

# Update Breast Cancer 2021 Part 5 – Advanced Breast Cancer

## Update Mammakarzinom 2021 Teil 5 – fortgeschrittenes Mammakarzinom



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### Schlüsselwörter

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#### ABSTRACT

Despite the COVID 19 pandemic and mostly virtual congresses, innovation in the treatment of breast cancer patients continues at an unabated pace. This review summarises the current developments. Initial overall survival data for CDK4/6 inhibitor treatment in combination with an aromatase inhibitor as the first advanced line of therapy in treatment-naive postmenopausal patients have been published. Similarly, a tri-

al comparing trastuzumab-deruxtecan versus trastuzumab-emtansine revealed a clear benefit regarding progression-free survival. Understanding of biomarkers making checkpoint inhibitor therapy particularly effective is increasing, and new compounds such as oral selective estrogen receptor destabilisers (SERDs) are entering clinical development and completing the first phase III trials.

#### ZUSAMMENFASSUNG

Trotz der COVID-19-Pandemie und weitgehend virtueller Kongresse schreitet die Innovation in Bezug auf die Behandlung von Patientinnen mit Mammakarzinom mit ungebremster Geschwindigkeit fort. Dieser Übersichtsartikel fasst die aktuellen Entwicklungen zusammen. Die ersten Daten zum Gesamtüberleben für eine Therapie mit einem CDK4/6-Inhibitor in Kombination mit einem Aromatasehemmer bei nicht vorbehandelten, postmenopausalen Patientinnen in der ersten fortgeschrittenen Therapielinie wurden veröffentlicht. Ebenso zeigte eine Studie, die Trastuzumab-Deruxtecan mit Trastuzumab-Emtansin verglich, einen deutlichen Vorteil in Bezug auf das progressionsfreie Überleben. Die Kenntnisse über Biomarker, die eine Therapie mit einem Checkpoint-Inhibitor besonders effektiv machen, nehmen zu, und neue Substanzen wie die oralen selektiven Östrogenrezeptor-Destabilisatoren (SERDs) halten Einzug in die klinische Entwicklung und schließen die ersten Phase-III-Studien ab.

## Introduction

Almost 50 years ago, tamoxifen was one of the first targeted drugs to be approved for the treatment of patients with breast cancer [1]. Similarly, trastuzumab, a monoclonal antibody targeting HER2 was approved almost 25 years ago [2]. These targeted medications have profoundly improved the prognosis in breast cancer patients and changed the therapeutic landscape of breast cancer forever. Despite the initial success, it was obvious that a large percentage of patients would become resistant to these regimens. That is why new therapeutic options have been developed over the past decades, based on the specific knowledge of these resistance mechanisms. Assessment of CDK4/6 inhibitors is coming to an end in the sense that overall survival data are now also available for first-line therapy in pre- and postmenopausal patients. Moreover, convincing data are available on the new antibody drug conjugate (ADC) trastuzumab-deruxtecan. After the initial enthusiasm for immunotherapies, there is also increasing evidence on those situations when these treatments are more, or less, effective. The latest developments based on newly published, clinically significant trials, recent publications in international journals and international congresses such as ASCO 2021 and ESMO 2021 are presented below.

## Long-term Data on Treatment with CDK4/6 Inhibitors in HR-positive, HER2-negative Breast Cancer Patients

Long-term data on overall survival have now been published from some of the initial large-scale trials on CDK4/6 inhibitors [3–6]. While these data were collected through supplemental analyses in the PALOMA-3, MONALEESA-3 and MONALEESA-7 trials, the data presented by the MONALEESA-2 trial were the first on overall survival. Median follow-up times ranged from 54 months in MONALEESA-7 to 80 months in MONALEESA-2 (► **Table 1**). The primary analysis of overall survival demonstrated benefits in overall survival with hazard ratios ranging from 0.71 to 0.81. Long-term follow-up analysis, when the vast majority of patients were no longer on therapy, revealed that the hazard ratios remained similar over time (► **Table 1**).

The recent publication of the primary overall survival analysis of the MONALEESA-2 trial [3] was important in interpreting the treatment situation, as this trial only enrolled patients with first-line treatment and did not include patients with evident endocrine resistance. Thus, this patient population corresponds to most patients also treated in clinical practice. The MONALEESA-2 trial enrolled patients who were de novo metastatic or had a disease-free interval of more than 12 months following primary treatment. At the time of the overall survival analysis, these 668 patients had a median follow-up of 80 months and 400 deaths

► **Table 1** Summary of current trials with a CDK4/6 inhibitor in advanced treatment settings.

Trial	Combined partner	Focused on	Enrolment from to (n)	PFS 95%-CI	OS 95%-CI	median FU primary OS analysis	OS <sup>§</sup> 95% CI	median FU longest OS analysis <sup>§</sup>	References
MONALEESA-2	Ribociclib Letrozol	Pt. w/o endocrine resistance (first-line)	02/2014–03/2015 (n = 668)	0.56 (0.43–0.72)	0.76 (0.63–0.93)	80	0.76 ** (0.63–0.93)	80**	[6, 43, 44]
MONARCH 3	Abemaciclib Aromatase inhibitor	Pt. w/o endocrine resistance (first-line)	11/2014–11/2015 (n = 493)	0.54 (0.41–0.72)	Yet unknown	NA	NA	NA	[45]
PALOMA-2	Palbociclib Letrozol	Pt. w/o endocrine resistance (first-line)	02/2013–07/2014 (n = 666)	0.58 (0.46–0.72)	Yet unknown	NA	NA	NA	[46]
MONALEESA-7	Ribociclib Premenopausal endocrine therapy	Pt. w/o endocrine resistance (first-line)*	12/2014–08/2016 (n = 672)	0.55 (0.44–0.69)	0.71 (0.54–0.95)	34.6	0.76 (0.61–0.96)	53.5	[47, 48]
MONALEESA-3	Ribociclib Fulvestrant	Pt. with and w/o endocrine resistance	06/2015–06/2016 (n = 726)	0.593 (0.48–0.73)	0.72 (0.57–0.92)	39.4	0.73 (0.59–0.90)	56.3	[49, 50]
MONARCH 2	Abemaciclib Fulvestrant	Pt. with endocrine resistance	08/2014–12/2015 (n = 669)	0.553 (0.45–0.68)	0.757 (0.61–0.95)	47.7	0.757 ** (0.61–0.95)	47.7**	[51, 52]
PALOMA-3	Palbociclib Fulvestrant	Pt. with endocrine resistance	10/2013–08/2014 (n = 521)	0.46 (0.36–0.59)	0.81 (0.64–1.03)	44.8	0.81 (0.65–0.99)	73.3	[43, 44]
DAWNA-1	Dalpiciclib	Pt. with endocrine resistance	unknown (n = 361)	0.45 (0.32–0.64)	NA	NA	NA	NA	

\* Prior chemotherapy allowed in advanced treatment setting.

\*\* The analysis of the longest OS available is also the primary analysis.

§ If the long-term follow-up analyses are not the primary analyses, they must be considered exploratory.

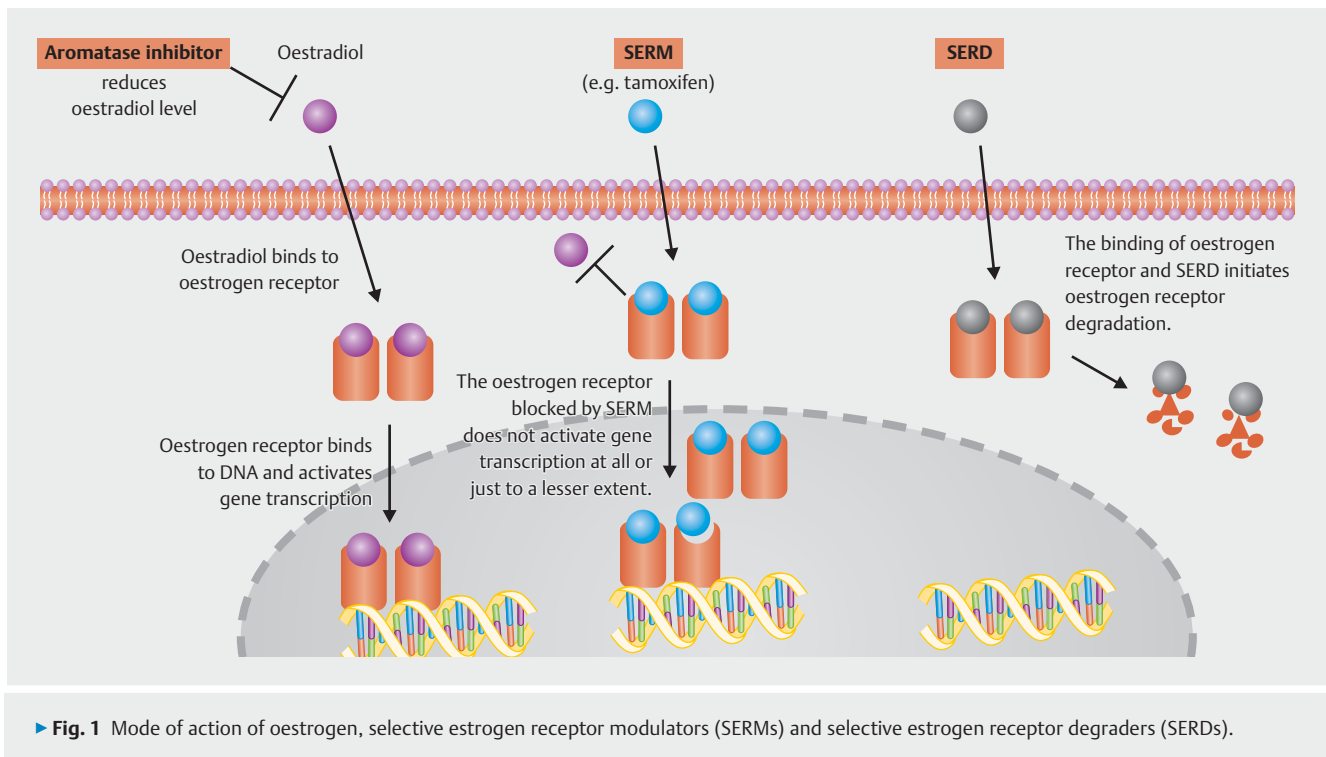
NA = not applicable (not published yet)

were recorded, 181 of which occurred in the ribociclib arm and 219 in the monotherapy arm at 1:1 randomisation. Thus, the benefit favouring the ribociclib arm was 24% with a hazard ratio of 0.74 (95% CI: 0.63–0.93) [3]. This difference was statistically significant. The therapeutic benefit was detectable across almost all subgroups, but in the analysis of de novo metastatic patients vs. patients after relapse a trend was noted, as the positive effect favouring ribociclib was mainly seen in the group of de novo patients [3].

Although there had already been data on first-line treatment from the other trials, this was the first study to collect these data for postmenopausal patients without specific resistance criteria when combined with an aromatase inhibitor. Thus, combined treatment with CDK4/6 inhibitors and endocrine therapy was confirmed as the standard first-line treatment.

The data from the PALOMA-2 and MONARCH 3 trials have not yet been published, but the current (as of December 2021) minimum follow-up times (PALOMA-2 trial: 88 months; MONARCH 3: 72 months) should indicate that these publications are imminent (► **Table 1**).

Apart from the large randomised phase III trials, another trial has now been presented, which had been conducted in China with the CDK4/6 inhibitor dalpiciclib developed for the Chinese market. Patients after progression on endocrine therapy could be randomised to fulvestrant monotherapy versus fulvestrant in combination with dalpiciclib. With a median follow-up of 10.7 months, the centrally calculated hazard ratio for progression-free survival was 0.45 (95% CI: 0.32–0.64) (► **Table 1**).



## Continued Development of Antihormonal Therapy

### Patient outcomes after CDK4/6 inhibitor therapy

With the establishment of CDK4/6 inhibitors as standard first-line therapy and the first evidence of benefit in early-stage patients [7], the question of meaningful treatment options following CDK4/6 inhibitor therapy is becoming increasingly important. Research is being vigorously pursued into molecular markers that can predict the efficacy of CDK4/6 inhibitor-based therapy. In addition, research is being conducted on the mechanism of progression under – or at the end of – CDK4/6 inhibitor-based therapy and how to harness it for subsequent treatments.

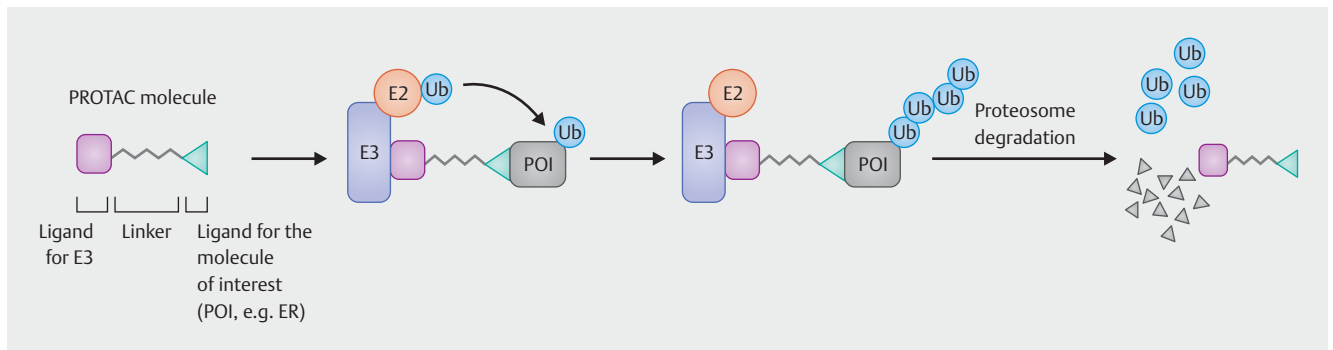
A number of biomarker analyses have already been carried out as part of the prospective randomised trials. In the PALOMA-3 study, for example, mutation analyses and amplification analyses of circulating tumour DNA (ctDNA) were correlated with progression-free survival. Amplifications in *FGFR1* and a *TP53* mutation appeared to be predictive for treatment with fulvestrant and palbociclib, while *TP53* and *ESR1* mutations seemed to play a role in treatment with fulvestrant alone [8]. Pooled ctDNA analyses from the MONALEESA trials identified several genes as possible predictors of better or worse ribociclib activity (*FRS2*, *MDM2*, *PRKCA*, *ERBB2*, *AKT1 E17K*, *BRCA1/2*, *CHD4*, *ATM* and *CDKN2A/2B/2C*) [9]. In the PADA-1 trial, patients treated with palbociclib and fulvestrant were shown to have a worse prognosis if an *ESR1* mutation was detected in the ctDNA or if the mutation load of *ESR1* mutations was not reduced [10]. These data and the known information on the efficacy of new anti-endocrine agents have led to

study designs making use of the knowledge of molecular mechanisms of progression, such as the SERENA-6 trial (see below).

### First phase III trial with oral SERDs (selective estrogen receptor degraders) in patients with advanced breast cancer positive

Fulvestrant was the first SERD approved for treatment of metastatic breast cancer. Together with aromatase inhibitors and tamoxifen as SERM, these three substances constitute the foundation of anti-endocrine therapy in breast cancer patients. The mode of action of these substances is summarised in ► **Fig. 1**.

Establishing the SERD fulvestrant clinically has been difficult. For a long time after approval (initially in 2004), the introduction of this drug was accompanied by difficulties in defining the correct dosage, and the EMA approval as first-line treatment in advanced stages was only granted in 2017 [11]. The only adjuvant trial with fulvestrant was terminated prematurely [12]. Partly responsible for this long development phase was a rather unfavourable pharmacokinetic profile, which requires intramuscular drug injection and, even with this mode of administration, it takes months for the plasma levels to stabilise [13]. This is the reason why the known dose of 500 mg is needed to reach adequate plasma levels even in the initial treatment period. This illustrates that the development of oral SERDs with more stable bioavailability could improve therapy. ► **Table 2** gives an overview of the SERDs under development. A press release recently announced that the EMBER trial of the oral SERD elacestrant met the primary study objective. Patients were included after treatment with a CDK4/6 inhibitor in combination with either an aromatase inhibitor or fulvestrant. Patients were then randomised to monotherapy with elacestrant or standard endocrine therapy (either fulvestrant or



► **Fig. 2** Mode of action of PROTACS such as ARV-471 degrading the oestrogen receptor.

► **Table 2** Current selective estrogen receptor degraders (SERDs).

SERD Substance Code (Name)	Name of study programme	References
LSZ102	unknown	[53]
G1T48 (rintodestrant)	PRESERVE	[54, 55]
RAD1901 (elacestrant)	EMERALD	[14, 56]
GDC-9545 (giredestrant)	...ERA (coopERA, lidERA, perseveERA)	[57–59]
SAR439859 (amcenestrant)	AMEERA	[60–62]
AZD9833 (camizestrant)	SERENA	[63]
LY3484356 (imlunestrant)	EMBER	[64–66]
Zn-c5	unknown	[67]
D-0502	unknown	[68]
ARV-471*	unknown	[15]
H3B-5942**	unknown	[69]

\* New class of SERD (Proteolysis Targeting Chimera, PROTAC)

\*\* New class of SERD (Selective Estrogen Receptor Covalent Antagonist; SERCA)

an aromatase inhibitor). The trial demonstrated that elacestrant significantly prolonged PFS [14]. The trial enrolled patients with and without somatic *ESR1* mutation, and the oral SERD had a benefit in both patients with and without the mutation.

### PROTAC – New class of substances made useful as SERD

In addition to the SERDs known to date, there are other substances with this effect belonging to a new class of drugs called PROTACs (Proteolysis Targeting Chimeras), which are hetero-bifunctional molecules with a ligand for a protein of interest (in this case the oestrogen receptor) on one side and another ligand on the other side acting as a substrate for the E3 ubiquitin ligase complex. This binds the protein to be degraded to the ubiquitin-proteasome system triggering the degradation (► **Fig. 2**). ARV-471 is a PROTAC targeted against the oestrogen receptor [15]. In a phase I trial, objective response was achieved in 4 out of 14 pa-

tients with advanced breast cancer and massive prior treatment. None of the patients experienced primary progression [15].

### Therapeutic sequences and their rationale

The importance of *ESR1* mutations as one of the resistance mechanisms against antihormonal treatment or combination therapy with CDK4/6 inhibitors has been postulated for some time [8, 10]. The SERENA-6 trial [16] is one example of studies making use of this knowledge. Existing and de novo *ESR1* mutations in ctDNA are measured before and during treatment with a CDK4/6 inhibitor plus an aromatase inhibitor. These patients are then randomised to continue CDK4/6 inhibitor therapy with the aromatase inhibitor or a SERD as new combined partner [16].

A number of therapeutic options have been and are being investigated in the post-CDK4/6 inhibitor setting. Although data on the efficacy of alpelisib in patients with *PIK3CA* mutations have already been collected with the SOLAR-1 trial [17], few patients received a CDK4/6 inhibitor prior to therapy with alpelisib and fulvestrant. This is why EPIK-B5, a prospective randomised trial still enrolling patients, is studying this question in patients after treatment with CDK4/6 inhibitors [18].

One trial that has already been conducted in this treatment setting did not achieve its study objective. The VERONICA trial was offered to patients with two or fewer lines of treatment and after CDK4/6 inhibitor therapy. Patients received either fulvestrant monotherapy or a combination of fulvestrant and venetoclax. Venetoclax is a Bcl-2 inhibitor already approved in patients with various haematological neoplasms. The trial did not reveal any difference in PFS between the randomisation arms (HR: 0.94; 95% CI: 0.61–1.45). In terms of overall survival, there was even a signal favouring monotherapy (HR: 2.56; 95% CI: 1.11–5.89).

It should be noted that CDK4/6 inhibitors will probably remain the standard of care in first-line treatment for a long time [19]. With this context in mind, it will be extremely important to understand the mechanisms of progression. Although the large CDK4/6 inhibitor trials have collected biomaterials, these may not be large enough to apply modern analytical techniques. One trial that may be of interest in this context is the HARMONIA, which compares ribociclib versus palbociclib in the group of PAM50 HER2 enriched patients. An extensive translational research programme is also being undertaken in this trial [20].

## Still Significant Progress in the Treatment of HER2-positive Breast Cancer Patients

### Trastuzumab-deruxtecan (T-DXd) versus T-DM1

With trastuzumab, the trastuzumab biosimilars, lapatinib, pertuzumab, T-DM1, neratinib, tucatinib and T-DXd, a wide range of drugs are available for the treatment of patients with HER2-positive breast cancer. Most of them improved the prognosis significantly, so that patients with HER2-positive breast cancer now belong to the group of patients with better prognosis compared to other molecular subtypes [21, 22]. Nevertheless, the introduction of new substances has always led to new advances. The latest compound to demonstrate clear benefits in a randomised trial was the receptor tyrosine kinase inhibitor tucatinib, which improved progression-free survival and overall survival in a population largely with pertuzumab and T-DM1 as prior treatment [23]. Data on T-DXd from a prospective randomised trial have also now been published. The study population had to have undergone prior treatment in the advanced therapeutic setting. Thus, almost all patients had received trastuzumab and about 61% also pertuzumab before the trial. The question tested was which of the antibody drug conjugates (ADC), T-DM1 or T-DXd, would result in better progression-free survival and overall survival. The question could be answered clearly: The hazard ratio for PFS was 0.28 (95% CI: 0.22–0.37;  $p = 7.8 \times 10^{-22}$ ) in favour of T-DXd. While the median progression-free survival under T-DM1 was 6.8 months, it had not yet been reached in the T-DXd group at the time of this analysis [24]. The trial thus not only established T-DXd as a new treatment standard in the corresponding therapeutic setting in which T-DM1 had previously been administered, but also demonstrated that there was a real medical need for T-DM1 in the sequence following pertuzumab. In the EMILIA study, the median PFS with T-DM1 was 9.6 months, but it must be remembered that these patients did not receive prior treatment with pertuzumab. Corresponding data from real-world registries are similar to the DESTINY-Breast03 trial, in which the median PFS was 7.7 months in second-line therapy after prior treatment with pertuzumab and 3.4 months in third-line therapy [25]. Hence, in this therapeutic setting, T-DXd significantly improved the treatment of HER2-positive breast cancer. Although the median PFS for T-DXd had not yet been reached, the 12-month PFS rate gives a clear indication. It was 34.1% with T-DM1 and 75.8% with T-DXd. However, it should be noted that the initial phase of the trial during therapy with T-DXd saw a number of deaths resulting from pneumonitis/interstitial lung disease (ILD) [26]. Although there were significantly more ILD cases as a side effect compared with T-DM1 (10.5% vs. 1.9%, a total of 27 cases under T-DXd) in the DESTINY-Breast03 trial, none of these side effects resulted in death [24]. Presumably, this is the consequence of stringent side-effect management, which requires that in respiratory symptoms onset, therapy is stopped immediately, diagnostic workup by high-resolution CT is performed, and corticosteroid therapy is initiated [27].

### Antibody-drug conjugates on the rise

ADC technology has fostered the clinical development of a number of new drugs, of which trial results are now slowly being published. One such study is the TULIP trial, which uses the ADC SYD985 and also trastuzumab-duocarmycin [28]. Duocarmycin is a DNA alkylane first isolated from streptomyces bacteria in the 1970s [29]. The TULIP trial enrolled 437 patients with advanced HER2-positive breast cancer who had completed at least two anti-HER2 regimens in the advanced treatment setting or already received T-DM1. Randomisation was 2:1 for treatment with SYD985 every three weeks versus treatment of physician's choice (lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + vinorelbine, trastuzumab + eribulin). More than 85% of patients had received prior treatment with T-DM1 and about 60% also with pertuzumab [28].

Comparison of both randomisation arms found better progression-free survival with trastuzumab-duocarmycin (SYD985). The hazard ratio was 0.64 (95% CI: 0.49–0.84;  $p = 0.002$ ) [28]. Overall survival revealed improvement without statistical significance (HR: 0.83; 95% CI: 0.62–1.09;  $p = 0.153$ ) [28].

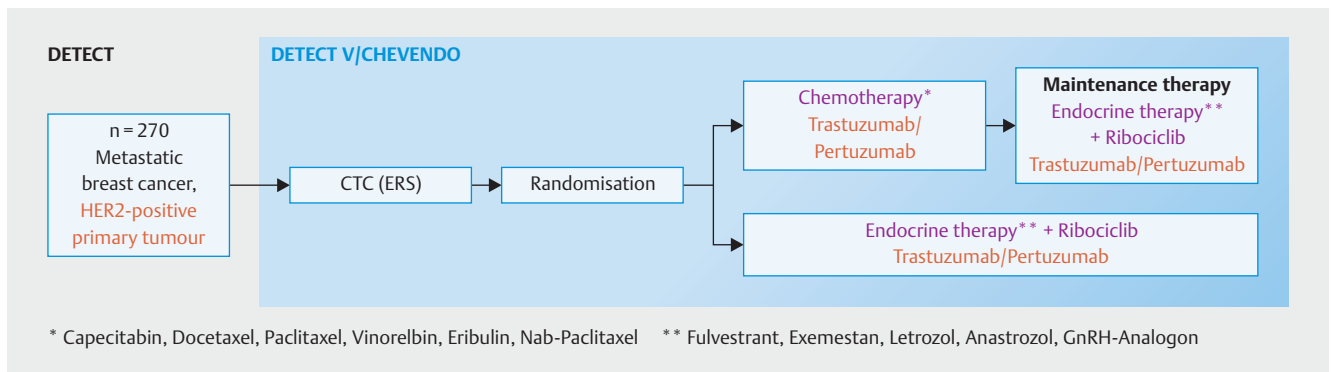
Interestingly enough, this treatment causes side effects that have not been the focus of breast cancer therapeutics so far. Conjunctivitis and keratitis were seen in about 38% of patients [28]. As with T-DXd, 7.6% of patients treated with SYD985 also developed pneumonitis.

The treatment options in patients with HER2-positive breast cancer will definitely undergo significant changes in the next few years. Tucatinib and T-DXd are two new, effective substances currently being tested in extensive trial programmes. The near future will show whether these drugs from the advanced therapeutic setting will also be included in the treatment of patients with early-stage disease. Enrolment in corresponding trials has already started.

### Endocrine therapy instead of chemotherapy combined with trastuzumab

In the sysucc-002 trial, patients with hormone receptor-positive, HER2-positive metastatic breast cancer were randomised undergoing first-line treatment were randomised between endocrine therapy plus trastuzumab and chemotherapy plus trastuzumab [30]. Almost two thirds of the 392 patients enrolled in the trial had visceral metastasis, about one quarter were diagnosed with de novo metastasis, and only about one quarter of the patients had previously received HER2-targeted therapy.

Analysis of progression-free survival revealed no significant difference between both arms (HR: 0.88, 95% CI: 0.71–1.09; log-rank: 0.25). Only patients with a disease-free period of less than 24 months experienced a non-significant benefit from chemotherapy (HR: 1.39, 95% CI: 0.97–1.98). There was no significant difference in overall survival. This study is the first phase III trial to directly compare chemotherapy with endocrine therapy in the context of HER2-targeted therapy in triple-positive metastatic breast cancer. Weaknesses of this study include the fact that neither a dual blockade with trastuzumab and pertuzumab was employed, which is the global standard in therapy, nor was a CDK4/6 inhibitor included. The DETECT-V trial (<http://www.detect-studien.de>, ► **Fig. 3**), which is actively enrolling patients in Ger-



► Fig. 3 DETECT-V study design.

many, takes this much more modern approach and patients can still be enrolled in it.

## Immunotherapies – Much Remains to Be Learned

### Checkpoint inhibitors and biomarkers

In some indications, PD-L1-positive cells must be identified. The indication for atezolizumab in advanced first-line treatment is linked to the presence of PD-L1-positive immune cells covering at least 1% of the tumour area. The indication for pembrolizumab is linked to a share of PD-L1-expressing immune and tumour cells (combined positive score, CPS) of at least 10. In neoadjuvant settings, PD-L1 expression is not predictive of pembrolizumab efficacy [31]. Although in the neoadjuvant KEYNOTE-522 trial the pCR rates increased with increasing PD-L1 expression, this was the case in both the arm with and the arm without pembrolizumab. Chemotherapy combined with a PD-1/PD-L1 therapeutic agent could also have an impact on efficacy, as the combination of atezolizumab and nab-paclitaxel in IMpassion130 resulted in a better prognosis [32], while in IMpassion131 the combination of atezolizumab and conventional soluble paclitaxel did not improve prognosis [33]. Similarly, tumour-infiltrating lymphocytes have been linked to both efficacy and prognosis in breast cancer patients [34, 35]. Immune-related markers of gene expression have previously been associated with response to chemotherapy [36, 37].

Data from a comprehensive translational analysis of the IMpassion130 trial have now been presented in light of this context [38]. The tumours of the patients enrolled in this trial were classified according to the following immunophenotypes [39]:

- Immune desert: Despite the presence of immune cells, these tumours do not have T-cells that could attack the malignancy. So there is no immune response.
- Immune-excluded phenotype: In these tumours, while there is indeed an increased number of immune cells, these are not localised in the parenchyma, but only in the stroma surrounding the tumour.

- Immune-inflamed phenotype: In these tumours, the numerous immune cells in the parenchyma appear to be in direct contact with the tumour cells.

Analysis of the IMpassion130 trial in relation to this classification revealed that in PD-L1 positivity, the hazard ratio for overall survival in the immune-inflamed phenotype showed the greatest effect favouring atezolizumab (HR: 0.61; 95% CI: 0.42–0.88) [38].

A classification dividing triple-negative tumours into subtypes based on their gene expression was also tested [40].

- BLIA: strong expression of genes of the immune system
- BLIS: high proliferation and glycolysis
- LAR: strong expression for the oestrogen and androgen pathway and strong expression for lipid metabolism genes.
- MES: strong expression for angiogenesis, myogenesis, oestrogen, and androgen signalling genes, TGF-beta, fibroblasts, and endothelial cells.

It was shown that the BLIA phenotype in particular predisposed to a response to atezolizumab therapy. The hazard ratio for overall survival was 0.54 (95% CI: 0.36–0.80).

Despite the success of immune checkpoint inhibitors and their use in standard treatment options, much remains to be learned about the pattern of efficacy of these therapies. Especially with the relevant side effect profile, everything should be tried to better assess the risk-benefit profile of this treatment. Identifying subgroups with particularly high and particularly low levels of efficacy could help.

### Pembrolizumab as newly approved treatment option

In the first-line treatment patients with advanced TNBC and a CPS score of 10 or more, data from the KEYNOTE-355 trial already showed that median progression-free survival improved from 5.6 months with chemotherapy to 9.7 months with chemotherapy + pembrolizumab (HR = 0.65; 95% CI: 0.49–0.86) [41]. These data have now been supplemented by further analysis of overall survival [42]. Another planned analysis called for a p-value of 0.0113. Indeed, median overall survival was prolonged from 16.1 months to 23.0 months (HR = 0.73; 95% CI: 0.55–0.95; p = 0.0093). Thus, a significant improvement in overall survival

has also been demonstrated. In the United States, pembrolizumab was available in May 2021 and in Europe in October 2021.

## Outlook

The MONALEESA-2 trial was the first to publish overall survival data in first-line treatment combined with an aromatase inhibitor in postmenopausal patients. Data from the MONARCH-3 and PALOMA-2 trials are still pending. Since the last patients were enrolled in July 2014 (PALOMA-2) and November 2015 (MONARCH 3) respectively, publication is expected soon. Only then can the entire study data be comprehensively assessed. The therapeutic benefit of T-DXd over T-DM1 is a significant step forward for the treatment of patients with advanced HER2-positive breast cancer. However, other trials are active – also with another very effective anti-HER2 drug (tucatinib) – studying the benefit in first-line treatment versus pertuzumab, and also trials in the (neo-)adjuvant setting. It may become complex in this context how new therapeutic sequences will establish themselves.

The path towards treatment based on molecular markers is already well underway with new trials such as SERENA-6. Additional trials related to the PI3K pathway and homologous recombination are underway to explore whether these approaches will result in better personalised therapy.

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### Correction

#### Update Breast Cancer 2021 Part 5 – Advanced Breast Cancer

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In the above-mentioned article, the institute details were mixed up for two authors. Correct is:

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