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Update Breast Cancer 2018 (Part 4) – Genomics, Individualized Medicine and Immune Therapies – in the Middle of a New Era: Treatment Strategies for Advanced Breast Cancer

Update Mammakarzinom 2018 (Teil 4) – Genomforschung, individualisierte Medizin und Immuntherapien – mitten in einer neuen Ära: Therapie des fortgeschrittenen Mammakarzinoms

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ABSTRACT

New therapeutic developments aimed at treating women with advanced breast cancer currently focus both on identifying patients eligible for targeted therapeutic concepts and on the continuing development of immune therapies. The data on CDK4/6 inhibitors are now complete and consistent in this class of substances (palbociclib, ribociclib and abemaciclib). Further pathways under investigation are PI3K and AKT signalling pathways along with diverse approaches to their inhibition. Initial study results were also presented recently on both mechanisms of action. Insights into the PARP inhibitors, moreover, are increasing; studies in this respect are also examining in which population they can be used most effectively. This review offers a summary of the recent studies and an outline of the latest developments.

ZUSAMMENFASSUNG

Neue Therapieentwicklungen zur Behandlung von Patientinnen mit fortgeschrittenem Mammakarzinom konzentrieren sich zurzeit sowohl auf die Identifikation von Patientinnen für zielgerichtete Therapieansätze als auch auf die Weiterentwicklung von immuntherapeutischen Ansätzen. Die Datenlage zu den CDK4/6-Inhibitoren konnte vervollständigt werden und ist konsistent in dieser Klasse von Substanzen (Palbociclib, Ribociclib und Abemaciclib). Weitere Signalwege, die untersucht werden, sind der PI3K-und der AKT-Signalweg sowie verschiedene Ansatzpunkte zu deren Hemmung. Für beide Wirkmechanismen liegen auch erste Studienergebnisse vor, die vor Kurzem vorgestellt wurden. Außerdem wachsen die Erkenntnisse zu den PARP-Inhibitoren, für die auch untersucht wird, in welcher Population sie am effektivsten eingesetzt werden können. Dieser Review-Artikel soll die aktuellen Studien zusammenfassen und einen Ausblick der neuesten Entwicklungen geben.

Introduction

Metastatic breast cancer is still a therapeutic situation in which the prognosis is especially unfavourable [1]. In recent years, however, treatments have been introduced for individual subgroups which in terms of survival have demonstrated a significant effect. Hence, HER2-positive metastatic breast cancer no longer has one of the poorest prognoses and could now belong to the group with the best prognosis [2]. This is partly due to the introduction of new anti-HER2 drugs [3–5]; however, improved patient care could also be responsible for such an achievement. New drugs such as mTOR and CDK4/6 inhibitors have also been introduced for other subtypes such as hormone receptor-positive HER2-negative metastatic breast cancer and have brought an improvement in progression-free survival [6–9]. The most promising introduction of a new substance class for triple-negative or *BRCA1/2*-mutated breast cancer is the PARP inhibitors, which have demonstrated an improvement in progression-free survival in several studies, also compared to conventional chemotherapy [10–13]. Last but not least, various efforts have been made above all in metastatic breast cancer to improve the monitoring of the disease. In this respect the methods have been developed more in the direction of molecular analysis so that individual tumour-specific properties such as tumour mutations or gene expression on circulating tumour cells in the blood can be detected [14, 15].

This review will explain new aspects of metastatic disease based on the latest publications and congresses that have taken place in 2018. In doing so, special attention is paid to the implementation of targeted therapy which attempts to maximise the effect on the disease at the same time as minimising the adverse effects so that quality of life remains as high as possible.

Advanced Breast Cancer – the HER2-Positive Patient

The survival of patients with HER2-positive metastatic cancer has improved significantly in recent years due to the use of anti-HER2 monoclonal antibodies, dual blockade with trastuzumab and pertuzumab, and treatment with antibody-toxin conjugates (T-DM1) [3, 5, 16]. Compared to docetaxel/trastuzumab-based therapy, dual blockade with pertuzumab and trastuzumab combined with docetaxel resulted in substantially prolonged survival at an additional 15.7 months [4, 16].

It was previously unclear whether the addition of pertuzumab to trastuzumab and chemotherapy beyond the first-line setting offered any benefit. The PHEREXA study was thus designed to investigate the addition of pertuzumab to a combination of trastuzumab and capecitabine as second-line therapy following first-line treatment comprising taxane and trastuzumab in patients with HER2-positive metastatic breast cancer [17]. Capecitabine was administered at a dose of 1000 mg/m^2 body surface area in the experimental arm versus 1250 mg/m^2 in the standard arm. The primary endpoint of the study was PFS; secondary endpoints were overall survival and adverse effects. In the final analysis, the difference in PFS was 2.8 months with hazard ratio (HR) of 0.83 (95% confidence interval [CI]: 0.68 to 1.02) and comparative survival 9.1 months with HR of 0.78 (95% CI: 0.6 to 0.98). Hence, there was no significant PFS advantage but a signal for improved overall survival [17]. Due to the small sample size, however, the study could not be analysed with sufficient statistical certainty and the control arm did not comply with current standards for second-line T-DM1 therapy. The taxanes, with trastuzumab and pertuzumab, thus remain the first-line standard. Such treatment can also be considered for second-line management in patients who have not previously undergone dual blockade with trastuzumab and

pertuzumab. So far, no data are available on treatment with pertuzumab beyond progression.

Additional studies into advanced HER2-positive breast cancer are described under "Antibody-drug conjugates".

Advanced Breast Cancer – the Triple-Negative Patient

The disruption of homologous recombination (HRD; homologous repair deficiency) is of particular importance in breast cancer. HRD can develop either as a result of *BRCA1/2* mutations and mutations in other genes involved in homologous recombination or even without such mutations, and lead to variable tumour responses under treatment [18–22]. BRCA1/2 mutations are associated with a higher pCR rate after neoadjuvant chemotherapy [18, 23–25], especially platinum-based chemotherapy [24, 26]. For a new substance class, namely the PARP inhibitors, breast cancer patients were also selected for the respective treatments based on a *BRCA1/2* mutation due to a high level of efficacy with PARP inhibitor therapy. PARP inhibitors block enzymes that are involved in the repair of single-stranded DNA. The efficacy in patients with metastatic breast cancer and *BRCA1/2* mutations has been established in several studies [10–13]. One question is the extent to which treatment with PARP inhibitors is effective in triple-negative disease irrespective of a *BRCA1/2* mutation, given that two of the PARP inhibitors are approved for ovarian carcinoma even without a proven mutation in a platinum-sensitive tumour. This question was addressed by the Brightness study, though not in metastatic, but rather primary breast cancer. Triple-negative patients (TNBC) were recruited to this study irrespective of *BRCA1/2* mutation status and treated either with paclitaxel or with paclitaxel + carboplatin, or with paclitaxel + carboplatin + veliparib. In all three arms, this treatment was followed by doxorubicin and cyclophosphamide [27]. During the initial analysis it was found that the addition of carboplatin to paclitaxel increased the pCR rate, whereas the addition of veliparib brought no further increase in the pCR [27]. Another analysis recently examined the relationship between HRD and the effectiveness of the treatments in this study [28]. Higher pCR rates were noted in patients with HRD across all three treatment arms. However, the patients receiving carboplatin were found to have higher pCR rates in both the HRD-positive and the HRD-negative subgroups. The treatment with doxorubicin and cyclophosphamide in all patients could explain the missing correlation between the HRD status and the randomisation arms [28]. It could also be the case that the specific tests for identifying HRD do not suffice for PARP inhibitor therapy. Whereas there are genetic markers associated specifically with triple-negative breast carcinoma [29–34], these markers must not necessarily be associated with HRD and, conversely, a tumour with HRD need not necessarily be triple-negative. New tests for HRD which utilise whole-genome sequencing, for instance, could deliver comprehensive answers to these questions [35].

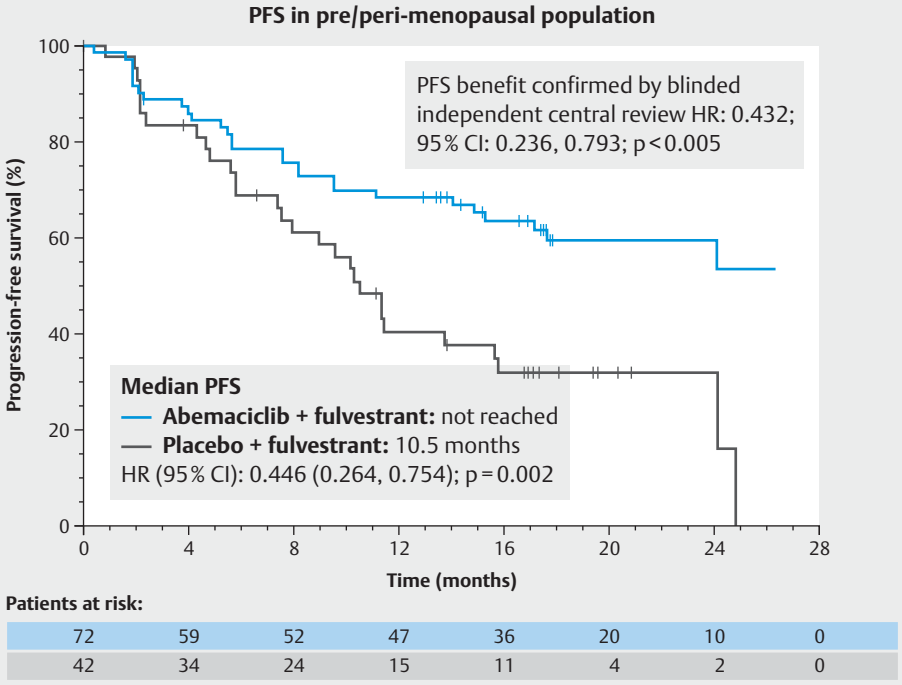
Another study, which in turn focused on patients with *BRCA1/2* mutation, employed talazoparib neoadjuvantly as monotherapy [36]. A total of 20 patients with *BRCA1/2* mutation were included in the study (17 patients with TNBC and three with hormone receptor-positive breast cancer). In 59% of the 17 patients evaluated, talazoparib resulted in a pCR [36]. Haematological toxicity was reported as a typical adverse effect and led to a dose reduction in more than half of the patients. Nevertheless, the possibility of chemotherapy-free treatment appears to be of great interest in this specific group of patients.

Approval is expected in Europe in the near future for PARP inhibitors in the indication of *BRCA1/2*-mutated metastatic breast cancer, thus opening up a new therapeutic option for these patients. The extent to which this treatment can be used in other tumours which either have a germ-line mutation in one of the other genes involved in homologous recombination [37] or in which another type of HRD has been detected, remains to be seen.

Advanced Breast Cancer – the HER2-Negative, Hormone Receptor-Positive Patient

CDK4/6 inhibitors regulate the G1/S-phase transition of the cell cycle which the cells must undergo in order to divide. With respect to the oral CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib, extended study programmes are in place consisting of ongoing or completed studies for improving the efficacy of endocrine therapy in hormone-receptor positive/HER2-negative breast cancer [6, 7]. In prospective, randomised phase III studies, all three CDK4/6 inhibitors were found to almost double the progression-free survival when combined compared to endocrine therapy alone. The relative improvement in the effect was demonstrated both in first-line therapy and subsequent treatment lines. The increased efficacy was confirmed both in young premenopausal and in postmenopausal patients, as well as patients with distant visceral and purely osseous metastases. The Breast Committee of the Working Group of Gynaecologic Oncology (AGO), which issues updated therapeutic guidelines on the treatment of breast cancer every year, therefore lists combined treatment with CDK4/6 inhibitors as the highest-level recommendation [38].

In terms of progression-free survival, the efficacy of the CDK4/6 inhibitor abemaciclib with fulvestrant was already shown in the past to be better than that of fulvestrant plus placebo (16.4 vs. 9.3 months; HR 0.553; 95% CI: 0.449, 0.681; $p < 0.0000001$) [39]. An analysis of the premenopausal and perimenopausal patients has now been presented [40]. Patients could be enrolled in the Monarch 2 study if they had not yet received chemotherapy for their metastatic disease and progressed while receiving neoadjuvant endocrine therapy, or within 12 months after or during adjuvant endocrine therapy in the metastatic setting. After approval, the patients were given 500 mg fulvestrant and 150 mg ademaciclib or placebo twice daily; premenopausal patients additionally received a GnRH analogue. The primary endpoint of the study was disease-free survival as assessed by the investigator [39]. Given the known efficacy of CDK4/6 inhibitors the efficacy of abemaciclib had also been anticipated by the study designers, resulting in 2 : 1 randomisation of the patients in the study. A total of 114 of the participating patients were premenopausal. The median survival of the patients in the placebo arm was 10.5 months, and no study endpoint was reached in the treatment group, meaning



▶ **Fig. 1** Progression-free survival of premenopausal and perimenopausal patients in the Monarch 2 study (after [40]).

that progression-free survival exceeded the period assumed by the study designers (HR 0.446; 95% CI: 0.264 to 0.754; p = 0.002). As in the analysis of the entire study group, the most frequent adverse effects were diarrhoea (treatment group 87.3% vs. placebo group 23.8%), neutropenia (59.2 vs. 7.1%) and leukopenia (43.7 vs. 4.8%) [40]. The study confirms the results of the Monaleesa 7 study which already demonstrated the outstanding efficacy of CDK4/6 inhibitors regardless of the age of the patients [41] (▶ **Fig. 1**).

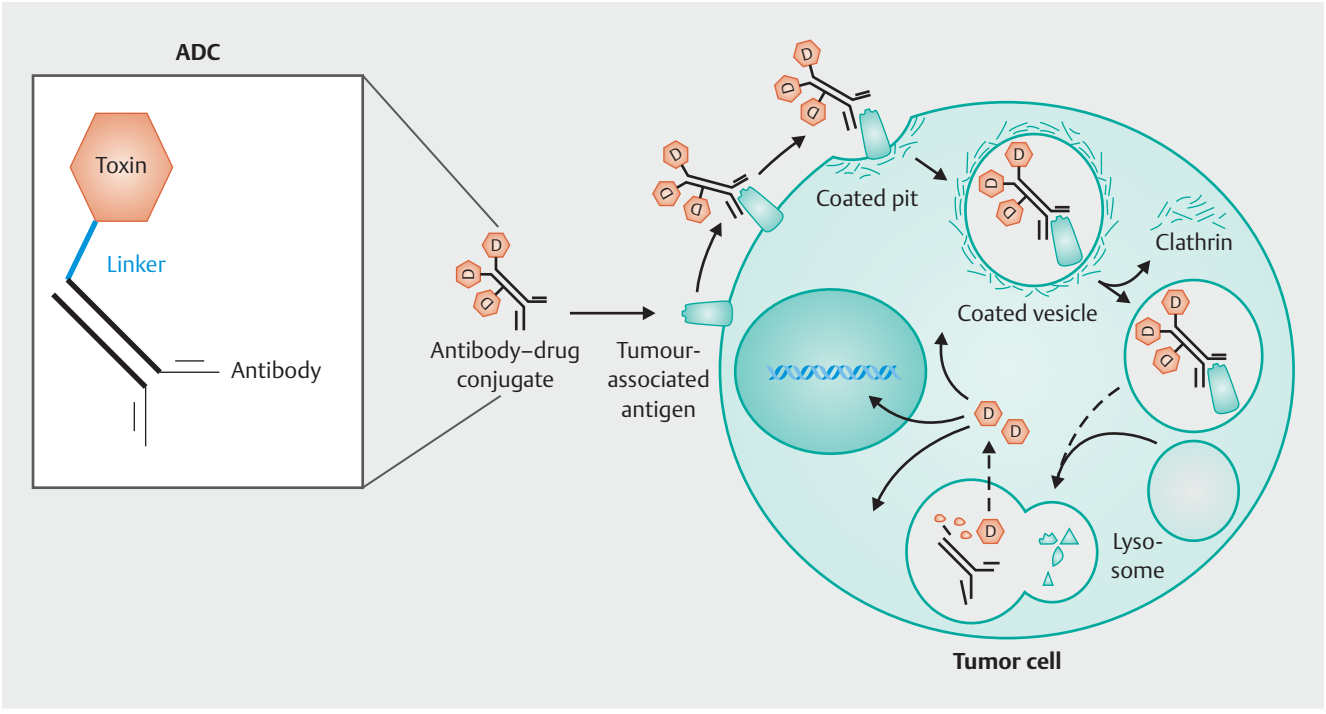
The progression-free survival of premenopausal and perimenopausal women was significantly prolonged by the administration of ademaciclib plus fulvestrant compared to fulvestrant alone [40].

The findings of the Monaleesa 3 study also demonstrated the efficacy of CDK4/6 inhibitors [42]. This study included postmenopausal patients with hormone receptor-positive HER2-negative breast cancer who had received no more than one endocrine treatment in the metastatic setting. The participants were given either 600 mg ribociclib (three weeks of treatment/one-week break) with fulvestrant or fulvestrant with placebo. The patients in this study were likewise randomised at a ratio of 2 : 1. The endpoint of the study was not reached in the treatment subgroup of patients who had not undergone endocrine therapy in the metastatic setting (compared to 18.3 months in the patients receiving standard treatment with fulvestrant alone) [42]. In the group that had already undergone treatment, median progression-free survival was still significantly longer at 14.6 months compared to 9.1 months. The reported adverse effects here were also grade 3/4 neutropenia (53.4 vs. 0%), elevated ALT and AST (6.6 vs. 1.9% and 4.8 vs. 1.2%) or a prolonged QTcF of over 480 ms on ECG (5.6 vs. 2.5%) [42]. The Monaleesa 3 study thus adds to the clinical data on the efficacy of ribociclib in combination with fulvestrant, positively supplementing the evidence in support of this combination as both first-line and second-line treatment and therefore increasing the flexibility of clinical management.

Interesting new data have been published on molecular profiles in relation to progression under CDK4/6 inhibitor therapy. Turner et al. presented an analysis from the well-known Paloma 3 study (palbociclib + fulvestrant versus fulvestrant monotherapy) of resistance mutations based on DNA circulating in the blood [43]. To this end, blood was tested in 193 women in whom CDK4/6-associated genes were examined before and after treatment. Whereas no *RB1* mutations were identified at the start of therapy, they were found in 4.8% of the patients after palbociclib and in none of the patients who had been treated with fulvestrant alone. *PIK3CA* and *ESR1* mutations occurred more frequently under both treatments and could be driver mutations for therapy resistance [43].

Advanced Breast Cancer – Antibody-Drug Conjugates

Immune toxins or antibody-drug conjugates are highly complex molecules whose basic structure is similar to that of the already established T-DM1: a monoclonal antibody conjugated with a cytotoxic moiety via a linker. One such molecule is illustrated in



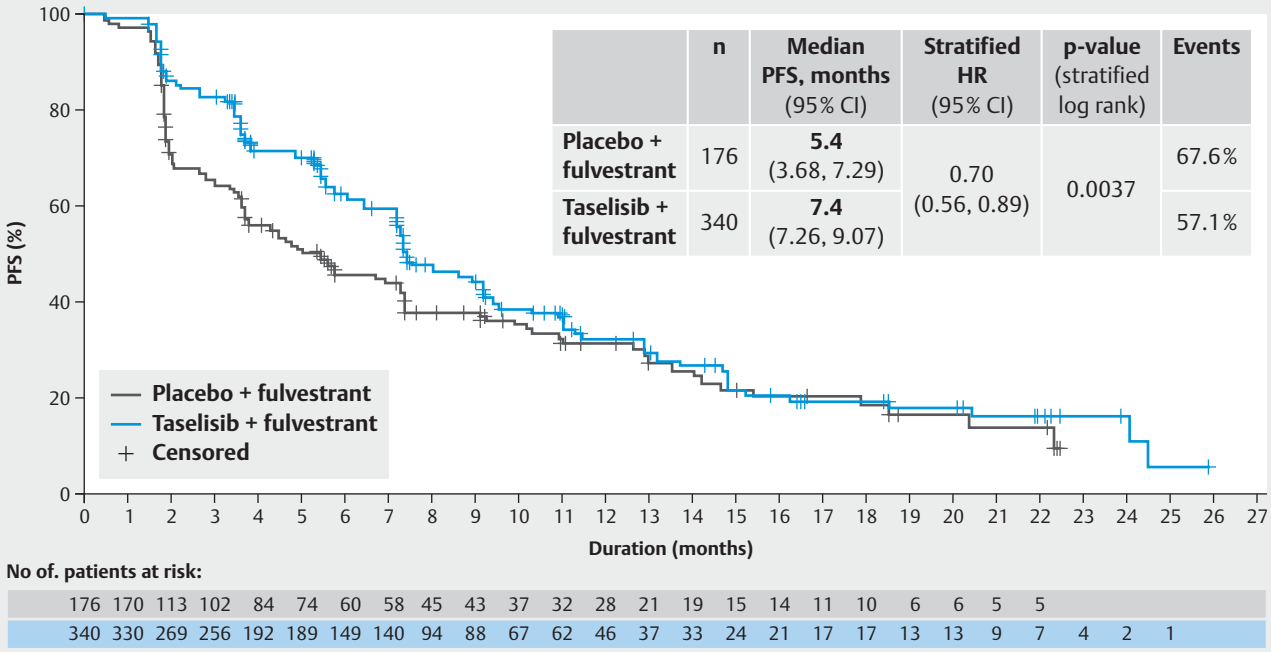
▶ **Fig. 2** Schematic diagram of an antibody-drug conjugate (antibody drug conjugate).

▶ **Fig. 2**. The data on three new, very promising antibody-drug conjugates were recently presented.

Bardia et al. studied sacituzumab-govitecan in metastatic hormone receptor-positive/HER2-negative breast cancer that had proved resistant to at least one or more prior treatments and was progressive (NCT01631552) [44]. The conjugate consists of SN-38, the active metabolite of the cytostatic irinotecan, conjugated with a humanised monoclonal antibody against TROP2 (trophoblast cell-surface antigen 2) The patients received sacituzumab-govitecan at a dose of 10 mg/kg on days 1 and 8 of a 21-day cycle until progression or unacceptable toxicity [44] A total of 54 patients with an average age of 54 years were treated between February 2015 and June 2017. Most patients had undergone at least two previous anti-hormonal treatments with CDK4/6 inhibitors and/or cytostatic drugs. By 31 December 2017, 16 patients had died, 27 were under long-term follow-up, and 11 were still on treatment. The median number of applications was 11. The treatment was generally tolerated well and there were no treatment-related deaths. Toxicity of grade ≥ 3 and ≥ 10 % entailed neutropenia and leukopenia. There was one incident in each case of grade ≥ 3 diarrhoea and febrile neutropenia. The overall response rate (ORR) was 31 % (17 partial remissions) and the clinical benefit rate (partial remission + stable disease > 6 months) was 48 %. In the patients given CDK4/6 inhibitors, the ORR was 24 % (9 partial remissions in 37 patients) [44]. The development of antibody-drug conjugates appears to offer great promise in the treatment of cancer. Active substances can be combined with trastuzumab, particularly for treating HER2-positive breast carcinomas.

One such new conjugate is SYD985, whereby trastuzumab is conjugated with duocarmazine. Saura et al. recently revealed the first set of efficacy data for patients who were heavily pretreated [45]. The dose-escalation stage of the phase I study was already complete; recent, preliminary efficacy data from the breast cancer extension cohorts and safety data were therefore presented. The patients were given 1.2 mg/kg body weight of SYD985 intravenously every three weeks until disease progression or unacceptable toxicity. Tumour evaluation scans were performed every six weeks. Expression of HER2 could be high or low, and the patients had to have received three or more previous anti-HER2 therapies, mostly including trastuzumab-emtansine. A total of 99 patients were included. SYD985 revealed an ORR of 33 % and mean PFS of 9.4 months. At the time of database lock, eight patients had been receiving SYD985 (16 %) for more than one year and five patients (10 %) were still on treatment. Efficacy was demonstrated even in heavily pretreated patients with low HER2 expression, including hormone receptor-positive (n = 32) and triple-negative breast cancer (n = 17). The safety profile was acceptable and adverse effects mainly of grade 1 and grade 2 were observed – most frequently tiredness, dry eyes and increased lacrimation. The most commonly reported grade 3/4 adverse drug reactions included neutropenia (6 %) and conjunctivitis (4 %).

Data are also available on an active substance conjugated with trastuzumab. Iwata et al. presented a multicentre, open phase II study with trastuzumab-deruxtecan (DS-8201a) in which treatment was administered to patients with HER2-positive but also HER2-non-overexpressing metastatic breast cancer, among others, who had previously received T-DM1 and were resistant to treatment [46]. DS-8201a is an HER2-targeted antibody-drug conjugate incorporating a humanised HER2 antibody that is attached to a topoisomerase-I inhibitor (deruxtecan) with a high ra-



	n	Median PFS, months (95% CI)	Stratified HR (95% CI)	p-value (stratified log rank)	Events
Placebo + fulvestrant	176	**5.4** (3.68, 7.29)	0.70 (0.56, 0.89)	0.0037	67.6%
Taselisib + fulvestrant	340	**7.4** (7.26, 9.07)			57.1%

No of. patients at risk:

176	170	113	102	84	74	60	58	45	43	37	32	28	21	19	15	14	11	10	6	6	5	5		
340	330	269	256	192	189	149	140	94	88	67	62	46	37	33	24	21	17	17	13	13	9	7	4	2	1

PFS was defined as the time from randomization to first disease progression as determined by investigator using RECIST V1.1, or death from any cause.
RECIST: Response Evaluation Criteria In Solid Tumors

▶ **Fig. 3** Progression-free survival in the SANDPIPER study in patients with a *PIK3CA* mutation (after [51]).

tio of active substance to antibody of 7 : 8. Data from the phase I study were already presented at the SABCS, revealing a manageable safety profile and promising anti-tumour activity [47]. In the presented study [46], the response rate in patients with HER2 overexpression was 64.2% and in those with non-overexpression 38.5% [46].

Advanced Breast Cancer – the PI3K/AKT Pathway

The PI3-kinase/AKT/mTOR signalling pathway plays an important role in regulating the malignant growth of breast carcinomas and thus is also a starting point for therapeutic interventions [48]. Everolimus is an approved mTOR inhibitor that has long been available in this context. A variety of new substances that target this signalling pathway are undergoing clinical development [49, 50].

Baselga et al. recently presented the results of the SANDPIPER study involving hormone receptor-positive, HER2-negative metastatic cancer patients who were given the PI3K inhibitor taselisib (GDC-0032) or placebo in each case combined with fulvestrant [51]. The study did reach its primary endpoint of a significant improvement in the PFS from 5.4 to 7.4 months in patients with an activating mutation in the PI3K signalling pathway (HR 0.7) (▶ **Fig. 3**) but, given the rather moderate advantage and distinctly increased rate of adverse effects (diarrhoea, hyperglycaemia, skin rash), the results were viewed with reservation. Further clinical development of the substance appears questionable [51].

Another therapeutic approach in the PI3 kinase/AKT/mTOR signalling pathway is the inhibition of AKT kinase. New AKT inhibitors are already being investigated in phase I and phase II clinical trials into the treatment of advanced cancers. Promising substances were presented in two talks at the ASCO in June 2018. Schmid et al. presented the results of their phase II study PAKT into AZD5363 (capivasertib), a highly selective oral AKT inhibitor, combined with paclitaxel in 140 patients with triple-negative breast cancer [52]. Whereas in the group without a modified PI3 kinase/AKT/mTOR signalling pathway the median overall survival from paclitaxel plus AZD5363 was 16.6 months vs. 13.2 months from paclitaxel alone (HR 0.84), the difference in the group with a modified PI3 kinase/AKT/mTOR signalling pathway was much greater: in the group given the AKT inhibitor, the median had not yet been reached and the HR was 0.37. Despite the small sample size of only 28 patients in this group with a modification, the result confers with another study: in the Lotus study, the oral AKT inhibitor ipatasertib was examined in combination with paclitaxel in 124 randomised patients. The initial results were already published [53] and an updated analysis has now been presented [54]. A greater advantage was also noted here from using the AKT inhibitor in patients with a modified PI3 kinase/AKT/mTOR signalling pathway: the PFS was increased from 4.9 to 9.0 months (HR 0.44) whereas in the entire group a difference of only 4.9 versus 6.2 months was noted (HR 0.6). A trend towards improved

overall survival was also observed. The final analysis of overall survival is expected in 2019. The results of the Lotus study offer a good rationale for the current, ongoing phase III study, IPATunity130 (NCT03337724), involving ipatasertib. Above all, the AKT inhibitors could generally be of clinical value in the future with respect to inhibiting the PI3 kinase/AKT/mTOR signalling pathway.

The Liquid Biopsy

In recent years, the detection of circulating tumour cells (CTCs) or tumour DNA (cfDNA) in the blood – also known as liquid biopsy – has attracted a great deal of attention. Whereas CTCs can be isolated and cultivated while still viable, cfDNA is obtained from apoptotic tumour cells. The liquid biopsy has in the meantime been thoroughly standardised. CTCs are detected through immunomagnetic beads, density gradient centrifugation or large filters. Furthermore, the Cell Search™ automated CTC detection system, which is approved by the FDA, can be used. Mass spectrometry, digital polymerase chain reaction (PCR) and next generation sequencing (NGS) permit detection of cfDNA. Both point mutations (single nucleotide variants) and insertions/deletions (indels), fusion genes and gene amplifications (copy number variations) are thereby detected [55 – 57].

A major advantage of the liquid biopsy is that it can be repeated at any time with a low risk of complications for the patient. This permits real-time recording of changing tumour biology (real-time biopsy) while chemotherapy is ongoing, for example. Unlike the classic tumour biopsy, the liquid biopsy also illustrates not only a small section of the generally very heterogeneous tumour or metastasis but rather represents a cross-section of the tumour biology of the parts of the tumour that are currently most active or all metastases. For this reason, the re-evaluation of predictive markers (e.g. of oestrogen and progesterone receptors and HER2 by means of CTCs or cfDNA) plays an important role. The great potential of liquid biopsy in the re-evaluation of therapeutically relevant markers was recently demonstrated in the study by Vidula et al. [58]. A comparative analysis revealed that survival in the patients with metastatic breast cancer who received treatment adapted to the genomic modifications was only significantly better than under standard therapy if the genomic analysis was performed on the cfDNA and not on the tumour tissue. The mutations were found more frequently in the cfDNA than in the tumour tissue, indicating genomic evolution of the breast carcinoma [59]. It was also noted that mutations in the Ras-Raf-ERK (MAPK) metabolic pathway detected through the cfDNA were the strongest independent prognostic factors for time to progression.

With respect to the prognostic significance of liquid biopsy, data for breast cancer are available mainly on the CTCs [56, 60 – 64]. Hence, CTC detection with Cell Search™ is associated with a poorer disease course. CTC detection five years after adjuvant chemotherapy is associated with a significantly increased risk of late relapse [65]. The possible clinical consequences could be extended endocrine therapy. In metastatic breast cancer the detection of five or more tumour cells, irrespective of the molecular subtype, is linked to significantly shorter progression-free survival (PFS) and overall survival [66]. Persistent CTC in patients with metastatic breast cancer during ongoing therapy is unfavourable as far as the further clinical course is concerned. Furthermore, the dynamics of the CTC count offer a much earlier indication of the therapeutic response, i.e. after only one month, compared to imaging, which usually permits a valid statement to be made only after three months [60].

In summary, liquid biopsy is currently being evaluated in clinical trials with a view to estimating prognosis, predicting therapeutic response and monitoring treatment. Based on the data available so far, it can be assumed that both CTCs and cfDNA could be used to personalise systemic therapies. As a prognostic factor, the detection of CTCs has already been included in the AGO recommendations as a clinically valid marker [38].

Outlook

In the treatment of metastatic breast cancer, myriad advances have been made which are promising with respect to improving progression-free survival or even overall survival. Nevertheless, it must be assumed that in most patients the condition will not be curable and the course will be chronic. Quality of life and individual planning of the treatment sequences are therefore particularly important. Networks and real-world registries could help to thus improve therapy and patient care [67 – 74]. It was shown only recently that an intensive basis for communication between patient and physician can positively influence the course of the disease [75]. Hence, in the ongoing development of treatments it is essential to focus not only on the medication and adverse effects but also, primarily, on patient communication and information.

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Conflict of Interest

A. D. H. received honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene and Pfizer. N. N. received consultancy honoraria from Janssen-Cilag and travel support from Novartis. F. O. received speaker and consultancy honoraria from Amgen, Celgene, TEVA, AstraZeneca, Novartis, Roche, and MSD. F.-A. T. received honoraria from AstraZeneca, Genomic Health and Novartis. H.-C. K. received honoraria from Carl Zeiss meditec, TEVA, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche and Genomic Health. P. H. received honoraria, unrestricted educational grants and research funding from Amgen, AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer and Roche. P. A. F. received honoraria from Roche, Pfizer, Novartis and Celgene. His institution conducts research for Novartis. H. T. received honoraria from Novartis, Roche, Celgene, TEVA, Pfizer and travel support from Roche, Celgene and Pfizer. J. E. received honoraria from Roche, Celgene, Novartis, Pfizer, Pierre Fabre, TEVA and travel support from Celgene, Pfizer, TEVA and Pierre Fabre. M. P. L. has participated on advisory boards for AstraZeneca, MSD, Novartis, Pfizer, Genomic Health and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac and Eisai. V. M. received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Pfizer, Pierre-Fabre, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Roche, Pierre Fabre, Amgen,

Daiichi-Sankyo and Eisai. E. B. received honoraria from Novartis and Hexal for consulting and clinical research management activities. A. S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuckschwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. W. J. received honoraria and research grants from Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, Sanofi, Daiichi Sankyo, Tesaro. F. S. participated on advisory boards for Novartis, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer. A. W. participated on advisory boards for Novartis, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene. D. L. received honorarium from Amgen, AstraZeneca, Celgene, Lilly, Loreal, MSD, Novartis, Pfizer, Tesaro M. W. received speakers honoraria and consultant fees from Novartis, Amgen, Celgene, Roche, Genentech, AstraZeneca, and Pfizer. S. Y. B. received honoraria from Pfizer, and Novartis. T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Celgene, Roche, Novartis and Pfizer.

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