Update Breast Cancer 2020 Part 4 – Advanced Breast Cancer

Update Mammakarzinom 2020 Teil 4 – fortgeschrittenes Mammakarzinom

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ABSTRACT

Substances with good effectiveness that intervene in specific signalling pathways have been used increasingly in recent years in the treatment of patients with advanced breast cancer, and new therapies and approaches have now been added, which actually relate to quite specific changes, such as the treatment of patients with HR+/HER2 tumours with a *PIK3CA*

mutation. The treatment of patients with a *BRCA1* or *BRCA2* mutation has also been improved by the introduction of PARP inhibitors. Attempts are now being made increasingly to extend treatment indications based on molecular patterns, to identify other patients who could benefit from a treatment and to integrate the newly established treatment methods in existing therapy sequences. This review articles summarises the latest information in this connection.

ZUSAMMENFASSUNG

Nachdem in den letzten Jahren bei der Behandlung von Patientinnen mit fortgeschrittenem Mammakarzinom zunehmend Substanzen mit einer guten Effektivität zum Einsatz kommen, welche spezifische Signalwege angreifen, sind nun neue Therapien und Ansätze hinzugekommen, die sich tatsächlich auf ganz spezifische Veränderungen beziehen wie die Behandlung von Patientinnen mit HR+/HER2− Tumoren mit einer *PIK3CA*-Mutation. Ebenso ist die Behandlung von Patientinnen mit einer *BRCA1*- oder *BRCA2*-Mutation durch die Einführung der PARP-Inhibitoren verbessert worden. Nun wird zunehmend versucht, Therapieindikationen aufgrund molekularer Muster auszudehnen und weitere Patientinnen zu identifizieren, die von einer Therapie profitieren könnten, und die neu etablierten Therapiemethoden in bestehende Therapiesequenzen einzubinden. Diese Übersichtsarbeit fasst die neuesten Erkenntnisse in diesem Zusammenhang zusammen.

Introduction

In the last few years, a few targeted therapies have been developed for patients with metastatic breast cancer and subsequently introduced into clinical practice [1 – 4]. Some of these therapies, such as the CDK4/6 inhibitors or pertuzumab and T-DM1, had already been developed for subgroups of patients that could be identified by immunohistochemistry. Other drugs, such as the PI3K inhibitor alpelisib or the PARP inhibitors, require testing for genetic changes in the tumour or in the germline in addition for the indication. This focused approach to ensure that patients are selected for whom effectiveness will be particularly high and that patients who do not have this characteristic are spared the side effects is the optimal procedure when introducing new drugs. This review article summarises the latest developments in advanced breast cancer and in the area of biomarkers based on the latest presentations (e.g., ASCO, AACR 2020) and publications.

Treatment of Patients with Advanced HER2-Positive Breast Cancer

Effective treatment of cerebral metastases

The treatment of patients with HER2-positive advanced breast cancer is characterised by the use of targeted anti-HER2 drugs [5]. Trastuzumab, pertuzumab and T-DM1 are very effective anti-HER2 drugs used in the treatment of HER2-positive breast cancer. The tyrosine kinase inhibitors lapatinib and neratinib also have their place. Just in the past year, the tyrosine kinase inhibitor tucatinib was presented through the prospective randomised phase III study HER2CLIMB [6]. In patients with advanced breast cancer, who all had pretreatment with trastuzumab, pertuzumab and T-DM1, a comparison between therapy with trastuzumab + capecitabine and tucatinib + trastuzumab + capecitabine showed that progression-free survival and overall survival were improved. A new analysis has now been presented, which focussed on the 291 patients who already had cerebral metastases at the start of the study. In these patients, a clinically significant advantage was seen for the triple combination. In patients who were treated with tucatinib + trastuzumab + capecitabine, the median CNS-related progression-free survival was prolonged from 4.2 to 9.9 months. The hazard ratio was 0.32 (95% CI: 0.22–0.48) [7]. The median overall survival was prolonged from 12.0 to 18.1 months. The hazard ratio was 0.58 (79% CI: 0.40–0.85). Similar differences between the treatment arms were also seen in groups of patients who had either active or stable brain metastases. It can be concluded that the addition of tucatinib to treatment with capecitabine and trastuzumab is also associated with a marked improvement of the clinical treatment situation in patients with cerebral metastases.

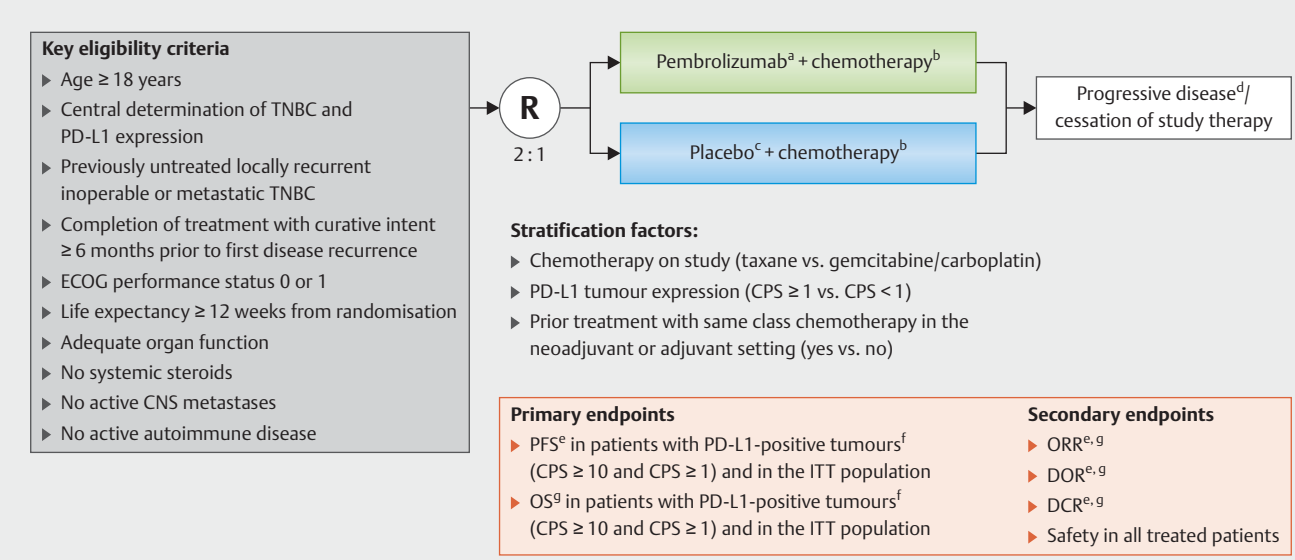
High activity in the area of treatment development for HER2-positive patients

Other anti-HER2 drugs, which are currently being developed for clinical use, include, for example, pyrotinib, margetuximab and trastuzumab-deruxtecan.

Slightly improved progression-free survival was shown for margetuximab, which is an anti-HER2 antibody optimised for ADCC (antibody-dependent cell-mediated cytotoxicity) [8]. In the case of this antibody, the ADCC is dependent on a germline variant of genes CD16 and CD32; patients who will benefit most from such therapy can possibly be identified with this.

An improvement in progression-free survival was found for treatment with pyrotinib and capecitabine compared with treatment with lapatinib and capecitabine [9]. This was confirmed in the PHOEBE phase III study [10]. In the study, after pretreatment with trastuzumab and taxanes, patients were treated either with lapatinib and capecitabine or with pyrotinib and capecitabine. The median progression-free survival was prolonged from 6.8 to 12.5 months (hazard ratio: 0.39; 95% CI: 0.56).

Many studies are currently being conducted with the antibody-drug conjugate (ADC) trastuzumab-deruxtecan. In a single-arm early phase I/II study, this anti-HER2 ADC produced a median progression-free survival of 14.8 months (95% CI: 13.8–16.9), even after several previous treatment lines [11]. This drug could also be effective in patients with low expression of HER2 (score 1+ or 2+). It is therefore being tested not only in HER2-positive patients (e.g., in the post-neoadjuvant therapy setting, in the metastatic situation after T-DM1 and in comparison with T-DM1, and others), but also in patients with an expression of HER2 that suffices to bind the antibody but without classic overexpression of HER2.



▶ **Fig. 1** KEYNOTE-355 study design. [a] Pembrolizumab 200 mg intravenous (i. v.) every 3 weeks (Q3W); [b] Chemotherapy dosing regimens are as follows: nab-paclitaxel 100 mg/m^2 i. v. on days 1, 8, and 15 every 28 days, paclitaxel 90 mg/m^2 i. v. on days 1, 8, and 15 every 28 days, gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days; [c] Normal saline; [d] Treatment may be continued until confirmation of progressive disease; [e] Based on RECIST v 1.1 assessed by a central imaging vendor; [f] PD-L1 assessed at a central laboratory using PD-L1 ICH 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1-positive tumour cells, lymphocytes, and macrophages divided by total number of tumour cells × 100); [g] To be presented at a later date. CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; PD-L1: programmed death ligand 1; R: randomized; TNBC: triple-negative breast cancer. Modified after: [45].

Treatment of Patients with Advanced TNBC or BRCA-Associated Breast Cancer

Immunotherapies

Since atezolizumab in combination with nab-paclitaxel is already licensed in the first treatment line for patients with metastatic breast cancer, the results of the KEYNOTE-355 study, which tests the PD-1 antibody pembrolizumab also in the first treatment line, have also been published [45].

The KEYNOTE-355 study included patients with advanced TNBC who had not yet had any pretreatment in the metastatic stage. The study compared a combination of chemotherapy and pembrolizumab with chemotherapy alone. The permitted chemotherapy included nab-paclitaxel, paclitaxel or gemcitabine/carboplatin. The study design is shown in ▶ **Fig. 1**. The primary study aim was the progression-free survival, for which a hierarchical procedure was chosen with regard to PD-L1 testing (for a summary of PD-L1 testing see [12]). This means that the population that has a CPS score ≥ 10 is tested primarily and if significance is reached, the greater population with a CPS score of ≥ 1 was tested. A total of 847 patients were randomised, of whom 566 were to be treated with pembrolizumab + chemotherapy and 281 with chemotherapy alone (2 : 1 randomisation).

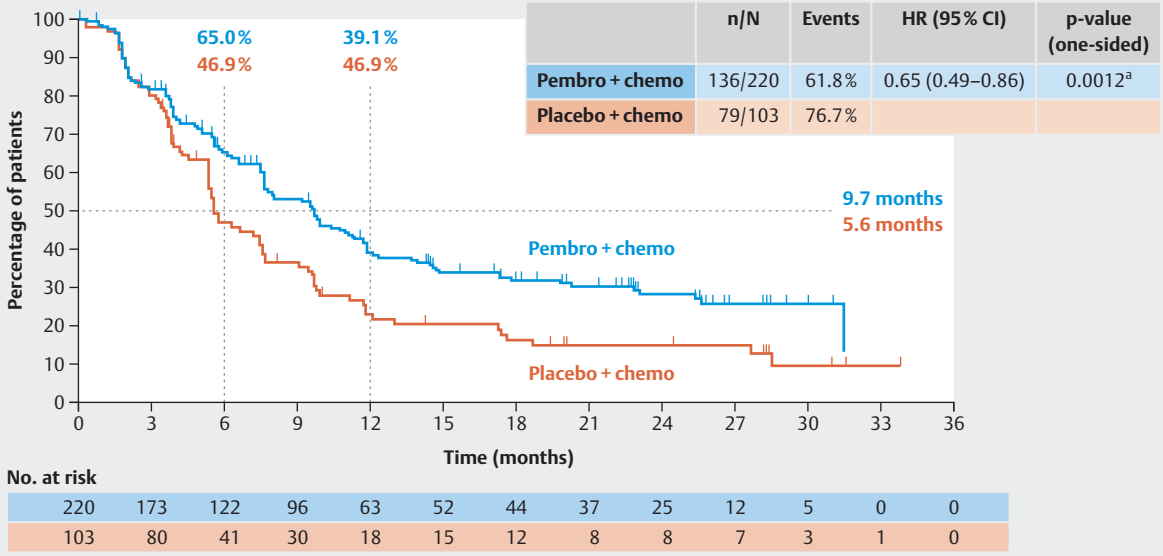
Of the 847 patients, 323 had a CPS score of ≥ 10 (38.1 %) and 636 patients had a CPS score > 1 % (75.1 %).

The primary study aim was reached when the CPS ≥ 10 tumours were analysed. In this TNBC cohort the addition of pembrolizumab to the chemotherapy prolonged the median PFS from 5.6 to 9.7 months. The hazard ratio was 0.65 (95 % CI: 0.49–0.86, p = 0.0012). The population with CPS ≥ 1 could therefore be examined. Here the median PFS was 5.6 vs. 7.6 months and the hazard ratio was 0.74 (95 % CI: 0.61–0.90, p = 0.0014). Since the required p-value in these multiple consecutively planned tests was 0.0011, this result was not formally statistically significant. The Kaplan-Meier curves of these analyses are shown in ▶ **Fig. 2** and **3**. Analyses of overall survival are not yet available. There was no new information about the side effect profile. Thus, data are now available showing that pembrolizumab can be combined with different chemotherapy drugs in the KEYNOTE-355 treatment situation.

Chemotherapy as a trigger of an immune response

For some chemotherapy agents and certain dosing schedules it is already known that modulation of the immune system can take place [13]. Eribulin and vinorelbine are two of these drugs for which it is suspected that they can have an immunological effect in this way. In a preclinical study, for instance, triple-negative breast cancer cell lines were incubated together with immune cells of the innate immune defence system with eribulin, vinorelbine, docetaxel, paclitaxel and ixabepilone and the immune reaction was measured using the gene expression profile of cytokines and immune checkpoint genes. This showed that eribulin and vinorelbine but not the taxanes can stimulate interferon expression in the immune cells [14].

Against this background, combinations of checkpoint inhibitors with these chemotherapy drugs would be of particular inter-

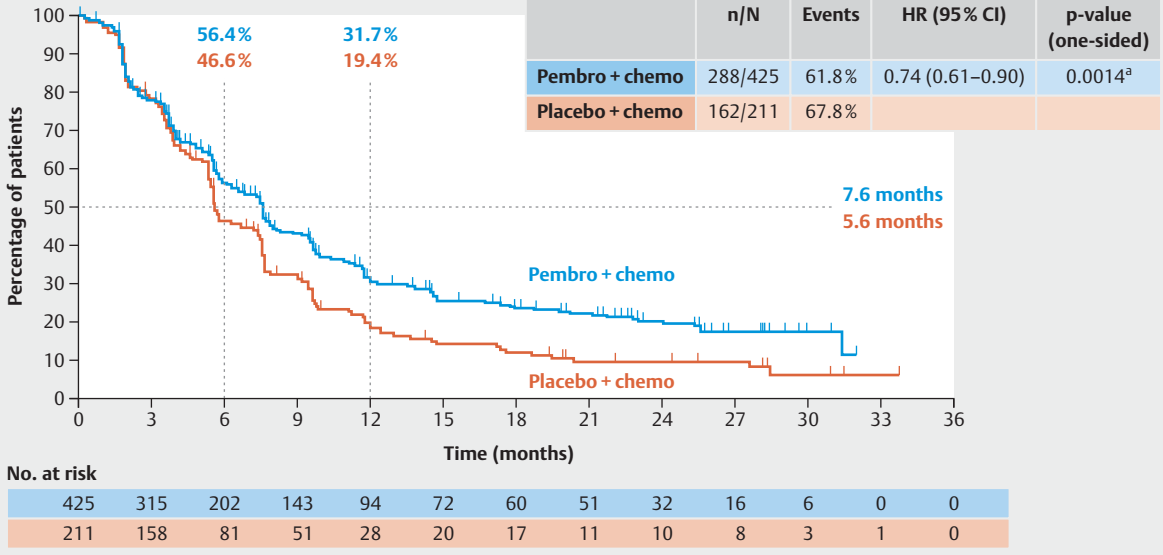


	n/N	Events	HR (95% CI)	p-value (one-sided)
Pembro + chemo	136/220	61.8%	0.65 (0.49–0.86)	0.0012[a]
Placebo + chemo	79/103	76.7%		

No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

▶ **Fig. 2** Progression-free survival in the KEYNOTE-355 study in the population of patients with a tumour CPS score of ≥ 10 (primary analysis). [a] Prespecified p-value boundary of 0.00411 not met. Hazard ratio (CI) analysed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cut-off December 11, 2019. HR: hazard ratio; CI: confidence interval. Modified after: [45].



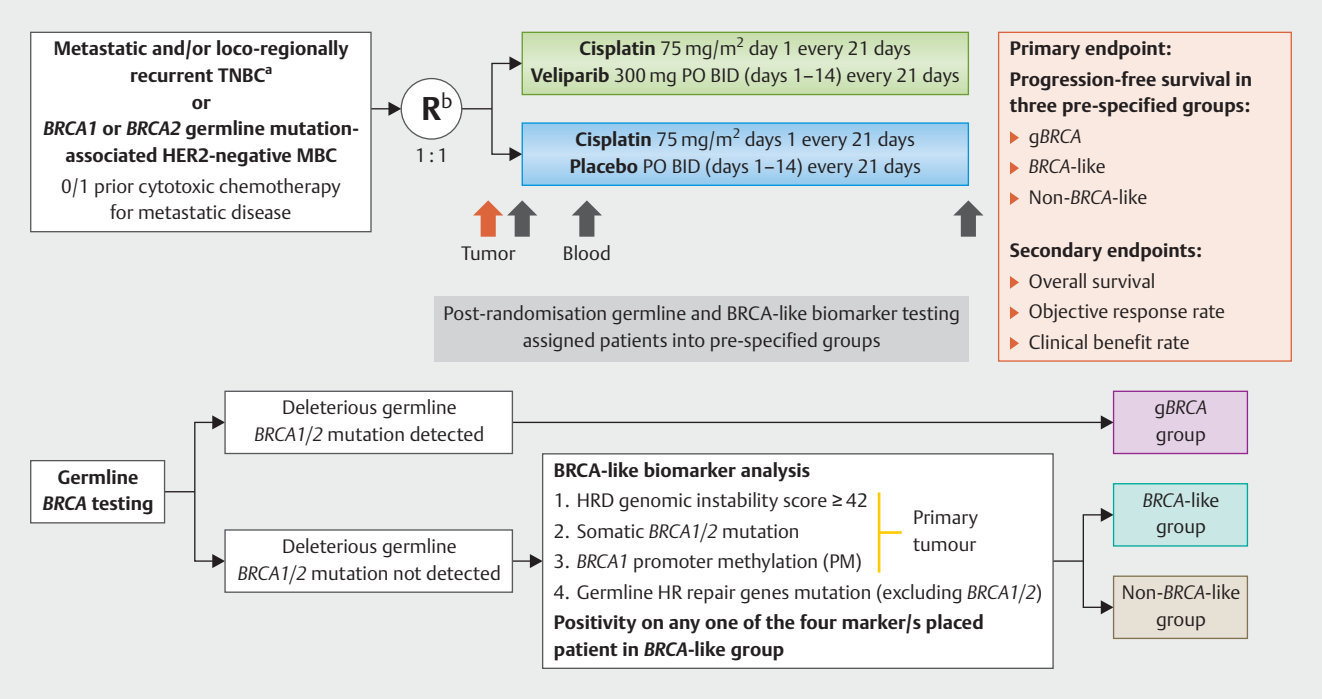
	n/N	Events	HR (95% CI)	p-value (one-sided)
Pembro + chemo	288/425	61.8%	0.74 (0.61–0.90)	0.0014[a]
Placebo + chemo	162/211	67.8%		

No. at risk

425	315	202	143	94	72	60	51	32	16	6	0	0
211	158	81	51	28	20	17	11	10	8	3	1	0

▶ **Fig. 3** Progression-free survival in the KEYNOTE-355 study in the population of patients with a tumour and CPS score of ≥ 1. [a] Prespecified p-value boundary of 0.00411 not met. Hazard ratio (CI) analysed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cut-off December 11, 2019. HR: hazard ratio; CI: confidence interval. Modified after: [45].

est. In the phase-I/II ENHANCE1 study a combination of eribulin and pembrolizumab was tested for toxicity and efficacy [15]. This study included 167 patients with advanced TNBC with 0–2 previous treatments. No new unexpected toxicities were seen in addition to those that were expected because of the eribulin therapy or pembrolizumab therapy. A response rate of 25.8% was seen in patients in the first treatment line and in 21.8% in higher treatment lines [15]. These response rates are promising and thus this combination could be further developed in further phase III studies.



▶ **Fig. 4** SWOG-S1416 study design. [a] TNBC defined as oestrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical (ICH) nuclear staining of ≤ 1 % and HER2 negative per ASCO/CAP guidelines; [b] Randomization stratified by number of prior cytotoxic regimens for metastatic disease (0 vs. 1). BID: bis in die; MBC: metastatic breast cancer; TNBC: triple-negative breast cancer. Modified after: [46].

PARP inhibitors in patients with HRD markers other than *BRCA1* and *BRCA2*

The PARP inhibitors olaparib and talazoparib are licensed for the treatment of HER2-negative patients with advanced breast cancer if a germline BRCA1/2 mutation has been found [16, 17], which is the case in ca. 10 % of cases of TNBC and in ca. 4–5 % of HER2-negative HR-positive patients [18 – 22]. For veliparib, which can be combined with chemotherapy in a nearly regular dose, it was shown that the addition of veliparib to chemotherapy with carboplatin and paclitaxel can improve the prognosis of patients with HER2-negative advanced breast cancer if a BRCA1/2 germline mutation had been found [23] (BROCADE study).

A small phase II study has now been reported (SWOG S1416), which treated HER2-negative patients either with veliparib and cisplatin or with cisplatin alone. Patients were included if they were treated in the first or second treatment line and could be assigned to one of the following groups [46].

- Group 1 (germline BRCA group): germline mutation in BRCA1/2
- Group 2 (BRCA-like group): tumour mutation in BRCA1/2, germline mutation in one of 36 DNA repair genes (BROCA-HR), BRCA1 promoter hypermethylation, myChoice score of ≥ 42
- Group 3 (BRCA-unlike): patients could not be assigned to either of the other two groups.

The study design is shown in ▶ **Fig. 4**. The addition of veliparib did not confer any benefit in the group of BRCA-unlike patients, and also not in the group of patients with a BRCA1/2 germline mutation. The absence of a difference in the group of patients with the BRCA1/2 germline mutation was initially surprising, but it must be considered that this group of 37 patients was small and that olaparib and talazoparib had been licensed during the study for the treatment of patients with a BRCA1/2 germline mutation. In the BRCA-like group (group 2), however, a statistically significant difference was seen with a median progression-free survival of 4.2 months in patients treated with cisplatin and 5.9 months in patients who had been treated with cisplatin + veliparib (hazard ratio: 0.53; 95 % CI: 0.34–0.83). This shows that apart from the group of patients with a germline mutation in BRCA1/2 there are other BRCA-like characteristics (HRD score, mutations in other genes, *BRCA1* hypermethylation) that could define efficacy of PARP inhibitors.

The TBCRC-048 study (Olaparib Extended Study) is another small phase II study, which addressed a similar question [24]. Patients were included in this study who had a germline or tumour mutation in one of the following genes: *ATM, ATR, BARD1, BRIP1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, RAD51D* and other unnamed genes or a somatic tumour mutation in BRCA1/2. The patients were treated with olaparib monotherapy. Most germline mutations (87 % of the patients) were found in *ATM, CHEK2, PALB2* or tumour mutations in *BRCA1/2*. The response rate was 33 % in the group of patients who had a germline mutation outside BRCA1/2. It was interesting that all 11 patients in whom a germline PALB2 mutation was present benefited from the olaparib therapy (ORR 82 %, CBR 100 %). In patients with a tumour mutation in BRCA1 or BRCA2 31 % had a response to the olaparib therapy [24].

Treatment of Patients with Advanced HER2-Negative, Hormone Receptor-Positive Breast Cancer

Aromatase inhibitor or fulvestrant as combination partner in the hormone-sensitive situation

The therapy sequence in patients with advanced HER2-negative hormone receptor-positive breast cancer is becoming ever more important given the increasing treatment options [25–27]. Not only the sequence in the metastatic situation is of importance but also the way anti-hormone therapies are used in the adjuvant setting. Treatment with CDK4/6 inhibitors has become established as standard in the first treatment line of advanced breast cancer. The efficacy of this treatment has been confirmed both in combination with aromatase inhibitors and with fulvestrant. The choice of endocrine combination partner is particularly important, however, because treatments after the CDK4/6 inhibitors could possibly use fulvestrant as combination partner. The efficacy of the PI3K inhibitor alpelisib was already established some time ago in the SOLAR-1 study. In this study, a combination of fulvestrant with alpelisib was compared with fulvestrant therapy alone [28]. Progression-free survival was prolonged from 5.7 months to 11.0 months in patients with *PIK3CA* mutations. The combination partner fulvestrant could thus be of benefit in the second therapy line after CDK4/6 inhibitors for possible treatment with the PI3K inhibitor alpelisib. The CDK4/6 inhibitors are effective in different treatment situations both in combination with fulvestrant or aromatase inhibitors [29–37]. The 3 studies that recruited hormone-sensitive patients and tested a combination with an aromatase inhibitor (MONALEESA-2, MONARCH-3 and PALOMA-2) all had as a requirement that the patients had no progression on (neo-) adjuvant therapy and that the conclusion of the (neo-) adjuvant therapy had to be at least 12 months previously [32, 34, 36]. Against this background, these studies showed a clear benefit for disease-free survival even when an aromatase inhibitor was again combined with a CDK4/6 inhibitor in the metastatic situation. Nevertheless, real-world data suggest that fulvestrant is often preferred as anti-hormonal therapy in the first palliative treatment line for recurrence [25]. In this connection, the PARSIFAL study published at ASCO 2020 is of particular importance [38]. This study compared treatment with palbociclib + fulvestrant in this described hormone-sensitive situation (similar to MONALEESA-2, MONARCH-3, PALOMA-2) with treatment with palbociclib-letrozole. The primary study aim was progression-free survival. 486 patients in total were included and randomised 1 : 1. A statistically significant difference was not found between the two arms with regard to progression-free survival (hazard ratio = 1.13 [95 % CI: 0.89–1.45]). There was also no difference with regard to overall survival, where the hazard ratio was 1.0 (95 % CI: 0.68–1.48) [38]. When interpreting these data, it must be borne in mind that this study initially investigated fulvestrant for superiority, which was not demonstrated. This study then looked at non-inferiority, which likewise was not confirmed. A treatment decision should always therefore depend on the overall view of the disease and the planned therapy sequences.

Alpelisib after CDK4/6 inhibitor treatment

In the Solar-1 study, which showed an improvement in PFS by addition of alpelisib in patients with a *PIK3CA* mutation of the tumour, only a few patients had received previous treatment with a CDK4/6 inhibitor. Only 7 patients received treatment with alpelisib and fulvestrant and 10 patients received placebo and fulvestrant. The median progression-free survival was 5.5 months in patients treated with alpelisib and 1.8 months in those who had been treated with fulvestrant alone [28]. It is therefore clear that better evidence was needed for this group of patients. This evidence was delivered by the recently presented BYLIEVE study in which patients were included who were to be treated again with anti-hormonal therapy following treatment with a CDK4/6 inhibitor [39]. This non-randomised study consisted of several cohorts, of which only cohort A has been presented to date. Cohort A included 112 patients who had previously received treatment with a CDK4/6 inhibitor and an aromatase inhibitor. In the BYLIEVE study all patients received the combination of alpelisib and fulvestrant. Naturally, a tumour mutation in the *PIK3CA* gene had to be found in all patients. The primary end point was the number of patients who had no breast cancer disease progression after 6 months. This number was 50.4 % (95 % CI: 41.2–59.6). The median progression-free survival (secondary end point) was 7.3 months (95 % CI: 5.6–8.3) [39]. It should be noted critically, however, that the BYLIEVE study is not a prospective randomised study that compares the combined treatment consisting of alpelisib and anti-hormonal therapy with a different therapy. Overall, treatment with alpelisib and fulvestrant could represent the preferred treatment option after therapy with a CDK4/6 inhibitor based on the available data for patients with a *PIK3CA* mutation in the tumour. With regard to the side effects, it must be noted that clinically significant hyperglycaemic episodes and skin rashes occur in approximately one third of the patients, often necessitating interdisciplinary management.

Biomarkers

Tumour mutational burden and pembrolizumab

The KEYNOTE-119 study is a study in which patients with advanced TNBC in later treatment lines were treated either with pembrolizumab alone or with chemotherapy [40]. Even though the primary study aim, namely, superiority of pembrolizumab compared with chemotherapy, was not reached, the study showed clearly that pembrolizumab was all the more effective the higher the CPS score was (PD-L1 positivity in immune cells and tumour) [40]. The median overall survival was 14.9 months in patients with a CPS ≥ 20 and 12.7 months in patients with a CPS ≥ 10, 10.7 and 9.9 months with CPS ≥ 1, when no limitations were made with regard to the CPS scores [40].

The tumour mutational burden (TMB) was also discussed in this context as a biomarker for the response to immunotherapy [41–44]. The TMB status of 253 of the 601 patients in the KEYNOTE-119 study was determined. 26 patients (10.3 %) had a TMB ≥ 10 mutations per megabase pair (mut/Mb). The response rate with pembrolizumab was numerically higher (14.3 %) in patients with a high TMB than in patients with a low TMB (12.7 %). The dif-

ference between the two treatment arms (pembrolizumab vs. chemotherapy) with regard to overall survival also appeared to be greater in patients with a high TMB (hazard ratio: 0.58; 95% CI: 0.21–1.57) than in patients with a low TMB (hazard ratio: 0.81; 95% CI: 0.61–1.07).

Whether and how TMB can be established as a biomarker in patients with breast cancer remains to be seen.

Outlook

Tucatinib and trastuzumab-deruxtecan are two substances that are entering clinical practice for HER2-positive advanced breast cancer. This could further markedly improve the treatment situation of patients with a HER2-positive tumour. In patients with TNBC, a therapy advantage was shown with pembrolizumab for a second checkpoint inhibitor (after atezolizumab) in first-line therapy. With regard to treatment with PARP inhibitors an attempt is being made to expand the treatment indication to other mutations or HRD signals. For HER2-negative HR-positive tumours, following CDK4/6 inhibitor therapy, a further targeted therapy (PI3K inhibition) has entered clinical practice with alpelisib. The trend of the last few years is thus confirmed, showing that drug development is progressing at high speed and hardly a year passes in which new substances are not presented for all subtypes of metastatic breast cancer with promising new data from clinical studies.

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Conflict of Interest

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. F. O. received speaker and consultancy honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Celgene, Cellex, Eisai, Gilead, Hexal, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Novonordisc, Riemser, Roche, Servier, Shire, Tesaro, Teva. H.-C. K. received honoraria from Carl Zeiss meditec, TEVA, Theraclion, Novartis, Amgen, Astra Zeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche and Genomic Health. P. A. F. received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, Merck-Sharp & Dohme, Eisai, Puma and Teva. His institution conducts research with funding from Novartis and Biontech. H. T. received honoraria from Novartis, Roche, Celgene, Teva, Pfizer and travel support from Roche, Celgene and Pfizer. J. E. received honoraria from AstraZeneca, Roche, Celgene, Novartis, Lilly, Pfizer, Pierre Fabre, Teva, Daiichi-Sankyo and travel support from Astra, Celgene, Daiichi-Sankyo, Lilly, Novartis, Pfizer, Teva, Pierre Fabre. M. P. L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, 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, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi Sankyo and Eisai, Lilly, Tesaro and Nektar. E. B. received honoraria from Novartis, Hexal and onkowissen.de for consulting, clinical research management or medical education 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, Daichi, 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, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene. D. L. received honoraria from Amgen, AstraZeneca, Celgene, Lilly, Loreal, MSD, Novartis, Pfizer, Tesaro, Teva 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. M. T. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Genomic Health and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, and AstraZeneca M. W. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and Roche. J. H. reports receiving speakers bureau honoraria from Celgene, Novartis, and Roche, and is a consultant/advisory board member for Amgen, Celgene, Novartis and Roche.

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