Thieme

Update Breast Cancer 2020 Part 5 – Moving Therapies From Advanced to Early Breast Cancer Patients

Update Mammakarzinom 2020 Teil 5 – Einführung von Substanzen aus der metastasierten Therapiesituation in die frühe Therapiesituation

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ABSTRACT

In recent years, significant progress has been made in new therapeutic approaches to breast cancer, particularly in patients with HER2-positive and HER2-negative/hormone receptor-positive (HR+) breast cancer. In the case of HER2-positive tumours, these approaches have included, in particular, treatment with pertuzumab, T-DM1, neratinib and, soon, also tucatinib and trastuzumab deruxtecan (neither of which has yet been authorised in Europe). In patients with HER2−/HR+ breast cancer, CDK4/6 inhibitors and the PIK3CA inhibitor alpelisib are of particular importance. Further novel therapies, such as Akt kinase inhibitors and oral SERDs (selective estrogen receptor down regulators), are already being investigated in ongoing clinical trials. These therapeutic agents are not only being introduced into curative, (neo-)adjuvant therapeutic settings for HER2-positive tumours; a first favourable study on abemaciclib as an adjuvant therapy has now also been published. In patients with triple-negative breast cancer, after many years of negative study results with the Trop-2 antibody drug conjugate (ADC) sacituzumab govitecan, a randomised study has been published that may represent a significant therapeutic advance. This review describes the latest developments in breast cancer subsequent to the ESMO Congress 2020.

ZUSAMMENFASSUNG

Bei neuen Therapieansätzen des Mammakarzinoms sind insbesondere bei Patientinnen mit HER2-positiven und den HER2-negativen/hormonrezeptorpositiven (HR+) Mammakarzinom in den letzten Jahren deutliche Fortschritte gesehen worden. Bei HER2-positiven Tumoren muss in dem Zusammenhang Pertuzumab, T-DM1, Neratinib und bald auch Tucatinib und Trastuzumab-Deruxtecan (beide in Europa noch nicht zugelassen) genannt werden. Bei den Patientinnen mit HER2−/HR+ Mammakarzinom sind insbesondere die CDK4/6-Inhibitoren und der PIK3CA-Inhibitor Alpelisib zu nennen. Weitere, neue Therapien, wie Akt-Kinase-Inhibitoren und orale SERDs (selective estrogen receptor down-regulators), werden bereits in laufenden klinischen Studien untersucht. Nicht nur bei den HER2-positiven Tumoren halten die Therapien Einzug in die kurative, (neo-)adjuante Therapiesituation, sondern es wurde nun eine erste positive Studie mit Abemaciclib in der adjvuanten Situation vorgestellt. Bei Patientinnen mit einem triple-negativen Mammakarzinom ist nach vielen Jahren von negativen Studienergebnissen mit dem Trop-2 Antikörper-Wirkstoff-Konjugat (antibody drug conjugate, ADC) Sacituzumab-Govitecan eine randomisierte Studie veröffentlicht worden, die einen deutlichen Therapiefortschritt bedeuten kann. Diese Übersichtsarbeit beschreibt die neuesten Entwicklungen beim Mammakarzinom nach dem ESMO-Kongress 2020.

Introduction

Care for patients with breast cancer is complex and incorporates prevention, early detection, treatment and follow-up. Significant progress has been made in each of these areas in recent years [1–9].

Evidence has been accumulating that risk prediction for the disease can now differentiate relatively well between validated, genuine risk genes and genes from analytical panels that have no straightforward association with breast carcinoma. As a result, a major study to clarify the findings has been published.

The speed with which new therapies are being introduced is accelerating significantly. For example, the effectiveness of the antibody drug conjugate sacituzumab govitecan was recently demonstrated in a randomised study for triple-negative breast cancer (TNBC), and studies on the tyrosine kinase inhibitor tucatinib and the antibody drug conjugate trastuzumab-deruxtecan are currently being conducted for HER2-positive breast cancer. In patients with HER2−/HR+ breast cancer, new targeted combinations and also new anti-oestrogenic agents are being tested following the introduction of CDK4/6 inhibitors and the PI3K inhibitor alpelisib.

Significant developments in healthcare have also been made in the field of digital medicine, partly as a result of the COVID 19 pandemic. This review summarises and reflects upon such recent developments, as presented in scientific publications and at recent congresses such as the ESMO Congress 2020.

Neoadjuvant Therapy

Immune therapies in neoadjuvant therapy

The KEYNOTE-522 study, a large randomised neoadjuvant study, showed that supplementation of therapy with pembrolizumab in triple-negative breast cancer resulted in an improvement in the pathological complete remission rate (pCR) from 51.2% to 64.8% [10–12].

Similar results have now been reported with atezolizumab [13]. The IMpassion031 study included patients with early TNBC whose primary tumour was at least 2 cm in size. Another requirement was that patients' PD-L1 status had to be determinable. However, it did not have to be positive. Patients were treated with chemotherapy of 12 cycles of weekly nab-paclitaxel followed by dose-dense therapy with biweekly doxorubicin (60 mg/m^2) com-

bined with cyclophosphamide (600 mg/m^2). The patients also received atezolizumab at 840 mg or placebo every 2 weeks. After surgery, therapy with atezolizumab was completed with 11 three-weekly cycles of 1200 mg in the atezolizumab arm. A total of 333 patients were randomised and 307 patients underwent surgery. The pCR rate in the placebo arm was 41.1%, while the pCR rate in the atezolizumab arm was 57.6% (16.5% difference, 95% CI: 5.9–21.7%, p = 0.0044). In the subgroup analysis based on PD-L1 status (positive if at least 1% of immune cells exhibited staining), pCR rates of 68.8% (atezolizumab arm) and 49.3% (placebo arm) were observed in the group with positive PD-L1 status (difference 19.5%, 95% CI: 4.2–34.8%). In patients with PD-L1-negative breast cancer, pPCR rates of 47.4% (atezolizumab arm) and 34.4% (placebo arm) were achieved (difference 13.3%, 95% CI: − 0.9–27.5%) [13]. Survival parameters (event-free survival, disease-free survival and overall survival) with a median observation period of about 20 months were also reported. On the basis of very few events and wide confidence intervals, the atezolizumab arm showed a numerical (statistically non-significant) advantage over the placebo arm. No new side-effect profiles were reported. Thus, in the neoadjuvant setting in TNBC, two randomised trials, one on pembrolizumab [11] and the other on atezolizumab [13], have now shown a significant improvement in pCR rate.

▶ **Table 1** provides an overview of the neoadjuvant, randomised trials that are investigating therapy with a PD1 or PD-L1 inhibitor.

Adjuvant Treatment of Patients with Breast Cancer

The last time a novel anti-hormonal therapy was introduced in the adjuvant setting was almost 20 years ago. At that time, findings of an absolute difference in disease-free survival of 2% comparing 5 years of anastrozole to 5 years of tamoxifen [14] led in 2002 to authorisation in the USA. The hazard ratio in the initial analysis with a median follow-up period of 33.3 months was 0.83 (95% CI: 0.71–0.96) [14]. The hazard ratio in the final analysis with a 10-year follow-up was 0.86 (95% CI: 0.76–0.97) for the first 5 years (total population) and 0.83 (95% CI: 0.72–0.95) for hormone receptor positive tumours [15]. It should be noted that the ATAC study included some patients with unknown hormone receptor status (approximately 8%) [14]. Beyond this first study on the use of an aromatase inhibitor in the adjuvant setting, mention should likewise be made of the large number of other studies in the adjuvant setting that have also investigated letrozole and exemestane [16, 17]. Regardless of the successes achieved by the introduction of aromatase inhibitors almost 20 years ago, the majority of deaths in breast cancer patients occur in the HR+/HER2− group of patients, as these make up the largest percentage of all breast cancers. Improving the treatment of these patients would have a major impact on the overall population. Following the promising data on CDK4/6 inhibitors (CDK4/6i) in the metastatic setting, trials have also been initiated for all three CDK4/6i in the adjuvant setting [18 – 22]. The first two of these studies (PALLAS and MonarchE) have now been presented at the ESMO Congress 2020 [23, 24].

PALLAS

The PALLAS study included 5760 patients who had to fulfil the following criteria (selection):

- HR+/HER2−
- UICC stage II or III
- Completion of all primary therapy options
- Primary diagnosis not more than 12 months ago
- Initiation of adjuvant endocrine therapy (ET) less than 6 months previously

Most patients had a UICC stage of IIB (33.4%) or III (48.7%). A very high percentage had received chemotherapy (82.6%). The percentage of patients with a negative nodal status was 13.0% [23].

Patients were treated with endocrine therapy (ET) ± palbociclib for 2 years. Afterwards, the scheduled endocrine therapy is completed as a monotherapy.

The results of this study were negative. In an interim analysis, a “futility” analysis was performed after the 351 events pre-specified to terminate the study. At a median follow-up period of 23.7 months, the hazard ratio was 0.93 (95% CI: 0.76–1.15) with invasive relapse-free 3-year survival rates (iDFS) of 88.2% (palbociclib + ET arm) vs. 88.5% (endocrine monotherapy arm).

MonarchE

The MonarchE study investigating abemaciclib yielded a different result. Patients were included in this study if they had more than 3 affected lymph nodes or 1–3 affected lymph nodes and a tumour size of at least 5 cm, a grade 3 tumour or a Ki-67 index of ≥ 20%.

Again, most patients in this study had a UICC stage of IIB (13.8%) or III (approx. 72%). Patients received standard-of-care adjuvant endocrine therapy with or without abemaciclib for 2 years. At the time of the first interim analysis, invasive disease-free survival was assessed after 323 events and a median follow-up time of 15.5 months. The analysis revealed a significant advantage in favour of the combination therapy. The hazard ratio was 0.72 (95% CI: 0.56–0.92), with 2-year invasive relapse-free survival rates of 92.2% and 88.7%, respectively. ▶ **Fig. 1** presents the Kaplan-Meier curve for the results. ▶ **Fig. 2** shows a comparison of the Kaplan-Meier curves of the ATAC study [14] and the MonarchE study [25] at the time of initial publication.

PENELOPE-B study

The PENELOPE-B study [26] – initially reported to be negative via a press release – is another adjuvant CDK4/6i study. This study included patients who did not achieve pCR after neoadjuvant chemotherapy and had an unfavourable prognostic profile based on a clinical-pathologic stage – estrogen/grade (CPS-EG) score [27]. PENELOPE-B included patients who had a CPS-EG score of 3 or higher or a score 2 and ypN+ disease. The PENELOPE-B study was the only placebo-controlled study, and therapy with palbociclib lasted 1 year. The final analysis of the study has now been published [28].

NATALEE study

One study still open for recruitment is the NATALEE study [19]. This study is evaluating ribociclib therapy over 3 years in a population of patients at a lower and higher risk of relapse. The number

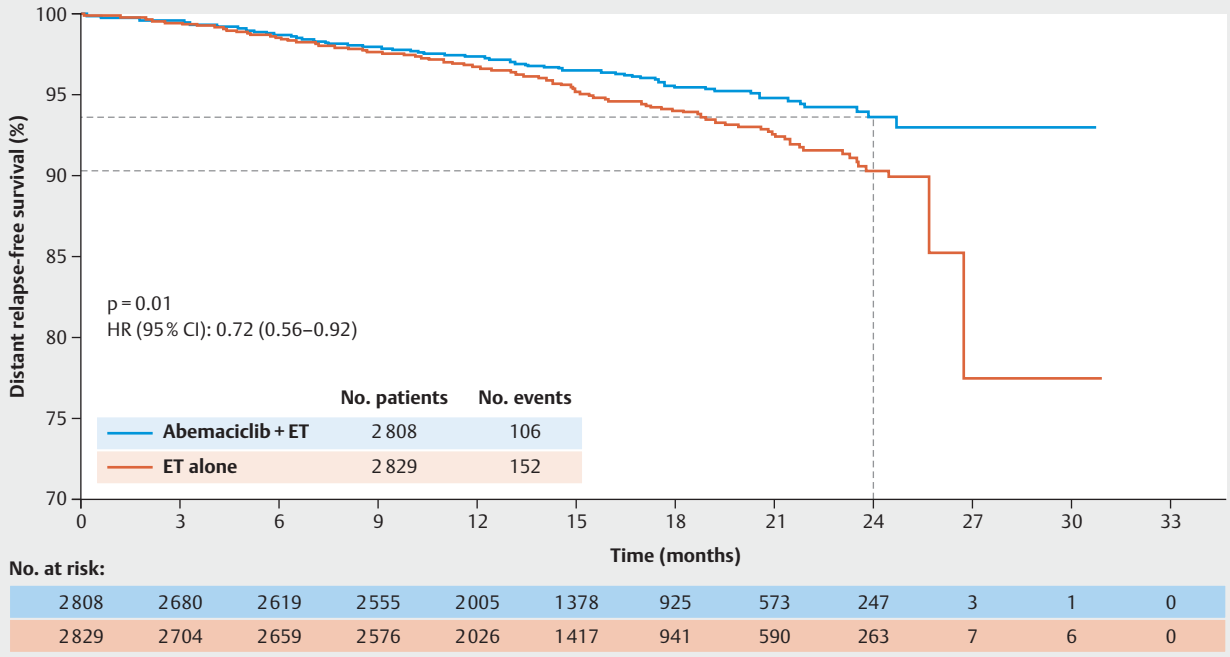
▶ **Table 1** Overview of neoadjuvant studies (reported and as yet unreported) involving a PD1 or PD-L1 inhibitor.

Name of study	Population	Number of patients	Date of first publication	Which therapies are compared with each other?	pCR rates in the study arms	Survival data from both arms	Reference no.
GeparNuevo	Triple-negative breast cancer	174	1 August 2019	Durvalumab or placebo in addition to nab-paclitaxel followed by EC	47/88 (54.4%) in the durvalumab arm vs. (44.2%) in the placebo arm	As yet unpublished	[54]
KEYNOTE-522	Triple-negative breast cancer	602	27 Feb. 2020	Pembrolizumab vs. placebo plus paclitaxel and carboplatin	64.8% in the pembrolizumab arm vs. 51.2% in the placebo arm	Event-free survival with an HR in favour of the pembrolizumab arm (HR = 0.63; 95% CI: 0.43–0.93*)	[11]
KEYNOTE-756	Oestrogen receptor positive, HER2–	Planned: 1140	26 May 2019	Pembrolizumab vs. placebo with neoadjuvant chemotherapy and adjuvant endocrine therapy	As yet unpublished	As yet unpublished	[55]
NeoTrip	Triple-negative breast cancer	280	12 Dec. 2019	Atezolizumab vs. placebo with carboplatin and nab-paclitaxel	43.5% with atezolizumab vs. 40.8% with chemotherapy alone	As yet unpublished	[56]
IMpassion031	Triple-negative breast cancer	455	20 Sep. 2020	Atezolizumab vs. placebo with chemotherapy	95/165 (58%) vs. 69/168 (41%)	Event-free survival (HR = 0.76, 95% CI: 0.40–1.44) Disease-free survival (HR = 0.74, 0.32–1.70) Overall survival (HR = 0.69, 0.25–1.87)	[13]
GeparDouze	Triple-negative breast cancer	Planned: 1520	As yet unpublished	Atezolizumab vs. placebo with neoadjuvant chemotherapy	As yet unpublished	As yet unpublished	[57]
CheckMate 7A8	Hormone receptor positive, HER2-negative, postmenopausal	Planned: 136	As yet unpublished	Nivolumab, abemaciclib, palbociclib and anastrozole	As yet unpublished	As yet unpublished	[58]
APTneo	HER2-positive	Planned: 650	As yet unpublished	Atezolizumab vs. placebo with trastuzumab, pertuzumab, carboplatin and paclitaxel, or sequential therapy with anthracycline	As yet unpublished	As yet unpublished	[59]

* Statistically not significant in accordance with the pre-specified analysis plan including interim analyses

of patients was recently increased from approximately 4000 patients [29] to 5000 patients [19]. In the PENELOPE-B and MonarchE studies patients were administered a CDK4/6 inhibitor for one year or two years respectively. The NATALEE study, in contrast, will provide information on a longer duration of therapy of three years. Another study, the ADAPTcycle study, is being conducted in Germany, comparing adjuvant chemotherapy with endocrine-based therapy (2 years of ribociclib), while the ADAPTlate study is investigating the use of abemaciclib 2–6 years after initial diagnosis.

▶ **Table 2** compares the inclusion and exclusion criteria of the various adjuvant CDK4/6 inhibitor studies.



▶ **Fig. 1** Remote metastases-free survival in the MonarchE study (data from [24]).

Treatment of Patients with Metastatic Breast Cancer

Immunotherapies IMpassion131, IMpassion130, KEYNOTE-355

The PD-L1 inhibitor atezolizumab has now been authorised for patients with advanced triple-negative breast cancer following the findings of the IMpassion130 trial, which revealed an improvement in progression-free survival and overall survival in patients with immune cell (IC) PD-L1-positive tumours [30, 31]. Similarly, the KEYNOTE-355 study showed that the addition of pembrolizumab to chemotherapy significantly improved progression-free survival. In the USA, pembrolizumab has already been authorised for this indication.

The IMpassion130 study selected nab-paclitaxel as combination therapy for atezolizumab. Various chemotherapies (nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin) were permitted in the KEYNOTE-355 study. Based on a subgroup analysis of combination partners, the KEYNOTE-355 study found no differences between the chemotherapy options with which pembrolizumab was combined.

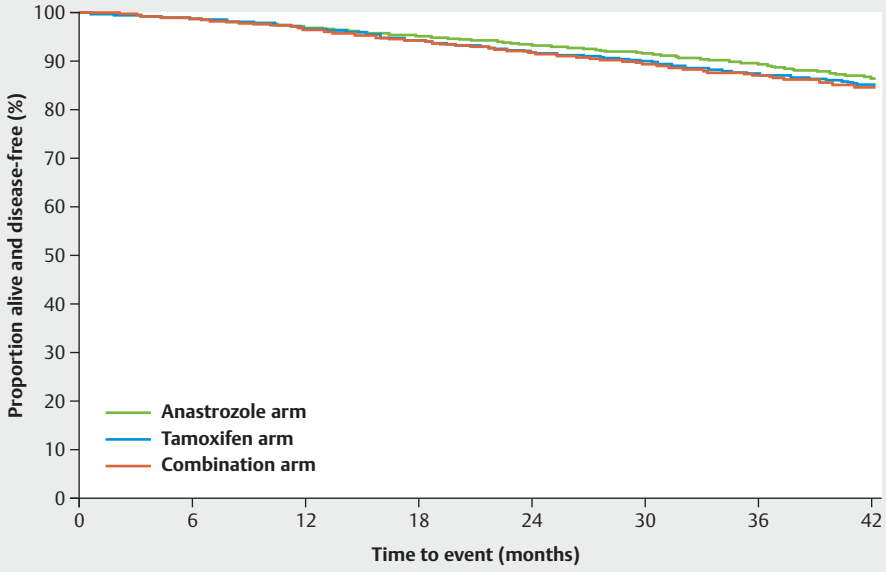
The IMpassion131 study [32] investigated a study population similar to that of IMpassion130, but whose subjects were randomised to paclitaxel + atezolizumab or to paclitaxel monotherapy (+ placebo) at a 2 : 1 ratio [32]. A total of 651 patients were recruited, of which 292 had tested positive for PD-L1 (immune cells positive in ≥ 1 %). Neither in the PD-L1-positive population nor in the overall population was a benefit observed for progression-free survival or overall survival [32].

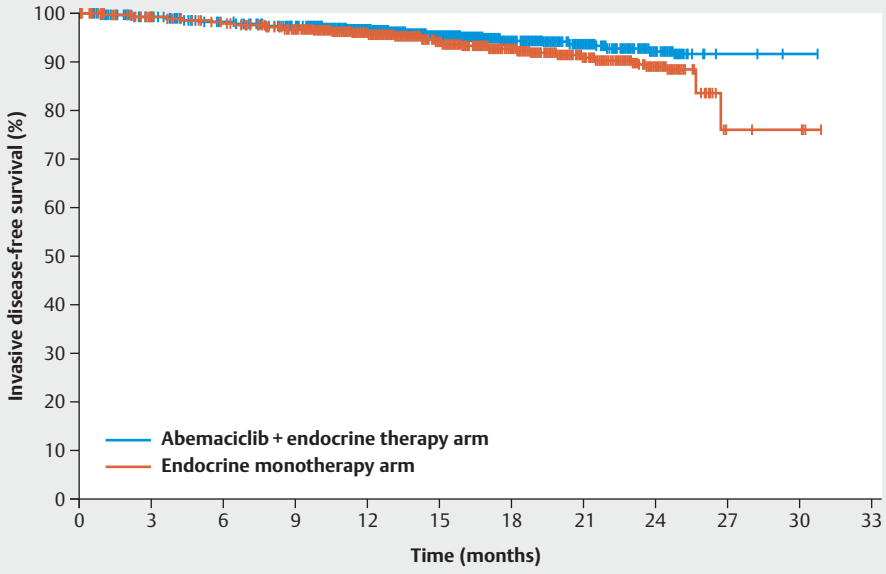
It has been suggested that the lack of effect of atezolizumab in combination with paclitaxel may have been due to cortisone, which was co-administered during therapy with soluble paclitaxel. Ultimately, however, such an explanation must be regarded as speculative. It is known that different chemotherapies have different effects on the immune system [33] and also interact differently with PD1/PD-L1 inhibitors [34].

Convincing data on sacituzumab govitecan in TNBC patients (ASCENT study)

There have already been significant therapeutic successes in the field of antibody drug conjugates (ADC) in HER2-positive patients [35 – 37]. An epithelial glycoprotein (Trop-2) that is expressed by breast cancer cells and is associated with a poorer prognosis has now been identified in patients with triple-negative breast cancer, as well as potentially in the future in other subtypes [38, 39]. The ADC sacituzumab govitecan acts on this target, with SN-38, a cytostatic agent similar to irinotecan but highly potent, as a payload. In the USA, sacituzumab govitecan has already been authorised on the basis of positive data from the early therapeutic study [40].

ASCENT is a randomised phase III study in which TNBC patients with ≥ 2 prior chemotherapies are treated with either sacituzumab govitecan or a chemotherapeutic treatment of physician choice [60]. A total of 529 patients were included. The study was terminated early due to a significant difference between the treatment arms.





▶ **Fig. 2** Comparison of disease-free survival in the ATAC study with a 33.3-month follow-up and invasive disease-free survival in the MonarchE study with a 15-month follow-up (data from [24]).

All included patients had previously received a taxane, approx. 7–8% had received a PARP inhibitor and approx. 26–29%, a PD1/PD-L1 inhibitor.

A clear difference was observed between the randomised arms of the study. Patients receiving chemotherapy of physician choice progressed at a median of 1.7 months (95% CI: 1.5–2.6), while patients receiving treatment with sacituzumab govitecan did not progress until 5.6 months (95% CI: 4.3–6.3). The corresponding hazard ratio was 0.41 (95% CI: 0.32–0.52, $p < 0.0001$). A clear difference in overall survival was also observed. The median time to death for patients in the chemotherapy arm was 6.7 months (95% CI: 5.8–7.7), while the median time to death for patients in the sacituzumab-govitecan arm was 12.1 months (95% CI 10.7–14.0). The hazard ratio was 0.48 (95% CI: 0.38–0.59, $p < 0.0001$). ▶ **Fig. 3** presents the Kaplan Meier curves.

The most common side effects (all grades) were neutropoenia (63%), anaemia (34%), vomiting (29%), diarrhoea (59%) and fatigue (45%). However, these led in only 4.7% of patients to premature discontinuation of therapy.

Overall survival analysis of the SOLAR-1 study

The PI3K inhibitor alpelisib was recently approved after it had been shown to improve median progression-free survival from 5.7 months to 11 months in patients with HER2−/HR+ metastatic

▶ **Table 2** Comparison of inclusion and exclusion criteria of (post-)adjuvant therapy studies with CDK4/6 inhibitors.

Criterion	PALLAS	MonarchE	NATALEE	PENELOPE-B
Age	≥ 18 years	≥ 18 years	≥ 18 years	≥ 18 years
Tumour stage	AJCC stage II: ▪ T0/T1 N1 ▪ T2 N0 ▪ T2 N1 ▪ T3 N0 or AJCC stage III ▪ T0/T1 N2 ▪ T2 N2 ▪ T3 N1/N2	T1–T4 and N1 with ▪ ≥ 4 ipsilateral positive axillary lymph nodes ▪ 1–3 ipsilateral positive axillary lymph nodes and at least one of the following criteria: – G3 – tumour size ≥ 5 cm – Ki-67 ≥ 20 %	▪ T0/T1 N2 ▪ T2 N2 ▪ T3 N1/N2 or ▪ T0/T1 N1 ▪ T2 N1 or ▪ T3 N0 or T2 N0 with – G3 or – G2 and Ki-67 ≥ 20 % or oncotype DX ≥ 26, PAM50 high risk, MammaPrint high risk, EndoPredict high risk	≥ ypT1 or ≥ ypN1 After at least 16 weeks of neoadjuvant chemotherapy
Tumour biology	HR+/HER2−	HR+/HER2−	HR+/HER2−	HR+/HER2− and CPS-EG score of ≥ 3 or CPS-EG of 2 with N+
Study schedule	Randomisation within 12 months of initial diagnosis and a maximum of 6 months after the commencement of endocrine therapy	Randomisation within 16 months of surgery and at least 21 days after the last chemotherapy and at least 14 days after the final radiotherapy	Randomisation within 18 months of initial diagnosis and no more than 6 months after the commencement of endocrine therapy or "high risk" on the basis of a gene expression test (Onkotype DX, Prosigna, MammaPrint or EndoPredict)	Randomisation within 16 weeks of surgery or maximum 10 weeks after completion of radiotherapy
ECOG	≤ 1	≤ 1	≤ 1	≤ 1
ECG	QTcF < 480 ms	No limit specified	QTcF < 450 ms	QTcF < 480 ms

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ECG = electrocardiography, GFR = glomerular filtration rate, INR = International normalized ratio, QTcF = QT interval corrected with the Fridericia formula, ULN = upper limit of normal

breast cancer and with a somatic *PIK3CA* mutation who had previously received endocrine therapy (hazard ratio: 0.65, 95 % CI: 0.50–0.85) [41]. Data on overall survival have now been reported revealing 181 patients died (out of a total of 341 patients) [42].

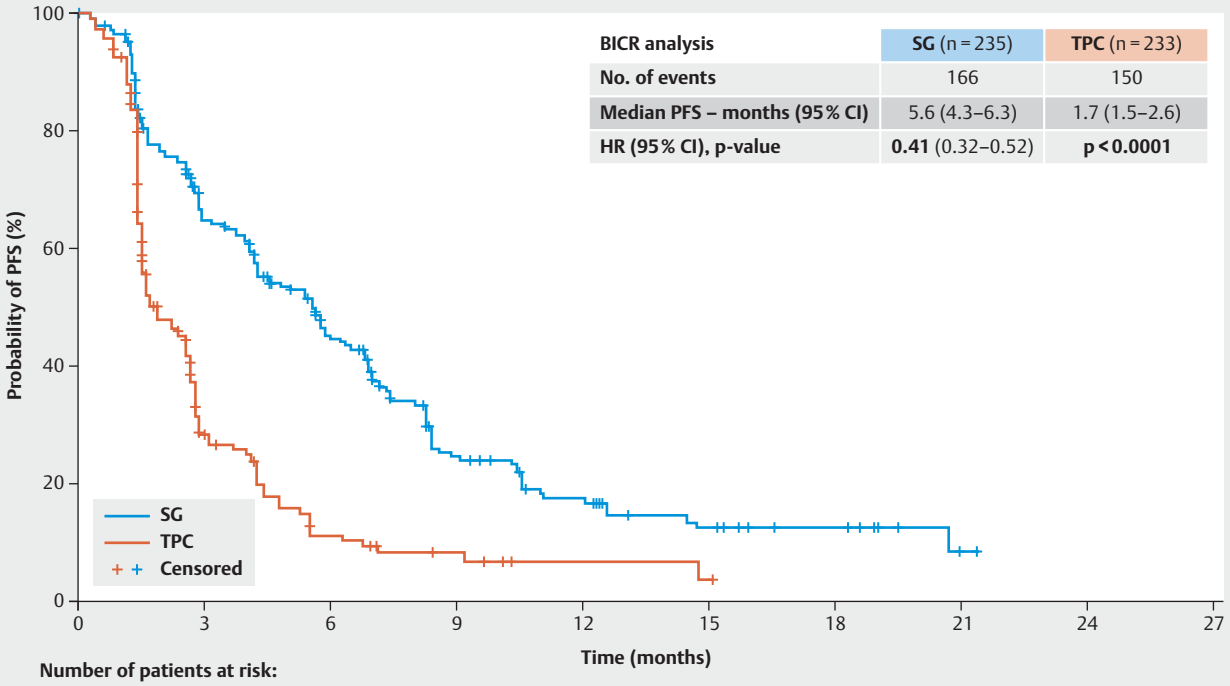
Even if the addition of alpelisib to fulvestrant improved overall survival from 31.4 months (95 % CI: 26.8–41.3) to 39.3 months (95 % CI: 34.1–44.9), this difference was not statistically significant (HR = 0.86, 95 % CI: 0.64–1.15, p = 0.15). A subgroup analysis suggested that a significant part of the effect was attributable to patients with a lung or liver metastasis. In this subgroup of 190 patients, the difference in median overall survival was almost 15 months (37.2 vs. 22.8 months, HR = 0.68, 95 % CI: 0.46–1.00) [42].

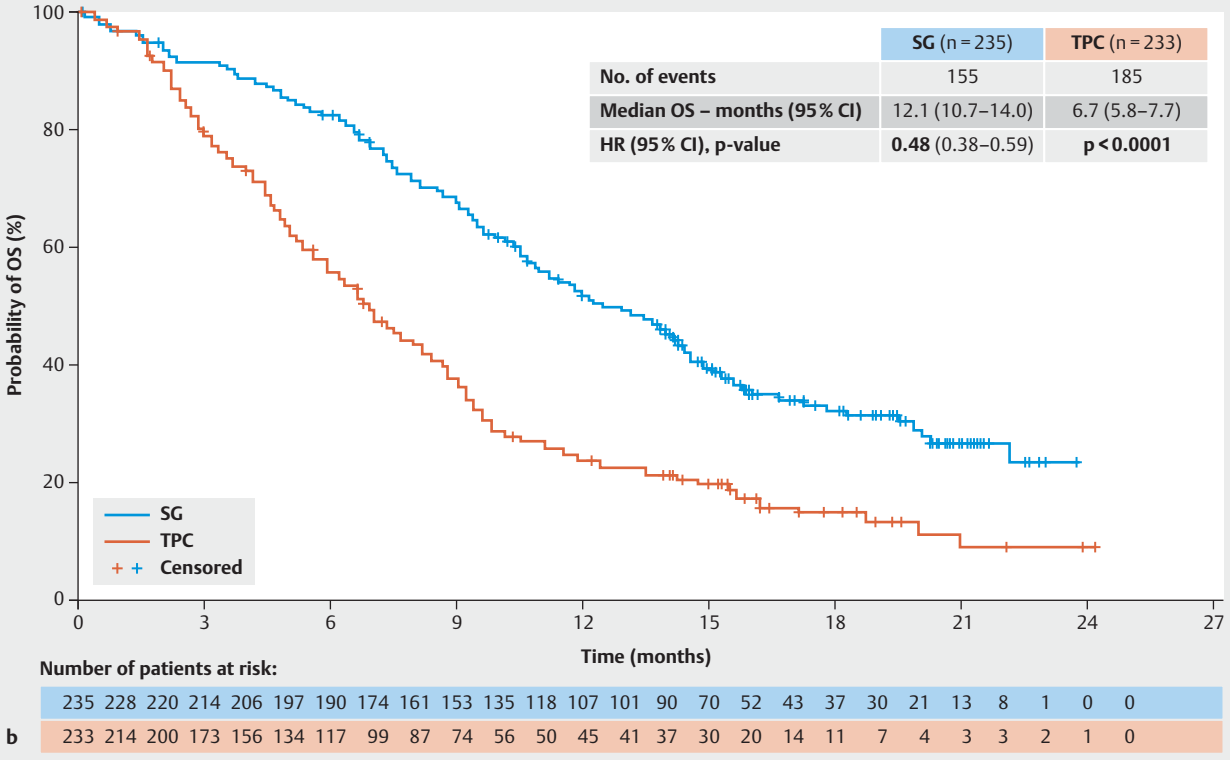
As testing is one of the prerequisites for alpelisib therapy, testing and methodology are increasingly a focus of interest. Mutations can be analysed from DNA extracted from paraffin-embedded tumours as well as from circulating DNA (ctDNA). According to its protocol [41], the SOLAR-1 study tested for the following mutations: C420R, E542K, E545A, E545D (only 1635G>T), E545G, E545K, Q546E, Q546R, H1047L, H1047R and H1047Y. Alpelisib is likely to be effective against tumours with a number of other different mutations, but prospective data on this should be awaited. It should be noted, however, that mutations other than those mentioned are very rare, as the vast majority of mutations in PIK3CA are restricted to three so-called hotspots.

Focus on quality of life

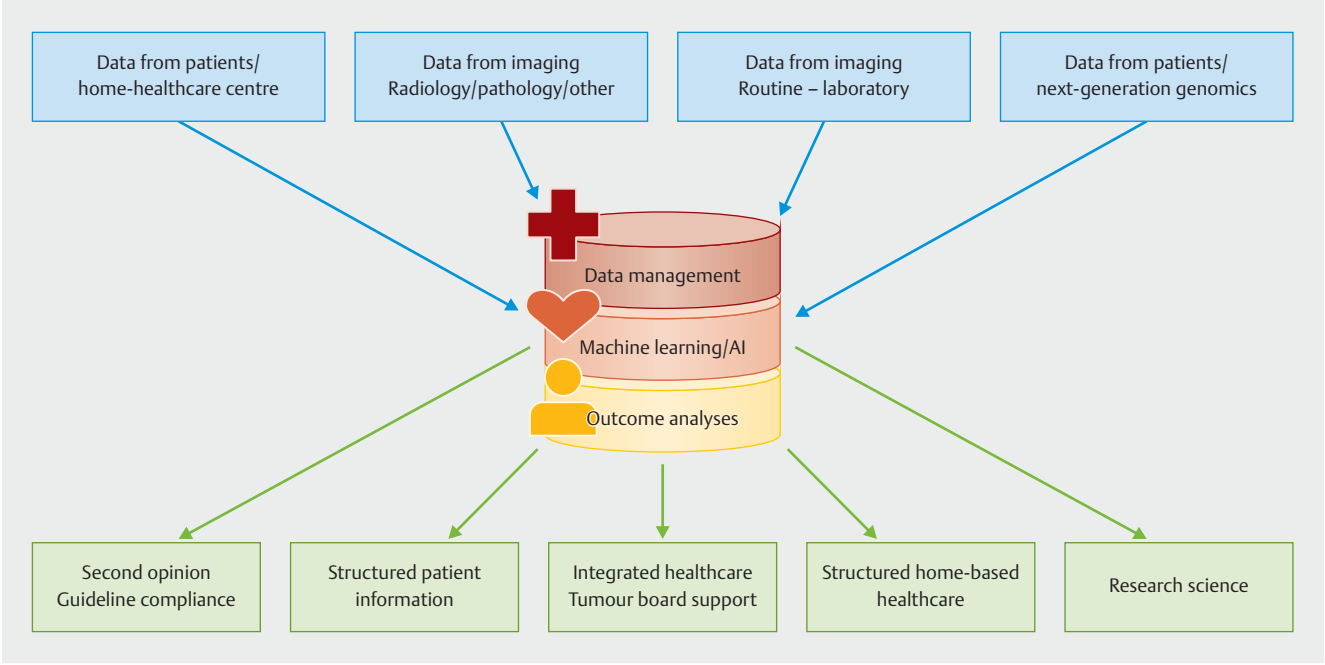
Quality of life is a particular focus of treatment for patients with advanced cancer. If possible, therapy should have a positive effect on quality of life. At a minimum, the patient's quality of life should be maintained and not worsened. This can be achieved by successful symptomatic treatment or by delaying progression. It has been established that progression is associated with a deterioration in quality of life [43]. Treatment with novel substances is often associated with an intensification of therapy or with the introduction of an additional concomitant drug. Critical assessment of quality of life is therefore important. Several analyses on quality of life have been published on CDK4/6 inhibitors that are widely used in early lines of therapy in advanced breast carcinoma [44]. Most such analyses revealed combination therapy and endocrine monotherapy were associated with similar quality-of-life scores [45 – 47], while one study revealed a benefit for combination therapy [48]. Recently, a pooled analysis of all ribociclib studies was performed [49]. Reviewing all studies, this analysis showed that combination therapy can significantly delay deterioration in quality of life. In subgroup analyses, which generate hypotheses, the effect was greatest in patients between 45 and 60 years of age and in patients with visceral metastases [49].

For patients with HER2-positive breast cancer who have already been treated with all standard options, further treatment options with tucatinib and trastuzumab deruxtecan will most likely be available in the future (after a pending authorisation in





▶ **Fig. 3** Progression-free survival (**a**) and overall survival (**b**) for randomisation arms in the ASCENT study (SG = sacituzumab govitecan; TPC = treatment of physician's choice. Data from [60], survival rates were added).



▶ **Fig. 4** Perspectives for digital medicine.

Europe) [37, 50]. Quality-of-life data have recently been published for the randomised HER2CLIMB study [51]. In this analysis, in which almost half of all patients had brain metastases, the addition of tucatinib to trastuzumab and chemotherapy did not result in any difference in quality of life [51] despite a more unfavourable side-effect profile [50]. It is worth noting that significant benefits in progression-free survival and overall survival had already been reported for tucatinib when comparing the randomisation arms [50].

Digital Medicine

Catalysed in part by the COVID-19 pandemic, the prospects for digital medicine have once again undergone a transformation. The pandemic has highlighted the obvious advantages of collecting data digitally and providing care to patients, without them having to physically attend medical appointments in a hospital or in private practice. However, it was clear even before the pandemic that shifting appointments to monitor therapies and illnesses to the patients' own homes had the potential to improve the quality of life of patients and reduce the burden on the healthcare system [52]. In addition, modern smart sensory systems are enabling patients to collect medically relevant information [53]. The ability to record ECG data, conduct blood analyses, monitor activity and sleep patterns as well as other information via smart phones and smart watches and to use this information for patient care is opening up new perspectives in both care and research.

Collecting information about patients' conditions allows caregivers to communicate with patients about such information and to analyse the data to gain new insights into patient groups. Data from private practice and from hospitals can be merged with other healthcare-related data. Such datasets can be managed and analysed using machine learning to conduct outcome-oriented research. The findings could enable compliance with guidelines and improve the information provided to patients, patient care, home-based care and medical research in equal measure. ▶ **Fig. 4** illustrates a possible network of this type.

Outlook

Some of the studies presented in this review are relevant to clinical practice; they either describe therapies that for the first time are clearly effective in disease settings where no effective therapies previously existed (sacituzumab govitecan in patients with pretreated, advanced TNBC), or they answer specific issues of particular interest to clinicians. Thus, the issue as to whether atezolizumab can also be successfully combined with paclitaxel – disproved by the IMpassion131 study – has been resolved for the time being. Atezolizumab should still be combined with nab-paclitaxel. The IMpassion031 study has now resulted in data from a second, larger study in the neoadjuvant therapeutic setting involving checkpoint blockade. It remains to be seen how rapidly these therapies can be granted authorisation. Such authorisation would require demonstration of a clear benefit with regard to the increased rate of side effects described above.

Finally, new methods of care, such as digital medicine, offer the prospect that healthcare can increasingly be shifted into the home. It is hoped that scientific studies will be conducted to establish the extent to which this will improve patients' quality of life. To date, the personal contact between doctors and patients has been the most important factor in establishing good therapy compliance and trust in the necessary therapeutic measures.

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Conflict of Interest

M. P. L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, Exact Sciences and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Exact Sciences, AstraZeneca, medac and Eisai. **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. **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. **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. **W. J.** received honoraria and research grants from Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, Sanofi, Daichi, Tesaro. **E. B.** received honoraria from Novartis, Hexal and onkowissen.de for consulting, clinical research management or medical education activities. **E. S.** received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Tesaro, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH, Onkowissen TV. **M. T.** has participated on advisory boards for AstraZeneca, Clovis, Eisai, GSK, Lilly, MSD, Novartis, Pfizer, Exact Sciences, Pierre-Fabre and Roche and has received honoraria for lectures from Clovis, Daiichi Sankyo, GSK, Lilly, MSD, Roche, Novartis, Pfizer, Exact Sciences, and AstraZeneca and has received trial funding by Exact Science. **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.-C. K.** has received honoraria from Carl Zeiss meditec, Teva, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche, MSD, SurgVision, Onkowissen and Genomic Health. **M. U.** received honoraria from AbbVie, Amgen, Astra Zeneca, Celgene, Daichi Sankyo, Eisai, Lilly, MSD Merck, Mundipharma, Myriad Genetics, Pfizer, PUMA Biotechnology, Roche Sanofi Aventis, Novartis, Pierre Fabre – all honoraria to the institution/employer. **N. H.** reports receipt of honoraria or consultation fees from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Lilly, MSD, Novartis, Odonate, Pfizer, Roche, Sandoz/Hexal and Seattle Genetics. **N. D.** has received honoraria from MSD, Roche, AstraZeneca, Teva, Mentor, and MCI Healthcare. **C. T.** has participated on advisory boards, lectures for Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Lilly, MSD, Mundipharma, Medapharm, Novartis, Pfizer, Pierre-Fabre, Roche, Tesaro, and Vifor. **M. W.** has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and 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. **D. L.** received honoraria from Amgen, AstraZeneca, Celgene, Lilly, Loreal, MSD, Novartis, Pfizer, Tesaro, Teva. **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. The remaining authors have no conflict of interest to declare for this specific article.

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