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Update Breast Cancer 2020 Part 2 – Advanced Breast Cancer: New Treatments and Implementation of Therapies with Companion Diagnostics

Update Mammakarzinom 2020 Teil 2 – fortgeschrittenes Mammakarzinom: neue Substanzen und Einzug diagnostik-abhängiger Therapien

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ABSTRACT

For patients with locally advanced or metastatic breast cancer, new and effective therapies such as CDK4/6 inhibitors, PARP inhibitors and a PD-L1 inhibitor have been introduced in recent years. This review presents an update on the available studies with their data. In addition, two innovative anti-HER2 therapies are presented (trastuzumab-deruxtecan and tucatinib) for which the results from new studies have been reported. Molecular tests offer the possibility of defining patient populations or also monitoring courses of therapy. This can help identify patients with specific characteristics in order to provide them with individually targeted therapy within the framework of studies. In a large study, the benefit of such a biomarker study was able to be described for the first time.

ZUSAMMENFASSUNG

Für Patientinnen mit einem lokal fortgeschrittenen bzw. metastasierten Mammakarzinom wurden in den letzten Jahren neue und effektive Therapien wie CDK4/6-Inhibitoren, PARP-Inhibitoren und ein PD-L1-Inhibitor eingeführt. In dieser Übersichtsarbeit wird ein Update zu den vorhandenen Studien mit ihrer Datenlage gegeben. Ebenso werden 2 innovative Anti-HER2-Therapien dargestellt (Trastuzumab-Deruxtecan und Tucatinib), für die die Ergebnisse aus neue Studien berichtet worden sind. Molekulare Tests bieten die Möglichkeit, Patientinnenpopulationen zu definieren oder auch Therapieverläufe zu monitorieren. Dieses kann helfen, Patientinnen mit spezifischen Eigenschaften zu identifizieren, um diesen eine individuelle zielgerichtete Therapie im Rahmen von Studien zukommen zu lassen. In einer großen Studie konnte der Nutzen einer solchen Biomarkerstudie zum ersten Mal beschrieben werden.

Introduction

Significant advancements have been made in recent years in the case of patients with advanced or metastatic breast cancer. In addition to studies which have shown an improvement in overall survival (OS) for the addition of CDK4/6 inhibitors [1–4], companion diagnostics were established for some studies which can select the patient population in which the therapy has an effect and also identifies the patients in whom the therapy does not have an effect and can thus spare these patients from the adverse effects of the therapy. This means the studies on the PARP inhibitors with regard to a mutation in *BRCA1* or *BRCA2* [5,6], a study on immunotherapy with atezolizumab and another study on the treatment of patients with HER2-negative, hormone-receptor-positive breast cancer with the PI3K inhibitor alpelisib [7]. This overview summarises the latest developments on this basis and reports on current findings, taking recent congresses such as the San Antonio Breast Cancer Symposium 2019 into account. New therapies for patients with HER2-positive breast cancer are also presented, as are findings on the comparison between a CDK4/6-inhibitor-based therapy and chemotherapy and the benefit of biomarkers.

Treatment of Patients with Advanced HER2-positive Breast Cancer

Trastuzumab-deruxtecan

Trastuzumab-deruxtecan (DS-8201a, T-Dxd) is a newly developed substance from the class of antibody-drug conjugates (ADC) [8] which is already known in our field through T-DM1. The new substance is composed of the monoclonal antibody trastuzumab and the cytostatically active DXd which are chemically bound through a linker [9]. In comparison to T-DM1, there is a higher ratio of cytostatic molecule to antibody molecule in the case of T-Dxd, as well as a very stable linker which ensures an easy release of active substance in the cell, as a result of which a potentially cytotoxic effect on the neighbouring cells is also expected. The cytostatic agent which is split intracellularly is a topoisomerase-1 inhibitor. There were already data published in 2019 from a phase I study available [10]. In a recently published phase II study with 184 evaluable patients following pretreatment with T-DM1 and a median of 6 previous therapies, an impressive response rate of 60.9% was seen (95% confidence interval [CI]: 53.4–68) as was a percentage of patients without progression after 6 months of 76.1% (95% CI: 69.3–82.1). The progression-free survival (PFS) was 14.8 months (95% CI: 13.8–16.9). The most common adverse effect was nausea, generally grade I and II. However, 13.6% of patients developed interstitial lung disease with a total of 4 (2.2%) deaths [11]. This adverse effect of interstitial lung disease can evidently be favourably influenced by early detection and treatment. Phase III studies with this substance in various treatment situations are currently ongoing. There are also indications that trastuzumab-deruxtecan is effective in tumours which do not show any overexpression but rather only expression of HER2. Studies investigating this issue are also currently ongoing. The substance has been approved in the USA since the end of December 2019.

Tucatinib

Tucatinib is a tyrosine kinase inhibitor which is specifically directed against HER2. In San Antonio, the results of the HER2Climb study were presented: it involved 612 patients who had all been pretreated with trastuzumab/pertuzumab as well as with T-DM1 and who had already received a median of 4 lines of therapy [12]. The patients were treated with capecitabine and trastuzumab plus placebo or tucatinib. The study was positive for the primary endpoint of progression-free survival with a risk reduction (RR) in the overall collective of 46% ($p < 0.00001$). The survival in the treatment group after 12 months was 33% compared to 12% in the control group. The median overall survival was 7.8 months in the treatment group and 5.6 months in the control group. About 48% of the patients in the study had brain metastases and also in this subgroup, a clear advantage for progression-free survival was identified, with a similar hazard ratio (HR) of 0.46. In the subgroup with brain metastases, 25% of the patients on tucatinib and 0% of

the patients on placebo were still without disease progression after one year. This corresponds to earlier data which had indicated good efficacy in CNS metastases as well [13]. The most frequent adverse effects in the HER2Climb study were diarrhoea, transaminase elevation and hand-foot syndrome. The number of therapy discontinuations was overall low: 3% for placebo and 6% for tucatinib administration.

It can thus be assumed that the combination of capecitabine, trastuzumab and tucatinib will be a new, valuable therapeutic option following pretreatment with trastuzumab/pertuzumab as well as T-DM1, as soon as approval is available.

Margetuximab

Margetuximab is a modified antibody against HER2 which is intended to impart increased immunity for the antibody-dependent cellular toxicity. In addition, adaptive immunity is to be induced. In the phase III "SOPHIA" study with 536 intensively pretreated patients, the combination with margetuximab plus chemotherapy was noted to be slightly superior to the administration of trastuzumab and chemotherapy [14]. The progression-free survival was extended from 4.9 to 5.8 months (HR 0.76, $p < 0.033$). Patients with a genetic variant of the FC receptor appear to benefit more from the substance, however the substance must still define its significance in everyday clinical practice.

Treatment of Patients with Advanced TNBC Breast Cancer

Additional interim analysis of the IMpassion130 study

The IMpassion130 study compared therapy with atezolizumab and nab-paclitaxel with nab-paclitaxel alone in patients with advanced, triple-negative breast cancer (TNBC) in first-line therapy. After the first interim analysis after 12.9 months of median follow-up in the main analysis (PD-L1 immune-cell-positive and -negative) had not shown any significant advantage in overall survival (HR = 0.84, 95% CI: 0.69–1.02; $p = 0.08$), but in the subgroup analysis of the PD-L1 immune-cell-positive tumours, a clinically significant difference in the median overall survival of 9.5 months (15.5 months with nab-paclitaxel and 25 months with atezolizumab and nab-paclitaxel) [15] was demonstrated, the next interim analysis has now been published [16]. This second interim analysis showed a nearly 6-month longer median follow-up, and in the overall survival comparison, it showed an HR of 0.86 (95% CI: 0.72–1.02, $p = 0.078$). In the comparison in the PD-L1 immune-cell-positive subgroup, the median overall survival times were 18 months with nab-paclitaxel and 25 months with atezolizumab and nab-paclitaxel [16]. Thus the results of the first interim analysis were able to be confirmed in the sense that little had changed with regard to effect sizes.

PARP inhibitors

Patients with a *BRCA1* mutation develop TNBC more often than patients without a *BRCA1/2* mutation [17]. However, about 50% of breast cancers in patients with a *BRCA1* mutation are not triple-negative [17]. In patients with *BRCA2*-positive breast cancer, this connection was not able to be proven. For this reason, the greater proportion of patients with a *BRCA1/2* mutation are hormone-receptor-positive [18]. In view of this, patients with positive and negative hormone receptor were included in the large phase III studies on the treatment of patients with advanced HER2-negative breast cancer with a *BRCA1/2* mutation [5,6]. Both studies were positive for the overall population. A third study has now been added which compared the PARP inhibitor veliparib in combination with carboplatin and paclitaxel with chemotherapy alone. In this study as well, the therapy with the PARP inhibitor had significantly better progression-free survival (HR = 0.705; 95% CI: 0.566–0.877; $p = 0.002$) [19]. In the PARP inhibitor group, a probability of progression-free survival of 26% was able to be observed in this population after 3 years [19], while this was 10% or lower in the other two studies [5,6]. Even if the numbers of cases at the time of the observation were small, the question arises as to whether long-term disease control can be achieved with the PARP inhibitor therapies in a portion of the patients.

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

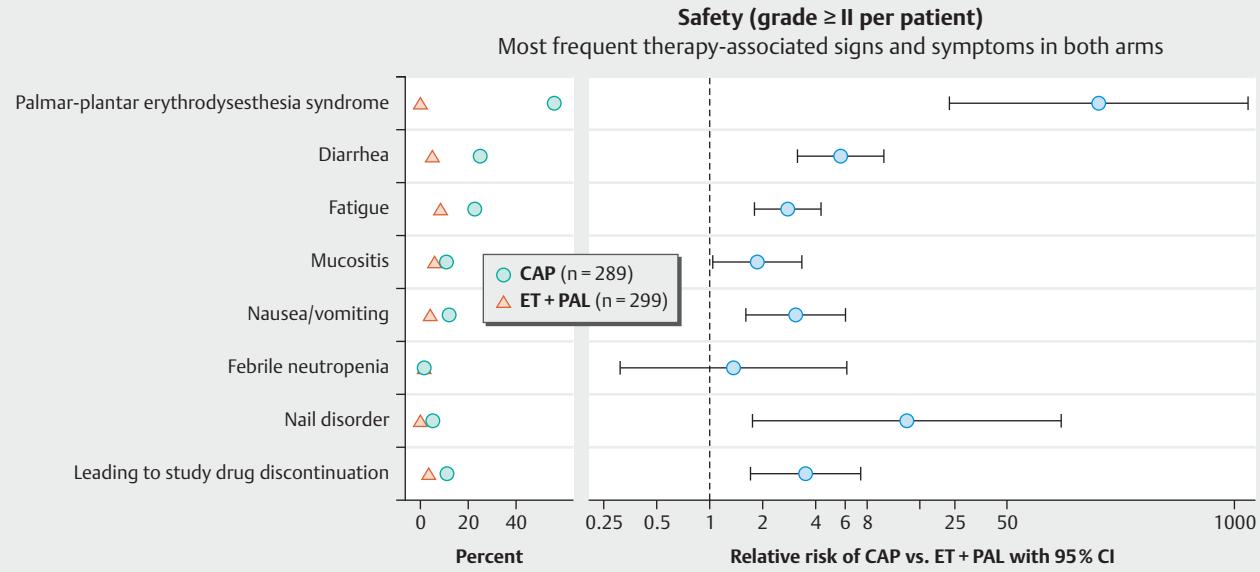
Comparison of the CDK4/6-based therapies with chemotherapy

The combination of CDK4/6 inhibitors with an anti-hormonal therapy is considered nowadays to be the new standard in the treatment of metastatic hormone-receptor-positive HER2-negative breast cancer. Phase III studies with palbociclib, ribociclib and abemaciclib in combination with aromatase inhibitors or with fulvestrant demonstrate a significant improvement of the PFS and, to some extent, of overall survival. In addition, the toxicity profile is relatively favourable in comparison to chemotherapy. In international guidelines, the endocrine combination therapy is therefore recommended nowadays, with the exception of patients with a so-called visceral crisis or high need for rapid remission.

However, there are only a few results available to date on the direct comparison between the endocrine combination therapy and a monochemotherapy in this setting.

The PEARL study compared the combination of exemestan or fulvestrant plus palbociclib versus a monochemotherapy with capecitabine in patients with metastatic, hormone-receptor-positive, HER2-negative breast cancer [20]. The results do not demonstrate any significant difference in the PFS between the two therapies (endocrine therapy [ET] with palbociclib 7.4 months, capecitabine 9.4 months, HR = 1.09, 95% CI: 0.9–1.31). However, the toxicities in the chemotherapy group were significantly higher, particularly with a higher rate of hand-foot syndrome, diarrhoea, fatigue and anaemia (▶ **Fig. 1**).

A Korean study (Young PEARL) investigated this question in premenopausal patients [20]. In this study, the combination of palbociclib, exemestan and leuprorelin demonstrated a significantly elevated PFS rate (HR = 0.659, 95% CI: 0.43–0.954, $p = 0.046$).



▶ **Fig. 1** PEARL study: Comparison of the toxicity of a monochemotherapy with capecitabine versus the combination of exemestan or fulvestrant, plus palbociclib (data from [20]).

On the basis of the present data, it cannot be definitively assessed at present which therapeutic sequence is optimal for a patient with metastatic, hormone-receptor-positive, HER2-negative breast cancer and which patient would still benefit from chemotherapy.

Biomarkers

Prediction of late recurrences in hormone-receptor-positive breast cancer patients

The "Clinical Treatment Score at 5 years" (CTS5) was developed to be able to estimate, by means of clinical-pathological parameters, the risk for the late development of a distant recurrence (DR) in patients with hormone-receptor-positive breast cancer after completing 5 years of endocrine therapy [21]. The data set of the ATAC study (n = 4735) was used here to generate the CTS5 [22], the data from the BIG 1–98 studies (n = 6711) [23] were used to validate the CTS5.

To calculate the CTS5, node status, tumour size, grading and patient age were entered into a CTS5 calculator (www.cts5-calculator.com). Then one obtains a score and the resultant risk of developing a distant metastasis within 5–10 years after completing 5 years of endocrine therapy. A differentiation is made here between three risk groups with corresponding cut-off values: low risk (≤ 5%), intermediate risk (5–10%) and high risk (> 10%).

In the TAILORx study, 10273 node-negative, hormone-receptor-positive patients were divided into 3 risk groups using the Oncotype DX® multigene assay in order to evaluate the benefit of chemoendocrine therapy (CET) versus ET alone. In doing so, cut-off values which are lower than the previous commercial values were used (low risk recurrence score [RS] 0–10, intermediate risk RS 11–25 and high risk RS 26–100). The results of the study published in 2018 [24] which have been much discussed by now were able to show that, in a patient aged > 50 years with an RS up to 25, there is no benefit for chemotherapy. The situation was somewhat different for the patient group aged ≤ 50 years since in this group, there is a reduced benefit starting at an RS of 16 [24].

The question now arises whether the CTS5 could also be validated in a more current patient collective, namely that of the TAILORx study, and whether the risk classification according to the Oncotype DX® corresponds with that of the CTS5. For this purpose, 7353 patients from the TAILORx study were identified who had not suffered any DR after 5 years of ET [25].

The patients were divided into two groups according to their therapy: 4069 patients with an ET (RS 0–10 and 11–25) and 3284 patients with a CET (RS 11–25 and RS 26–100). The proportion of patients with an RS of 26–100 was 629 patients and thus represented the smallest group [25].

75.5% of the ET group was able to be allocated to the CTS5 low risk group, 23.2% to the intermediate group and 1.3% of the high risk group. The risk for a DR was, correspondingly, 2.5, 5.2 and 4.3%. In the group receiving chemoendocrine therapy, 2.4% of the patients with a risk of a distant recurrence of 9.5% were able to be identified for CTS5 high risk. Thus the CTS5 confirmed the risk classification using Oncotype DX® [25].

A second analysis was performed adjusted to age. Here, the patients were differentiated not only according to their therapy but also according to the age of ≤ 50 and > 50 years.

Overall, it can be concluded that the TAILORx cohort demonstrated a lower risk of a DR (RS 0–25, ET: 3.1% and RS 11–100 CET: 3/8%), however the CTS5 also had high predictive power for the prognosis regarding a DR. The highest prognostic significance

▶ **Table 1** Therapy cohorts of the PLASMAMATCH study depending on the therapy-relevant mutation.

Therapy cohorts	Cohort A (only ER pos.)	Cohort B	Cohort C (only ER pos.)	Cohort D
No. of patients	74	20	18	19
Mutation	ESR1 mutation	HER2 mutation	AKT1 mutation	AKT-1 (ER-) PTEN
Therapy	Fulvestrant 500 mg d1/ d15 q28d*	Neratinib+ fulvestrant (if ER pos.)	Capivasertib + fulvestrant	Capivasertib
CRR	8.1% (6/74)	25% (5/20)	22% (4/18)	10.5% (2/19)
Efficacy	**no**	**yes**	**yes**	**no (yes for AKT-1)****
PFS in months	2.2 (1.7–5.3)	5.4 (3.4–9.1)	10.2 (3.2–18.2)	3.4 (1.8–5.5)

* Initial fulvestrant 500 mg d1, d8, d15 (loading dose)

** Response rate 33% (2 of 6)

was in the intermediate and high-risk group (RS11–100) according to the Oncotype DX. In patients with an RS of 0–10 (low risk), the prognostic significance was not significant [25]. A further limitation must be made for the CTS5 in the group of patients aged ≤ 50 in which it was less prognostic overall than in the group aged > 50 years. Thus at present, the CTS5 should not yet be used in this group.

"Liquid biopsy"

In recent years, the "liquid biopsy" using circulating tumour cells (CTCs) or circulating (ct-) DNA has become increasingly important in the breast cancer clinical study landscape. While CTCs are primarily used for therapy monitoring, the mutation analysis of the ctDNA plays a major role in therapy selection. The advantage of the "liquid biopsy" is that it can be easily repeated at any point in time through a simple blood draw, for example, for the re-evaluation of therapy-related markers. The need was recently confirmed within the scope of the AURORA study which investigated the molecular profile between the primary tumour and corresponding metastases [26]. In 30% of patients with a luminal primary tumour, a change in the subtype in the case of metastasis was seen which could mean a change in the therapeutic concept, where applicable.

If the representative biopsy of the metastasis is not possible, the liquid biopsy can be used, whereby the comparability of the prognostic and predictive significance between CTCs and ctDNA in the primary as well as in the metastatic breast cancer situation is still unclear.

In a neoadjuvant study, Radovich et al. investigated the prognostic significance of CTCs and ctDNA in 196 patients with TNBC and no pathological complete remission (pCR) following the neoadjuvant situation [27]. The clinical follow-up was 17.2 months. The detection of ctDNA correlated with a significantly lower DFS, distant DFS and OS. By contrast, the detection of CTCs was associated only with a trend for a worse clinical outcome. The CTC positivity did not correlate with the detection of ctDNA. This underscores the possible differences in the tumour-biological significance. If patients were positive for both markers, they had the worst prognosis. By contrast, if there was no evidence of CTC and ctDNA, the OS was the highest (2-year survival rate [YSR] 76 vs. 51%, $p = 0.0074$). These data confirm the clinical relevance of ctDNA for the detection of a prognostically relevant minimal residual disease. The further characterisation with regard to therapy-relevant mutations could additionally contribute to the selection of a suitable postneoadjuvant therapeutic strategy in this patient collective. It is planned to prospectively investigate this question as part of the PERSEVERE trial. If a therapy-relevant mutation is proven, the patients with non-pCR receive targeted postneoadjuvant therapy.

The concept of therapy selection based on ctDNA was already investigated in the metastatic setting within the scope of the PlasmaMatch study [28]. Overall, ctDNA specimens from a total of 1044 metastatic patients were investigated for therapy-relevant mutations. The ctDNA analysis lasted 13 days on average. The most frequently detected genetic changes were ESR-1 (27.7%), AKT1 (4.29%) followed by HER2 mutations (2.7%). In the case of hormone-receptor-positive breast cancer, ESR-1 and PIK3CA mutations were detected in particular. HER2 mutations were also found in HER2-negative breast cancer [29]. 131 patients were able to be treated with molecular genetic therapy, depending on the detected mutation (▶ **Table 1**). The therapeutic strategy was assessed as effective if at least 3 or more out of 16 patients in the respective therapy cohort responded (exception: cohort A: 13 out of 78). The results show that if a HER2 mutation is present, neratinib may be a promising approach. The AKT inhibitor capivasertib is a possible therapeutic strategy if an AKT mutation is present, independent of hormone receptor status. Conversely, the escalation of the fulvestrant dose if an ESR1 mutation is present was not effective.

These data prove the potential benefit of the strategy of selecting effective therapies based on the tumour mutations of the ctDNA. For this reason, intensive efforts for comprehensive and quality-assured ctDNA determination as well as for the implementation of molecular tumour boards for senological patients should be made.

Supportive Therapy and Patient Participation

Drug therapies are steadily advancing. However, they are only optimal if associated adverse effects are sufficiently controlled and supportive therapies prevent early discontinuation, preserve quality of life, and reduce long-term toxicities.

Taxanes are standard in neo/adjuvant as well as in metastatic therapy. In the case of EBC, there is currently a trend for dose-

dense therapy, particularly if there is greater node involvement [30]. A traditional adverse effect of taxanes is sensory neuropathy. According to published studies, the prevalence is 15–30% and the long-term (chronic) neuropathy is indicated at 2–4%. However, the corresponding follow-up is lacking in numerous studies. Chronic neuropathy appears far more frequently when treating patients as part of aftercare. A prospective study was recently presented in which the rate of persistent sensory peripheral neuropathy in the clinical setting and the influence on quality of life was analysed [31]. 176 patients with therapy containing taxanes (52% paclitaxel; 47% docetaxel) received questionnaires on quality of life (EORTC) as well as on chemotherapy-induced peripheral neuropathy. With a median time since the last taxane of 30 months, the total neuropathy rate (74.4%) was significantly higher than in previous studies. Subsequently, in months 6–24 after therapy, a rate of 82.5% (n = 52) was noted; in months 25–48, a rate of 74.6% (n = 47) was noted and in months 49–120, a rate of 64% (n = 32) was noted. The moderate and severe neuropathy, in contrast to no or mild neuropathy, led to a decrease in the average quality of life scores from 75 to 50 (p = 0.0062). Existing diabetes mellitus was the only comorbidity with a significant association with higher neuropathy scores (p = 0.03). In addition, higher neuropathy scores were seen under paclitaxel in comparison to docetaxel (p = 0.0001) [31]. The results should be included in the information provided to patients. In patients with diabetic neuropathy, alternative therapies should be considered. In addition, prophylactic measures (e.g. vibration training and balance exercises) as well as the early introduction of supportive therapies should be explained.

Another chemotherapy toxicity is ovarian insufficiency in premenopausal patients. Here the addition of GnRH analogues to chemotherapy independent of hormone receptor status can be considered [32]. Currently the OPTION study with 227 premenopausal patients with early breast cancer in whom quality of life with and without GnRH analogues on chemotherapy was documented at the start of therapy, after 3, 6, 12, 18, 24 months and then every 5 years demonstrated a significant worsening in quality of life on chemotherapy due to increased menopausal symptoms (p = 0.02) [33]. This should be integrated into the informational discussion. However, over the long term, there was an improvement – even if not significant – in quality of life and adverse endocrine symptoms.

Moreover, it should also be taken into account that in Germany, the age at first pregnancy is steadily rising and increasingly more women who have not yet completed family planning are confronted with the diagnosis of breast cancer and its consequences. Depending on the individual chemotherapeutic agents, the dosage, the duration of therapy, the form of application and concomitant therapies such as simultaneous radiation therapy, the amenorrhoea rate in women aged 20–34 years is 10% and in women aged 35–39, it is 30%. As part of a current analysis, stress due to the subject of fertility, the use of fertility-preserving strategies and the impact of concerns regarding fertility on the therapeutic decision were analysed in 419 breast cancer patients aged ≤ 45 years [34]. Overall, 32% of patients (n = 133) were worried about fertility – 73% of those aged ≤ 35 years, 28% of those aged 36–40 and 13% of those aged > 40 years (p < 0.01). Of these patients, 88% had in-depth discussions with their attending physicians. In 16% (n = 67), concern about fertility influenced the therapeutic decision (3% switched to another chemotherapy, 1% had no hormone therapy, 8% had hormone therapy < 5 years). In total, only 29 patients (7%) utilised fertility-preserving measures, such as cryopreservation of embryos (n = 14), eggs (n = 14) or GnRH analogues (n = 12). Accordingly, a need for optimisation with regard to counselling and the initiation of measures is advisable.

In recent years, significant advancements in antiemesis have been achieved. However, an investigation of 58 000 male and female patients upon a visit to an emergency department showed that 10% of them visited the emergency department due to acute chemotherapy-associated nausea or emesis [35]. Supportive therapies can only be as good as they are also used. Particularly in the case of therapies containing anthracycline and platinum, NK1 receptor antagonists (NK1-RA) and a combination with 5-HT3 antagonists are recommended. In a study with 402 patients with ≥ 1 completed cycle of anthracycline and cyclophosphamide who received netupitant and palonosetron (NEPA) orally or i. v. and dexamethasone orally, only 1% of the patients required acute treatment of chemo-induced nausea and vomiting [35]. There was no inpatient admission as a result. The risk for acute treatment was 5× and 8× higher, respectively, in the case of other antiemetic prophylaxes.

In an interim analysis of the NIS AkyPRO [36] the quality of life within the framework of a generally highly emetogenic chemotherapy on NEPA was documented in the largest subgroup (n = 986/2500). Over 84% of the patients reported that vomiting had no influence on everyday life.

Data which substantiate a comparability of oral and intravenous NEPA with regard to tolerability and efficacy were presented in another work [37]. As compared to other NK1-RA, NEPA i. v. has a safety-relevant advantage. No hypersensitivity and no reactions at the injection sites were reported.

Outlook

As described in the recently published cancer statistics in the United States, the mortality for all types of cancer has decreased by 2.2%, more than ever before [38]. Since the early 1990s, breast cancer has also had a steady decrease in cancer mortality (▶ **Fig. 2**). Until the end of the 1990s, the yearly decrease was over 3% and since then, it has been between 1.3 and 1.9%. The studies reported in this work support the fact that such steady successes regarding the continual reduction in breast cancer mortality can be achieved. It can be assumed that, with improved prevention, estimation of prognosis, new therapies in the adjuvant situation and the advent of digitisation, a further reduction in mortality can also be achieved in the coming years.

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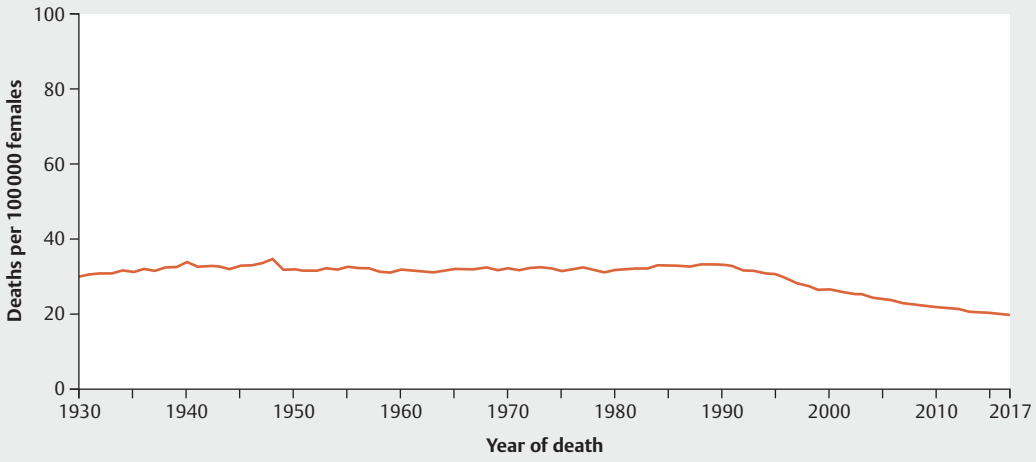

▶ **Fig. 2** Breast cancer deaths annually per 100 000 women in the United States (data from [38]).

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, Novo Nordisk, 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, Genomic Health, Theramex, ClinSol and onkowissen.de, travel support from Carl Zeiss meditec, Novartis, Amgen, Astra Zeneca, Pfizer LIV Pharma, Genomic Health, Tesaro and Daiichi-Sankyo and owns stock from Theraclion and Phaon Scientific. 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 Astra Zeneca, Roche, Celgene, Novartis, Lilly, Pfizer, Pierre Fabre, Teva and travel support from Celgene, Pfizer, Teva and 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 and medical education activities MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac, onkowissen.de, ClinSol and Eisai. V. M. received speaker honoraria from Amgen, Astra Zeneca, 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, 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, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai, Celgene, Teva, Hexal, AstraZeneca, Sirtex, MSD and received honoraria for lectures from Novartis, Pfizer, Aurikamed, RocheAmgen, Eisai, Lilly, AstraZeneca, Genomic Health, ClinSol, onkowissen.de. D. L. received honoraria from Amgen, AstraZeneca, ClinSol, Celgene, Lilly, Loreal, MSD, Novartis, onkowissen.de, 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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