

Update Breast Cancer 2021 Part 4 – Prevention and Early Stages

Update Mammakarzinom 2021 Teil 4 – Prävention und frühe Krankheitsstadien



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Schlüsselwörter

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ABSTRACT

This past year has seen new and effective options for further improving treatment outcome in many patients with early-stage breast cancer. Patients with hormone receptor-positive disease benefited significantly from the addition of the CDK4/6 inhibitor abemaciclib to endocrine adjuvant therapy. In triple-negative disease, data were presented for two treatment regimens. Patients with advanced disease (stage 2 and 3) benefit from neoadjuvant treatment with the immune checkpoint inhibitor pembrolizumab in combination with standard che-

motherapy, regardless of PD-L1 expression. When neoadjuvant therapy has failed to achieve the desired remission in BRCA1 and BRCA2 mutations, the administration of the PARP inhibitor olaparib has demonstrated an impressive response. Other data address translational issues in HER2-positive breast cancer and neoadjuvant therapy approaches with the oral SERD giredestrant and the PARP inhibitor talazoparib. This review presents and analyses the findings of this year's most important study outcomes.

ZUSAMMENFASSUNG

Im vergangenen Jahr wurden für viele Patientinnen mit Mammakarzinom in frühem Krankheitsstadium neue und effektive Optionen für eine weitere Verbesserung der Behandlungsergebnisse gezeigt. Für Patientinnen mit hormonrezeptorpositiver Erkrankung zeigte sich ein signifikanter Zusatzeffekt durch den Einsatz des CDK4/6-Inhibitors Abemaciclib zusätzlich zur endokrinen adjuvanten Therapie. Bei triple-negativer Erkrankung wurden Daten für 2 Therapieprinzipien gezeigt. Patientinnen mit fortgeschrittener Erkrankung (Stadium 2 und 3) profitieren von dem neoadjuvanten Einsatz des Immuncheckpoint-Inhibitors Pembrolizumab unabhängig von der PD-L1-Expression in Kombination mit einer Standardchemotherapie. Bei BRCA1- oder BRCA2-Mutation wurde ein eindrucksvoller Benefit durch den Einsatz des PARP-Inhibitors Olaparib gezeigt, wenn die neoadjuvante Therapie nicht zur gewünschten Remission geführt hat. Weitere Daten betreffen translationale Fragestellungen beim HER2-positiven Mammakarzinom sowie neoadjuvante Therapieansätze mit dem oralen SERD Giredestrant und dem PARP-Inhibitor Talazoparib. In dieser Übersichtsarbeit werden die Ergebnisse der wichtigsten Studienergebnisse dieses Jahres vorgestellt und bewertet.

Introduction

In patient with early breast cancer, the gradual progress in adjuvant therapy has resulted in a significant improvement in the chances of cure. Important interventions such as dose-dense chemotherapy, pertuzumab and T-DM1 in HER2-positive cancer, GnRH agonists in premenopausal hormone receptor-positive disease, and carboplatin to optimise chemotherapy in triple-negative cancer have been incorporated in recent years. The focus is on new targeted drugs to further optimise adjuvant therapy and also on de-escalation of therapeutic measures through better identification of patients at risk, the reduction of medications and better supportive therapy. These were also prominent topics at recent congresses such as ASCO 2021 and ESMO 2021, which will be summarised in this review.

Ten Breast Cancer Risk Genes You Should Know

Since the 1990s, *BRCA1* and *BRCA2* genotyping has been part of counselling healthy women seeking consultation for hereditary breast and ovarian cancer. Following the large-scale trials published in early 2021, evidence is accumulating on which genes should be genotyped in panel testing. One commentary identified 10 genes for cancer-susceptibility [1]. *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2* are clearly defined and validated breast cancer risk genes [2, 3]. The data for *TP53* also clearly indicate that it is a gene for breast cancer-susceptibility [1], but the low prevalence in these large-scale trials prevented researchers from calculating the corresponding risk [2, 3]. Three other genes (*BARD1*, *RAD51C* and *RAD51D*) mainly increase the risk of hormone receptor-negative breast cancer [2, 3]. Even if they do not significantly increase the lifetime risk because of this, hormone receptor-negative breast cancer is highly significant. The identification of mutation carriers is not only important for the prevention of breast cancer, but also to identify women at significantly increased risk of ovarian cancer. In terms of the risk genes stated, there is a large overlap with *BRCA1*, *BRCA2*, *PALB2*, *RAD51C* and *RAD51D* [4]. In addition,

BRIP1 should be genotyped, which, although not clearly associated with breast cancer risk [5], is useful in identifying women at high risk of ovarian cancer [4]. Thus, the following 10 genes could be regarded as a gene panel on which testing and counselling should focus.

- *ATM*
- *BARD1*
- *BRCA1*
- *BRCA2*
- *BRIP1*
- *CHEK2*
- *PALB2*
- *RAD51C*
- *RAD51D*
- *TP53*

The function of these genes is summarised in ► **Table 1**. With the growing knowledge of which genes are validated risk factors in the development of breast cancer, potential attempts are also being made to apply this knowledge to the treatment of breast cancer. The effects of *BRCA1/2* mutations in the neoadjuvant and adjuvant setting have already been reported in past studies. While chemotherapy in the neoadjuvant setting appears to improve efficacy [6–8], the reported effect on prognosis is inconsistent [9]. There are similar studies for other genes such as *PALB2* or *CHEK2* describing the effect on the prognosis of breast cancer patients, but no effects resulting in clinical implications [10–12]. However, mutations in *PALB2* may be an indicator of response to olaparib, as most TNBC patients with a *PALB2* mutation responded to olaparib therapy in a small study [13].

However, data from the metastatic setting have been lacking to date. PRAEGNANT, a recently published registry study, reported a mutation frequency of 5% for *BRCA1/2* mutations in patients with metastatic breast cancer [14]. Another about 5% of the patients carried a mutation in one of the other known breast cancer risk genes [14].

In this study, the difference in progression-free survival and overall survival between patients with and without a germ line mutation in one of the breast cancer risk genes was not statistically significant [14].

Non-endocrine Based Treatment in Early Stages of the Disease

Two important studies, the OlympiA study and the survival data from the KEYNOTE-522 study, have recently been published [15, 16]. Both demonstrated clinically important advances in the treatment of patients with triple-negative breast cancer (TNBC), and the OlympiA trial also in the treatment of patients with HER2-negative, hormone receptor-positive breast cancer.

Better event-free survival in TNBC patients with pembrolizumab statistically significant

The KEYNOTE-522 study has already been published concerning one of its study objectives. In the KEYNOTE-522 trial, patients with stage 2 and 3 triple-negative breast cancer underwent neoadju-

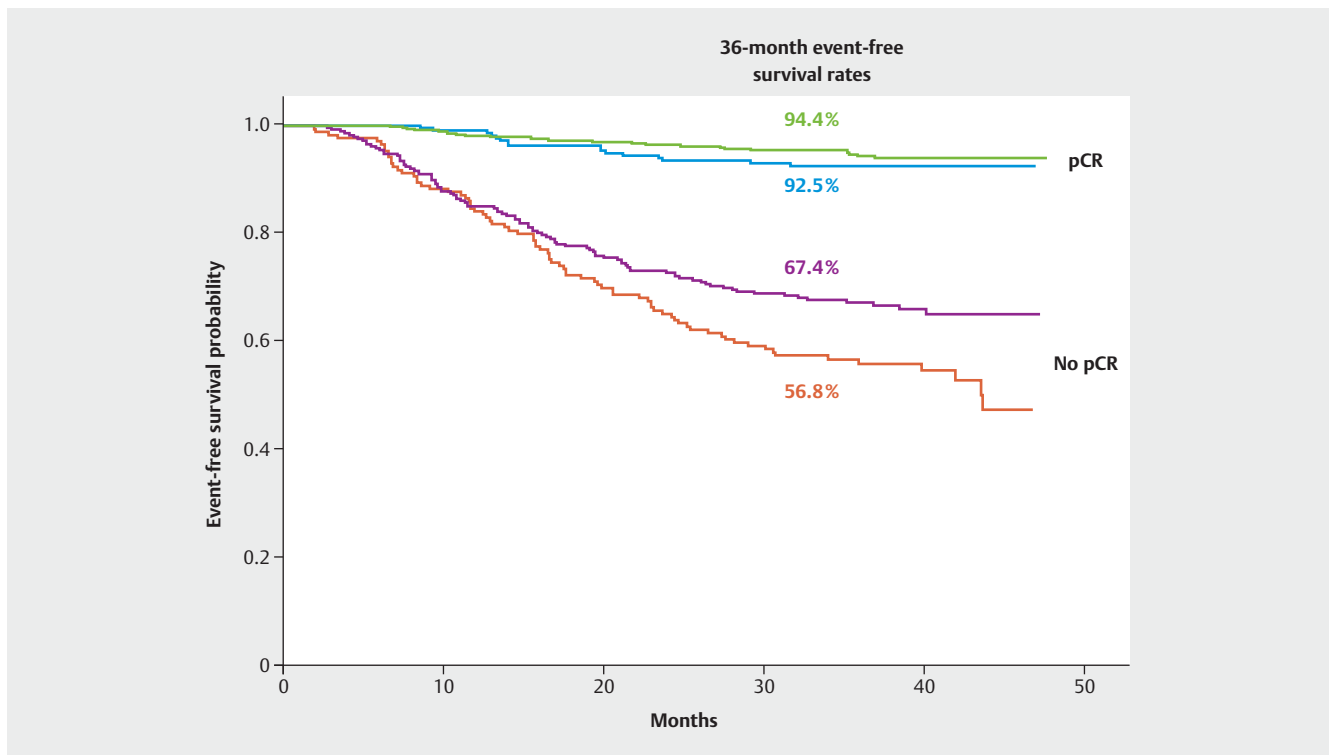
► **Table 1** Functional classification of the validated breast cancer risk genes.

Name of gene	involved in homologous recombination	involved in other DNA repair mechanisms	validated breast cancer risk gene
<i>ATM</i>	X		X
<i>BARD1</i>	X		X
<i>BRCA1</i>	X		X
<i>BRCA2</i>	X		X
<i>BRIP1</i>		X	
<i>CHEK2</i>		X	X
<i>PALB2</i>	X		X
<i>RAD51C</i>	X		X
<i>RAD51D</i>	X		X
<i>TP53</i>		X	X

vant treatment with standard chemotherapy including carboplatin and were compared with patients who also received supplemental pembrolizumab. Pembrolizumab treatment was continued in the pembrolizumab plus chemotherapy arm for six months following surgery [17]. In the final analysis of all 1174 patients participating in the survival analyses, the pCR rate was 55.6% in the chemotherapy arm and 63.0% in the pembrolizumab plus chemotherapy arm. Thus, the pembrolizumab plus chemotherapy arm benefited by 7.5% [18]. The fourth interim analysis presented robust data on the probability of event-free survival. With a median follow-up of 39.1 months, it was shown that the addition of pembrolizumab decreased the risk of relapse or death by 37% (hazard ratio: 0.63; 95% CI: 0.48–0.82) [15]. This effect was statistically significant ($p = 0.00031$). The probability of event-free survival at 36 months is 76.8% in the chemotherapy arm and 84.5% in the pembrolizumab plus chemotherapy arm. Interestingly enough, the relative benefit was present and similar in both patients with and without a pCR (► **Fig. 1**). Although there was no statistically significant difference in overall survival, probably due to the still short follow-up period, the numerical difference at 3 years was 2.8% (89.7% in the pembrolizumab arm and 86.9% in the chemotherapy arm). The hazard ratio (HR) was 0.72 (95% CI: 0.51–1.02) [15]. More analyses with longer follow-up time are expected.

Neoadjuvant data with durvalumab support the integration of PD-1/PD-L1 inhibitors into the treatment of early-stage disease

Although the phase II GeparNuevo trial with 174 patients is much smaller than the KEYNOTE-522 trial, the results recently presented support the role of immuno-oncological regimens in patients with stage 2 and 3 TNBC [19]. Invasive disease-free survival (iDFS), distant disease-free survival (dDFS) and overall survival were secondary study objectives. The hazard ratios were 0.48 (95% CI: 0.24–0.97; $p = 0.0398$) for iDFS, 0.31 (95% CI: 0.13–0.74, $p = 0.0078$) for dDFS and 0.24 (95% CI: 0.08–0.72; $p = 0.0108$)



► **Fig. 1** Event-free survival in the KEYNOTE-522 trial by randomisation arm and pCR group (data from [15]).

for overall survival. There was no evidence that this effect was limited to the group of patients with or without pCR or that the benefit of the checkpoint inhibitor was reflected in the attainment of pCR alone, even though the trial was not designed to draw such conclusions.

Olaparib in adjuvant settings

Since the PARP inhibitors olaparib and talazoparib have already been approved in the metastatic setting for HER2-negative patients with a *BRCA1* or *BRCA2* germ line mutation, the OlympiA trial for patients at high risk for relapse in the early stages of the disease has tested whether 12 months of adjuvant therapy with olaparib can improve iDFS. With a median follow-up of 2.5 years and 1836 patients randomised, iDFS was shown to improve with a HR of 0.58 (95% CI: 0.41–0.82). The probability of disease-free survival (iDFS) at 36 months was 77.1% for the placebo arm and 85.9% for the olaparib arm [16]. Although the comparison showed no statistically significant difference in terms of overall survival, the mortality rate was reduced by 32% (HR: 0.68; 95% CI: 0.44–1.05; $p=0.02$) [16]. 18% of the enrolled patients had hormone receptor-positive breast cancer. While the treatment effect was numerically smaller in this group (HR: 0.70; 95% CI: 0.49–1.21) than in the TNBC cohort (HR: 0.52; 95% CI: 0.39–0.69), no heterogeneity was demonstrated for the subgroups. One explanation might be the small number of cases.

Both the OlympiA trial and the KEYNOTE-522 trial are groundbreaking because they are changing the treatment landscape for

patients with triple-negative breast cancer and HER2-negative, hormone receptor-positive breast cancer.

Talazoparib in neoadjuvant settings

After a small, neoadjuvant trial ($n=13$) in patients with a *BRCA1/2* mutation achieved a median reduction in tumour volume of 88% with talazoparib monotherapy [20], the question arose as to how this therapy would fare in a larger group of patients. This question was tested in the NeoTALA trial [21]. This study analysed 48 HER2-negative patients with a germ line *BRCA1/2* mutation and treated with 0.75 mg talazoparib per day as neoadjuvant monotherapy for 24 weeks. 45.8% of this population achieved a pCR. Especially against the backdrop of its markedly better tolerance compared to chemotherapy [22], this information is helpful to continue the development of corresponding therapeutic concepts.

Role of carboplatin in the treatment of TNBC patients

It was already known from the trials GeparSixto and CALGB 40603 that adding carboplatin to anthracycline- and taxane-based neoadjuvant chemotherapy increased pCR rates from 37–46% to 53–60% [23, 24]. In the GeparSixto trial, the addition of carboplatin to anthracycline- and taxane-based intensive neoadjuvant chemotherapy improved relapse-free survival in the TNBC population with a HR of 0.54 (95% CI: 0.34–0.93). Overall survival improved with a HR of 0.60 (95% CI: 0.32–1.12) [25]. In the CALGB 40603 trial, platinum-free chemotherapy did not differ in survival from platinum-based neoadjuvant chemotherapy [26]. Survival data from the BrightNESS study have now been published in this con-

text [27]. In the BrighTNess study, patients were randomised into three treatment arms. Patients with early TNBC were enrolled regardless of their *BRCA1/2* mutation status. The patients initially received either paclitaxel monotherapy, a combined regimen with paclitaxel and carboplatin or a regimen with paclitaxel, carboplatin and veliparib. All patients then received four cycles of doxorubicin and cyclophosphamide. The 4-year event-free survival of 78.2% in the paclitaxel-carboplatin-veliparib arm was comparable to the 79.3% survival in the paclitaxel-carboplatin arm. At 68.5%, the paclitaxel-monotherapy arm was markedly lower [27]. Overall, the BrighTNess trial therefore confirmed the efficacy of platinum-based chemotherapy in the neoadjuvant treatment of patients with triple-negative breast cancer. However, the interpretation of the data is complicated by the fact that the risk reduction obtained relative to the first event mainly concerned locoregional recurrence, less so distant metastasis.

Treatment of Early-Stage HER2-positive Tumour Patients

De-escalating anti-HER2 therapy

The duration of adjuvant anti-HER2 treatment with trastuzumab has been under discussion for some time. Treatment with trastuzumab in the (neo-)adjuvant setting over one year is well established by now [28–30]. The question of whether a two-year course of therapy would be better was clearly answered in the negative [31]. However, some other studies have been conducted comparing a one-year trastuzumab regimen with a shorter course of treatment [32–37]. The PERSEPHONE, HORG and PHARE trials compared one year of trastuzumab with a six-month course. The SOLD and Short-HER trials shortened adjuvant treatment even further, comparing a one-year course of trastuzumab with a nine-week regimen.

Recently, a meta-analysis of these data (12 months versus shorter therapy) in a non-inferiority design has been published. This analysis covered more than 11 300 patients [38] and included three comparisons: all trials comparing 6 months with 12 months, and trials comparing 9 weeks with 12 months. The cut-off for non-inferiority was seen at a hazard ratio of 1.19 to 1.25, depending on which of the three analyses was performed. This corresponded to an absolute difference of 2% in invasive disease-free survival.

The meta-analysis confirmed the non-inferiority of 6 months versus 12 months. However, the non-inferiority of 9 weeks versus 12 months could not be confirmed [38]. Moreover, the quite extensive data on 12 months of trastuzumab in patients with early-stage disease raises doubts that adjuvant trastuzumab treatment for 6 months could become a new standard in the treatment of HER2-positive patients. The authors suggested that in the individual treatment setting – if necessary – it could be decided together with the patients whether treatment should be continued after 6 months, as the extension to 12 months only provided a marginal additional benefit of 0.7%. Yet, it must also be taken into account that the treatment combination of the studies in the meta-analysis is rare nowadays. Many patients receive dual therapy (trastuzumab and pertuzumab) in the neoadjuvant setting, and in the ab-

sence of complete remission may receive T-DM1 as postneoadjuvant treatment. Patients with trastuzumab mono often undergo de-escalation of chemotherapy with 12 cycles of paclitaxel according to the APT study. It is currently unclear whether in de-escalation of chemotherapy, further de-escalation may also be achieved by shortening the trastuzumab treatment period.

De-escalation of chemotherapy

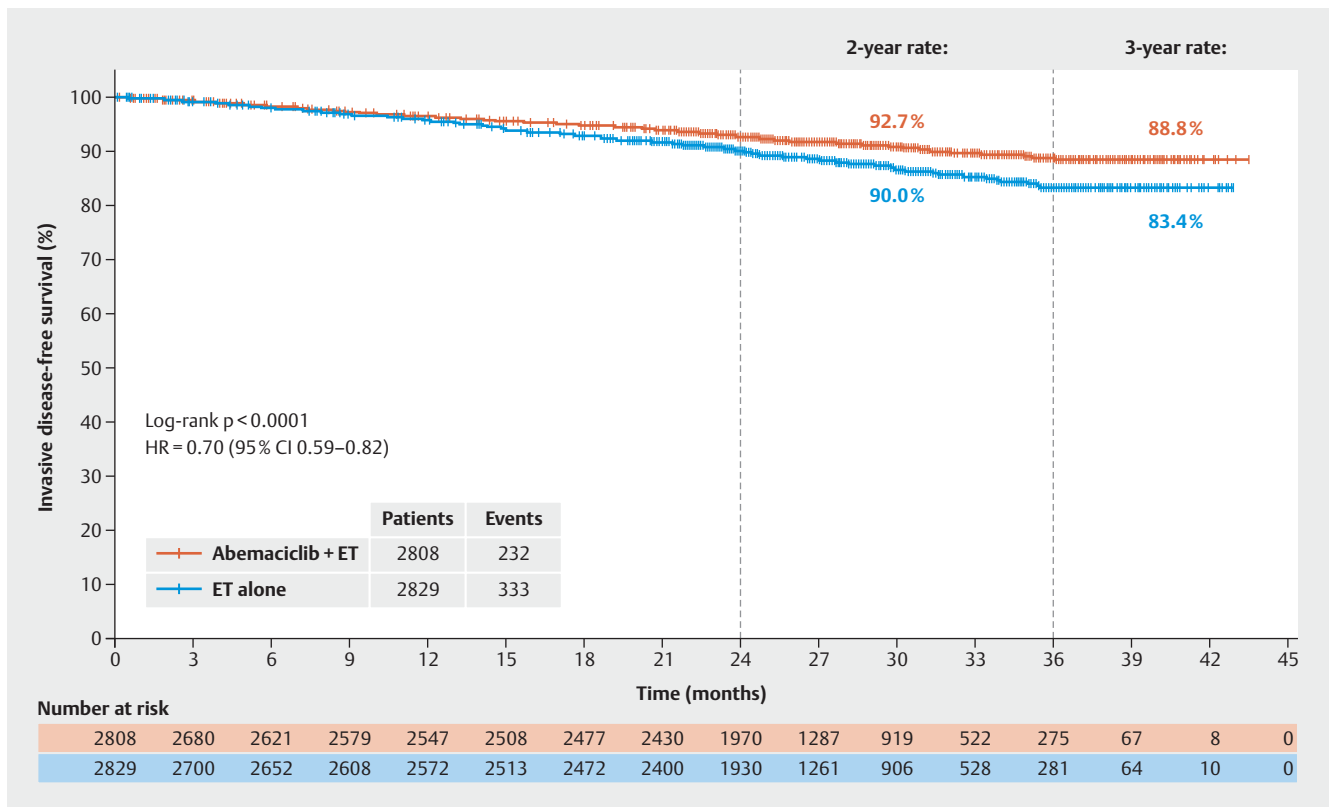
ADAPT-HER2+HR is another trial addressing the de-escalation of anti-HER2 treatment [39]. This trial compared chemotherapy-free, neoadjuvant treatment with trastuzumab and pertuzumab (T+P) versus treatment with paclitaxel, trastuzumab and pertuzumab (T+P+Pac). Accordingly, both arms followed a de-escalating strategy compared to the standard treatment. The T+P arm achieved a pCR rate (ypT0/is ypN0) of 34.4% compared to a pCR rate of 90.5% in the T+P+Pac arm [39]. Despite the markedly low pCR rate in the T+P arm, it is of great interest which patients achieved a pCR without the addition of chemotherapy. For this reason, translational analyses have been performed despite the rather small number of cases, a total of 134 patients.

This allowed patients with highly HER2-expressing tumours, with non-basal-like tumours, with early treatment response, and patients with specific gene expression profiles to be identified as promising for a chemotherapy-free treatment regimen [39]. Nevertheless, these and other de-escalation studies are inadequate to replace the current standard.

Endocrine-based Treatment in Early-Stage Disease

CDK4/6 inhibitors in adjuvant therapy

After the monarchE trial with its rather short median follow-up of 15.5 months in terms of invasive disease-free survival (HR: 0.72; 95% CI: 0.56–0.92; favouring combined abemaciclib therapy) revealed positive data [40], the treatment was considered a possible option in patients with HER2-negative, hormone receptor-positive breast cancer, although the observation period was deemed too short to draw firm conclusions about the long-term value of the treatment. In San Antonio, data were published in 2020 with a longer median follow-up of 19.1 months (HR: 0.713; 95% CI: 0.583–0.871). Now another analysis with a median follow-up (FU) of 27.1 months has been presented [41]. In this analysis, the HR was 0.70 (95% CI: 0.59–0.82). The disease-free survival rate after 3 years was 83.4% in the standard endocrine treatment arm and 88.8% in the combination arm with abemaciclib. This corresponds to an absolute difference of 5.4% (► Fig. 2). Altogether, it can be stated that the relative improvement of the prognosis does not change much from analysis to analysis, which speaks for the stability of these outcomes. At the time of the 27-month follow-up analysis, 90% of the patients were already no longer on therapy, making it more likely that the difference between both randomisation arms would be maintained. In view of these current data, on 13 October 2021, the US Food and Drug Administration approved abemaciclib in the US for patients with HER2-negative, hormone receptor-positive breast cancer and positive lymph



► Fig. 2 Invasive disease-free survival at a median follow-up of 27 months (data from [41]).

nodes and a Ki-67 $\geq 20\%$ (as determined by the FDA approved test “MIB-1 pharmDx [Dako Omnis]”). It remains to be seen which criteria will be adopted by the European regulatory authority, as this definition does not cover the complete study population of the monarchE trial. Even though Ki-67 is an excellent prognostic marker and can also predict response to chemotherapy, this marker has not yet been established in routine practice in all treatment centres [42–45].

In the wake of the negative outcomes of the PenelopeB and PALLAS trials with palbociclib, the monarchE trial with abemaciclib is the first adjuvant trial to demonstrate the adjuvant benefit of CDK4/6 inhibitor-based therapy. The NATALEE trial (TRIO033) is another study that has recruited 5000 patients and will answer the question of whether the addition of the third CDK4/6 inhibitor ribociclib in the adjuvant setting will have a positive impact on disease-free survival.

Selective estrogen receptor degraders (SERD) in early-stage disease

Initial clinical experience with SERDs was gained in trials for advanced disease [46–51]. For a general introduction to the topic of “oral SERDs”, see Lüftner D, Schütz F, Stickeler E et al. Update Breast Cancer 2021 Part 5 – Advanced Breast Cancer. *Geburtshilfe Frauenheilkd* 2022; 82: 215–225. doi:10.1055/a-1724-9569.

Recently, data from an interim analysis of the neoadjuvant coopERA trial have been presented. The coopERA trial compared 14-day neoadjuvant induction treatment with the peroral SERD giredestrant versus anastrozole in terms of reduction in proliferation as measured by Ki-67. After these initial 14 days, the respective anti-hormonal therapy was continued together with palbociclib for 16 weeks. In the cohort treated with giredestrant, the proliferation factor Ki-67 was reduced by 80% versus 67% in the cohort treated with anastrozole. With a p-value of 0.0222, the trial did not achieve the p-value of 0.01029 needed for formal statistical significance. Nevertheless, these outcomes are promising and support the rationale of studying this substance in other therapeutic settings. The lidERA trial, which compares adjuvant 5-year treatment with giredestrant versus guideline-based 5-year adjuvant endocrine treatment as chosen by the physician [52], is currently being initiated internationally. The AMEERA-6 trial of the oral SERD amcenestrant, which is being tested in an adjuvant setting in a study population that has prematurely completed adjuvant endocrine therapy and is therefore at high risk of relapse, will start soon [53].

The field of oral SERDs has seen some new developments, such as the use of PROTAC (Proteolysis Targeting Chimera) technology [54]. These hetero-bifunctional molecules bind a ligand for a protein of interest (in this case the oestrogen receptor) on one side and the E3 ubiquitin ligase complex on the other. This triggers oestrogen receptor breakdown. A neoadjuvant study is now also being planned with this substance [55].

Outlook

The challenges lie in optimising treatment in high-risk diagnoses such as triple-negative breast cancer, which relapses early despite all measures to the contrary, and luminal cancer which relapse even late in the course of treatment. Developments, such as immune checkpoint inhibitors and PARP inhibitors, open up new and effective treatment options in biologically defined subgroups. For luminal cancer, continued development of endocrine-based therapy with oral selective estrogen receptor degrading substances (oral SERDs) and CDK4/6 inhibitors promises higher cure rates. On the other hand, we know that the improved prognosis in early breast cancer has come at the cost of massive overtreatment. Therefore, it is also important to de-escalate where possible. Possible approaches include the development of less neurotoxic taxanes, the avoidance of anthracyclines in many indications, antibody treatment alone with the avoidance of chemotherapy in some HER2-positive cancers, toxicity reduction through the use of antibody-substance conjugates in HER2-positive and triple-negative cancers, and also the identification of patients with luminal cancers (ER-pos./HER2-neg.) who can be adequately treated with adjuvant endocrine therapy alone.

Early-stage breast cancer still remains a challenge. The heterogeneity of this disease requires personalised treatment concepts with escalation where necessary and de-escalation where possible.

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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.

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