Thieme

Update Breast Cancer 2022 Part 5 – Early Stage Breast Cancer

Update Mammakarzinom 2022 Teil 5 – Brustkrebs in frühen Krankheitsstadien

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ABSTRACT

The treatment of patients with early stage breast cancer has changed in recent years due to the introduction of pembrolizumab, olaparib, and abemaciclib. These and other drugs with the same class of active ingredient are currently in trial for various indications. This review article summarizes the latest results that have either been presented at major conferences such as the ESMO 2022 or published recently in international journals. This includes reports on newly discovered breast cancer genes, atezolizumab in neoadjuvant therapy in HER2-positive patients, long-term data from the APHINITY study, and on how preoperative peritumoral application of local anesthetics can influence the prognosis. We also present solid data on dynamic Ki-67 from the ADAPT studies.

ZUSAMMENFASSUNG

Die Behandlung von Patientinnen mit Mammakarzinom in frühen Krankheitsstadien hat sich in den letzten Jahren durch die Einführung von Pembrolizumab, Olaparib und Abemaciclib verändert. Diese und weitere Substanzen dieser Wirkstoffklassen werden derzeit in verschiedenen Indikationen getestet. Diese Übersichtsarbeit fasst die neuesten Ergebnisse zusammen, die entweder auf den großen Kongressen wie dem ESMO 2022 oder kürzlich in internationalen Fachzeitschriften veröffentlicht worden sind. Es wird berichtet von neu entdeckten Brustkrebsgenen, Atezolizumab in der Neoadjuvanz bei HER2-positiven Patientinnen, Langzeitdaten aus der Aphinity-Studie und vom Effekt von Lokalanästhetika, die präoperativ peritumoral appliziert wurden, auf die Prognose. Ebenso werden solide Daten zum dynamischen Ki-67 aus den ADAPT-Studien vorgestellt.

Introduction

After many years of efforts to de-escalate the treatment of patients with early stage breast cancer, in recent years olaparib, pembrolizumab, and abemaciclib have been introduced as drugs that once again escalate the treatment of this patient group; however, they do so in a manner specific to the cancer subtype, with attempts made to define the patient group that will benefit from the greatest efficacy. In this context, the question of prognosis gains special importance. As long-term observation data becomes increasingly available, this may help us to gain a better understanding of the prognosis for patients with hormone receptor-positive (HRpos)/HER2-negative (HER2neg) breast cancer. The de-escalation concepts remain valid, of course, depending on the given situation. New data on this have also become available. In this article we present these topics, as well as current aspects of prevention and treatment for HER2-positive patients with early stage breast cancer.

Prevention

Largest study on new risk variants now published

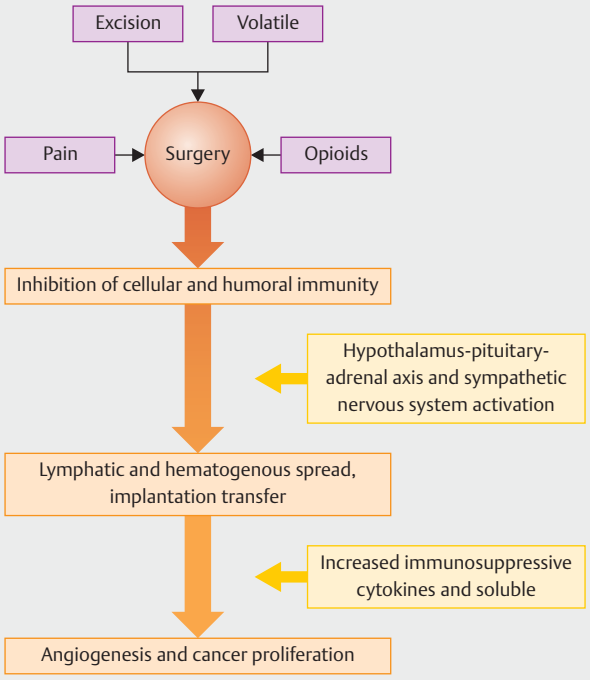
In addition to the high-risk genes BRCA1 and BRCA2, over the past 15 years other moderate to low-penetrance gene variants have been described, which may explain up to 40% of the familial breast cancer risk. In studies on this topic, familial breast cancer risk is defined as a risk that is twice as high as normal due to the person's family history. The largest part of this risk is accounted for by single nucleotide polymorphisms (SNPs), which occur commonly in the population. Due to the large number of variants being investigated, in order to describe these risks it was necessary to conduct increasingly large-scale studies with increasingly large numbers of cases – not only because of the sometimes marginal influence of individual variants, but also because of the difficulties in dealing with multiple tests when performing a large number of statistical tests. The largest study conducted to date in this context has now been published [1]. This study includes data from 160 500 breast cancer patients and 226 196 control subjects. Accordingly, it comprises both clinical and genetic information for a total of 386 696 individuals. In this study, 17 gene loci were identified in 14 previously unknown genes. The remaining 124 genes identified in the study were in gene regions that were already known. ▶ **Table 1** gives an overview of the newly identified genes which may play an important role in the genesis of breast cancer.

During the COVID-19 pandemic, the scientific community shifted its focus to the issue of making and using mRNA vaccines. Before the pandemic, some efforts had been made to use these platforms for the rapid manufacture of cancer vaccines [2–4], in order to develop, for example, vaccines against possible neoantigens, for therapeutic or preventive purposes [5–7]. With breast cancer, too, it is known that a clinically relevant proportion of patients develop a significant immune response, which researchers have been able to associate with the treatment efficacy or the prognosis [8–10]. However, antigens that are known to occur in breast tumors are also the focus of experimental vaccines [11]. Data on a new vaccine based on a DNA plasmid have now been published for the first time [12]. In this phase I study, a DNA plasmid coding for the intracellular domain of the HER2 receptor was tested in various doses [12]. The patients enrolled in the study who received the highest dose also recorded the greatest response in terms of a type 1 immune response. At the end of the three-monthly intradermal injections, some of the patients showed a residual immune response after 16 weeks. These data show that in the near future this type of treatment is ripe for fur-

▶ **Table 1** Newly discovered gene loci that have been found to have an association with breast cancer risk (according to [1]).

Chromosome	Gene name closest to the variant	HR
2p22.1	*SLC8A1*	0.97 (0.96, 0.98)
5q13.2	*LINC02056**	0.96 (0.95, 0.98)
5q35.2	*CPEB4**	0.97 (0.96, 0.98)
6p21.2	*CDKN1A*	0.97 (0.96, 0.98)
6q22.31	*HSF2**	1.05 (1.03, 1.07)
6q27	*AFDN*	1.06 (1.04, 1.07)
7p21.2	*ENSG00000224330**	1.03 (1.02, 1.04)
8p22	*PCM1*	1.03 (1.02, 1.04)
10q21.1	*PRKG1*	1.03 (1.02, 1.04)
11q23.1	*ALG9*	1.03 (1.02, 1.04)
11q23.3	*PCSK7*	1.06 (1.04, 1.08)
12q13.3	*INHBE*	0.97 (0.96, 0.98)
15q22.2	*TLN2*	1.03 (1.02, 1.05)
18p11.21	*LDLRAD4*	1.03 (1.02, 1.05)
20q11.23	*PHF20*	1.05 (1.03, 1.07)
10q26.11	*DENND10*	0.86 (0.81, 0.90)
17p13.2	*ZZEF1*	1.13 (1.09, 1.18)

* Variants located in the gene neighborhood



▶ **Fig. 1** Possible mechanisms by which a surgical intervention can influence tumor biology (data from [14], https://creativecommons.org/licenses/by/4.0/).

ther investigation in clinical studies, in both the therapeutic and preventive fields. Given that to date primary prevention has mainly been focused on hormone receptor-positive tumors, with this kind of approach it would be possible to also focus on cancers of the more aggressive subtypes, such as HER2-positive tumors.

New Surgical Data with New Approaches

Does preoperative infiltration with local anesthetic affect the prognosis?

A recently published randomized study from India investigating the influence of local anesthetics on the prognosis in primary breast cancer patients [13] is the subject of heated debate.

The study hypothesized that the preoperative, peritumoral application of local anesthetic can have an influence on the prognosis in breast cancer patients. In fact, there was a discussion around several possible factors that might influence molecular signaling pathways in the surgical setting, such as administration of opioids, stress, and hypoxia, among others [14]. ▶ **Fig. 1** gives an overview of these factors. Similarly, it is hypothesized that local anesthetics could block some of these unwanted molecular changes [14].

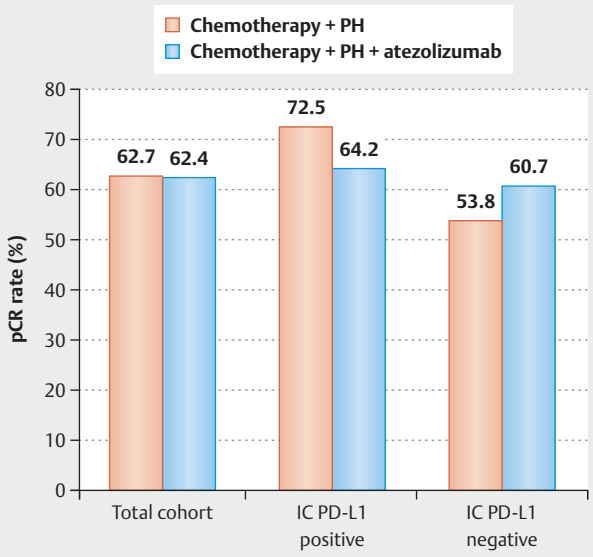
In this recently published study, a total of 1583 breast cancer patients were randomized to undergo preoperative peritumoral injection of local anesthetic versus no application of local anesthetic. The median observation period was 72 months. With regard to both relapse-free survival and overall survival, the differences observed were in favor of preoperative peritumoral injection of local anesthetic. The hazard ratio (HR) for relapse-free survival was 0.74 (95% CI: 0.58–0.95) and the HR for overall survival was 0.53 (95% CI: 0.53–0.94 [14]. Considering the inadequate presentation of the study population and lack of evidence concerning the actual mechanisms involved, the study results need to be published in full and reproduced in further studies before they can be adopted in clinical practice.

New Data on Patients with HER2-Positive Breast Cancer Not Clinically Relevant

Atezolizumab in neoadjuvant therapy

Pembrolizumab has been approved for neoadjuvant and adjuvant treatment of triple-negative breast cancer (TNBC) in patients with a high risk of relapse [15, 16]. It significantly improves event-free survival, and the data also point to an improvement in overall survival times; however, this difference is not yet statistically significant [15]. Previously, we did not have any data on other molecular subtypes (HER2-positive and hormone receptor-positive). Now the Impassion050 study has been published – a neoadjuvant study investigating the addition of atezolizumab to neoadjuvant therapy in HER2-positive breast cancer [17].

As standard, the patients were given dose-dense doxorubicin and cyclophosphamide, followed by treatment with paclitaxel in combination with trastuzumab and pertuzumab. The patients



▶ **Fig. 2** pCR rates in the Impassion050 study (data from [17]).

were randomized to additionally receive either atezolizumab or a placebo. Analyzes were to be carried out both on the study cohort as a whole and on the subpopulations of PD-L1-positive and PD-L1-negative patients. The rates of pathological complete remission (pCR) for these populations are set out in ▶ **Fig. 2**. In the overall study cohort, no difference was observed between the two randomization arms. The pCR rates were 62.7% in the placebo arm and 62.4% in the atezolizumab arm. In the pCR rate analysis for the Immune Cell (IC)PD-L1-positive subcohort (primary study objective), a difference of 8.3% was observed (72.5% in the placebo arm and 64.2% in the atezolizumab arm). In the IC-PD-L1-negative arm, by contrast, the effect on pathological complete remission was numerically reversed (with a pCR rate of 53.8% in the placebo arm and 60.7% in the atezolizumab arm). None of the differences between the randomization arms were formally statistically significant. Nevertheless, this study shows how important it is to gain a better understanding of how immunotherapies work. To date, none of the studies investigating the triple-negative subgroup have been able to demonstrate an association between PD-L1 positivity and a potentially reduced response. In patients with metastatic disease, it has been shown that the addition of pembrolizumab to a chemotherapy regimen results in even greater benefit in terms of progression-free survival or overall survival the higher the rate of PD-L1 expression (CPS score) [18]. In the neoadjuvant setting, the response to chemotherapy or a treatment combining chemotherapy and pembrolizumab was better the higher the rate of PD-L1 expression (CPS score) [15, 16]. However, this effect was observed both in patients undergoing chemotherapy alone and in those receiving the combination with pembrolizumab; this means that the indication for neoadjuvant pembrolizumab does not depend on diagnostics for PD-L1 expression.

Pertuzumab in long-term follow-up

Pertuzumab can be used in the neoadjuvant and adjuvant setting. In the neoadjuvant setting, the rate of pCR is increased by approximately 20% [19–21]. In the adjuvant setting, a disease-free survival (DFS) benefit was reported in the Aphinity study with a median follow-up of 45.4 months (HR in favor of combination therapy at 0.81; 95% CI: 0.66–1.00). Subgroup analysis by nodal status showed that patients with positive lymph node status in particular benefited from the therapy (HR = 0.77; 95% CI: 0.62–0.96), and patients with negative nodal status benefited less (HR = 1.13; 95% CI 0.68–1.86). The third interim analysis for overall survival has now been published, with a median follow-up of 8.4 years [22]. Just as in previous analyzes, the evaluation in terms of overall survival did not achieve statistical significance with an HR of 0.83 (95% CI: 0.68–1.02); however, the addition of pertuzumab did result in a numerical benefit. This effect was somewhat more pronounced in the nodal-positive patients (HR = 0.80, 95% CI: 0.63–1.00). In nodal-negative patients, an HR of 0.99 (0.64–1.55) indicates that pertuzumab has no effect on overall survival. Exploratory analyzes of disease-free survival (DFS) showed very similar results to the previous studies, especially with regard to the greater treatment effect in nodal-positive patients.

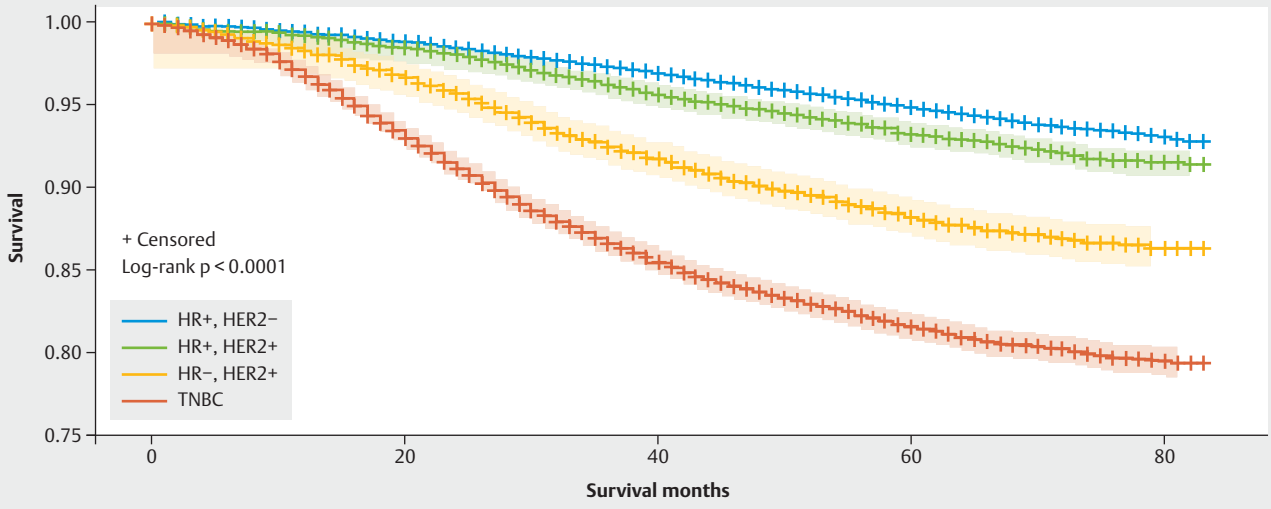
Thus, the data on pertuzumab have not changed much and the current treatment recommendations [23], advising treatment in patients with nodal-positive disease and allowing individual treatment decisions in patients with nodal-negative disease, remain valid according to this analysis.

Optimizing Adjuvant Therapy in Patients with HR-Positive/HER2-Negative Breast Cancer – Old Studies/New Studies

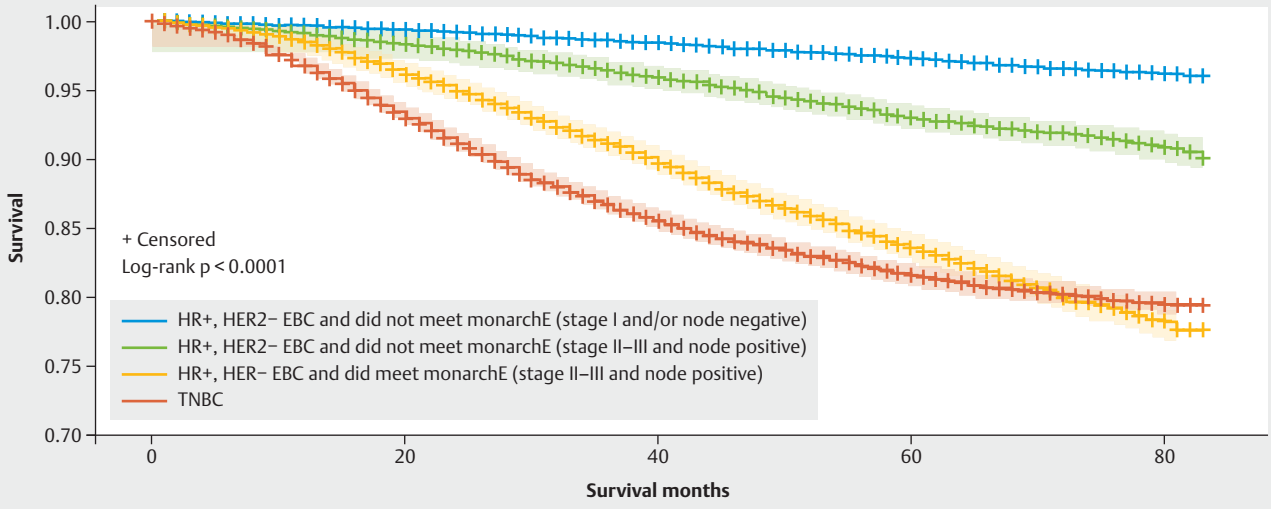
Long-term data on the duration of aromatase inhibitor therapy after 2–3 years of tamoxifen

The treatment of patients with early stage breast cancer has improved significantly over the past decades. The prognosis is generally good for this patient group, especially for those who are hormone receptor-positive. However, since the latter account for the largest proportion of all breast cancer patients in absolute terms, they are also implicated in the largest proportion of breast cancer deaths. This is why it is especially important to continue optimizing the therapy for this treatment group.

Some of the major adjuvant endocrine therapy studies which recruited their cohorts some time ago are now reporting their long-term follow-up results. One of these is the DATA study which investigated the duration of aromatase inhibitor therapy. The study cohort consisted of postmenopausal patients who had already received treatment with tamoxifen for 2–3 years. The patients were randomized into two groups, with one group receiving anastrozol treatment for 3 years, and the other receiving anastrazol for 6 years [24]. A total of 1912 patients were enrolled, and the 10.1 year follow-up has just been published. In absolute terms, disease-free survival in year 10 was improved by 3.1% (HR = 0.86, 95% CI: 0.72–1.01; p = 0.073). Treatment efficacy



	190954	157136	100099	49134	6791
	27555	22252	13582	6687	994
	11610	9243	5569	2702	412
a	29207	22851	13874	6813	1015



	140884	116344	74505	36747	5099
	25422	20729	13115	6426	894
	24648	20063	12479	5961	798
b	29207	22851	13874	6813	1015

▶ **Fig. 3** **a** Breast cancer-specific survival according to groups defined by hormone receptor status and HER2 status (data from [26]). **b** Survival rates for TNBC patients and for HRpos/HER2neg patients who do and do not meet the inclusion criteria for the MonarchE study (data from [26]).

was highest in progesterone receptor-positive patients and in groups for which the prognosis was considered poor due to nodal positivity or large tumor size. Accordingly, the hazard ratio in patients with positive axillary lymph node status and a tumor of at least 2 cm was 0.64 (95% CI: 0.47–0.88; p = 0.005). This shows that the need for therapy is greatest in the group of patients who have a poor prognosis. As with most adjuvant endocrine studies, the DATA study did not provide any evidence of benefit for overall survival [24].

Prognosis and medical need in adjuvant HRpos/HER2neg patient group

The new adjuvant endocrine therapy studies are also focused on patients with an elevated risk of relapse. For example, the Mon-

archE study only enrolled patients who had at least 4 positive lymph nodes, or 1–3 positive lymph nodes in combination with a tumor of at least 5 cm or a tumor grading of 3. Patients with 1–3 positive lymph nodes and a Ki-67 of at least 20% were also enrolled [25].

An analysis that made use of the American SEER database was able to show how patients with these characteristics fared in terms of breast cancer-specific survival compared to other patient groups. Over 342 000 patients in disease stages I–III took part in the analysis [26]. Compared to early-stage patients with positive HER2 status or with TNBC, patients with HR-positive/HER2-negative breast cancer clearly had the best breast cancer-specific survival (▶ **Fig. 3a**). With the focus on HRpos/HER2neg patients, sorting patients according to the MonarchE study inclusion and exclusion criteria showed that the patients channeled into the study MonarchE study made up approximately 13% of all the HRpos/HER2neg patients investigated in this analysis [26]. Moreover, it was shown that after 6 years, patients with triple negative disease had a similar prognosis to those who were eligible for the MonarchE study (▶ **Fig. 3b**) [26]. This means that the improvement in invasive disease-free survival achieved by adding abemaciclib to the adjuvant therapy represents a significant improvement in therapy options. This study showed that adding abemaciclib resulted in an improvement in invasive relapse-free survival, with a hazard ratio of 0.71, 95% CI: 0.58–0.87; p = 0.0009 [25]. While the study on adjuvant use of palbociclib yielded negative results [27 – 29], the NATALEE study (adjuvant use of ribociclib) [30, 31] has yet to be assessed; an interim analysis of this study is expected soon.

Dose-Dense Chemotherapy

More data with long-term follow-up

Increasing the dose intensity of adjuvant chemotherapy has become widely established. A meta-analysis of data from over 40 000 patients showed that a dose-dense chemotherapy regimen reduced the 10-year relapse risk (28.0% vs. 31.4%), as well as the 10-year mortality (22.1% vs. 24.8) [32]. As most of these studies recruited their patient cohort 10 to 20 years ago, some of them are now reporting their long-term results. One such study is the FIM2 study, which now has a median follow-up time of 15.2 years [33]. All patients in this study had to have a positive lymph node status. Otherwise, patients with both hormone receptor-positive and hormone receptor-negative tumors were eligible to enroll in the study.

The GIM2 study, with four randomization arms, addressed two research aims: firstly to compare dose-dense chemotherapy with epirubicin/cyclophopsphamide (EC) every 2 weeks versus every 3 weeks, and secondly to investigate the addition of 5-fluorouracil (FEC) (2 × 2 factorial design).

A comparison between the two arms receiving 5-FU and the two arms not receiving 5-FU did not reveal any difference in terms of relapse-free survival (HR = 1.12; 95% CI: 0.98–1.29) or overall survival (HR = 1.13; 95% CI: 0.94–1.36) [33], as previously reported [34].

After 15 years, a consistent effect could be observed in the comparison between the (F)EC arms followed by paclitaxel every 2 weeks versus every 3 weeks; the absolute difference after 15 years was 9% for relapse-free survival (HR = 0.77; 95% CI: 0.67–0.89) and 7% for overall survival (HR = 0.72; 95% CI: 0.60–0.86) [33]. These long-term results showing very clear absolute differences in this nodal-positive population serve to highlight the value of dose-dense chemotherapy, which has also been accorded a "++" recommendation by the German Gynecological Oncology Group (AGO) [23].

Biomarkers

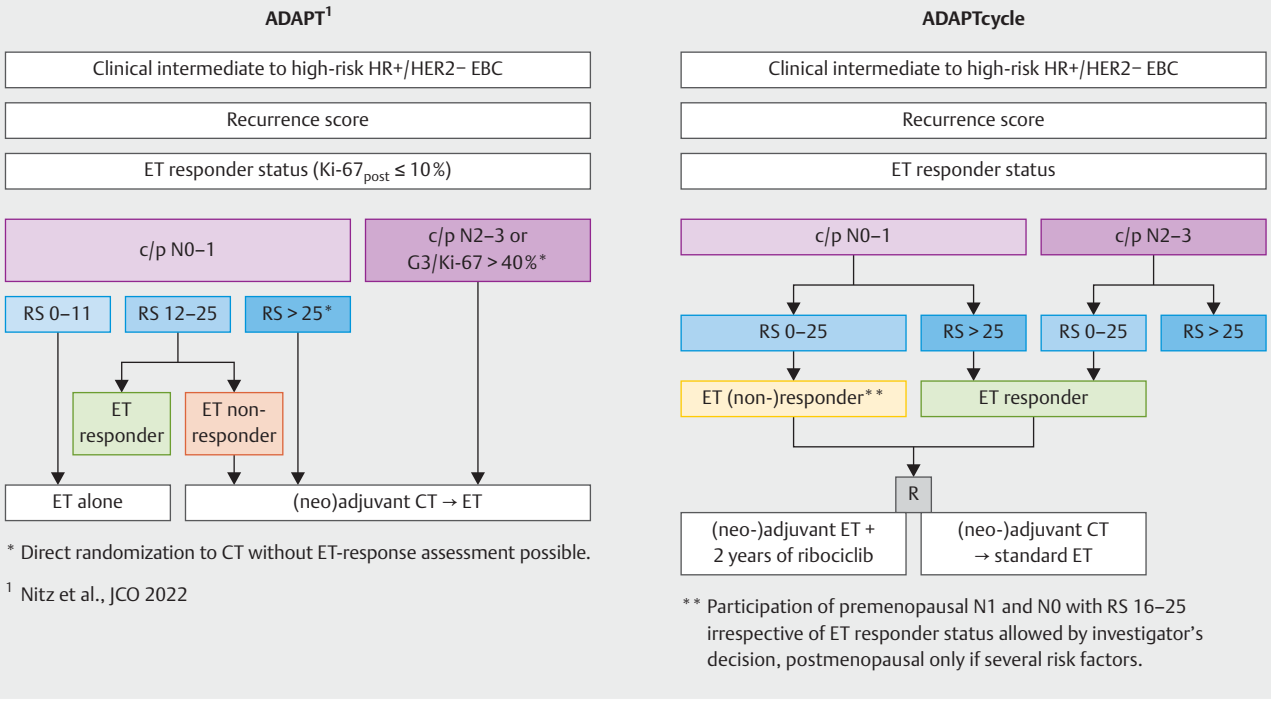
ADAPT study program with solid data on Ki-67 changes during preoperative endocrine therapy

The ADAPT study program comprises various studies addressing the question of dynamic changes in Ki-67 during initial endocrine therapy. Extensive data from the ADAPT1 and ADAPTCycle studies have now been published. The study designs are presented in ▶ **Fig. 4**. Data have been published for over 5900 patients in total (3666 from ADAPT1 and 2272 from ADAPTCycle) [35]. A particular point of interest was the response of hormone receptor-positive tumors depending on the patient's age and whether or not they received endocrine therapy. The postmenopausal patient group included women who were treated with either tamoxifen or aromatase inhibitors. In the younger/premenopausal patient group, the women were treated with either tamoxifen, tamoxifen + ovarian function suppression (OFS), or aromatase inhibitors + OFS. A Ki-67 score ≤ 10% after endocrine therapy was considered favorable for the prognosis. These response rates (rate of patients with Ki-67 ≤ 10% after endocrine therapy) are set out in ▶ **Fig. 5**. The highest response rates were seen in the postmenopausal patients treated with aromatase inhibitors (81.5% in the ADAPT study and 77.9% in the ADAPTCycle study), and in premenopausal patients treated with aromatase inhibitors + OFS (76.9% in the ADAPTCycle study). Treatment with tamoxifen as monotherapy led to significantly lower response rates in both the postmenopausal patients (42.5–56.3%) and the premenopausal patients (32.0–40.1%) [35]. With regard to prognosis, it was shown that the Ki-67 response rate had a greater effect on the prognosis for patients aged 50 or under (HR = 0.63, 95% CI: 0.24–1.65) than it did for patients aged over 50 (HR = 0.78; 95% CI: 0.54–1.12).

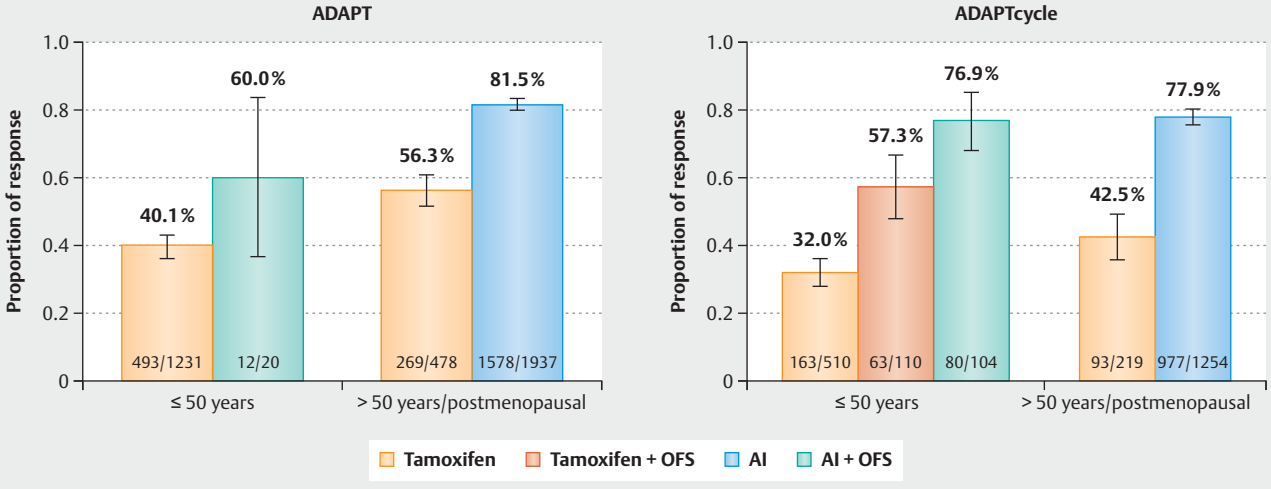
Accordingly, these preliminary biomarker data from the ADAPT studies provide a good basis for further research on the concept of dynamic Ki-67. For premenopausal women in particular, these molecular data are consistent with the clinical results showing that the best disease-free survival times were achieved through treatment with aromatase inhibitors + OFS [36]; this corresponds to the group that had the largest reduction in Ki-67 in the ADAPTCycle study [35].

Margetuximab and polymorphisms in Fc gamma receptor IIIa

It is known that antibodies such as trastuzumab act in part via the ADCC mechanism (antibody-dependent cell-mediated cytotoxicity). Both the characteristics of the antibodies and the character-



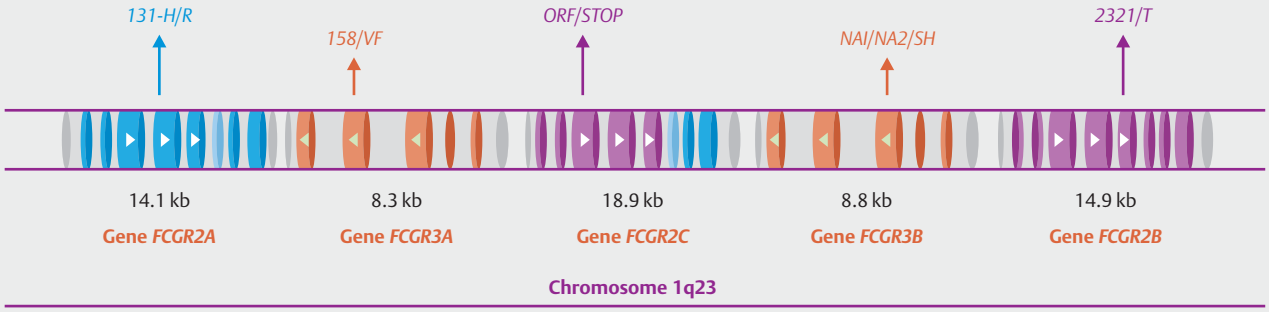
▶ **Fig. 4** Diagram of the ADAPT study programs ADAPT1 and ADAPTCycle (Source: https://wsg-online.com/studien/).



▶ **Fig. 5** Response rate (Ki-67 ≤ 10% after endocrine therapy) in the ADAPT studies (data from [35]).

istics of the patient's Fc receptor can have an influence on efficacy. Thus, it has been shown that reduced ADCC induction by trastuzumab can result in a reduced effect [37]. Polymorphisms in Fc gamma receptors 2 and 3 (▶ **Fig. 6**) correlating to differing efficacy of trastuzumab have also been described in some studies; however, this effect has not been observed in other studies [38–41]. The drug margetuximab [42] was developed in order to make the ADCC action component of the anti-HER2 antibodies independent of genetic variants of the Fc gamma receptor. The final overall survival data of SOPHIA have now been published.

Results for the total cohort of the SOPHIA study did not show any difference between trastuzumab and margetuximab. The hazard ratio for overall survival was 0.95 (95% CI: 0.77–1.17). However, for the subcohort who were carriers of the homozygous gene CD16A-158FF, overall survival was better with margetuximab (HR = 0.72; 95% CI: 0.52–1.00), while conversely for the rarer ge-



▶ **Fig. 6** Structural map of the genes for Fc gamma receptors 2 and 3, with locations of the polymorphisms discussed above ([45], cc commons license). Similar gene sequences have similar colors. [rerif]

notype CD16-158VV, overall survival results were better with trastuzumab (HR = 1.77 95 % CI: 1.01–3.12 [43].

Based on the Fc gamma receptor data from the SOPHIA study [43] as well as data from the study by Pivot et al. [37], these biomarkers are a very interesting topic for future research. Consequently, in the NeoOn study, AGO-B is investigating whether a real-time ADCC test is able to predict the efficacy of ontruzant [44].

Outlook

Over the past few years some additional therapies and diagnostics have become available in the neoadjuvant setting. These include pembrolizumab for TNBC patients with a high risk of relapse, olaparib for HER2-negative patients with a high risk of relapse, and abemaciclib for HR-positive/HER2-negative patients with a high risk of relapse. Other current adjuvant studies include the NATALEE study (ribociclib in the adjuvant setting) which has now finished recruiting, and the lidERA study (adjuvant giredestrant), which is currently recruiting. Further studies are planned, such as the CAMBRIA-1 study (adjuvant camizestrant) and the EMBER-4 study (adjuvant imlunestrant).

Because many of these drugs are being developed in parallel, there is a lack of evidence regarding the combination or sequence of these substances. This means it is unclear whether olaparib should be combined with pembrolizumab, given the relevant indication. Similarly, abemaciclib and olaparib may be competitively indicated in the eligible patients. In this context we need additional evidence, where applicable from real world records.

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Conflict of Interest

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