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Update Breast Cancer 2022 Part 3 – Early-Stage Breast Cancer

Update Mammakarzinom 2022 Teil 3 – Brustkrebs in frühen Krankheitsstadien

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ABSTRACT

This review summarizes recent developments in the prevention and treatment of patients with early-stage breast cancer. The individual disease risk for different molecular subtypes was investigated in a large epidemiological study. With regard to treatment, new data are available from long-term follow-up of the Aphinity study, as well as new data on neoadjuvant therapy with atezolizumab in HER2-positive patients. Biomarkers, such as residual cancer burden, were investigated in the context of pembrolizumab therapy. A Genomic Grade Index study in elderly patients is one of a group of studies investigating the use of modern multigene tests to identify patients with an excellent prognosis in whom chemotherapy may be avoided. These and other aspects of the latest developments in the diagnosis and treatment of breast cancer are described in this review.

ZUSAMMENFASSUNG

In dieser Übersichtsarbeit werden neueste Entwicklungen in der Prävention von Brustkrebs und Behandlung von Patientinnen mit frühen Krankheitsstadien mit Mammakarzinom zusammengefasst. Die Ermittlung von individuellen Erkrankungsrisiken nach molekularen Subtypen wurde in einer großen epidemiologischen Studie untersucht. Im Bereich der Behandlung gibt es neue Daten zur Langzeitnachbeobachtung der Aphinity-Studie ebenso wie neue Daten zur neoadjuvanten Therapie von HER2-positiven Patientinnen mit Atezolizumab. Biomarker wie Residual Cancer Burden wurden im Zusammenhang mit einer Pembrolizumab-Therapie untersucht. Eine Untersuchung des Genomic-Grade-Indexes bei älteren Patientinnen reiht sich ein in die Gruppe von Studien, die versucht, durch moderne Multigentests Patientinnen zu identifizieren, bei denen eine Chemotherapie vermieden werden kann, weil diese eine exzellente Prognose haben. Diese und weitere Aspekte der neuesten Entwicklungen bei der Diagnostik und Therapie des Mammakarzinoms werden in dieser Übersichtsarbeit beschrieben.

Introduction

The majority of international congresses have been held online in the past two years, but this year the ASCO Congress 2022 was once again held in person. This Congress, as well as other events and current publications, are summarized in this review and placed in the context of current therapies.

With regard to prevention, interventions are becoming increasingly individualized. With regard to treatments, new drugs such as abemaciclib, olaparib and pembrolizumab are entering the clinical arena for the treatment of early-stage breast cancer patients. As these drugs become more widely used, biomarkers are being sought that can, on an individual basis, determine the effectiveness of new treatments or the patient's prognosis with conventional treatments. In this context, new data exist on multigene testing and chemotherapy in older patients. Understanding which patient groups would benefit most from immunotherapy with checkpoint inhibition could also assist in making individualized treatment decisions.

Prevention

Well-known but still a big unknown – reproductive traits as risk factors for breast cancer

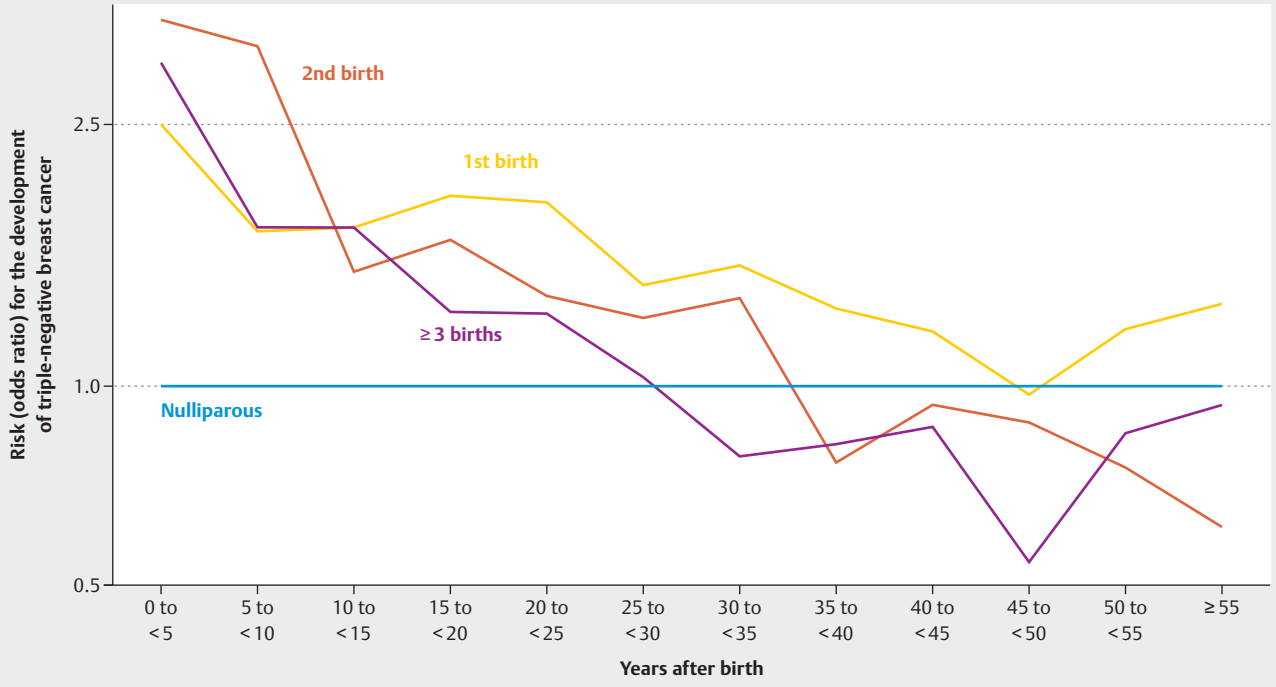
As with the individualization of breast cancer treatment, prevention and early detection increasingly take account of individual risks not only for the disease itself but also for mortality after diagnosis. In this context, molecular characteristics often serve as surrogate markers for the relevant studies.

For example, in those at high risk of triple-negative disease, more extensive preventive measures may be warranted compared with women at increased risk of breast cancer but who have a good prognosis. Similarly, prevention could be individualized for different subtypes of breast cancer.

Several risk factors have already been studied from this perspective. For example, it has been clear for a long time that women with a *BRCA1* germ line mutation are most likely to develop triple-negative breast cancer, and conversely women with triple-negative breast cancer have high rates of *BRCA1/2* mutation [1–5]. However, other breast cancer risk genes such as *BRCA2, BARD1* and *PALB2* have also been associated with an increased risk of triple-negative breast cancer in particular [6–8]. Some low-penetrance risk genes were found to have an association with poor prognosis or specific molecular subtypes [9–15].

Non-genetic risk factors focus on mammographic density [16–18] and reproductive factors [19–27]. In addition, in particular the age at menarche and at menopause, as well as the number of children, are well-established risk factors, as is the duration of breastfeeding [19, 21].

Regarding reproductive risk factors, a large study has now been published that examined reproductive factors in relation to risk for the various molecular subtypes of breast cancer [28]. This work examined more than 23 000 breast cancer patients and more than 71 000 healthy controls from 31 population-based studies. It was reported that women with at least one pregnancy had a lower risk of luminal like and HER2-positive breast cancer.



▶ **Fig. 1** Odds ratio for developing triple-negative breast cancer for patients who have had one, two, and three deliveries relative to women who have not delivered a baby [28].

However, this effect did not occur until about 10 years after the last birth. Pregnancies increased the risk of triple-negative breast cancer for decades after the last birth [28], before approaching or falling below the risk of nulliparous women. ▶ **Fig. 1** shows the risk development of a diagnosis of triple-negative breast cancer over time after delivery, compared to women who reported not given birth [28].

The data from this large epidemiological study are significant because they disaggregate breast cancer risk over time. For centuries, pregnancy has been thought to reduce the risk of breast cancer [29]. While this is true for most postmenopausal patients and also for most molecular subtypes, the situation is different for triple-negative breast cancer [28]. In this case, the risk seems to remain elevated for many decades after pregnancy. This is particularly important because subsequent pregnancy may lead to a significant increase in the incidence of this subtype, which carries a poor prognosis.

Molecularly, the mechanisms leading to mammary gland transformation during pregnancy and lactation have also been associated with proliferation of epithelial stem cells in the breast [30–33]. The RANK/RANKL/OPG pathway appears to play a significant role not only in bone metabolism but also in the transformation of the mammary gland during pregnancy [33], and is associated with other risk factors for the development of breast cancer [34].

Future studies must show exactly which molecular mechanisms are responsible for these observations and whether these correlations can be utilized in breast cancer prevention.

Data on Ovarian Suppression in Combination with Tamoxifen

The choice of anti-hormonal adjuvant therapy in premenopausal patients is still under discussion. Simplified, national treatment recommendations call for patients at low risk of relapse to receive tamoxifen, and patients at intermediate risk of relapse to receive tamoxifen in combination with ovarian suppression. Patients at high risk of relapse may be treated with an aromatase inhibitor in combination with ovarian suppression [35]. Most of the evidence is drawn from the SOFT and TEXT studies [36–39]. The long-term follow-up data from the Korean ASTRRA study have now been published [40].

Ovarian suppression in combination with tamoxifen – long-term data consolidate the evidence

The ASTRRA study enrolled patients who were under 46 years of age, had stage I to III disease at diagnosis, and had received (neo)-adjuvant chemotherapy. A total of 1282 patients were randomized to treatment with tamoxifen for 5 years, or treatment with tamoxifen for 5 years and goserelin for 2 years. The median follow-up time in the recently reported analysis was 8.9 years. The previously observed disparity is again apparent in this analysis. Treatment with tamoxifen and ovarian suppression showed better disease-free survival with a hazard ratio of 0.67 (95% CI: 0.51–0.87). Absolute disease-free survival rates at 8 years were 80.2% for tamoxifen alone and 85.4% for patients with ovarian suppres-

sion, an absolute reduction of 5.2%. This difference did not translate into overall survival in a statistically significant manner, although it should be noted that survival in the recruited group of patients was excellent, with an OS rate at 8 years of 96.5% in the OFS group and 95.3% in the tamoxifen group (HR = 0.78; 95% CI: 0.49–1.25 [40]. In subgroup analyses, the effects were more pronounced in patients aged 40 to 45 years and in HER2-negative patients.

Thus, the ASTRRA study contributes to the body of data that has emerged from the other studies in the treatment setting, namely that the addition of OFS improves disease-free survival, but probably not overall survival. The decision to treat the known side effects of OFS (goserelin in this case) should always be made individually in consultation with the patient.

Anti-HER2 Therapies in the Neoadjuvant and Adjuvant Setting

More than any other molecular subtype, treatment for HER2-positive early-stage breast cancer has improved the prognosis of affected patients with the introduction of new drugs. Not only trastuzumab, but also pertuzumab [41], trastuzumab-emtansine (T-DM1) [42], and neratinib [43, 44] are approved for adjuvant treatment of patients with HER2-positive early-stage breast cancer.

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% [45–47]. 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 of 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 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). Now, after a second interim analysis, the third interim analysis for overall survival has been published with a median follow-up of 8.4 years [48]. Just as in previous analyses, the evaluation in terms of overall survival did not achieve statistical significance with an HR of 0.83 (95% CI: 0.68–1.02), but there was a numerical advantage for the addition of pertuzumab. 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 analyses 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 [35] advising treatment in patients with nodal-positive disease and allowing individual treatment decisions in patients with nodal-negative disease remain valid after this analysis.

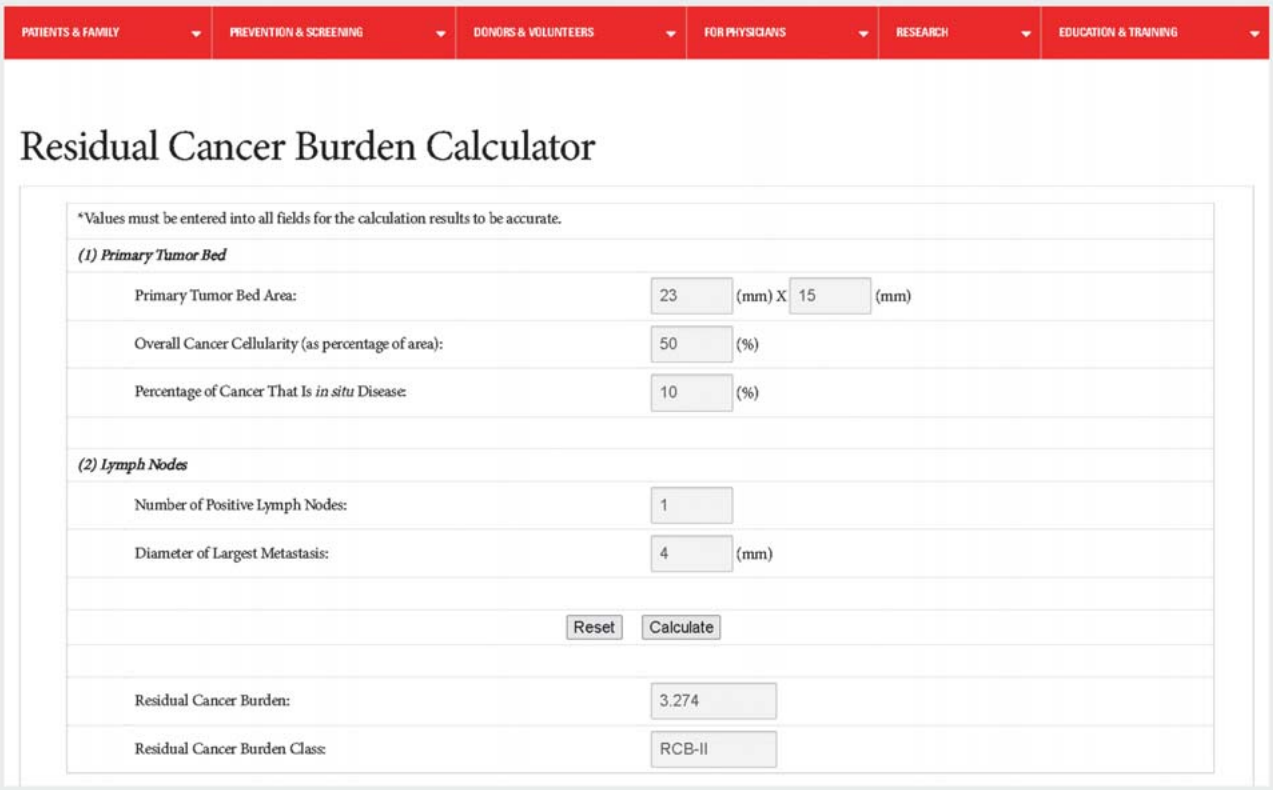
Atezolizumab in the neoadjuvant setting

While data exist from a large randomized study of pembrolizumab (KEYNOTE-522 study) for patients with early-stage triple-negative breast cancer [49, 50], and pembrolizumab is approved for neoadjuvant in combination with chemotherapy followed by adjuvant treatment, there are relatively few data for patients with hormone receptor-positive disease and patients with HER2-positive disease. Now, the results of IMpassion050 with reference to pCR have been published [51]. In the IMpassion050 study, 454 HER2-positive patients were enrolled and randomized to neoadjuvant therapy with either dose-dense chemotherapy with doxoribicin/cyclophosphamide followed by therapy with paclitaxel in combination with trastuzumab and pertuzumab, or to the same therapy in combination with atezolizumab. Overall, there was no difference in the pCR rate. It was 62.4% in patients with atezolizumab and slightly higher at 62.7% in patients without atezolizumab. Interestingly, in patients without atezolizumab, there was a significant difference between patients who were PD-L1-positive (pCR: 72.5%) and who were PD-L1-negative (pCR: 53.8). The difference was less in patients who received atezolizumab in addition to chemotherapy (64.2% in PD-L1 positivity and 60.7% in PD-L1 negativity) [51].

This result is surprising. However, not all discussions about the accuracy of PD-L1 testing are over, and in the KEYNOTE-522 study, the CPS score was also not predictive of the efficacy of pembrolizumab. However, it is noteworthy that in the IMpassion050 study, treatment without atezolizumab had the highest overall pCR rates in the PD-L1-positive population. Surprisingly, a similar effect was seen in IMpassion131 [52] with respect to overall survival. Patients with paclitaxel monotherapy had the best numerical overall survival in that study. There was no statistical difference. In breast cancer, there are now treatment scenarios where PD-L1 expression must be present in order to determine effectiveness (first-line advanced triple-negative breast cancer), whereas in patients undergoing neoadjuvant/adjuvant treatment, such a determination is not necessary. However, there may also be combination therapies for which PD-L1 determination is not necessary. More evidence is needed to understand these relationships [53].

Pembrolizumab in Patients with Triple-Negative Early Breast Cancer – the Search for Biomarkers

For the treatment of patients with early-stage triple-negative breast cancer at increased risk of recurrence, pembrolizumab was approved as a neoadjuvant treatment in combination with chemotherapy followed by monotherapy in the adjuvant setting to complete one year of treatment. In the KEYNOTE-522 study, it was shown that not only the pCR rate is increased, but that even patients without pCR drew some benefit in terms of event-free survival [49, 50, 54, 55]. This was surprising because it was previously thought that the effect on prognosis was mainly mediated by pCR [56–59]. Similarly, in the KEYNOTE-522 study, patients with pCR had an excellent prognosis, which was only slightly better in patients treated with pembrolizumab (3-year event-free rate: 94.4 vs. 92.5%; HR = 0.73; 95% CI: 0.39–1.36). Given the side effects, there



▶ **Fig. 2** Online Residual Cancer Burden Calculator [64].

is often discussion as to whether, in light of this, there are patients who benefit more or less from adjuvant pembrolizumab therapy, or whether there are groups of patients for whom the adjuvant treatment can be omitted. In this context, a preliminary understanding of possible biomarkers is provided by an analysis of the KEYNOTE-522 study using the "Residual Cancer Burden" (RCB) score [60]. The RCB score [61–63] is calculated from several parameters that summarize the response to chemotherapy. For example, it can be determined with an online calculator [64] (▶ **Fig. 2**).

An analysis of efficacy in terms of event-free survival in the KEYNOTE-522 study demonstrated that the effect on prognosis may well differ between RCB groups. Patients with pCR (RCB-0) had excellent prognostic data, which was already known. In general, prognosis was worse depending on RCB category for patients in both the pembrolizumab arm and the control arm with increasing category (increasing residual tumor) (▶ **Fig. 3**). The clearest benefit for the addition of pembrolizumab was seen in the group of patients with RCB category 2. Here, the HR was 0.52 (95% CI: 0.32–0.82), and the 3-year event-free survival rates were 55.9% for the control arm, and 75.7% for the pembrolizumab arm. Patients in the worst category (RCB-3) did not appear to benefit from pembrolizumab therapy.

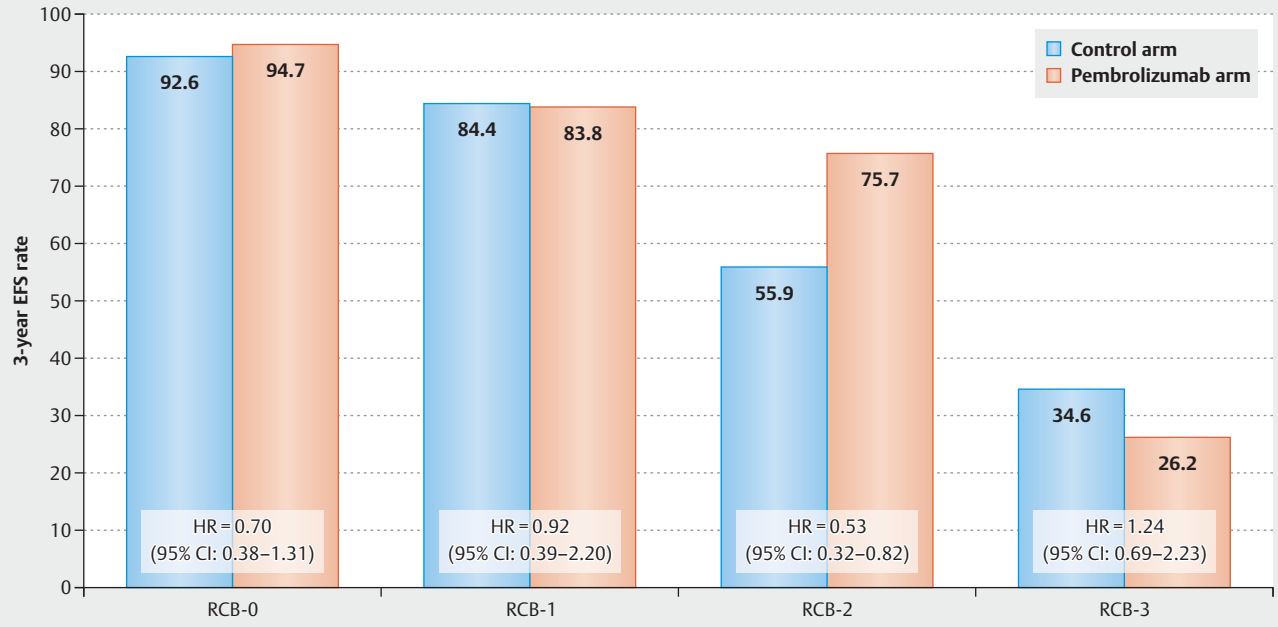
The use of RCB in clinical practice is not part of a treatment recommendation. However, this examination indicates that this biomarker/score could be further reviewed in future studies to plan therapy after neoadjuvant therapy.

Biomarkers

To date, a few treatments for early and advanced disease have been mandatorily linked to certain biomarkers. These include anti-HER2 therapies (positive HER2 status), endocrine therapies (positive hormone receptor status), alpelisib (somatic *PIK3CA* tumor mutation), talazoparib/olaparib (germ line mutation in *BRCA1/2*), and pembrolizumab/atezolizumab (PD-L1 expression in metastatic triple-negative breast cancer). Other biomarkers have not been mandatorily established. Prognostic tests, such as multigene testing, can be used to identify patients with early-stage disease who have an excellent prognosis in order to avoid adjuvant chemotherapy. In the United States, one biomarker used in the adjuvant approval of the CDK4/6 inhibitor abemaciclib therapy is the well-known Ki-67 score.

Ki-67 and abemaciclib in patients with HR+ HER2− breast cancer

Ki-67 has been described as a proliferative marker since the 1980s [65]. Its role as a prognostic and predictive factor for pCR after neoadjuvant chemotherapy has been described in multiple studies [66–76]. However, its clinical use has not been mandatorily recommended to date. However, unlike in Europe, in 2021 the U.S. FDA determined that abemaciclib can be used as an adjuvant in patients with node-positive breast cancer and a Ki-67 ≥ 20%. This is not consistent with the regulatory situation in Europe,



▶ **Fig. 3** Event-free 3-year survival rates in the KEYNOTE-522 study by Residual Cancer Burden Group [60].

where patients with more than 3 affected lymph nodes but also patients with 1–3 affected lymph nodes can be prescribed abemaciclib if the tumor is ≥ 5 cm or is grade 3. This divergent approach is currently the subject of scientific debate [77, 78]. Although it is undisputed that Ki-67 is a significant prognostic factor, the MonarchE study, which provided adjuvant data for abemaciclib treatment, did not demonstrate that Ki-67 has predictive value for the efficacy of abemaciclib, but did not confirm its prognostic relevance [79]. The concerns that oppose the use of Ki-67 are mainly the reproducibility and comparability of results with the risk of not selecting the right patients for therapy. This problem, as described, does not exist in Europe.

Multigene tests in elderly patients

Recent years have seen the accumulation of an extensive body of data that has led to the routine use of several multigene tests in Germany. All multigene tests are more or less capable of identifying HR+/HER2− patients with an excellent prognosis [80 – 85]. However, no clear results could be obtained with regard to predicting the efficacy of chemotherapy. In the RXponder study, the recurrence score was not able to predict the benefit of chemotherapy compared with adjuvant endocrine therapy without prior chemotherapy [86]. There is little data on this topic in older female patients.

Against this background, the recently published ASTER-70s study provided new insights. In this study, the Genomic Grade Index (GGI) was determined [87, 88]. The Genomic Grade Index was developed to characterize tumor grading with gene expression analyses. Quantitative PCR is used to determine 97 cell cycle and proliferation genes, and tumors are classified as high, intermediate (equivocal), and low.

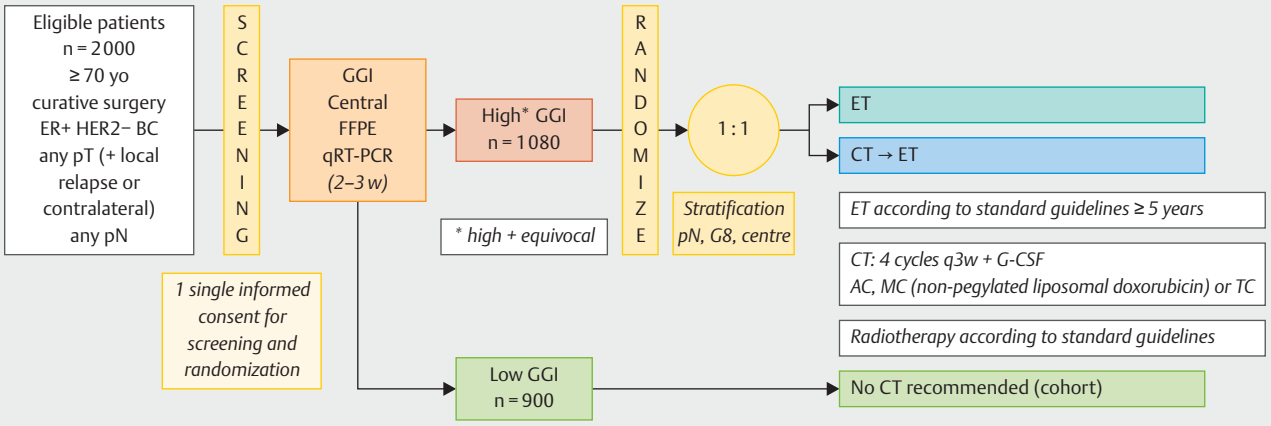
The ASTER-70s study (▶ **Fig. 4**) [89] enrolled patients who were at least 70 years of age and had HR+ HER2− breast cancer without metastases, either as a new diagnosis or as local recurrence. After determination of the GGI, no further chemotherapy was recommended for patients with a low GGI, and randomization was performed for patients with an intermediate or high GGI. One treatment arm was treated with chemotherapy followed by adjuvant hormonal therapy. In the alternative treatment arm, patients received adjuvant endocrine treatment alone [89]. Nearly 1100 patients were randomized. With a median follow-up of almost 6 years, a trend could be seen in favor of therapy with chemotherapy (HR = 0.79, 95 % CI: 0.60–1.03), which did not meet the threshold of statistical significance. Among older patients, lack of adherence to therapy was relatively high in the chemotherapy arm (20.5 %) compared with the randomization arm without chemotherapy (0.6 %) [89]. In such cases, a per protocol analysis is always useful, yielding an HR of 0.73 (95 % CI: 0.55–0.98).

Although the study was negative overall, it does provide evidence to suggest that there are older patients who may benefit from chemotherapy if they are at high risk of relapse (as determined here by GGI).

Outlook

In recent years, there has been a significant increase in data on multigene testing and treatment decisions for or against chemotherapy. Some studies such as the OPTIMA study (with PAM50) are currently still recruiting and will certainly supplement the data.

With respect to neoadjuvant/adjuvant therapy with pembrolizumab, biomarkers could help identify groups of patients who do



▶ **Fig. 4** Study design of the ASTER-70s study.

not need adjuvant therapy. However, this needs to be addressed in future studies.

For patients with HER2-negative HR-positive breast cancer, the preliminary phase of the Natalee study, which is evaluating ribociclib in the adjuvant setting in patients at increased risk of recurrence, is awaited.

In the near future, these and other studies will expand the treatment options for patients in the early stages of the disease.

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Conflict of Interest

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