

Update Breast Cancer 2022 part 3 - early-stage breast cancer

Tanja N. Fehm, Manfred Welslau, Volkmar Müller, Diana Lüftner, Florian Schütz, Peter A. Fasching, Wolfgang Janni, Christoph Thomssen, Isabell Witzel, Erik Belleville, Michael Untch, Marc Thill, Hans Tesch, Nina Ditsch, Michael P. Lux, Bahriye Aktas, Maggie Banys-Paluchowski, Andreas Schneeweiss, Cornelia Kolberg-Liedtke, Andreas D. Hartkopf, Achim Wöckel, Hans-Christian Kolberg, Nadia Harbeck, Elmar Stickeler

Angaben zur Veröffentlichung / Publication details:

Fehm, Tanja N., Manfred Welslau, Volkmar Müller, Diana Lüftner, Florian Schütz, Peter A. Fasching, Wolfgang Janni, et al. 2022. "Update Breast Cancer 2022 part 3 - early-stage breast cancer." *Geburtshilfe und Frauenheilkunde* 82 (09): 912-21. <https://doi.org/10.1055/a-1912-7105>.

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

Update Mammakarzinom 2022 Teil 3 – Brustkrebs in frühen Krankheitsstadien



Authors

Tanja N. Fehm¹, Manfred Welslau², Volkmar Müller³, Diana Lüftner⁴, Florian Schütz⁵, Peter A. Fasching⁶, Wolfgang Janni⁷, Christoph Thomssen⁸, Isabell Witzel³, Erik Belleville⁹, Michael Untch¹⁰, Marc Thill¹¹, Hans Tesch¹², Nina Ditsch¹³, Michael P. Lux¹⁴, Bahriye Aktas¹⁵, Maggie Banys-Paluchowski¹⁶, Andreas Schneeweiss¹⁷, Cornelia Kolberg-Liedtke¹⁸, Andreas D. Hartkopf⁷, Achim Wöckel¹⁹, Hans-Christian Kolberg²⁰, Nadia Harbeck²¹, Elmar Stickeler²²

Affiliations

- 1 Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany
- 2 Onkologie Aschaffenburg, Aschaffenburg, Germany
- 3 Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany
- 4 Immanuel Hospital Märkische Schweiz & Medical University of Brandenburg Theodor-Fontane, Brandenburg, Buckow, Germany
- 5 Gynäkologie und Geburtshilfe, Diakonissen-Stiftungs-Krankenhaus Speyer, Speyer, Germany
- 6 Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
- 7 Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany
- 8 Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
- 9 ClinSol GmbH & Co KG, Würzburg, Germany
- 10 Clinic for Gynecology and Obstetrics, Breast Cancer Center, Gynecologic Oncology Center, Helios Klinikum Berlin Buch, Berlin, Germany
- 11 Agaplesion Markus Krankenhaus, Department of Gynecology and Gynecological Oncology, Frankfurt am Main, Germany
- 12 Oncology Practice at Bethanien Hospital, Frankfurt am Main, Germany
- 13 Department of Gynecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany
- 14 Klinik für Gynäkologie und Geburtshilfe, Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten, St. Vincenz Krankenhaus GmbH, Germany
- 15 Department of Gynecology, University of Leipzig Medical Center, Leipzig, Germany
- 16 Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

- 17 National Center for Tumor Diseases (NCT), Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany
- 18 Department of Gynecology and Obstetrics, University Hospital Essen, Essen, Germany
- 19 Department of Gynecology and Obstetrics, University Hospital Würzburg, Würzburg, Germany
- 20 Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany
- 21 Breast Center, Department of Gynecology and Obstetrics and CCC Munich LMU, LMU University Hospital, Munich, Germany
- 22 Department of Gynecology and Obstetrics, RWTH University Hospital Aachen, Aachen, Germany

Key words

breast cancer, early stage, adjuvant treatment, neoadjuvant treatment, chemotherapy, endocrine therapy

Schlüsselwörter

Brustkrebs, Frühstadium, adjuvante Therapie, neoadjuvante Therapie, Chemotherapie, endokrine Therapie

received 20. 7. 2022

accepted after revision 31. 7. 2022

Bibliography

Geburtsh Frauenheilk 2022; 82: 912–921

DOI 10.1055/a-1912-7105

ISSN 0016-5751

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Peter A. Fasching, MD

Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen EMN, Friedrich Alexander University of Erlangen-Nuremberg Universitätsstraße 21–23, 91054 Erlangen, Germany
peter.fasching@fau.de



Deutsche Version unter:

<https://doi.org/10.1055/a-1912-7105>

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 di-

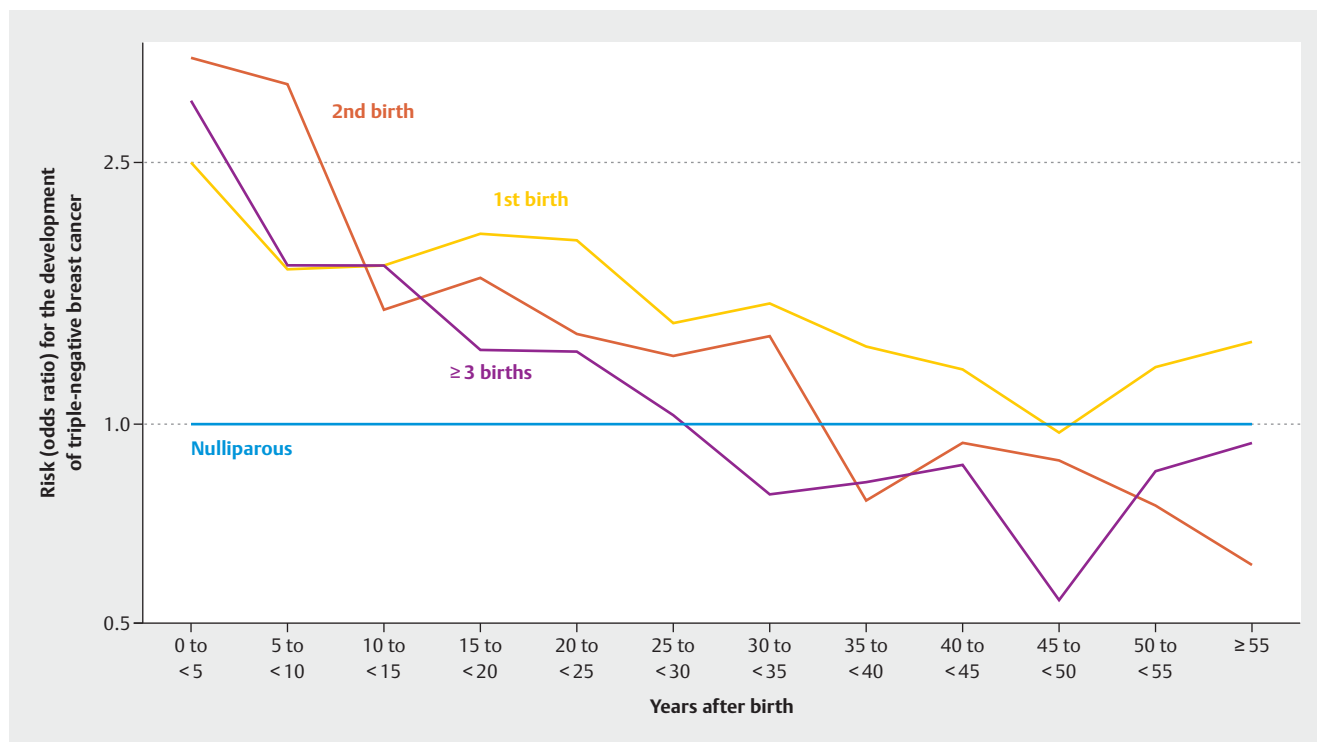
agnosis. In this context, molecular characteristics often serve as surrogate markers for the relevant studies.

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 suppression.

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 doxorubicin/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

PATIENTS & FAMILY
PREVENTION & SCREENING
DONORS & VOLUNTEERS
FOR PHYSICIANS
RESEARCH
EDUCATION & TRAINING

Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed	
Primary Tumor Bed Area:	<input type="text" value="23"/> (mm) X <input type="text" value="15"/> (mm)
Overall Cancer Cellularity (as percentage of area):	<input type="text" value="50"/> (%)
Percentage of Cancer That Is <i>in situ</i> Disease:	<input type="text" value="10"/> (%)
(2) Lymph Nodes	
Number of Positive Lymph Nodes:	<input type="text" value="1"/>
Diameter of Largest Metastasis:	<input type="text" value="4"/> (mm)
<input type="button" value="Reset"/> <input type="button" value="Calculate"/>	
Residual Cancer Burden:	<input type="text" value="3.274"/>
Residual Cancer Burden Class:	<input type="text" value="RCB-II"/>

► **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.

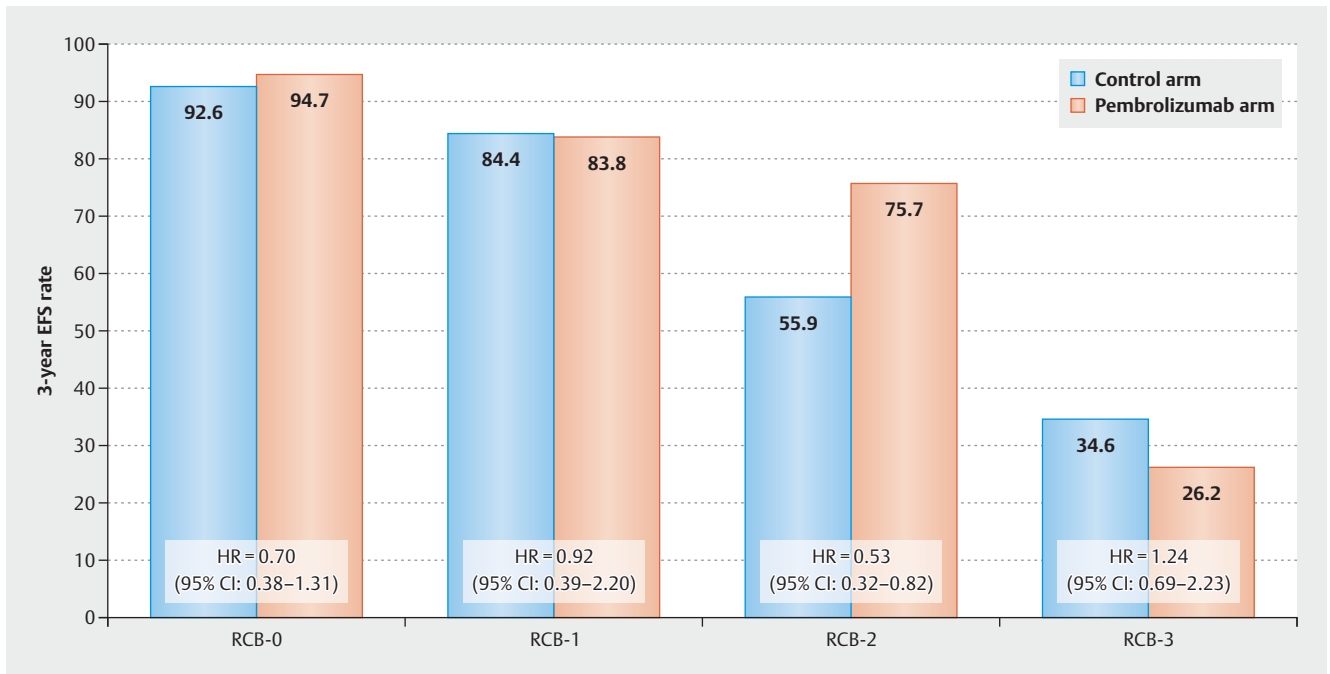
The use of RCB in clinical practice is not part of a treatment recommendation. However, this examination indicates that this biomarker/score could be further reviewed in future studies to plan therapy after neoadjuvant therapy.

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 $\geq 20\%$. 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.

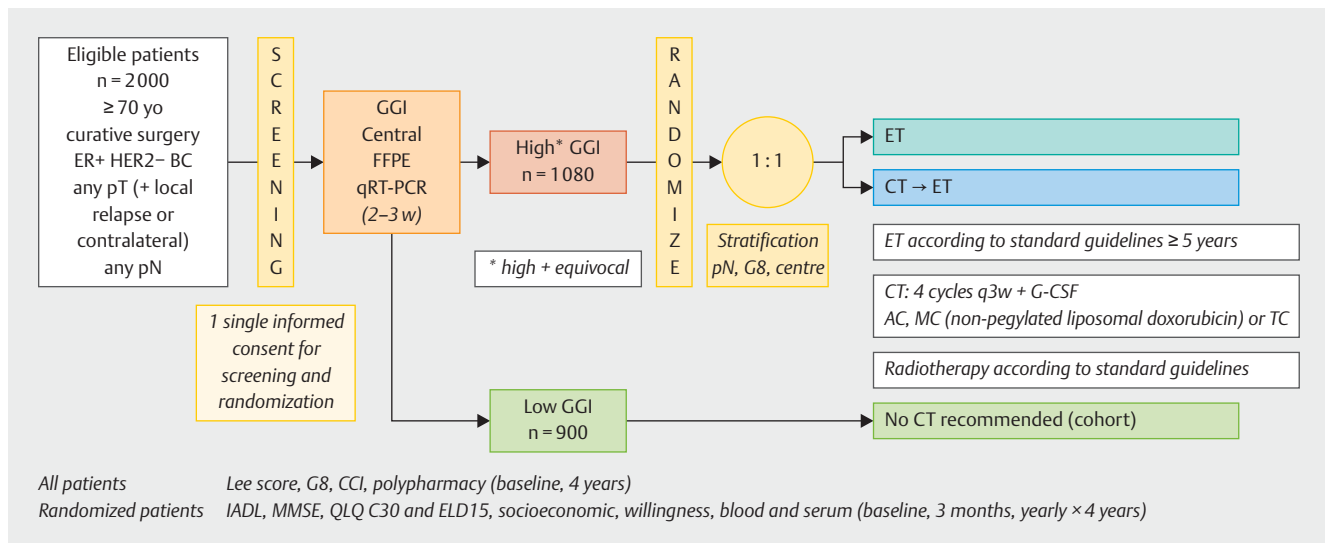
The ASTER-70s study (► **Fig. 4**) [89] enrolled patients who were at least 70 years of age and had HR+ HER2- breast cancer without metastases, either as a new diagnosis or as local recurrence. After determination of the GGI, no further chemotherapy was recommended for patients with a low GGI, and randomization 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.

Acknowledgements

This work was done in part thanks to grants from onkowissen.de, Gilead, Novartis, Pfizer, Roche, and MSD. None of the companies had any part in the preparation and recommendations of this manuscript. The authors are solely responsible for the content of the manuscript.

Conflict of Interest

B. A. received honoraria and travel grants from AstraZeneca, Gilead, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo and Pfizer.

C. K.-L. received honoraria from Roche, AstraZeneca, Celgene, Novartis, Pfizer, Lilly, Hexal, Amgen, Eisai, and SonoScape as well as honoraria for consultancy work from Phaon Scientific, Novartis, Pfizer, and Celgene as well as research assistance from Roche, Novartis, and Pfizer. Travel grant from Novartis and Roche, employment at Palleos Healthcare, and Managing Director and partner at Phaon Scientific.

M. B.-P. received honoraria for lectures and advisory role from Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkowissen, Seagen, AstraZeneca, Eisai, Amgen, Samsung, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Pintuition, Pierre Fabre, and study support from Mammotome, Endomag and Merit Medical.

E. B. received honoraria from Gilead, Ipsen, Sanofi, Sandoz, SunPharma, AstraZeneca, Novartis, Hexal, BMS, Lilly, Pfizer, Roche, MSD, BBraun and onkowissen.de for clinical research management and/or medical education activities.

N. D. has received honoraria from MSD, Roche, AstraZeneca, Teva, Pfizer, Novartis, Seagen, Gilead, MCI Healthcare.

P. A. F. reports personal fees from Novartis, grants from Biontech, personal fees from Pfizer, personal fees from Daiichi Sankyo, personal fees from AstraZeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from SeaGen, personal fees from Roche, personal fees from Hexal, personal fees from Agendia, personal fees from Gilead.

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.

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.

N. H. received honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, Exact Sciences, Gilead, Lilly, MSD, Mylan, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Seagen.

W. J. has received research Grants and/or honoraria from Sanofi-Aventis, Daiichi Sankyo, Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, GSK, Eisai, Cellgene and Johnson & Johnson.

H.-C. K. has received honoraria from Pfizer, Novartis, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, Teva, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lily, Surg-Vision, Onkowissen, Gilead, Daiichi Sankyo and MSD, travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro and owns stock of Theraclion SA and Phaon Scientific GmbH.

D. L. received honoraria from Amgen, AstraZeneca, Eli Lilly, High5md, Gilead, GSK, Loreal, MSD, Novartis, Onkowissen, Pfizer, Seagen, Teva.

M. P. L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, Gilead, Exact Sciences, Pierre Fabre, Grünenthal, Daiichi Sankyo, PharmaMar and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, AstraZeneca, and Eisai. He is editorial board member of medactuell from medac.

V. M. received speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, GSK, Pfizer, MSD, Medac, Novartis, Roche, Teva, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead. Consultancy honoraria from Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Sanofi, Seagen, Gilead. Institutional research support from Novartis, Roche, Seagen, Genentech. Travel grants: Roche, Pfizer, Daiichi Sankyo.

E. S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Tesaro, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH, Onkowissen TV.

A. S. received research grants from Celgene, Roche, honoraria from Amgen, AstraZeneca, Aurikamed, Bayer, Celgene, Clinsol, Connect-medica, Gilead, GSK, I-MED, Lilly, MCI Deutschland, Metaplan, MSD, Nanostring, Novartis, Onkowissen.de, Promedicis, Pfizer, Pierre Fabre, Roche, Seagen, Streamedup, Teva, Tesaro, Thieme and travel support from Celgene, Pfizer, Roche.

F. S. participated on advisory boards for Novartis, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer.

H. T. received honoraria from Novartis, Roche, Celgene, Teva, Pfizer, AstraZeneca and travel support from Roche, Celgene and Pfizer.

C. T. received honoraria for advisory boards and lectures from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Gilead, Lilly, MSD, Mylan, Nanostring, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen, Vifor.

M. T. has participated on advisory boards for AstraZeneca, Clovis, Daiichi Sankyo, Eisai, Gilead Science, GSK, Lilly, MSD, Novartis, Organon, Pfizer, Pierre Fabre, Seagen and Roche and has received honoraria for lectures from Amgen, Clovis, Daiichi Sankyo, Eisai, GSK, Lilly, MSD, Roche, Novartis, Organon, Pfizer, Seagen, Exact Sciences, Viatrix, Vifor and AstraZeneca and has received trial funding by Exact Sciences and Endomag Manuscript support was done by Amgen, ClearCut, pfm medical, Roche, Servier, Vifor.

M. U. All honoraria went to the institution/employer: Abbvie, Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Lilly, MSD, Myriad Genetics, Pfizer, Roche, Sanofi Aventis, Novartis, Pierre Fabre, Seagen; Gilead.

M. W. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and Roche.

I. W. has participated on advisory boards for Novartis, Daiichi Sankyo, Lilly, Pfizer and received speaker honoraria from AstraZeneca, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche.

A. W. participated on advisory boards for Novartis, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene.

References

- [1] Lakhani SR, Reis-Filho JS, Fulford L et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clin Cancer Res* 2005; 11: 5175–5180. doi:10.1158/1078-0432.CCR-04-2424
- [2] Couch FJ, Hart SN, Sharma P et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015; 33: 304–311. doi:10.1200/JCO.2014.57.1414
- [3] Fasching PA, Loibl S, Hu C et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the Gepar-Quinto Study. *J Clin Oncol* 2018; 36: 2281–2287. doi:10.1200/JCO.2017.77.2285
- [4] Fasching PA, Yadav S, Hu C et al. Mutations in BRCA1/2 and Other Panel Genes in Patients With Metastatic Breast Cancer-Association With Patient and Disease Characteristics and Effect on Prognosis. *J Clin Oncol* 2021; 39: 1619–1630. doi:10.1200/JCO.20.01200
- [5] Shimelis H, LaDuca H, Hu C et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. *J Natl Cancer Inst* 2018; 110: 855–862. doi:10.1093/jnci/djy106
- [6] Breast Cancer Association Consortium, Mavaddat N, Dorling L et al. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. *JAMA Oncol* 2022; 8: e216744. doi:10.1001/jamaoncol.2021.6744
- [7] Hoyer J, Vasileiou G, Uebe S et al. Addition of triple negativity of breast cancer as an indicator for germline mutations in predisposing genes increases sensitivity of clinical selection criteria. *BMC Cancer* 2018; 18: 926. doi:10.1186/s12885-018-4821-8
- [8] Kraus C, Hoyer J, Vasileiou G et al. Gene panel sequencing in familial breast/ovarian cancer patients identifies multiple novel mutations also in genes others than BRCA1/2. *Int J Cancer* 2017; 140: 95–102. doi:10.1002/ijc.30428
- [9] Escala-Garcia M, Guo Q, Dork T et al. Genome-wide association study of germline variants and breast cancer-specific mortality. *Br J Cancer* 2019; 120: 647–657. doi:10.1038/s41416-019-0393-x
- [10] Stevens KN, Fredericksen Z, Vachon CM et al. 19p13.1 is a triple-negative-specific breast cancer susceptibility locus. *Cancer Res* 2012; 72: 1795–1803. doi:10.1158/0008-5472.CAN-11-3364
- [11] Stevens KN, Vachon CM, Lee AM et al. Common breast cancer susceptibility loci are associated with triple-negative breast cancer. *Cancer Res* 2011; 71: 6240–6249. doi:10.1158/0008-5472.CAN-11-1266
- [12] Broeks A, Schmidt MK, Sherman ME et al. Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: findings from the Breast Cancer Association Consortium. *Hum Mol Genet* 2011; 20: 3289–3303. doi:10.1093/hmg/ddr228
- [13] Fasching PA, Pharoah PD, Cox A et al. The role of genetic breast cancer susceptibility variants as prognostic factors. *Hum Mol Genet* 2012; 21: 3926–3939. doi:10.1093/hmg/dds159
- [14] Escala-Garcia M, Abraham J, Andrulis IL et al. A network analysis to identify mediators of germline-driven differences in breast cancer prognosis. *Nat Commun* 2020; 11: 312. doi:10.1038/s41467-019-14100-6
- [15] Fagerholm R, Khan S, Schmidt MK et al. TP53-based interaction analysis identifies cis-eQTL variants for TP53BP2, FBXO28, and FAM53A that associate with survival and treatment outcome in breast cancer. *Oncotarget* 2017; 8: 18381–18398. doi:10.18632/oncotarget.15110
- [16] Vachon CM, Scott CG, Tamimi RM et al. Joint association of mammographic density adjusted for age and body mass index and polygenic risk score with breast cancer risk. *Breast Cancer Res* 2019; 21: 68. doi:10.1186/s13058-019-1138-8
- [17] Hack CC, Emons J, Jud SM et al. Association between mammographic density and pregnancies relative to age and BMI: a breast cancer case-only analysis. *Breast Cancer Res Treat* 2017; 166: 701–708. doi:10.1007/s10549-017-4446-7
- [18] Vachon CM, Pankratz VS, Scott CG et al. The contributions of breast density and common genetic variation to breast cancer risk. *J Natl Cancer Inst* 2015. doi:10.1093/jnci/dju397
- [19] Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; 13: 1141–1151. doi:10.1016/S1470-2045(12)70425-4
- [20] Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. *CA Cancer J Clin* 2014; 64: 186–194. doi:10.3322/caac.21225
- [21] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; 360: 187–195. doi:10.1016/S0140-6736(02)09454-0
- [22] Rudolph A, Song M, Brook MN et al. Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int J Epidemiol* 2018; 47: 526–536. doi:10.1093/ije/dyx242
- [23] Brouckaert O, Rudolph A, Laenen A et al. Reproductive profiles and risk of breast cancer subtypes: a multi-center case-only study. *Breast Cancer Res* 2017; 19: 119. doi:10.1186/s13058-017-0909-3

- [24] Yang XR, Chang-Claude J, Goode EL et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst* 2011; 103: 250–263. doi:10.1093/jnci/djq526
- [25] Milne RL, Gaudet MM, Spurdle AB et al. Assessing interactions between the associations of common genetic susceptibility variants, reproductive history and body mass index with breast cancer risk in the breast cancer association consortium: a combined case-control study. *Breast Cancer Res* 2010; 12: R110. doi:10.1186/bcr2797
- [26] Stickeler E, Aktas B, Behrens A et al. Update Breast Cancer 2021 Part 1 – Prevention and Early Stages. *Geburtshilfe Frauenheilkd* 2021; 81: 526–538. doi:10.1055/a-1464-0953
- [27] Huober J, Schneeweiss A, Hartkopf AD et al. Update Breast Cancer 2020 Part 3 – Early Breast Cancer. *Geburtshilfe Frauenheilkd* 2020; 80: 1105–1114. doi:10.1055/a-1270-7208
- [28] Jung AY, Ahearn TU, Behrens S et al. Distinct reproductive risk profiles for intrinsic-like breast cancer subtypes: pooled analysis of population-based studies. *J Natl Cancer Inst* 2022. doi:10.1093/jnci/djac117
- [29] Ramazzini B. *De morbis artificum diatriba*. 1700
- [30] Kiechl S, Schramek D, Widschwendter M et al. Aberrant regulation of RANKL/OPG in women at high risk of developing breast cancer. *Oncotarget* 2017; 8: 3811–3825. doi:10.18632/oncotarget.14013
- [31] Sigl V, Jones LP, Penninger JM. RANKL/RANK: from bone loss to the prevention of breast cancer. *Open Biol* 2016. doi:10.1098/rsob.160230
- [32] Sigl V, Owusu-Boaitey K, Joshi PA et al. RANKL/RANK control Brca1 mutation-driven mammary tumors. *Cell Res* 2016; 26: 761–774. doi:10.1038/cr.2016.69
- [33] Wunderle M, Ruebner M, Haberle L et al. RANKL and OPG and their influence on breast volume changes during pregnancy in healthy women. *Sci Rep* 2020; 10: 5171. doi:10.1038/s41598-020-62070-3
- [34] Mintz R, Wang M, Xu S et al. Hormone and receptor activator of NF-kappaB (RANK) pathway gene expression in plasma and mammographic breast density in postmenopausal women. *Breast Cancer Res* 2022; 24: 28. doi:10.1186/s13058-022-01522-2
- [35] Ditsch N, Wöcke A, Untch M et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022. *Breast Care* 2022. doi:10.1159/000524879
- [36] Francis PA, Pagani O, Fleming GF et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. *N Engl J Med* 2018; 379: 122–137. doi:10.1056/NEJMoa1803164
- [37] Regan MM, Francis PA, Pagani O et al. Absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with hormone receptor-positive (HR+) HER2-negative breast cancer (BC): Results from TEXT and SOFT. *J Clin Oncol* 2018; 36 (Suppl.): Abstr. 503
- [38] Pagani O, Regan MM, Walley BA et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; 371: 107–118. doi:10.1056/NEJMoa1404037
- [39] Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; 372: 436–446. doi:10.1056/NEJMoa1412379
- [40] Baek SY, Noh WC, Ahn S-H et al. Adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: 8-year follow-up of the randomized ASTRRA trial. *J Clin Oncol* 2022; 40: 506–506. doi:10.1200/JCO.2022.40.16_suppl.506
- [41] von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; 377: 122–131. doi:10.1056/NEJMoa1703643
- [42] von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2019; 380: 617–628. doi:10.1056/NEJMoa1814017
- [43] Chan A, Moy B, Mansi J et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. *Clin Breast Cancer* 2021; 21: 80–91.e7. doi:10.1016/j.clbc.2020.09.014
- [44] Martin M, Holmes FA, Ejlertsen B et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1688–1700. doi:10.1016/S1470-2045(17)30717-9
- [45] Fasching PA, Hartkopf AD, Gass P et al. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis. *Breast Cancer Res Treat* 2019; 173: 319–328. doi:10.1007/s10549-018-5008-3
- [46] Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32. doi:10.1016/S1470-2045(11)70336-9
- [47] Gianni L, Pienkowski T, Im YH et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800. doi:10.1016/S1470-2045(16)00163-7
- [48] Loibl S, Jassem J, Sonnenblick A et al. Updated Results of Aphinity at 8.4 years median follow up. *ESMO Virtual Plenary* 2022; July 14, 2022
- [49] Schmid P, Cortes J, Dent R et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med* 2022. doi:10.1056/NEJMoa2112651
- [50] Schmid P, Cortes J, Pusztai L et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med* 2020; 382: 810–821. doi:10.1056/NEJMoa1910549
- [51] Huober J, Barrios CH, Niikura N et al. Atezolizumab With Neoadjuvant Anti-Human Epidermal Growth Factor Receptor 2 Therapy and Chemotherapy in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Primary Results of the Randomized Phase III IMPassion050 Trial. *J Clin Oncol* 2022. doi:10.1200/JCO.21.02772
- [52] Miles D, Gligorov J, Andre F et al. Primary results from IMPassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol* 2021; 32: 994–1004. doi:10.1016/j.annonc.2021.05.801
- [53] Jacob JB, Jacob MK, Parajuli P. Review of immune checkpoint inhibitors in immuno-oncology. *Adv Pharmacol* 2021; 91: 111–139. doi:10.1016/bs.apha.2021.01.002
- [54] Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC. *Ann Oncol* 2021. doi:10.1016/j.annonc.2021.06.014
- [55] Schmid P, Cortes J, Dent R et al. KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC). *Ann Oncol* 2019. doi:10.1093/annonc/mdz1394
- [56] Huang M, O'Shaughnessy J, Zhao J et al. Evaluation of Pathologic Complete Response as a Surrogate for Long-Term Survival Outcomes in Triple-Negative Breast Cancer. *J Natl Compr Canc Netw* 2020; 18: 1096–1104. doi:10.6004/jncn.2020.7550
- [57] Huang M, O'Shaughnessy J, Zhao J et al. Association of Pathologic Complete Response with Long-Term Survival Outcomes in Triple-Negative Breast Cancer: A Meta-Analysis. *Cancer Res* 2020; 80: 5427–5434. doi:10.1158/0008-5472.CAN-20-1792

- [58] Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384: 164–172. doi:10.1016/S0140-6736(13)62422-8
- [59] von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; 30: 1796–1804. doi:10.1200/JCO.2011.38.8595
- [60] Pusztai L, Denkert C, O’Shaughnessy J et al. Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: Exploratory analysis from KEYNOTE-522. *J Clin Oncol* 2022; 40: 503-503. doi:10.1200/JCO.2022.40.16_suppl.503
- [61] Symmans WF, Yau C, Chen YY et al. Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for High-risk Breast Cancer: An Analysis of Data From the I-SPY2 Randomized Clinical Trial. *JAMA Oncol* 2021; 7: 1654–1663. doi:10.1001/jamaoncol.2021.3690
- [62] Symmans WF, Wei C, Gould R et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. *J Clin Oncol* 2017; 35: 1049–1060. doi:10.1200/JCO.2015.63.1010
- [63] Symmans WF, Peintinger F, Hatzis C et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25: 4414–4422. doi:10.1200/JCO.2007.10.6823
- [64] MD Anderson Cancer Center. Residual Cancer Burden Calculator. Accessed July 16, 2022 at: <http://www3mdandersonorg/app/medcalc/indexcfm?pagename=jsconvert3> 2022
- [65] Gerdes J, Lelle RJ, Pickartz H et al. Growth fractions in breast cancers determined in situ with monoclonal antibody Ki-67. *J Clin Pathol* 1986; 39: 977–980. doi:10.1136/jcp.39.9.977
- [66] Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. *J Clin Oncol* 2005; 23: 7212–7220. doi:10.1200/JCO.2005.07.501
- [67] Viale G, Giobbie-Hurder A, Regan MM et al. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. *J Clin Oncol* 2008; 26: 5569–5575. doi:10.1200/JCO.2008.17.0829
- [68] Cheang MC, Chia SK, Voduc D et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst* 2009; 101: 736–750. doi:10.1093/jnci/djp082
- [69] Yerushalmi R, Woods R, Ravdin PM et al. Ki67 in breast cancer: prognostic and predictive potential. *Lancet Oncol* 2010; 11: 174–183. doi:10.1016/S1470-2045(09)70262-1
- [70] Fasching PA, Heusinger K, Haerle L et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. *BMC Cancer* 2011; 11: 486. doi:10.1186/1471-2407-11-486
- [71] Heusinger K, Jud SM, Haberle L et al. Association of mammographic density with the proliferation marker Ki-67 in a cohort of patients with invasive breast cancer. *Breast Cancer Res Treat* 2012; 135: 885–892. doi:10.1007/s10549-012-2221-3
- [72] von Minckwitz G, Schmitt WD, Loibl S et al. Ki67 measured after neoadjuvant chemotherapy for primary breast cancer. *Clin Cancer Res* 2013; 19: 4521–4531. doi:10.1158/1078-0432.CCR-12-3628
- [73] Penault-Llorca F, Radosevich-Robin N. Ki67 assessment in breast cancer: an update. *Pathology* 2017; 49: 166–171. doi:10.1016/j.pathol.2016.11.006
- [74] Fasching PA, Gass P, Haberle L et al. Prognostic effect of Ki-67 in common clinical subgroups of patients with HER2-negative, hormone receptor-positive early breast cancer. *Breast Cancer Res Treat* 2019; 175: 617–625. doi:10.1007/s10549-019-05198-9
- [75] Smith I, Robertson J, Kilburn L et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol* 2020; 21: 1443–1454. doi:10.1016/S1470-2045(20)30458-7
- [76] Nielsen TO, Leung SCY, Rimm DL et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst* 2021; 113: 808–819. doi:10.1093/jnci/djaa201
- [77] Dowsett M, Nielsen TO, Rimm DL et al. Ki67 as a Companion Diagnostic: Good or Bad News? *J Clin Oncol* 2022. doi:10.1200/JCO.22.00581
- [78] Tarantino P, Burstein HJ, Lin NU et al. Should Ki-67 be adopted to select breast cancer patients for treatment with adjuvant abemaciclib? *Ann Oncol* 2022; 33: 234–238. doi:10.1016/j.annonc.2021.12.004
- [79] Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol* 2021; 32: 1571–1581. doi:10.1016/j.annonc.2021.09.015
- [80] Buus R, Sestak I, Kronenwett R et al. Molecular Drivers of Oncotype DX, Prosigna, EndoPredict, and the Breast Cancer Index: A TransATAC Study. *J Clin Oncol* 2021; 39: 126–135. doi:10.1200/JCO.20.00853
- [81] Cardoso F, van’t Veer LJ, Bogaerts J et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med* 2016; 375: 717–729. doi:10.1056/NEJMoa1602253
- [82] Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351: 2817–2826. doi:10.1056/NEJMoa041588
- [83] Piccart M, van ’t Veer LJ, Poncet C et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol* 2021; 22: 476–488. doi:10.1016/S1470-2045(21)00007-3
- [84] Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 2018; 379: 111–121. doi:10.1056/NEJMoa1804710
- [85] Sparano JA, Gray RJ, Makower DF et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 2015; 373: 2005–2014. doi:10.1056/NEJMoa1510764
- [86] Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. *N Engl J Med* 2021; 385: 2336–2347. doi:10.1056/NEJMoa2108873
- [87] Toussaint J, Sieuwerts AM, Haibe-Kains B et al. Improvement of the clinical applicability of the Genomic Grade Index through a qRT-PCR test performed on frozen and formalin-fixed paraffin-embedded tissues. *BMC Genomics* 2009; 10: 424. doi:10.1186/1471-2164-10-424
- [88] Sotiriou C, Desmedt C. Gene expression profiling in breast cancer. *Ann Oncol* 2006; 17 (Suppl. 10): x259–x262. doi:10.1093/annonc/mdl270
- [89] Brain E, Viansone AA, Bourbonloux E et al. Final results from a phase III randomized clinical trial of adjuvant endocrine therapy ± chemotherapy in women ≥ 70 years old with ER+ HER2- breast cancer and a high genomic grade index: The Unicancer ASTER 70s trial. *J Clin Oncol* 2022; 40: 500-500. doi:10.1200/JCO.2022.40.16_suppl.500