

# Update Breast Cancer 2019 Part 4 – Diagnostic and Therapeutic Challenges of New, Personalised Therapies for Patients with Early Breast Cancer

## Update Mammakarzinom 2019 Teil 4 – diagnostische und therapeutische Herausforderungen neuer personalisierter Therapien für Patientinnen mit frühem Mammakarzinom



### Authors

Florian Schütz<sup>1</sup>, Peter A. Fasching<sup>2</sup>, Manfred Welslau<sup>3</sup>, Andreas D. Hartkopf<sup>4</sup>, Achim Wöckel<sup>5</sup>, Michael P. Lux<sup>6</sup>, Wolfgang Janni<sup>7</sup>, Johannes Ettl<sup>8</sup>, Diana Lüftner<sup>9</sup>, Erik Belleville<sup>10</sup>, Hans-Christian Kolberg<sup>11</sup>, Friedrich Overkamp<sup>12</sup>, Florin-Andrei Taran<sup>4</sup>, Sara Y. Brucker<sup>4</sup>, Markus Wallwiener<sup>1</sup>, Hans Tesch<sup>13</sup>, Tanja N. Fehm<sup>14</sup>, Andreas Schneeweiss<sup>15</sup>, Volkmar Müller<sup>16</sup>

### Affiliations

- 1 Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany
- 2 Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
- 3 Onkologie Aschaffenburg, Aschaffenburg, Germany
- 4 Department of Obstetrics and Gynecology, University of Tübingen, Tübingen, Germany
- 5 Department of Gynecology and Obstetrics, University Hospital Würzburg, Würzburg, Germany
- 6 Kooperatives Brustzentrum Paderborn, Klinik für Gynäkologie und Geburtshilfe Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten, Germany
- 7 Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany
- 8 Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
- 9 Charité University Hospital, Campus Benjamin Franklin, Department of Hematology, Oncology and Tumour Immunology, Berlin, Germany
- 10 ClinSol GmbH & Co KG, Würzburg, Germany
- 11 Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany
- 12 OncoConsult Hamburg GmbH, Hamburg, Germany
- 13 Oncology Practice at Bethanien Hospital Frankfurt, Frankfurt, Germany
- 14 Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany

15 National Center for Tumor Diseases, Division Gynecologic Oncology, University Hospital Heidelberg, Heidelberg, Germany

16 Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany

### Key words

breast cancer, adjuvant, neoadjuvant, chemotherapy, antihormone therapy, multigene tests

### Schlüsselwörter

Mammakarzinom, adjuvant, neoadjuvant, Chemotherapie, Antihormontherapie, Multigentests

received 24.7.2019

revised 4.8.2019


accepted 22.8.2019

### Bibliography

DOI <https://doi.org/10.1055/a-1001-9925>  
 Geburtsh Frauenheilk 2019; 79: 1079–1089 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

### 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@uk-erlangen.de](mailto:peter.fasching@uk-erlangen.de)

 Deutsche Version unter:  
<https://doi.org/10.1055/a-1001-9925>

## ABSTRACT

The further development of therapies for women with early breast cancer is progressing far more slowly than in the case of patients with advanced breast cancer and is additionally delayed compared to developments in metastatic breast cancer. Nonetheless, significant advancements have been able to be recorded recently. This review summarises the latest developments in view of the most recent publications and professional conferences. For hormone-receptor-positive patients, new aspects for the duration of antihormone therapy and with regard to the benefits of multigene tests have been published. In the case of HER2-positive patients, the value of post-neoadjuvant therapy and de-escalation of the therapy is discussed. In patients with triple-negative breast cancer, there is a question of whether the knowledge of the biological background of a homologous recombination deficiency (HRD) helps develop new therapies for this subtype. In particular the “use” of a *BRCA1/2* mutation or the biological characteristic HRD as a potential motive for therapy plays a role here in specifying the significance of platinum therapy and therapy with PARP inhibitors.

## ZUSAMMENFASSUNG

Die Weiterentwicklung der Therapien für Frauen mit einem frühen Mammakarzinom schreitet deutlich langsamer voran als bei Patientinnen mit fortgeschrittenem Mammakarzinom und ist zudem zeitlich versetzt zu Entwicklungen beim metastasiertem Mammakarzinom. Trotzdem konnten in letzter Zeit deutliche Fortschritte verzeichnet werden. Diese Übersichtsarbeit fasst die jüngsten Entwicklungen vor dem Hintergrund der neuesten Publikationen und Fachkongresse zusammen. Für hormonrezeptorpositive Patientinnen sind neue Aspekte für die Dauer der Antihormontherapie und in Bezug auf den Nutzen von Multigentests veröffentlicht worden. Bei HER2-positiven Patientinnen wird der Stellenwert einer post-neoadjuvanten Therapie und eine Deeskalation der Therapie diskutiert. Bei Patientinnen mit tripel-negativem Mammakarzinom stellt sich die Frage, ob das Wissen um den biologischen Hintergrund einer Defizienz der homologen Rekombination (HRD) dabei hilft, neue Therapien für diesen Subtyp zu entwickeln. Insbesondere die „Nutzung“ einer *BRCA1/2*-Mutation oder des biologischen Merkmals HRD als potenzielles Therapiemotiv spielen dabei eine Rolle, den Stellenwert der Platintherapie und einer Therapie mit PARP-Inhibitoren zu spezifizieren.

## Introduction

In recent years, a number of studies have been published on patients with breast cancer which represent particular challenges for patients as well as physicians. In the case of patients with early breast cancer, it is discussed whether multigene tests can help identify those patients in whom chemotherapy can definitively be avoided and vice-versa, whether patients with a poor prognosis can also benefit from chemotherapy. In particular, the assumption of costs by the health insurance companies for such tests has been the subject of controversy in discussions in recent years. Moreover, particularly in the case of HER2-positive breast cancer, opportunities have been created by modern, so-called post-neoadjuvant study concepts to offer patients not only effective therapies for which standard treatment has not yet been sufficient but also to better understand the molecular mechanisms of resistance of a neoadjuvant therapy. The latest study results, including against the background of the current conferences such as the conference of the American Society of Clinical Oncology, ASCO) in 2019 are summarised below.

## Prevention and Risk Factors

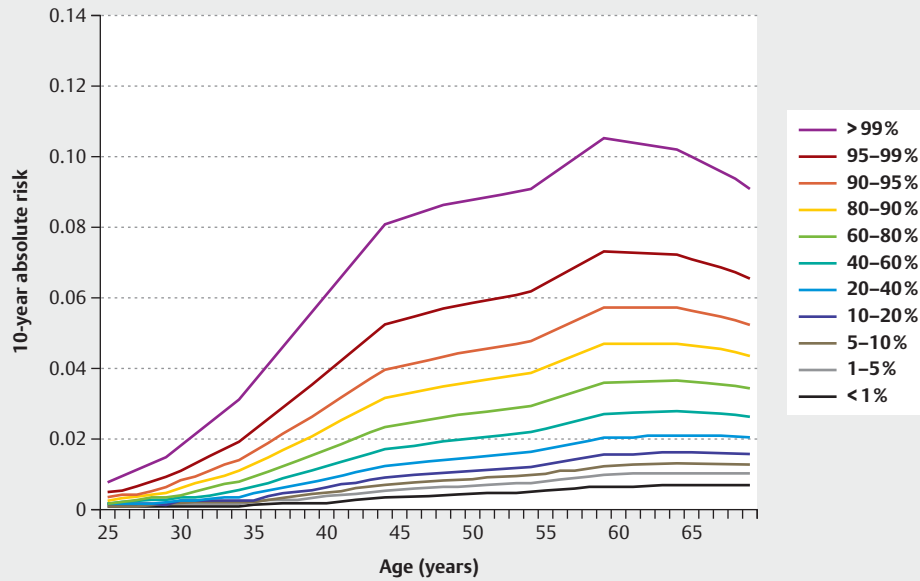
One of the most challenging undertakings in personalised medicine is undoubtedly individualised prevention for each patient. While prevention is one of the most important principles of medicine to prevent damage from occurring in the first place, it is difficult to identify those individuals for whom certain measures are useful.

With regard to genetic risk factors, approx. 200 validated risk loci have been described to date (highly penetrating, moderately

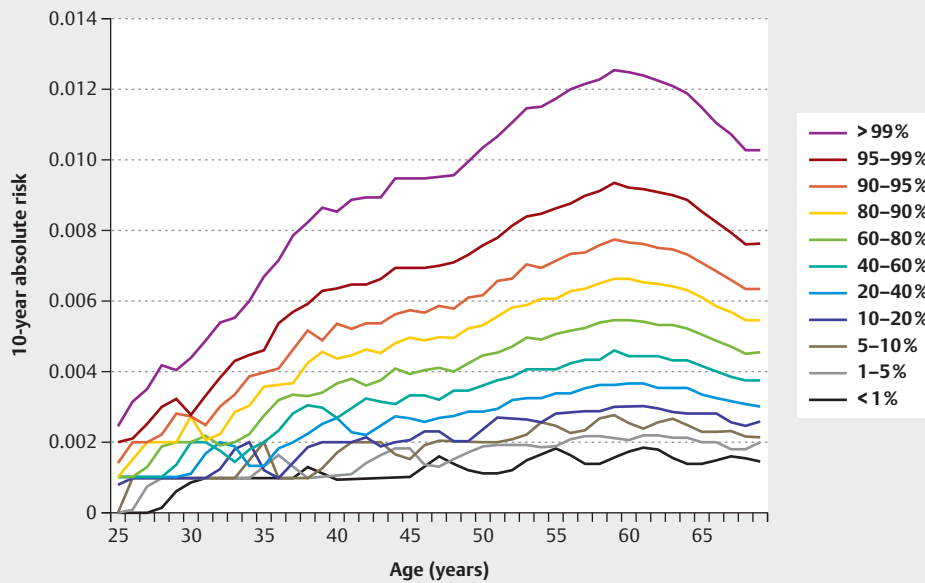
penetrating and low-penetrating genetic variants), which may explain 35–40% of the increased familial risk [1–14]. However, this also means that 60% of the increased familial risk cannot be explained by the mere genetic connections and it may still be some time until the interaction between genes or between genes and the environment can be connected in a usable way for the patient.

Nonetheless, the use of genetic and non-genetic risk information is more advanced than ever. There are some studies which attempt to decode the gene-gene interaction on the one hand and the gene-environment interaction on the other hand [15–29]. The two analyses which can most likely be used in clinical practice for patients are the use of as many risk variants as possible in order to define risk groups for patients with them [24, 30–32]. An example for practical implementation is shown in ► **Figs. 1** and **2**. These present that the 10% of 60-year-old women with the highest risk of at least 10% will develop hormone-receptor-positive breast cancer in the next 10 years. For the hormone-receptor-negative patients, the prediction is significantly reduced. Here it can be predicted for the 1% of women with the highest risk that they will develop a hormone-receptor-negative breast cancer with a probability of at least 1% [30].

The prediction could be optimised even further in combination with other risk factors, such as the analysis of mammographic density. In a large study in which 77 risk variants and the mammographic density were analysed, it was not able to be shown that the genetic variants which were responsible for the breast cancer risk could also explain the varying mammographic density. This means that both factors predict the risk independently of each other [15]. For the mammographic density, it is also known that it correlates with molecular characteristics of the breast cancer



► Fig. 1 Absolute 10-year risk depending on age for hormone-receptor-positive breast cancer (according to [30]).

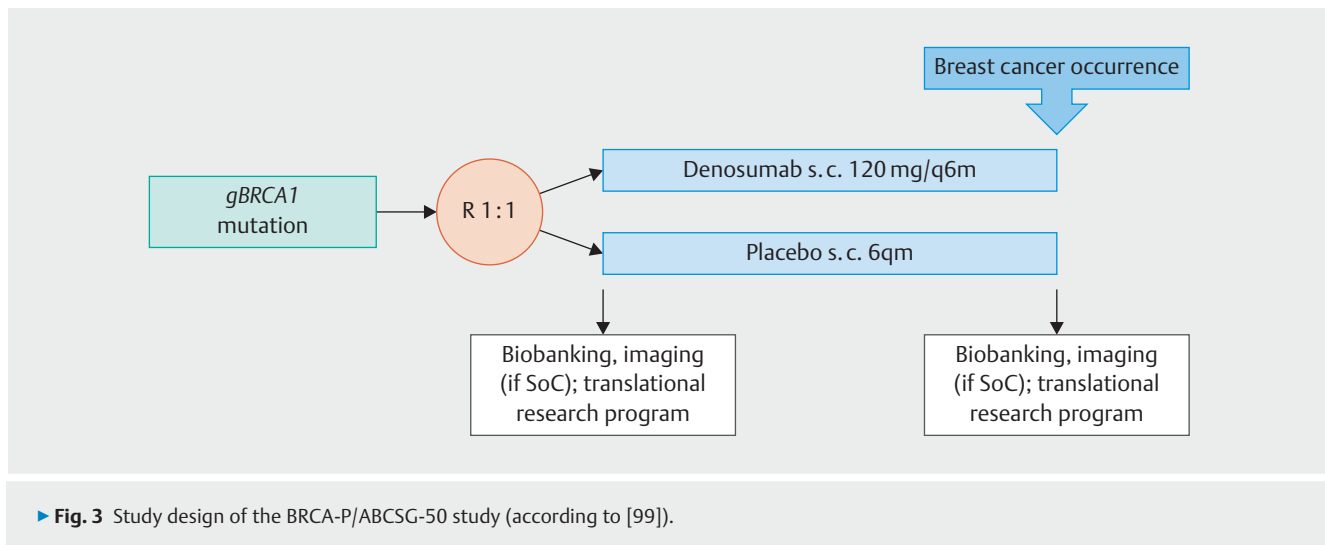


► Fig. 2 Absolute 10-year risk depending on age for hormone-receptor-negative breast cancer (according to [30]).

[33, 34]. This individualised assessment of risk factors may facilitate individualised early detection.

For women with a *BRCA1* mutation, entirely new options for prevention potentially open up. The great significance of the RANKL/RANK pathway in women with a *BRCA1* mutation has been known for some time [35–37].

A study on patients with *BRCA1* mutations receiving the anti-RANKL antibody denosumab was therefore already started on this basis. A total of 2918 patients who carry mutations are to be randomised. Recruitment began in July 2017 [38]. The study design is shown in ► Fig. 3.



## Early HER2-positive Breast Cancer

### Neoadjuvant experiences with anti-HER2 therapies

In the neoadjuvant therapy situation, combination therapy with chemotherapy + trastuzumab + pertuzumab is approved and results in rates for pathological complete remission (pCR) of approx. 40–50% [39,40]. The antibody-toxin conjugate (ADC) trastuzumab-emtansine (T-DM1) was able to demonstrate significant advantages for progression-free survival (PFS) and overall survival (OS) in a metastatic situation on the one hand [41] and recently also significant advantages for disease-free survival (DFS) in the post-neoadjuvant situation [42]. This raises the question of whether neoadjuvant therapy with T-DM1, for example, without classical chemotherapy but in combination with pertuzumab, provides an advantage for the patients. This issue was investigated within the scope of the neoadjuvant KRISTINE study. The KRISTINE study is a randomised, two-arm, open phase 3 study which compared 6 cycles of neoadjuvant therapy with docetaxel and carboplatin in combination with trastuzumab and pertuzumab ( $n = 223$ ) with the alternative with 6 cycles of T-DM1 and pertuzumab ( $n = 221$ ). Postoperatively the patients in the chemotherapy arm received 12 cycles of pertuzumab and trastuzumab, the patients in the T-DM1 arm received 12 cycles of T-DM1 and pertuzumab. For the patients in the T-DM1 arm who did not achieve pCR, adjuvant chemotherapy was recommended. The pCR rates (44.4 vs. 55.7% [ $p = 0.016$ ]) in favour of the chemotherapy arm had already been published two years ago [43]. Currently, the secondary endpoints of disease-free survival (DFS) and invasive disease-free survival (IDFS) were reported after a median follow-up observation period of 37 months. In the DFS, a significant difference was seen in favour of the T-DM1 arm (hazard ratio [HR]: 2.61; 95% CI: 1.36–4.98), whereby this was triggered primarily by the 15 patients who suffered progression on the neoadjuvant therapy. In the chemotherapy arm, no progression during the neoadjuvant therapy was observed. In 12 of these 15 patients, a heterogeneous HER2 diagnosis was noted which may have contributed to this result. By contrast, the IDFS was comparable (HR = 1.11;

95% CI 0.52–2.40). To understand this, it must be mentioned that the DFS was calculated after randomisation but the IDFS was calculated after surgery and thus the 15 patients with progression in the neoadjuvant situation, as listed above, did not influence the DFS and IDFS [44]. The results of the KRISTINE study certainly generate hypotheses, yet they indicate that a loss of efficacy through de-escalation may be able to be compensated with a therapy modification controlled by the biomarker “response”.

### De-escalation in anti-HER2-targeted therapies

The large number of drugs for the treatment of HER2-positive breast cancer represent the basis for considering a de-escalation of the therapies with regard to the duration of a therapy as well as the reduction of conventional chemotherapy. A new study regarding this issue was recently presented, the PREDIX study [45]. In this Swedish phase 3 study, patients were randomised either in the standard arm (103 patients; 6 × docetaxel, trastuzumab, pertuzumab → breast surgery → 2 × EC) or in the experimental arm (99 patients; 6 × trastuzumab-emtansine (T-DM1) → breast surgery → 4 × EC). After EC therapy, both arms received 11 × trastuzumab s.c. pCR was identified in the standard arm in 47% and in the experimental arms in 45% of the treated patients. In the hormone-receptor-negative patients, the rate was 67 and 59% and in the hormone-receptor-positive patients, the rate was 36% in both arms. No differences were significant. The known adverse effects of the drugs used were seen and here it could be noted that milder as well as serious adverse effects were found more rarely in the experimental arm [45]. Yet whether the ADC T-DM1 actually represents an effective option for treating breast cancer in a targeted manner and with few adverse effects must be seen in the connection with other studies. However, strategies must still be found to identify those patients who are predestined for such de-escalating therapy by using molecular, genetic, or imaging markers.

## Benefits of a stratified, post-neoadjuvant therapy in HER2-positive breast cancer

Neoadjuvant systemic therapy permits *in vivo* sensitivity testing in addition to a reduction in surgical morbidity (more breast conservation, fewer axillary lymphadenectomies) [46–48]. Based on the effect of the neoadjuvant systemic therapy on the primary tumour, its effect on the long-term prognosis can be estimated [49,50].

Patients with HER2-positive breast cancer who did not achieve any pathological complete remission in the breast and axilla on neoadjuvant systemic therapy (pCR, ypT0/is ypN0) have an increased risk of recurrence and mortality [51–53]. The phase 3 KATHERINE study included 1486 patients with primary HER2-positive breast cancer who had not achieved pCR following neoadjuvant standard therapy with at least one taxane and trastuzumab for at least 9 weeks. On a randomised basis, they postoperatively received either T-DM1 (3.6 mg/kg) or trastuzumab (6 mg/kg) every 3 weeks for 14 cycles. With a median follow-up period of 41 months, the switch to T-DM1 significantly improved the invasive disease-free survival after 3 years (primary endpoint), from 77.0 to 88.3% ( $\Delta$  11.3%; HR 0.50; 95% CI: 0.39–0.64;  $p < 0.0001$ ) as well as the metastasis-free survival (distant disease-free survival, DDFS) from 83.0 to 89.7% ( $\Delta$  6.7%; HR = 0.60; 95% CI: 0.45–0.79). This benefit was achieved at the expense of an increase in thrombopenia (grade  $\geq 3$   $\Delta$  + 5.7%), increased liver values (grade  $\geq 3$   $\Delta$  approx. + 1%) and polyneuropathy (grade  $\geq 3$   $\Delta$  + 1.4%) [42].

In addition, data from this study on quality of life were recently presented [54]. They were collected with the standardised and validated questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-Breast Cancer Module 23 (QLQ-BR23) during randomisation, on the first day of the 5th and 11th cycle, within 30 days after ending the study medication and after 6 and 12 months of follow-up observation. Overall, 612 (82%) and 640 (86%) patients in the trastuzumab and T-DM1 arms respectively were included in the assessment for whom quality-of-life parameters were surveyed at at least one additional time point, in addition to the baseline survey. The questionnaires after 6 and 12 months of follow-up observation were also available from more than 70% of the patients in both study arms. The slightly increased rate of adverse effects on T-DM1 in comparison to trastuzumab (all grades 99 vs. 93%; grade  $\geq 3$  26 vs. 15%) had only a minimal and transient influence on patients' quality of life. The mean value changes as compared to the baseline values were comparable and small in both treatment arms. On average, in both arms, no clinically significant worsening in the functional and symptom parameters was measured. Numerically, somewhat more patients in the T-DM1 arm than in the trastuzumab arm indicated a clinically significant worsening of individual quality-of-life parameters at individual points in time. However, these differences disappeared after 6 months of follow-up observation.

The data on quality of life thus confirm the superior efficacy of T-DM1 in comparison to trastuzumab in patients with HER2-positive breast cancer and invasive residual tumour following neoadjuvant chemo- and anti-HER2 therapy.

## Early Hormone-Receptor-Positive Breast Cancer

With regard to the adjuvant therapy of patients with a hormone-receptor-positive breast cancer, the duration, choice, and sequence of aromatase inhibitors (AI) or tamoxifen depend in particular on the menopause status, tolerance, and risk of recurrence. Another intensively discussed topic is expanded adjuvant endocrine therapy (years 5–10 or even beyond). In accordance with the recommendations of the AGO Breast Cancer committee, this is recommended in the first 5 years only in the case of higher risk with concomitantly good tolerance [55,56]. In premenopausal women, the expanded therapy is administered with a total of 10 years of tamoxifen according to the data of the ATLAS study [57]. In the postmenopausal situation, a switch can be made to an AI. In patients who had started with an AI, the data according to the ABCSG-16 study to date suggest an extension to 7 instead of 10 years [58].

The exact duration of the expanded endocrine therapy with aromatase inhibitors following an initial sequence therapy of tamoxifen followed by an aromatase inhibitor is additionally the focus of further investigations: In a prospective randomised study (NCT01064635) by Del Mastro et al. [59], various durations of treatment with an endocrine therapy with AI after tamoxifen were investigated. The collective consisted of postmenopausal patients with hormone-receptor-positive, primary breast cancer who had adjuvantly received 2–3 years of tamoxifen. Randomisation into two groups was performed: 2–3 years of further therapy with letrozole or 5 years of letrozole. The primary endpoint was the DFS. A total of 2056 patients were included in the study. Of these patients, 1030 received the brief therapy with letrozole for 2–3 years and 1026 patients received the longer, 5-year therapy. The baseline characteristics, in particular, age and node status (node-negative patients: 56 vs. 56%; (neo-)adjuvant chemotherapy: 53.4 vs. 54.1%) were homogeneously distributed in both groups. The median follow-up period was 10 years (8.6–11.4). The 8-year DFS rate was 80% (95% CI 77.3–82.7) and 85% (95% CI 82.9–87.6) in the case of brief or prolonged administration (HR: 0.82; 95% CI 0.68–0.98;  $p = 0.031$ ). This significant advantage did not change by adjusting the node status, age, or grading. However, the rate of diagnosed osteoporosis was twice as high in the group with prolonged therapy: 81 (8.3%) versus 47 (4.8%), which makes the necessary benefit/risk assessment clear. Therefore the further identification of the collective which actually benefits from expanded therapy is necessary for clinical practice. However, there is currently no sufficiently validated biomarker for a possible prediction [55]. Within the framework of a translational question from the aTTom study, it was now investigated whether the Breast Cancer Index (BCI) can be used for the individual therapeutic decision regarding expanded endocrine therapy [60]. Within the framework of the aTTom study – similarly to the ATLAS study – 6956 patients after at least four years of tamoxifen therapy were randomised to stop therapy or continue with another 5 years of tamoxifen. After an 8.9-year follow-up, the prolonged tamoxifen therapy demonstrated a benefit for the entire group with regard to the disease-free survival with an HR of 0.86 (95% CI 0.77–0.96

( $p = 0.006$ )). The BCI is a gene expression test consisting of a signature of 11 genes which contains 5 genes for tumour proliferation as well as 2 genes of the oestrogen signalling pathway. The BCI provides information on the cumulative prognosis of years 0–10, as well as on the risk of late distant metastasis (in years 5+) and on the prediction of the benefit of expanded endocrine therapy. The current analyses are based on a follow-up observation of the patients for a median of 12.6 years. The BCI result was available for a total of 1822 hormone-receptor-positive patients. Of these patients, 583 had a positive node status. While in the case of patients with a positive node status and low BCI result, no significant advantage through the 10-year therapy was able to be demonstrated (HR = 0.88; 95% CI: 0.65–1.18 and HR = 1.07; 95% CI: 0.69–1.65), an advantage for patients with a high BCI result was seen with an HR of 0.35 (95% CI: 0.15–0.86). The absolute difference in DFS through the extended therapy was 4.7% in node-positive patients ( $p = 0.388$ ),  $-0.2\%$  ( $p = 0.768$ ) at a low BCI score, and  $10.2\%$  ( $p = 0.027$ ) at a high BCI score. Even after adjusting age, tumour size, grading, ER and PR status, a significant interaction between BCI and therapy was seen ( $p = 0.01$ ). The authors concluded that the BCI gene expression test is predictive for the expanded endocrine therapy with 10 years of tamoxifen in node-positive patients.

With regard to the GIM4 study, a current discussion on the results [61] revealed that the expanded therapy with an AI beyond 5 years demonstrated only a minimal to no effect on the disease-free survival, however it substantially reduced secondary carcinomas. The advantages and disadvantages must still be discussed individually with the patient and a mutual therapeutic decision must be made. The high discontinuation rates after the 5th year must be taken into account here. The adherence or compliance here is 57.5% to a maximum of 85–90%, depending on the study. With regard to the Trans-aTTom study, it was discussed [61] that only the group of node-positive patients met the prespecified criteria for the analysis and thus no statement on the node-negative patients can be made. Even if there is now an option to avoid overtreatment, the results for the entire collective should be waited for and confirmed by another study with comparable therapy and length – only then will there be corresponding evidence. In addition, the benefit of the BCI test for patients with aromatase inhibitor therapy in the first 5 years remains open.

While BCI has not yet been broadly applied in clinical practice, data from a prospective, randomised study are available following the publication of the TAILORx study [62,63] which attempts to identify the hormone-receptor-positive patients who can definitively omit chemotherapy. Here the study showed that in patients under age 50, it is questionable as to whether chemotherapy can be omitted [62]. In the current discussion [61], it must be borne in mind that caution is called for in the interaction between age and risk score (RS) within the scope of the TAILORx study, since this is an exploratory analysis: The TAILORx study showed that endocrine therapy is not inferior to chemotherapy in the case of a recurrence score between 11 and 25 in patients over age 50 and between 11 and 16 in patients under age 50. The addition of clinical-pathological parameters should also allow an exemplary answer to the question as to whether the prognostic information (low risk – tumour  $\leq 3$  cm and G1,  $< 2$  cm and G2, or  $\leq 1$  cm and G3) or high

risk (if the criteria of the low-risk group are not met) [64] can be further improved. Through the addition of these parameters, the group of patients under age 50 with a recurrence score between 16 and 20 can be further differentiated: absolute risk reduction with chemotherapy in the case of an RS of 16–20 ( $n = 923$ ):  $-0.2\%$  (standard error [SE]  $\pm 2.1\%$ ) for low risk vs.  $6.5\%$  (SE  $\pm 4.9\%$ ) for high risk. This confirms once again that the meaningfulness of gene expression analyses should be considered in the context of clinical-pathological parameters. An intriguing question remains regarding whether women  $\leq 50$  years could possibly benefit from ovarian suppression with tamoxifen/AI instead of chemotherapy.

In summary, instruments are needed which integrate clinical and pathological factors as well as biomarkers from tumour tissue and blood and additional patient factors in order to ensure truly individualised therapeutic approaches.

With the introduction of CDK4/6 inhibitors in patients with hormone-receptor-positive breast cancer (summarised in [65]), in particular also because 2 studies showed a significant overall survival advantage [66–68], large adjuvant therapy studies have been started for all 3 approved CDK4/6 inhibitors. The study results are still all pending. However, similar to the case in the above studies, adherence is no doubt an important topic [69,70] which must be better understood and which could possibly be improved through digital patient support [71–74] or special communication programmes.

## Early, Triple-Negative Breast Cancer

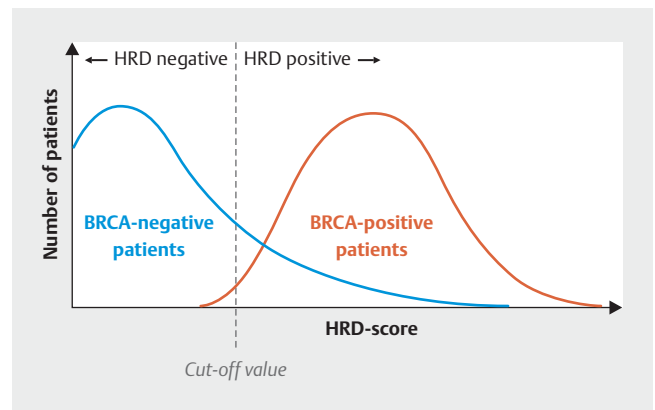
Patients with early, triple-negative breast cancer have the worst prognosis of all molecular subtypes, now that patients with a HER2-positive finding benefit so clearly from trastuzumab therapy that, by now, they represent a prognostically favourable group [75]. Since there are no points of attack for targeted therapy, chemotherapy is the only standard therapeutic option to date. However, a relatively high proportion of patients also responded to chemotherapy. Following neoadjuvant chemotherapy, approx. 40–50% of the TNBC patients achieve pCR. For these patients, it is known that they also have an excellent prognosis [32,76–83]. In the search for new targets for these patients, more and more about the biology of this breast cancer subtype is being understood. Some of these characteristics could soon help to better treat this form of breast cancer also in a non-metastatic primary situation.

Chemotherapy combinations containing platinum are increasingly being used in the case of this tumour biology, as a result of which the rate of pathological complete remissions (pCR) has been able to be significantly increased in the neoadjuvant setting. However, its effect on the long-term prognosis has not been definitively explained to date [79,84–87]. Here other biomarkers (apart from the triple-negative receptor status) could be helpful in identifying those patients who benefit the most from chemotherapy containing platinum. In view of this, the HRD score (HRD = Homologous Recombination Deficiency) is a marker of interest. Homologous recombination is necessary, among other things, to repair double-strand breaks, such as those caused by platinum derivatives [88]. Since *BRCA1* and *BRCA2* play an impor-

tant role in the repair of double-strand breaks, *BRCA1/2*-associated carcinomas are characterised by an elevated HRD score (► **Fig. 4**). Patients with a *BRCA1/2* germ line mutation (gBRCA) also more frequently develop triple-negative breast cancer and patients with a triple-negative breast cancer far more frequently have a *BRCA1/2* mutation [1, 3, 10, 80, 83]. Accordingly, in sporadic triple-negative tumours, there are frequently changes which resemble the pathological and molecular genetic characteristics of gBRCA mutated carcinomas (so-called “BRCAness”), and also increased HRD-positive tumours [89].

In the recently presented TRCBC-030 study, the extent to which the HRD score is associated with the response to neoadjuvant therapy either with paclitaxel or cisplatin was investigated [90]. Of 140 patients with triple-negative primary breast cancer (stage II–III, gBRCA-negative) randomised to 4× cisplatin 75 mg/m<sup>2</sup>, q3w vs. 12× paclitaxel 80 mg/m<sup>2</sup>, q1w, 68/95 (71.6%) patients had a usable test result (Myriad Genetics) of “HRD-positive” (score > 33). 15% of the patients in the carboplatin arm and 13% of the patients in the paclitaxel arm had a pCR. In neither of the two arms was a connection between therapeutic response and HRD positivity seen. Similar data were already demonstrated within the framework of the German GeparSixto study. In this study, the HRD positivity as well as the presence of a gBRCA1 mutation or gBRCA2 mutation were confirmed as markers for an overall better response to neoadjuvant systemic therapy, however they were not predictive for an explicit benefit through the addition of carboplatin [80, 91]. In routine clinical practice as well, similar effects with regard to platinum and gBRCA mutations in the neoadjuvant situation have been described [92].

Another recently presented study on the predictive value of the defective homologous recombination is the GeparOla study in which the effect of PARP inhibition with olaparib on pCR was investigated [93]. Only HRD-positive or *BRCA1/2*-positive (somatic or germ line mutation) women with early HER2-negative breast cancer were included. The patients received either 12× paclitaxel (80 mg/m<sup>2</sup>) weekly + olaparib 2× daily (PO) or 12× paclitaxel (80 mg/m<sup>2</sup>) weekly + carboplatin (AUC2) weekly (PCb), each followed by EC (90/600 mg/m<sup>2</sup>, q14d or q21d). The primary study endpoint was not the comparison of both arms, but rather the question of whether a pCR rate of at least 55% can be reached with the combination containing olaparib. 69 patients were randomised in the PO → C arm and 37 in the PCb → EC arm. In the PO arm, fewer therapeutic discontinuations and fewer adverse effects were seen than in the PCb arm. The pCR rate in the PO arm was 55.1% (90% CI: 44.5–65.3). Although the primary study endpoint was not reached with regard to the confidence interval, the pCR rate was comparable with that of the PCb arm (48.6%; 90% CI: 34.3–63.2). Interestingly, the olaparib combination in the hormone-receptor-positive patients was nearly as effective as in the hormone-receptor-negative patients with a pCR rate of 52.6% in comparison to 56.0%. By contrast, the therapy containing carboplatin appeared less effective in the hormone-receptor-positive women (20.0% pCR rate). In addition, the efficacy of olaparib was more pronounced in younger patients (<40 years) (pCR rate of 76.2%). With regard to the *BRCA1/2* status, a trend was once again confirmed that, if a *BRCA1/2* mutation is present, the pCR rate is higher overall on the one hand, and on the other hand,



► **Fig. 4** Distribution of the homologous recombination deficiency (HRD) score in patients with a pathogenic *BRCA1* or *BRCA2* germ line mutation (BRCA-pos.) and patients without germ line mutation (BRCA-neg.). The cut-off value classifies patients into an HRD-negative and HRD-positive group.

the PCb arm appeared to be less effective in patients with *BRCA1/2* wild type (pCR rate of 37.5). However, reference is made to the small number of cases in the individual groups and to the fact that this concerns purely numerical comparisons. In the previously published BrightNess study, no benefit from the addition of veliparib to carboplatin and paclitaxel was seen in triple-negative patients, independent of *BRCA1/2* status [87]. The GeparOla study now opens the perspective of investigating in further studies on whether paclitaxel should be supplemented with a PARP inhibitor in HRD-positive patients and whether in doing so, carboplatin can be omitted, in view of the increased adverse effects. However, there should be a focus on potential long-term toxicities of PARP inhibition, and not only the pCR but also the influence of the long-term prognosis should be taken into account.

### Checkpoint inhibition in early triple-negative breast cancer

It is already known that in patients with triple-negative breast cancer, an infiltration with lymphocytes (TILs) is associated with a higher pCR rate and a better prognosis [77, 94]. In the first lines of therapy in advanced breast cancer in the case of positivity of the immune cells in the tumour for PD-L1, a significant survival advantage was able to be demonstrated in the case of therapy with the anti-PD-L1 antibody atezolizumab and nab-paclitaxel versus therapy with nab-paclitaxel alone [95]. There are now the first indications of the efficacy from the neoadjuvant situation. In a press release, it was reported [96] that the Keynote-522 study [97] is positive with regard to one of the two primary endpoints (pCR). This means that the addition of the anti-PD-1 antibody pembrolizumab to chemotherapy was able to significantly increase the rate of pCR. 1174 triple-negative patients were recruited in the study [98].

## Outlook

With the introduction of the multigene tests in hormone-receptor-positive patients and the success of T-DM1 after failure of neoadjuvant chemotherapy with anti-HER2 combinations, significant advancements have been achieved in some patients with early breast cancer. The assessments of therapeutic success from the metastatic situation (CDK4/6 inhibitors) are still ongoing. It can also be expected for therapy programmes, such as with the PI3K inhibitor alpelisib, to be created. For triple-negative breast cancer, there is in fact an increasing understanding of the tumour biology, however except for the PARP inhibitors for tumours with *BRCA1/2* mutation, targeted therapies which could bring promising success are lacking. It thus remains to be seen whether new targeted therapies and, in particular, immunotherapies for patients with early breast cancer could mean an advancement in treatment.

## Acknowledgements

This work was developed in part as a result of support from Hexal and the PRAEGNANT network which is supported by Pfizer, Celgene, Daiichi Sankyo, Roche, Merrimack, Eisai, AstraZeneca, Hexal and Novartis. None of the companies played a role in the drafting of this manuscript. The authors alone are responsible for the content of the manuscript.

## Conflict of Interest

**A. D. H.** received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer. **F. O.** received speaker and consultancy honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Chugai, Celgene, Cellex, Eisai, Gilead, Hexal, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Riemsler, Roche, Tesaro, Teva. **H.-C. K.** received honoraria from Carl Zeiss meditec, Teva, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Janssen-Cilag, GSK, LIV Pharma, Roche and Genomic Health. **P. A. F.** received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, MSD, Eisai, Puma and Teva. His institution conducts research with funding from Novartis and Biontech. **M. W.** received speakers honoraria and consultant fees from Novartis, Amgen, Celgene, Roche, Genentech, AstraZeneca, and Pfizer. **H. T.** received honoraria from Novartis, Roche, Celgene, Teva, Pfizer and travel support from Roche, Celgene and Pfizer. **J. E.** received honoraria from AstraZeneca, Roche, Celgene, Novartis, Lilly, Pfizer, Pierre Fabre, Teva and travel support from Celgene, Pfizer, Teva and Pierre Fabre. **M. P. L.** has participated on advisory boards for AstraZeneca, MSD, Novartis, Pfizer, Eisai, Genomic Health and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, medac and Eisai. **V. M.** received speaker honoraria from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi Sankyo and Eisai, Lilly, Tesaro and Nektar. **E. B.** received honoraria from Novartis, Riemsler, Pfizer, Hexal, Amgen, and onkowissen.de for consulting, clinical research management or medical education activities. **A. S.** received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Zuckschwerdt Verlag GmbH, Georg Thieme Verlag, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH and promedicis GmbH. **W. J.** received honoraria and research grants from Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, Sanofi, Daiichi Sankyo, Tesaro. **F. S.** participated on advisory boards for Novartis, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer. **A. W.** participated on advisory

boards for Novartis, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene. **D. L.** received honorarium from Amgen, AstraZeneca, Celgene, Lilly, Loreal, MSD, Novartis, Pfizer, Tesaro, Teva. **T. N. F.** has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.

## References

- [1] 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
- [2] Couch FJ, Kuchenbaecker KB, Michailidou K et al. Identification of four novel susceptibility loci for oestrogen receptor negative breast cancer. *Nat Commun* 2016; 7: 11375
- [3] Couch FJ, Shimelis H, Hu C et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol* 2017; 3: 1190–1196
- [4] Garcia-Closas M, Couch FJ, Lindstrom S et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet* 2013; 45: 392–398, 398e1–398e2
- [5] Ghossaini M, Fletcher O, Michailidou K et al. Genome-wide association analysis identifies three new breast cancer susceptibility loci. *Nat Genet* 2012; 44: 312–318
- [6] Michailidou K, Beesley J, Lindstrom S et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet* 2015; 47: 373–380
- [7] Michailidou K, Hall P, Gonzalez-Neira A et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet* 2013; 45: 353–361, 361e1–361e2
- [8] Michailidou K, Lindstrom S, Dennis J et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017; 551: 92–94
- [9] Milne RL, Kuchenbaecker KB, Michailidou K et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat Genet* 2017; 49: 1767–1778
- [10] 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. doi:10.1093/jnci/djy106
- [11] Wu L, Shi W, Long J et al. A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer. *Nat Genet* 2018. doi:10.1038/s41588-018-0132-x
- [12] Wunderle M, Olmes G, Nabieva N et al. Risk, Prediction and Prevention of Hereditary Breast Cancer – Large-Scale Genomic Studies in Times of Big and Smart Data. *Geburtsh Frauenheilk* 2018; 78: 481–492
- [13] 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
- [14] 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
- [15] 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
- [16] 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. doi:10.1093/ije/dyx242
- [17] Muranen TA, Greco D, Blomqvist C et al. Genetic modifiers of CHEK2\*1100delC-associated breast cancer risk. *Genet Med* 2017; 19: 599–603



- [18] 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
- [19] Barrdahl M, Rudolph A, Hopper JL et al. Gene-environment interactions involving functional variants: Results from the Breast Cancer Association Consortium. *Int J Cancer* 2017; 141: 1830–1840
- [20] Schmidt MK, Hogervorst F, van Hien R et al. Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2\*1100delC Carriers. *J Clin Oncol* 2016; 34: 2750–2760
- [21] 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
- [22] Rudolph A, Milne RL, Truong T et al. Investigation of gene-environment interactions between 47 newly identified breast cancer susceptibility loci and environmental risk factors. *Int J Cancer* 2015; 136: E685–E696
- [23] Rudolph A, Fasching PA, Behrens S et al. A comprehensive evaluation of interaction between genetic variants and use of menopausal hormone therapy on mammographic density. *Breast Cancer Res* 2015; 17: 110
- [24] Mavaddat N, Pharoah PD, Michailidou K et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015. doi:10.1093/jnci/djv036
- [25] Jamshidi M, Fagerholm R, Khan S et al. SNP-SNP interaction analysis of NF-kappaB signaling pathway on breast cancer survival. *Oncotarget* 2015; 6: 37979–37994
- [26] Milne RL, Herranz J, Michailidou K et al. A large-scale assessment of two-way SNP interactions in breast cancer susceptibility using 46,450 cases and 42,461 controls from the breast cancer association consortium. *Hum Mol Genet* 2014; 23: 1934–1946
- [27] Nickels S, Truong T, Hein R et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. *PLoS Genet* 2013; 9: e1003284
- [28] 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
- [29] Vachon CM, Scott CG, Fasching PA et al. Common breast cancer susceptibility variants in LSP1 and RAD51L1 are associated with mammographic density measures that predict breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1156–1166
- [30] Mavaddat N, Michailidou K, Dennis J et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2018. doi:10.1016/j.ajhg.2018.11.002
- [31] Wöckel A, Lux MP, Janni W et al. Update Breast Cancer 2018 (Part 3) – Genomics, Individualized Medicine and Immune Therapies – in the Middle of a New Era: Prevention and Treatment Strategies for Early Breast Cancer. *Geburtsh Frauenheilk* 2018; 78: 1110–1118
- [32] Hartkopf AD, Müller V, Wöckel A et al. Update Breast Cancer 2019 Part 1 – Implementation of Study Results of Novel Study Designs in Clinical Practice in Patients with Early Breast Cancer. *Geburtsh Frauenheilk* 2019; 79: 256–267
- [33] 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
- [34] Heusinger K, Jud SM, Haberle L et al. Association of mammographic density with hormone receptors in invasive breast cancers: results from a case-only study. *Int J Cancer* 2012; 131: 2643–2649
- [35] Sigl V, Owusu-Boaitey K, Joshi PA et al. RANKL/RANK control Brca1 mutation. *Cell Res* 2016; 26: 761–774
- [36] Sigl V, Owusu-Boaitey K, Joshi PA et al. RANKL/RANK control Brca1 mutation-driven mammary tumors. *Cell Res* 2016; 26: 761–774
- [37] 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
- [38] ABCSG. ABCSG 50/BRCA-P: Schon drei Frauen randomisiert! 2019. Online: <https://www.abcsorg.org/abcs-g-50-brca-p-schon-drei-frauen-randomisiert/>; last access: 24.07.2019
- [39] 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
- [40] 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
- [41] Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791
- [42] von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2018. doi:10.1056/NEJMoa1814017
- [43] Hurvitz SA, Martin M, Symmans WF et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2018; 19: 115–126
- [44] Hurvitz SA, Martin M, Jung KH et al. Neoadjuvant Trastuzumab Emtansine and Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Three-Year Outcomes From the Phase III KRISTINE Study. *J Clin Oncol* 2019. doi:10.1200/JCO.19.00882
- [45] Bergh JCS, Andersson A, Bjohle J et al. Docetaxel, trastuzumab, pertuzumab versus trastuzumab emtansine as neoadjuvant treatment of HER2-positive breast cancer: Results from the Swedish PREDIX HER2 trial identifying a new potential de-escalation standard? *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.501
- [46] Fasching PA, Gass P, Hein A. Neoadjuvant Treatment of Breast Cancer – Advances and Limitations. *Breast Care (Basel)* 2016; 11: 313–314
- [47] Fernandez-Gonzalez S, Falo C, Pla MJ et al. The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. *Clin Breast Cancer* 2018; 18: 71–77
- [48] Fasching PA, Heusinger K, Haeberle L et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. *BMC Cancer* 2011; 11: 486
- [49] Robertson JFR, Dowsett M, Bliss JM et al. Peri-operative Aromatase Inhibitor treatment in determining or predicting Longterm Outcome in Early Breast Cancer-the POETIC\* Trial (CRUK/07/015) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. *Cancer Res* 2018; 78: Abstr. GS1-03
- [50] 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
- [51] 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
- [52] Schneeweiss A, Chia S, Hickish T et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer* 2018; 89: 27–35
- [53] Untch M, Fasching PA, Konecny GE et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol* 2011; 29: 3351–3357

- [54] Schneeweiss A, Loibl S, Mamounas EP et al. Patient-reported outcomes (PROs) from KATHERINE: A phase III study of adjuvant trastuzumab emtansine (T-DM1) versus trastuzumab (H) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer. *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.513
- [55] Liedtke C, Jackisch C, Thill M et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2018. *Breast Care (Basel)* 2018; 13: 196–208
- [56] Thill M, Liedtke C, Muller V et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2018. *Breast Care (Basel)* 2018; 13: 209–215
- [57] Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; 381: 805–816
- [58] Gnant M, Steger G, Greil R et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. *Cancer Res* 2018; 78: Abstr. GS3-01
- [59] Del Mastro L, Mansutti M, Bisagni G et al. Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of Gruppo Italiano Mammella (GIM). *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.504
- [60] Bartlett J, Sgroi D, Treuner K et al. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen–To offer more? (aTTom) trial. *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.505
- [61] Stearns V. Adjuvant Endocrine Therapy: Selecting the Optimal Path. 2019 ASCO Annual Meeting, Chicago 2019. Online: <https://meeting.library.asco.org/record/175033/video>; last access: 30.06.2019
- [62] 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
- [63] 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
- [64] Sparano JA, Gray RJ, Makower DF et al. Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer (EBC) by age and the 21-gene recurrence score (RS) in TAILORx. *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.503
- [65] Fasching PA, Schneeweiss A, Kolberg HC et al. Translational highlights in breast cancer research and treatment: recent developments with clinical impact. *Curr Opin Obstet Gynecol* 2019; 31: 67–75
- [66] Im SA, Lu YS, Bardia A et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med* 2019. doi:10.1056/NEJMoa1903765
- [67] Novartis. Novartis Kisqali significantly prolongs life in women with HR+/HER2- advanced breast cancer now in two distinct Phase III trials. Novartis Press Release 2019. Online: <https://www.novartis.com/news/media-releases/novartis-kisqali-significantly-prolongs-life-women-hrher2-advanced-breast-cancer-now-two-distinct-phase-iii-trials>; last access: 03.08.2019
- [68] Slamon DJ, Neven P, Chia S et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONA-LEESA-3. *J Clin Oncol* 2018. doi:10.1200/JCO.2018.78.9909
- [69] Nabieva N, Kellner S, Fehm T et al. Influence of patient and tumor characteristics on early therapy persistence with letrozole in postmenopausal women with early breast cancer: results of the prospective Evaluate-TM study with 3941 patients. *Ann Oncol* 2018; 29: 186–192
- [70] Nabieva N, Fehm T, Haberle L et al. Influence of side-effects on early therapy persistence with letrozole in post-menopausal patients with early breast cancer: Results of the prospective Evaluate-TM study. *Eur J Cancer* 2018; 96: 82–90
- [71] Basch EM, Deal AM, Dueck AC et al. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *J Clin Oncol* 2017; 35 (Suppl.): Abstr. LBA2
- [72] Hartkopf AD, Graf J, Simoes E et al. Electronic-Based Patient-Reported Outcomes: Willingness, Needs, and Barriers in Adjuvant and Metastatic Breast Cancer Patients. *JMIR Cancer* 2017; 3: e11
- [73] Tresp V, Overhage JM, Bundschuh M et al. Going Digital: A Survey on Digitalization and Large-Scale Data Analytics in Healthcare. *P IEEE* 2016; 104: 2180–2206
- [74] Wallwiener M, Matthies L, Simoes E et al. Reliability of an e-PRO Tool of EORTC QLQ-C30 for Measurement of Health-Related Quality of Life in Patients With Breast Cancer: Prospective Randomized Trial. *J Med Internet Res* 2017; 19: e322
- [75] Katzorke N, Rack BK, Haerberle L et al. Prognostic value of HER2 on breast cancer survival. *J Clin Oncol* 2013. doi:10.1200/jco.2013.31.15\_suppl.640
- [76] Untch M, Jackisch C, Schneeweiss A et al. NAB-Paclitaxel Improves Disease-Free Survival in Early Breast Cancer: GBC 69-GeparSepto. *J Clin Oncol* 2019. doi:10.1200/JCO.18.01842
- [77] Wurfel F, Erber R, Huebner H et al. TILGen: A Program to Investigate Immune Targets in Breast Cancer Patients – First Results on the Influence of Tumor-Infiltrating Lymphocytes. *Breast Care (Basel)* 2018; 13: 8–14
- [78] Schneeweiss A, Jackisch C, Schmatloch S et al. Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline-cyclophosphamide for patients with early breast cancer – GBC69 [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX Philadelphia (PA): AACR. *Cancer Res* 2018; 78: Abstr. GS3-05
- [79] Gass P, Lux MP, Rauh C et al. Prediction of pathological complete response and prognosis in patients with neoadjuvant treatment for triple-negative breast cancer. *BMC Cancer* 2018; 18: 1051
- [80] Hahnen E, Lederer B, Hauke J et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. *JAMA Oncol* 2017; 3: 1378–1385
- [81] Untch M, von Minckwitz G, Konecny GE et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer–outcome on prognosis. *Ann Oncol* 2011; 22: 1999–2006
- [82] Untch M, Fasching PA, Konecny GE et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer–results at the time of surgery. *Ann Oncol* 2011; 22: 1988–1998
- [83] 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 GeparQuinto Study. *J Clin Oncol* 2018. doi:10.1200/JCO.2017.77.2285

- [84] Sikov WM, Polley M-Y, Twohy E et al. CALGB (Alliance) 40603: Long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/- carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC). *J Clin Oncol* 2019. doi:10.1200/JCO.2019.37.15\_suppl.591
- [85] von Minckwitz G, Schneeweiss A, Loibl S et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; 15: 747–756
- [86] Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015; 33: 13–21
- [87] Loibl S, O'Shaughnessy J, Untch M et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrightNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; 19: 497–509
- [88] Scully R, Panday A, Elango R et al. DNA double-strand break repair-pathway choice in somatic mammalian cells. *Nature Reviews Molecular Cell Biology* 2019. doi:10.1038/s41580-019-0152-0
- [89] Sharma P, Barlow WE, Godwin AK et al. Impact of homologous recombination deficiency biomarkers on outcomes in patients with triple-negative breast cancer treated with adjuvant doxorubicin and cyclophosphamide (SWOG S9313). *Ann Oncol* 2018; 29: 654–660
- [90] Mayer EL, Abramson VG, Jankowitz RC et al. TBCRC030: A randomized phase II study of preoperative cisplatin versus paclitaxel in TNBC—Evaluating the homologous recombination deficiency (HRD) biomarker. *J Clin Oncol* 2019; 37 (Suppl.): Abstr. 507
- [91] Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response – final results from GeparSixto. *Ann Oncol* 2018. doi:10.1093/annonc/mdy460
- [92] Tutt A, Tovey H, Cheang MCU et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018; 24: 628–637
- [93] Fasching P, Jackisch C, Rhiem K et al. GeparOLA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). *J Clin Oncol* 2019; 37 (Suppl.): Abstr. 506
- [94] Denkert C, von Minckwitz G, Darb-Esfahani S et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol* 2018; 19: 40–50
- [95] Schmid P, Adams S, Rugo HS et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018; 379: 2108–2121
- [96] Merck. Merck's KEYTRUDA® (pembrolizumab) in Combination with Chemotherapy Met Primary Endpoint of Pathological Complete Response (pCR) in Pivotal Phase 3 KEYNOTE-522 Trial in Patients with Triple-Negative Breast Cancer (TNBC). 2019. Online: <https://www.mrknewsroom.com/news-release/oncology/mercks-keytruda-pembrolizumab-combination-chemotherapy-met-primary-endpoint-pa>; last access: 29.07.2019
- [97] Schmid P, Cortes J, Bergh JCS et al. KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs. placebo + chemo as neoadjuvant therapy followed by pembro vs. placebo as adjuvant therapy for triple-negative breast cancer (TNBC). *J Clin Oncol* 2018. doi:10.1200/JCO.2018.36.15\_suppl.TPS602
- [98] Clinicaltrials.gov. Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs. Placebo as Adjuvant Therapy in Participants With Triple Negative Breast Cancer (TNBC) (MK-3475-522/KEYNOTE-522). Online: <https://clinicaltrials.gov/ct2/show/NCT03036488> 2019; last access: 24.07.2019
- [99] ABCSG. ABCSG 50/BRCA-P Übersicht. Online: <https://www.abcs.org/abcs-studien/abcs-studien-open/abcs-studien-mammakarzinom-status-open/abcs-50-brca-p/abcs-50-brca-p-uebersicht/>; last access: 24.07.2019