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ABSTRACT

This review summarises not only the latest evidence on prevention, but also the current research on the treatment of early-stage breast cancer patients. Recent years have seen a growing body of evidence on the risk of high- and moderate-penetrance breast cancer susceptibility genes. A large international consortium has now been able to further refine the answer to the question of the significance of the so-called panel genes. Moreover, the data on treatment selection regarding endocrine efficacy and the decision for or against chemotherapy have also been advanced markedly. There is also new data on adjuvant CDK4/6 (cyclin-dependent kinase 4/6) inhibitors, which are standard in first-line treatment in patients with metastatic HER2-negative, hormone receptor-positive (HR+) breast cancer. For other therapies such as immune checkpoint inhibitors, which have successfully improved the rate of pathologic complete response (pCR) in neoadjuvant treatment settings for patients with triple-negative breast cancer (TNBC), there is a growing understanding of the quality of life and side effects. This is especially important in situations where patients could possibly be cured without such a regimen.

ZUSAMMENFASSUNG

In dieser Übersichtsarbeit werden nicht nur die neuesten Erkenntnisse zur Prävention, sondern auch die aktuellen Arbeiten zur Behandlung von Mammakarzinompatientinnen im frühen Krankheitsstadium zusammengefasst. In den letzten Jahren haben sich die Hinweise über hoch-penetrante und mittelgradig penetrante Risikogene für ein Mammakarzinom verdichtet. Nun konnte in einem großen internationalen Konsortium die Antwort auf die Frage nach der Wertigkeit der sogenannten Panelgene weiterentwickelt werden. Des weiteren sind auch die Daten zur Therapieselektion in Bezug auf endokrine Wirksamkeit und die Entscheidung für oder gegen eine Chemotherapie deutlich weiterentwickelt worden. Ebenso gibt es neue Daten zum adjuvanten Einsatz von CDK4/6-(Cyclin-dependent-kinase-4/6-)Inhibitoren, die in der 1. Therapielinie für Patientinnen mit metastasiertem HER2-negativem, hormonrezeptorpositiven (HR+) Mammakarzinom zum Therapiestandard gehören. Bei anderen Therapien wie den Immuncheckpoint-Inhibitoren, welche erfolgreich in der neoadjuvanten Therapiesituation bei Patientinnen mit einem triple-negativen Mammakarzinom (TNBC) die Rate an pathologischen Komplettremissionen (pCR) verbessern konnten, wächst das Verständnis für Lebensqualität und Nebenwirkungen. Dies ist von besonderer Bedeutung in einer Situation, in der Patientinnen potenziell auch ohne eine solche Therapie geheilt werden könnten.

Introduction

This review summarises the latest study outcomes in prevention and treatment of patients with early-stage breast cancer. Developments in recent years have shown that treatment innovations enter clinical practice at a rapid pace [1–6]. This paper includes full publications and presentations at the current major cancer and breast cancer meetings such as ESMO (European Society for Medical Oncology) 2020 and SABCS (San Antonio Breast Cancer Symposium) 2020. During the COVID-19 pandemic, these meetings were largely held in a virtual setting. Due to the pandemic, it is not just medical communication that has suffered. Far more significant is the drop in patient participation in screening and diagnostic procedures, the restrictions on planned interventions and procedures with medical indications, as well as the resulting decline in the patients' quality of life.

Prevention

Panel gene knowledge deepens

All inherited genetic risk factors can explain about 40% of a twofold increased familial risk of breast cancer [7–9]. Risk genes are divided into those with high, moderate and low penetrance. These largely comprise common polymorphisms for which over 150 genomic regions have been identified [10–27]. *BRCA1/2* accounts for about 16% and low-penetrance genes for about 18% of this familial risk [28]. Medium penetrance genes could explain about 4% of the twofold increase in familial risk [28]. Often these genes were included in so-called gene panels evaluated as part of genetic counselling and testing (e.g., *PALB2, ATM, CHEK2, …*). This has been the subject of much discussion in recent years and studies have been undertaken to quantify the risk of these genes [29, 30]. As is also evident from ▶ **Fig. 1**, in both papers the lifetime risk of moderate-penetrance risk genes was lower than for *BRCA1* or *BRCA2* (except *PALB2*) [31, 32]. In over 60 000 female breast
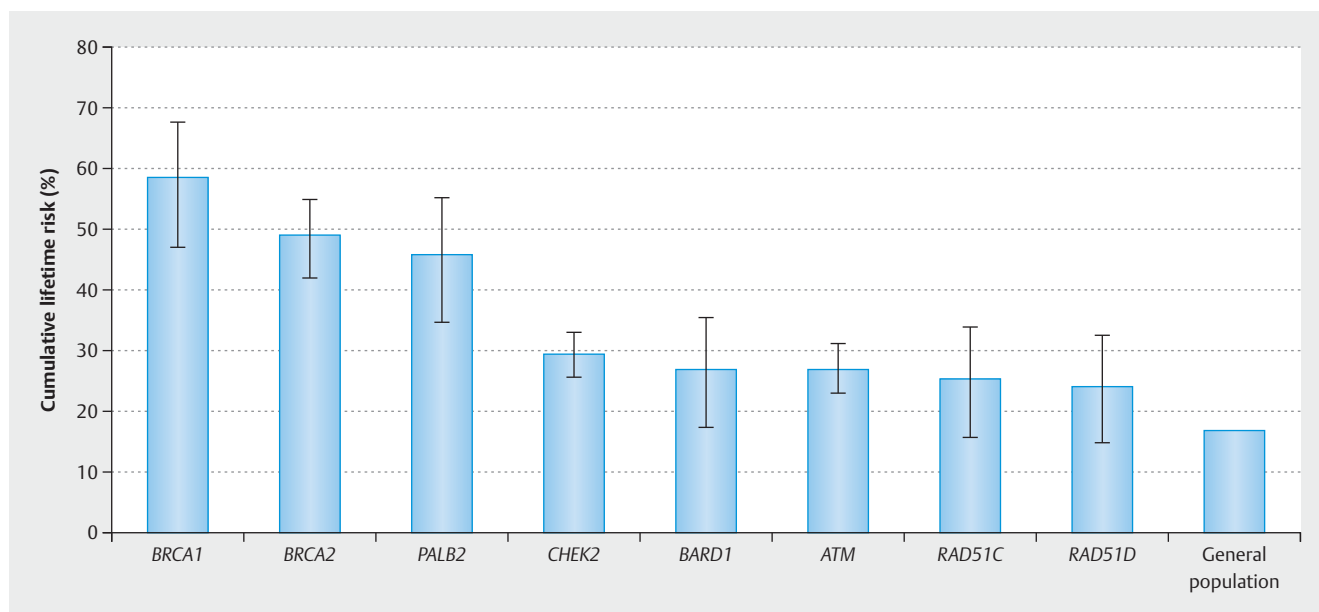
▶ **Fig. 1** Lifetime risk up to 80 years of age for the eight confirmed risk genes according to [31].

cancer patients and more than 53 400 healthy controls, 34 putative risk genes were sequenced and screened for protein truncating mutations and rare missense mutations [31]. The genes studied are listed in ▶ **Table 1**. *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2* clearly correlated with an increased risk of breast cancer. *BARD1, RAD51C, RAD51D*, and *TP53* also correlated with breast cancer risk, but not as markedly as those noted above. ▶ **Fig. 1** presents the cumulative lifetime risks according to Dorling et al. up to the age of 80 years. It becomes clear that in the risk range 45–60% *BRCA1, BRCA2* and *PALB2* together should be classified as high-penetrance risk genes, while the other confirmed risk genes with lifetime risks of 20–30% may be regarded as moderate risk genes. Ultimately, this paper, with more than 110 000 patients, provides the foundation for risk counselling. Even though no significant correlation was found for the remaining genes, this does not imply that they are not risk genes, but only that in this study design they did not attain risk ranges comparable to these eight confirmed genes. The role of these risk genes in the treatment of breast cancer is unclear. While carriers of the *BRCA1/2* mutation respond better to chemotherapy or PARP (poly-[ADP-ribose]-polymerase) inhibitors [33 – 38] in the neoadjuvant setting and to PARP inhibitors when metastasis is present [39 – 41], for the other mutations evidence that patients have a good chance of responding to olaparib therapy could only be found for *PALB2* [42].

Impact of diet and microbiome on breast cancer risk

It has already been established in some epidemiological studies that body weight impacts on the risk of breast cancer. Interestingly enough, in premenopausal women, a high BMI (body mass index) does not appear to be associated with increased risk. In postmenopausal women, on the other hand, a high BMI correlates with an increased risk of breast cancer [43 – 45]. Moreover, there seem to be other metabolic factors affecting the risk of breast

▶ **Table 1** The risk genes studied in over 60 000 breast cancer patients and more than 53 400 healthy controls.

ABRAXIS1	**CHEK2¹**	MSH6	RAD50
AKT1	EPCAM	MUTYH	**RAD51C²**
ATM¹	FANCC	NBN	**RAD51D²**
BABAM2	FANCM	NF1	RECQL
BARD1²	GEN1	**PALB2¹**	RINT1
BRCA1¹	MEN1	PIK3CA	STK11
BRCA2¹	MLH1	PMS2	**TP53²**
BRIP1	MRE11	PTEN	XRCC2
CDH1	MSH2		

¹ Breast cancer risk correlation with a p-value < 0.0001

² Breast cancer risk correlation with a p- value < 0.05

bold = confirmed breast cancer risk genes with high or moderate penetrance

cancer independently of BMI [43]. With regard to prognosis, it has also been established that obesity has a negative effect on the course of the disease and the molecular subtype [46, 47] This suggests a link between metabolism and breast cancer risk with more complex mechanisms. One study looking into this is the cohort study "NutriNet-Santé" [48]. It investigated the possible correlation between a high glycaemic index (a measure of the hyperglycaemic effect of food containing carbohydrates) and high glycaemic load with an increased risk of breast cancer. In the study, which was controlled by online questionnaires, more than 171 000 respondents were questioned every 6 months about diet and lifestyle, among other things. Over 81 000 women were evaluated in quintiles regarding the topic. 927 breast cancer cases

were observed. It was shown that unlike postmenopausal women in the lowest quintile of glycaemic load those in the highest quintile were at a significantly higher risk of breast cancer with a hazard ratio of 1.64 (95% CI: 1.06–2.55). Similarly, compared with the bottom quintile the share of diet with moderate and high glycaemic index in the top quintile correlated with an increased risk of breast cancer in pre- and postmenopausal women (HR = 1.48; 95% CI: 1.18–1.86) [48]. This study thus revealed that the composition of the diet can affect the risk of breast cancer. Since the analysis included BMI, height, physical activity, and other confounders as well, it can also be stated that this risk from diet is independent of these other parameters.

In the past, the gut microbiome has already been linked to the efficacy of immunotherapy in cancer patients [49]. The association between gut microbiome and breast cancer risk has also been studied [50] by now based on an existing large case-control study of over 130000 breast cancer cases and more than 110000 controls [51]. Moreover, studies were included that had investigated the correlation between genetic variants and the presence of specific microbiome patterns [52]. The 13 genetic variants correlating with specific microbiome patterns [52] were then studied by Mendelian randomisation for their correlation with breast cancer risk in the large case-control study [51]. In the overall population, the bacterial *genus ruminococcus* was identified as a risk factor. In triple-negative breast cancer (TNBC), bacteria of the *genus parabacteroides* have been identified as protective and unclassified bacteria of the *order bacteroidales* as risk factors [50]. However, as the interaction between health and the microbiome is not yet fully understood, it is difficult to establish a risk-reducing interventional strategy based on this data.

Neoadjuvant Therapy

Neoadjuvant treatment in patients with hormone receptor-positive HER2-negative tumours

Although pathologic complete response (pCR) generally predicts good outcome after neoadjuvant chemotherapy, this effect is most pronounced in patients with HER2-positivity or TNBC [53–57]. In patients with HR+/HER2− tumours, the interaction is less evident, which is why understanding resistance mechanisms in the neoadjuvant setting is of particular clinical relevance. An important clinical issue is whether chemotherapy is associated with a benefit in endocrine resistance or endocrine sensitivity. Ki-67 and multigene tests would seem to be promising biomarkers in this setting. The response to endocrine treatment resulting in Ki-67 decline within a few weeks was a significant prognostic marker, e.g. in the POETIC trial [58].

Absence of Ki-67 response under endocrine therapy and subsequent neoadjuvant chemotherapy

ALTERNATE is a new trial looking at these mechanisms. In this trial HER2−/HR+ patients with elevated Ki-67 levels persistently > 10% after initial neoadjuvant endocrine therapy underwent neoadjuvant chemotherapy. Data has been reported from this arm regarding the neoadjuvant chemotherapy [59]. Of the 1299 patients enrolled in the trial, 286 patients had a Ki-67 level > 10%

after renewed core needle biopsy under neoadjuvant endocrine therapy. 168 of these 286 patients underwent neoadjuvant chemotherapy, while the remaining patients were operated on directly. 14 patients with neoadjuvant treatment did not undergo surgery. Only 8 patients (4.8%; 95% CI: 2.1–9.2) achieved a pCR, despite the fact that more than 80% of the tumours tested Ki-67 > 20% [59]. In another trial in which the Ki-67 level was established before chemotherapy, the pCR rate in Ki-67 of 20% was a similar 8% [55]. Whether re-biopsy under endocrine therapy can provide more information than the initial Ki-67 level should be investigated further. The results of this trial cannot be applied in clinical practice when deciding for or against neoadjuvant chemotherapy or initial surgery.

Also in the ADAPT study HR+ HER2− patients were selected for a neoadjuvant chemotherapy based on a multigene test (OncotypeDX®) and a Ki-67 assessment after a 3-week endocrine treatment [60]. Eligible for neoadjuvant chemotherapy were patients with a recurrence score of > 25 or more than 3 positive lymph nodes and patients with > 10% Ki-67 positive cells in the repeat core needle biopsy 3 weeks after endocrine treatment [60]. Patients were randomised into one of two arms: 4 cycles of paclitaxel 175 mg/m^2 every 2 weeks followed by 4 cycles of epirubicin/cyclophosphamide every 2 weeks versus 8 cycles of Nab-paclitaxel 125 mg/m^2 weekly followed by 4 cycles of epirubicin/cyclophosphamide every 2 weeks. In the paclitaxel arm, the pCR rate was 12.9% and in the Nab-paclitaxel arm 20.8% (p = 0.002) [60]. Thus, after demonstrating better efficacy of Nab-paclitaxel versus paclitaxel in the neoadjuvant treatment of TNBC patients [61], it has now also been shown in HER2−, HR+ patients that the pCR rate could be almost doubled [61]. These outcomes confirm the pCR results of the GeparSepto trial in triple negative patients [62]. This trial also demonstrated a significant effect on metastasis-free survival [61].

Survival analysis update of the KEYNOTE-522 trial

The data from the third interim analysis (IA3) of the KEYNOTE-522 trial was presented at a meeting of the Oncologic Drugs Advisory Committee (ODAC) at the US Food and Drug Administration (FDA). This analysis was based on a total of 174 events. The hazard ratio was 0.65 (95% CI: 0.48–0.88; p = 0.0025). However, because of the numerous interim analyses, the p-value should have been 0.0021 [63]. Thus, the difference was not statistically significant. The corresponding Kaplan-Meier graph is shown in ▶ **Fig. 2**. Interestingly enough, the analysis regarding pCR was also repeated. While 602 patients participated in the initial analysis (pCR difference 13.6%), now all 1174 patients in the intention-to-treat population participated. The pCR rate in the chemotherapy arm was 55.6% and in the pembrolizumab + chemotherapy arm 63.0%. So the difference was only 7.5% [63].

Quality of life under neoadjuvant therapy with immune checkpoint inhibitors

With the KEYNOTE-522 trial, the NeoTRIP trial and the IMpassion031 trial, three larger prospective randomised trials involving patients with TNBC and neoadjuvant chemotherapy have been published [64–66]. Two trials revealed an increase in pCR irrespective of PD-L1 expression (KEYNOTE-522: 51.2% → 64.8% (in
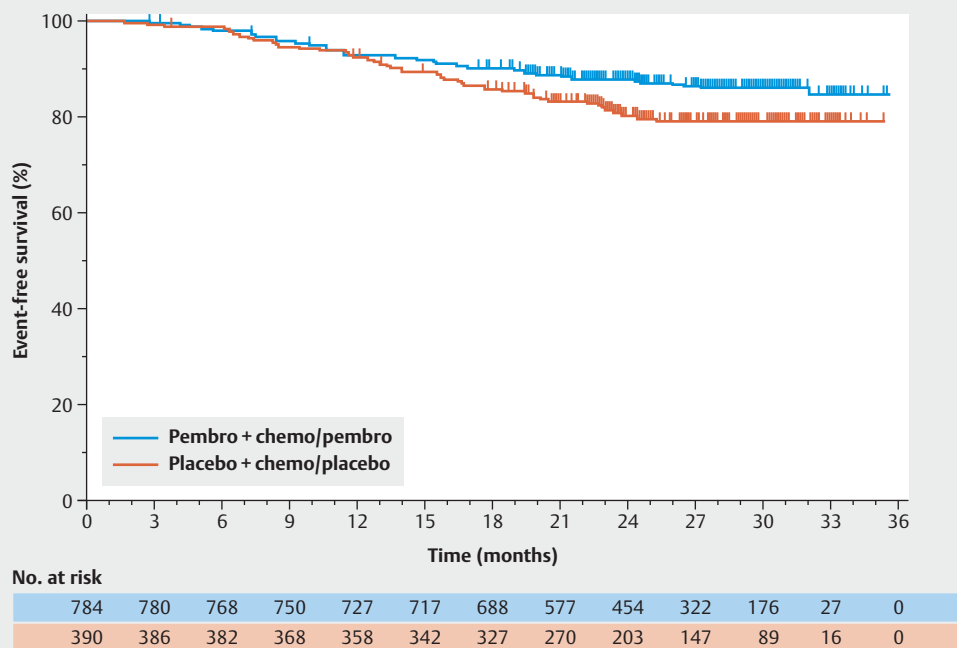
▶ **Fig. 2** Kaplan-Meier estimator for event-free survival in the KEYNOTE-522 trial at the third interim analysis (from [63]).

initial analysis); IMpassion031 41.1% → 57.6%). Since the sample comprised patients with excellent chances of being cured in case of pCR and because the possible, if any, survival benefit arising from the approx. 15% improvement in the pCR rate is still unclear, the side effects of the additional immune checkpoint inhibition are of particular interest. ▶ **Table 2** lists the incidence of side effects typically associated with immune checkpoint inhibitors. This data has now been supplemented by Patient Reported Outcomes (PRO, quality of life assessment) from the IMpassion031 trial [67]. This is true for both the neoadjuvant and adjuvant phases of the trial (patients in the atezolizumab arm received neoadjuvant atezolizumab in addition to chemotherapy and 11 adjuvant atezolizumab cycles every 3 weeks) [64]. ▶ **Figs. 3** and **4** present the changes from baseline for the EORTC-QLQC30 HrQoL (Health-related Quality of Life) total score and the fatigue subscale. It was found that the chemotherapy dosing interval affected the quality of life in both randomisation arms. In both randomisation arms, scores recovered after surgery, but there is the impression that patients in the atezolizumab arm had worse scores than patients in the arm without checkpoint inhibition. However, the authors emphasised that the analyses were purely descriptive and that the confidence intervals overlapped. They concluded that quality of life was similar in both randomisation arms [67]. Nevertheless, it must be noted that the numerical trend was consistent over the entire observation period and no statistical comparison was carried out. There is also no long-term follow-up data for long-term side effects.

▶ **Table 2** Adverse events of special interest (AESI) in the IMpassion031, NeoTRIP and KEYNOTE-522 trials [64–66]. The illustration is not intended to imply any comparison. The trial populations were quite different, e.g., with more patients without ECOG 0 in the KEYNOTE-522 trial.

	KEYNOTE-355	NeoTRIP	IMpassion031
No. of patients treated with PD-L1/PD-1 inhibitors	781	138	164
	% occurrence all grades		% occurrence all grades
Infusion reaction	16.9	8.0	10.4
Hypothyroidism	13.7	5.8	6.7
Hyperthyroidism	4.6	0.7	3.0
Adrenal failure	2.3	NR	0
Hypophysitis/ encephalitis	1.8	NR	0.6
Colitis	1.7	1.5	0.6
Hepatitis	1.4	0.7	1.2
Pneumonitis	1.3	NR	1.2

ECOG: Eastern Cooperative Oncology Group; NR: not reported; PD-L1: programmed death-ligand 1
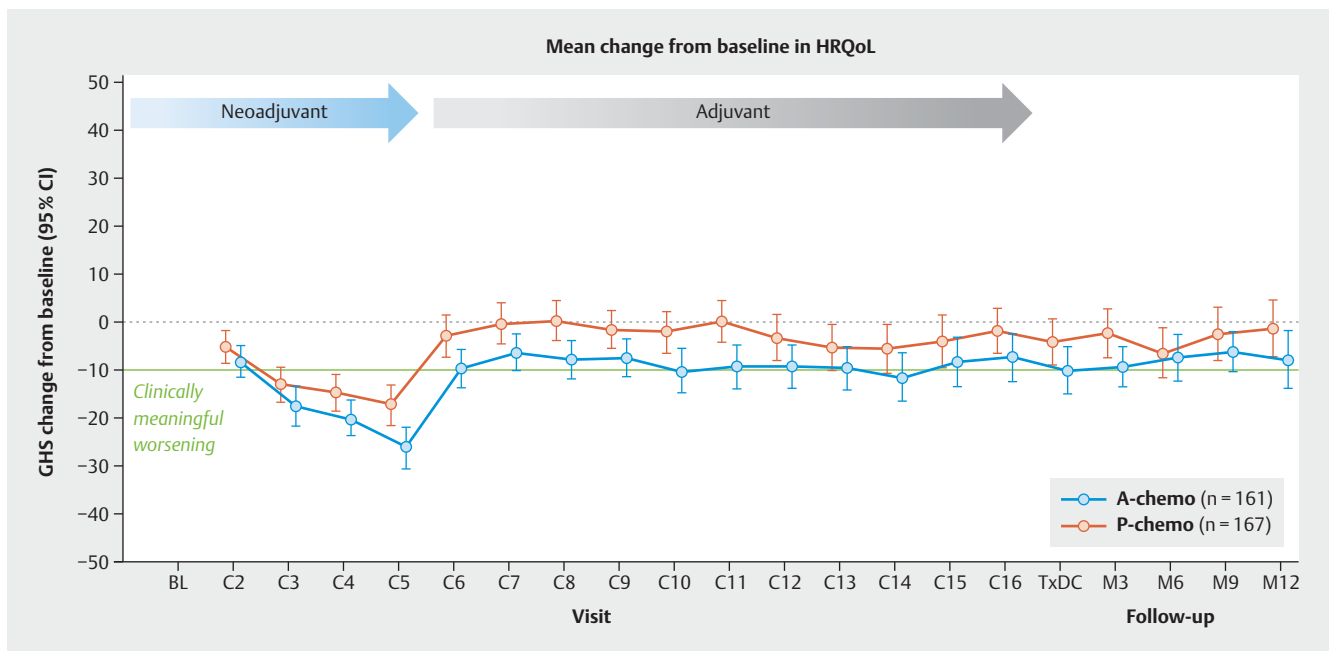
▶ **Fig. 3** Change in health-related quality of life (EORTC-QLQC30) [67].
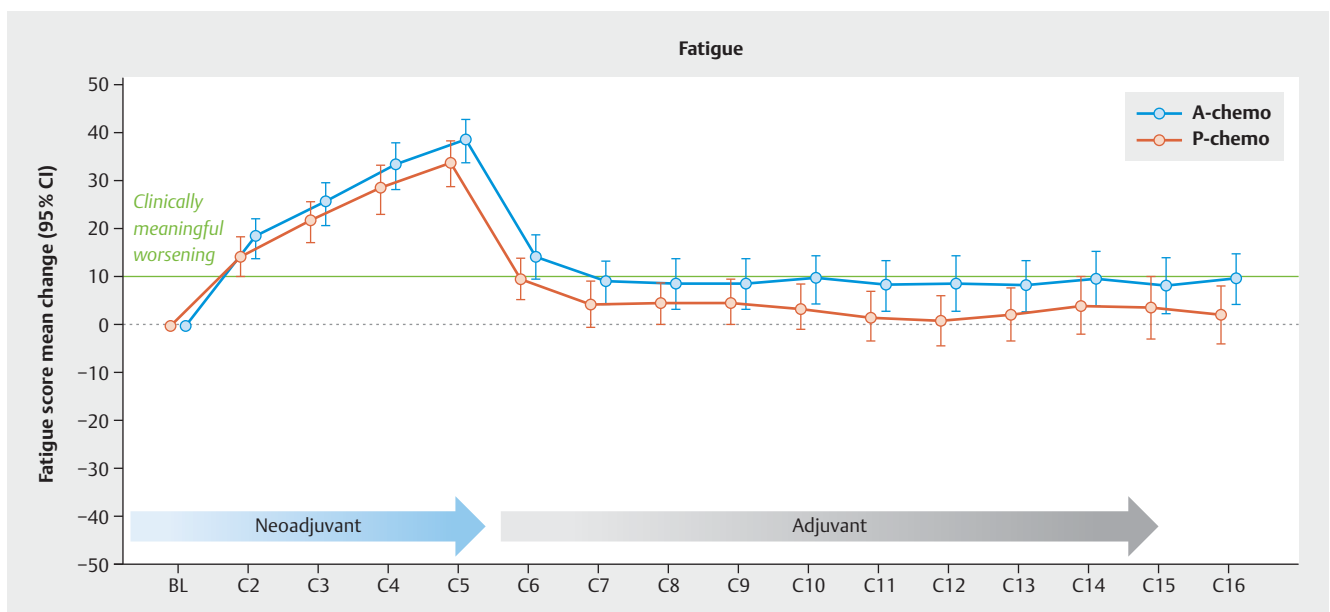
▶ **Fig. 4** Change in fatigue subscore (EORTC-QLQC30) [67].

Post-neoadjuvant Therapy

Prognostic models for patients after neoadjuvant chemotherapy

Pathologic complete response is an excellent predictor of prognosis post neoadjuvant chemotherapy, especially in patients with TNBC or HER2+ breast cancer [53–57]. However, for patients without pCR and even for a few patients with pCR, there could

be significant differences in prognosis. A number of papers have addressed this issue. The simplest approach is to follow the AJCC (American Joint Committee on Cancer) staging criteria, which can be used to classify patients into different prognostic groups after neoadjuvant chemotherapy [68].

These predictions can be improved by two additional models:

The CPS-EG score was developed precisely for this purpose [69, 70] and was also used in the PENELOPE-B trial as a predictive parameter for prognosis [71]. Later, the CPS-EG score was refined in-

to the Neo-Bioscore [72]. CPS-EG and Neo-Bioscore assign certain tumour characteristics before and after chemotherapy to arbitrary points, which are summed up to a total (score). These different scores may result in better prognostic prediction than the AJCC criteria alone [69–72]. The continuously calculated residual cancer burden (RCB) represents another tool for predicting patient prognosis following neoadjuvant chemotherapy [73]. Residual tumour diameter, percentage of residual cancer cells, percentage of in situ tumour parts, number of affected lymph nodes, and the largest diameter of an affected lymph node together are all entered into a regression model to calculate the RCB, which is then categorised into 4 RCB classes: RCB-0 (corresponding to ypT0 ypN0), RCB-I: (minimal residual tumour, corresponding to cases below the 40th percentile of the regression model), RCB-II (moderate residual tumour, corresponding to cases between the 40th to 87th percentiles of the regression model) and RCB-III (extensive residual tumour, corresponding to cases above the 87th percentile of the regression model) [73].

Another classification used in Germany is the regression grade according to Sinn [74, 75], where the categories of complete remission and invasive complete remission are combined with histopathologic criteria to classify the regression even further.

▶ Table 3 is a summary of the different classification systems.

Recently, a large trial comparing AJCC, RCB and the Neo-Bioscore was published [76]. This study enrolled 5328 patients undergoing neoadjuvant treatment by an international consortium. It was possible to apply the various classifications for residual cancer to 3730 of these patients. Both the Neo-Bioscore and the RCB classification categorised patients into prognostic groups that were better predictors of prognosis than AJCC staging alone [76]. Since the Neo-Bioscore also takes into account criteria prior to chemotherapy, it is possible to test whether this score has a prognostic potential within the subgroup of patients with pCR. In the analysis presented, this aspect could not be confirmed [76]. For the question in which AJCC stages the two scores can help to better predict prognosis, it was shown that the RCB score had its strength in patients with stage II TNBC and in HR+/HER2− patients with stage I breast cancer. The Neo-Bioscore, on the other hand, had additional prognostic value primarily in patients with stage I and III TNBC, in HR+/HER2− breast cancer and in stages II/III [76]. These analyses revealed that additional criteria can classify the prognosis following pCR much differently. Future studies should take this into account. Also, the integration of molecular markers such as the presence and amount of circulating tumour DNA [77] could provide additional information on how patients could be further treated in the absence of pCR post neoadjuvant chemotherapy.

Palbociclib in patients without pCR after neoadjuvant chemotherapy and high risk of relapse

The PENELOPE-B trial, a collaboration of the GBG (German Breast Group), the AGO-B (Arbeitsgemeinschaft Gynäkologische Onkologie-Brust), the NSABP (National Surgical Adjuvant Breast and Bowel Project) and the BIG (Breast International Group), studied whether adding palbociclib to standard anti-hormone therapy improves invasive relapse-free survival in patients with HR+/HER2− tumour without pCR [71]. This required a CPS-EG status of either ≥ 3 or 2

▶ Table 3 Different assessment methodologies of residual tumour burden regarding prognosis after neoadjuvant chemotherapy.

Characteristic	Assessment methodology		
	AJCC stage post chemotherapy	Residual Cancer Burden	Neo-Bioscore (formerly CPS-EG)
Tumour size prior to nCTX			+
Nodal status prior to nCTX			+
Molecular subtype prior to nCTX			+
Tumour grade prior to nCTX			+
Tumour size post nCTX	+	+	+
Tumour cellularity post nCTX		+	
No. of affected LN post nCTX	+	+	+
Size largest LN post nCTX		+	

AJCC: American Joint Committee on Cancer; nCTX: neoadjuvant chemotherapy

with positive lymph node status at the time of surgery. Patients were treated for 13 cycles (12 months) either by palbociclib in combination with endocrine therapy or by endocrine therapy alone and placebo. In the palbociclib arm, 80.5% of patients completed the 13 cycles of therapy, compared to 84.5% in the placebo arm. Thus, patient compliance under trial conditions was very good. With a mean age of 49 years, the patients were rather young and most of them had a CPS-EG score of ≥ 3 (59.4%). The primary endpoint of the trial was not met. With a median follow-up of 42.8 months, the hazard ratio was 0.93 (95% CI: 0.74–1.17; p = 0.525) in favour of the palbociclib arm. The interim analysis for overall survival also revealed no significant difference for the combination with palbociclib (HR = 0.87; 95% CI: 0.61–1.22; p = 0.420).

Possible reasons for not meeting the primary endpoint may be whether the treatment was too short, whether palbociclib differs significantly from abemaciclib, even after the negative PALLAS trial, and whether risk group selection differed too much. The PENELOPE-B trial is the trial with the longest follow-up, so it remains to be seen whether in trials like the MonarchE trial with its longer follow-up the benefit in favour of the CDK4/6 inhibitor will persist. Since the PALLAS and MonarchE trials treated several thousand patients who had received neoadjuvant chemotherapy, we expect important insight from the pCR, non-pCR and high versus low Ki-67 subgroups and the study of intrinsic subtypes in the residual invasive tumour component.

Neratinib following (neo-)adjuvant therapy of HER2-positive breast cancer

Neratinib, an oral tyrosine kinase inhibitor, binds to the intracellular domain of the EGF (epidermal growth factor) receptors HER1, HER2 and HER4. In the ExteNET trial, 2840 patients with HER2+ breast cancer following (neo-)adjuvant treatment with trastuzumab were treated for one year in the experimental arm with neratinib (240 mg/day) or in the other arm with placebo. The iDFS (invasive disease free survival) was significantly improved by this extended HER2-targeted treatment [78,79]. Since neratinib proved to be particularly effective in hormone receptor positive (HR+) cancers and when therapy was initiated within one year following trastuzumab (HR+ population/treatment initiated ≤ 1 year), approval in the US and Europe was granted with the corresponding restrictions. Further subgroup analyses after 8 years of follow-up were presented at the SABCS in December 2020 and recently published [80]. In the HR+/therapy start ≤ 1 year population, the 5-year iDFS rate was 90.8 vs. 85.7% in the neratinib arm (delta 5.1%, HR = 0.58; 95% CI: 0.41–0.82). In this subgroup, the estimated 8-year survival was also slightly more favourable with neratinib (91.5%) than in the control arm (89.4%). In the exploratory analysis of cases with residual tumour after neoadjuvant therapy (non-pCR), iDFS at 5 years with neratinib was 85.0% versus 77.6%. Moreover, fewer brain metastases were observed in the neratinib group. The reported data suggest a consistent effect of neratinib even after a longer follow-up of 8 years. Since the ExteNET trial was conducted before the HER2 blockade with trastuzumab and pertuzumab or T-DM1 (trastuzumab emtansine) was approved, extrapolation of this data to current practice is limited. After completion of their trastuzumab therapy, affected patients should be informed about the option of neratinib treatment, especially if there is an increased risk of recurrence (e.g. non-pCR), and, if necessary, instructed in the prevention and management of frequent diarrhoea.

Adjuvant Treatment of Breast Cancer Patients

CDK4/6 inhibitors in adjuvant therapy

In adjuvant therapy, several trials have studied the addition of a CDK4/6 inhibitor to endocrine treatment. The adjuvant trial with abemaciclib (MonarchE) has already been reported after an interim analysis [81]. Now the final analysis after 390 events in terms of invasive relapse-free survival has been presented [82]. This had a longer median follow-up time of 19.1 months than the interim analysis (15.5 months) and 67 additional events. A total of 5637 patients were randomised into two arms, either to endocrine treatment and placebo or to endocrine treatment and abemaciclib for 2 years. Various criteria for a high-risk population with an increased risk of recurrence had to be fulfilled [81]. At the time of analysis, more than 1400 patients had completed treatment, while almost 3300 patients were still on it [82]. The hazard ratio (HR = 0.713; 95% CI: 0.583–0.871) resembled that of the interim analysis (HR = 0.747; 95% CI: 0.598–0.932) [82]. In addition to this principal analysis, data was also presented relating to the subgroup of patients with Ki-67 ≥ 20% and other clinically unfavourable prognostic factors [83]. In this group with a very high risk of relapse, the hazard ratio was 0.643 (95% CI: 0.475–0.872), with a similar effect in the group with a high clinical risk of relapse and Ki-67 below 20% (HR = 0.685; 95% CI: 0.462–1.017) [83].

## Adjuvant chemotherapy in patients with hormone receptor-positive tumours

The TailorX trial established a data set for patients with early, node-negative, HR+ and HER2− breast cancer in which the subgroup of patients with excellent prognosis as determined by OncotypeDX demonstrated a benefit from additive adjuvant chemotherapy compared to endocrine therapy alone. In this trial, postmenopausal patients with a recurrence score of 11–25 were shown not to benefit from chemo- and endocrine therapy compared to endocrine therapy alone [84]. Initially, the clinical criterion tumour size and the pathohistologic criteria grading and Ki 67 were not evaluated in this analysis.

The RxPONDER trial (SWOG1007) recently presented was a similar trial, but with a node-positive (1–3 positive lymph nodes) population [85]. Similar to the TailorX trial, patients with early HR+/HER2− breast cancer with a recurrence score of ≤ 25 were randomised into a chemo-endocrine arm and an arm in which only standard anti-hormone therapy was administered. Patients with a recurrence score above 25 received chemotherapy followed by anti-hormone therapy. One of the most important issues in recent years has been whether the Recurrence Score would have an independent predictive effect in predicting the benefit of chemotherapy versus endocrine therapy alone. Therefore, the primary endpoint of the trial was the correlation between the continuous recurrence score and the randomisation arm. It was tested whether the difference between the randomisation arms would increase the higher the recurrence score was. If this primary analysis was negative, another primary analysis would study whether the recurrence score and the randomisation arm were independent prognostic factors in patients with a recurrence score of 0–25. This design is important when interpreting the trial.

The RxPONDER trial was evaluated with 5083 randomised patients and 410 events. Most patients were postmenopausal (66.8%), had one positive lymph node (65.5%) and a recurrence score of 14–25 (57.2%).

The primary analysis was negative (HR for the interaction variable: 1.02 [95% CI: 0.98–1.06; p = 0.30]) Thus, it can be concluded that in the RxPONDER trial, the recurrence score had no predictive value for the efficacy of chemotherapy followed by endocrine therapy compared to endocrine therapy alone. When analysing whether the respective randomisation arm and the recurrence score would predict patient prognosis, it was shown that both chemotherapy (compared to endocrine therapy) and the recurrence score had an independent prognostic effect. Chemotherapy resulted in a risk reduction for invasive relapse-free survival with a hazard ratio of 0.81 (95% CI: 0.67–0.96) and the recurrence score showed a hazard ratio of 1.06 (95% CI: 1.07–1.07) per incremental unit. In a further analysis, the benefit for the chemotherapy arm could be attributed almost entirely to the group of premenopausal patients. In this group, the hazard ratio favouring chemotherapy was 0.54 (95% CI: 0.38–0.76, p = 0.0004) and in the postmenopausal group 0.97 (95% CI: 0.78–1.22; p = 0.82).
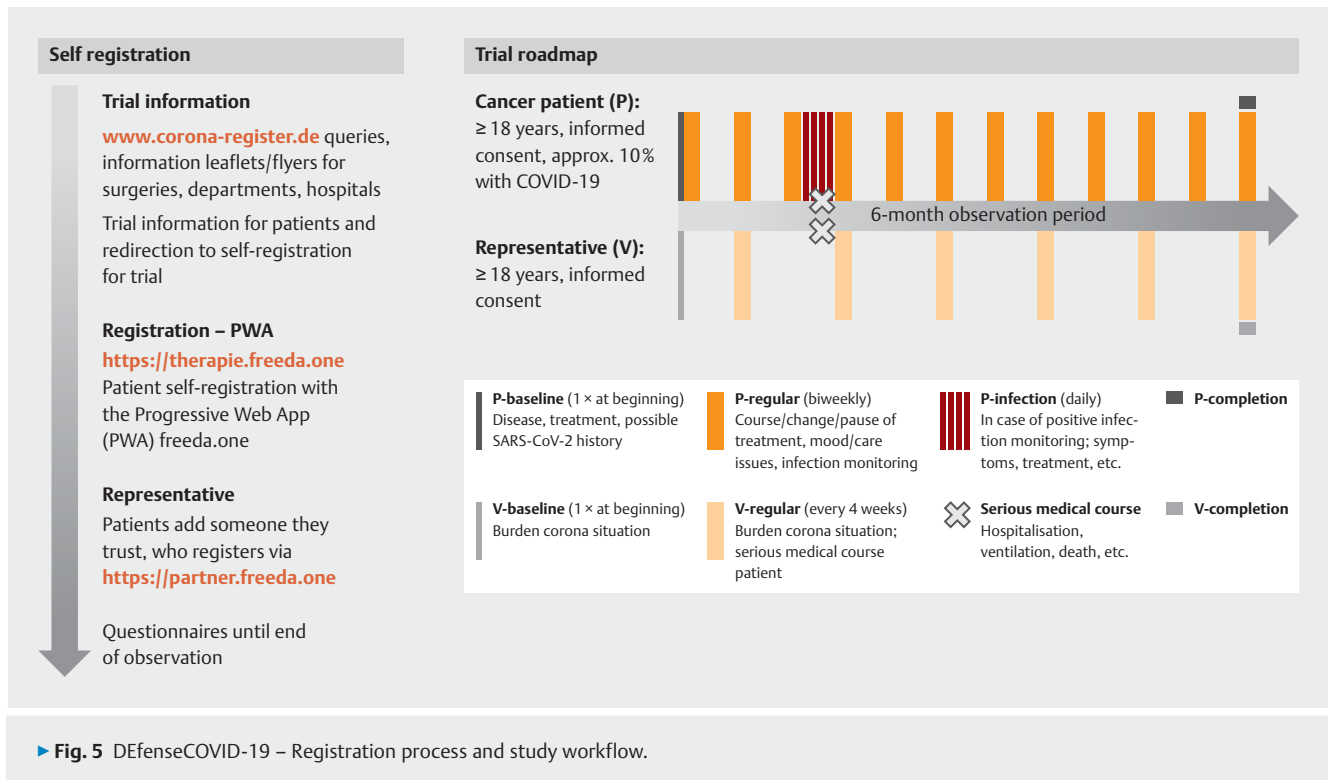
▶ **Fig. 5** DEfenseCOVID-19 – Registration process and study workflow.

In the premenopausal group, the difference also translated into better overall survival under chemotherapy with a hazard ratio of 0.47 (95% CI: 0.24–0.94; p = 0.032).

It is not known whether the effect of chemotherapy is due to the cytotoxicity or to an anti-hormonal effect by reducing ovarian function. It is also questionable whether a multigene assay is necessary at all in nodal-positive, premenopausal patients in order to make a decision for or against chemotherapy, since even the patients with only one affected lymph node and a very low score of 0–13 still benefited significantly from chemotherapy by 5% in absolute terms. A similar issue arose in postmenopausal patients, as the groups with a Recurrence Score of 0–13 and of 14–25 did not differ. Unfortunately, the study design specified chemotherapy for all patients with a recurrence score above 25, but it is certainly questionable whether a cut-off of 25 here identifies the group of HR+/HER2− high-risk patients who will benefit from chemotherapy. Also missing from this evaluation was information on tumour size, grading and Ki-67.

Breast Cancer During the COVID-19 Pandemic

In the COVID-19 pandemic triggered by the Severe Acute-Respiratory Syndrome Coronavirus type-2 (SARS-CoV-2), cancer patients constitute a special risk group, with the pandemic having implications in all areas of care and treatment of, e.g., breast cancer. Between March and April 2020, 23.8% fewer breast cancer cases were treated in German hospitals compared to the same period the previous year. It is possible that the pandemic has resulted in reduced oncological care, because cancer surgery had to be postponed or even cancelled altogether [86]. The professional societies DGHO

(German Society of Haematology and Medical Oncology), ESMO, ASCO, and others have developed guidelines and recommendations for the management and prioritisation of treatment interventions in breast cancer during the COVID pandemic [87 – 91].

According to the known current evidence, mortality rates for cancer patients with concomitant COVID-19 are significantly higher than in the general COVID-19 population, and are associated with increased age, male gender and prior conditions [92, 93]. The mortality rates published so far vary widely [94 – 96]. Currently, mortality rates of cancer patients with COVID-19 are much higher at 25–30% [92,93]. A meta-analysis of cohort studies of mortality in patients hospitalised for cancer and COVID-19 found a pooled 30-day mortality rate of 30% (95% CI: 25–35%), with a rate of 26% (95% CI: 22–31%) for the subgroup with solid tumours [93]. However, it should be noted that meta-analysis included mostly inpatient cases and that the cohorts came from different health care systems. For studies with a higher mean age, it was shown that there is a correlation between higher mortality rate and higher percentage of patients undergoing concurrent cancer treatment. But this could not be demonstrated for studies with a lower mean age [93]. In general, initial analyses of the COVID-19 and Cancer Consortium (CCC-19) registry demonstrated that cancer patients had an increased standardised incidence ratio (SIR) of mortality with chemotherapy (1.31 [1.00–1.69]) and a decreased SIR with endocrine therapy (0.62 [0.42–0.88]) < 2 weeks prior to COVID-19 onset. Targeted therapy 2–3 months prior to COVID-19 onset has also been reported to date to have a higher SIR (2.15 [1.14–3.68]). Decisive data on breast cancer treatment is still pending. Furthermore, little is known about subgroups of cancer patients and their potential impact on mortality associated

with COVID-19. It can also be assumed that patients with a cancer long in the past have risk profiles different from those patients who contracted SARS-CoV-2 infection while undergoing cancer treatment. Some cancer therapies, such as checkpoint inhibitors, markedly modulate the immune system; for this reason, it is necessary to closely monitor the course of SARS-CoV-2 infections in these patients [97]. Further insight into possible correlations between SARS-CoV-2 infection and cancer treatment is expected from the DEfenseCOVID-19 trial (www.corona-register.de).

The nationwide German self-registration trial DEfenseCOVID-19 aims to show whether certain cancer treatments pose a risk during SARS-CoV-2 infection. For this purpose, cancer patients who optionally have or have had a SARS-CoV-2 infection are enrolled in the trial and monitored for 6 months. Among other things, patients will answer specific questions about their cancer, course of treatment, prior conditions and possible SARS-CoV-2 infection (▶ Fig. 5). Serious medical events (including death) are also documented by a trusted third party designated by the cancer patient. In addition, data on the mental state of cancer patients during the pandemic is collected and published at regular intervals on the website www.corona-thermometer.de to provide updates on the ongoing trial. The strength of the trial is being able to include all COVID-19 cases in the trial, not just the serious courses. The data collected will be analysed in terms of morbidity and mortality following SARS-CoV-2 infection. By recognising particular risks, treatment decisions could be reconsidered and a risk-benefit analysis performed, taking into account any existing risk of infection. Recruitment started in Q4/2020 and is expected to continue until Q4/2021. Cancer patients are informed about the trial via the website www.corona-register.de and will continue to be informed about the trial and data protection aspects during the registration process before consenting to the trial.

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Conflict of Interest

E. S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Tesaro, Aurikamed GmbH, MCI Deutschland GmbH, bsh medical communications GmbH, Onkowissen TV.
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T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.
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