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Update Breast Cancer 2024 Part 2 – Patients with Early Stage Breast Cancer

Update Mammakarzinom 2024 Teil 2 – Patientinnen mit Frühstadien des Mammakarzinoms

OPEN ACCESS

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ABSTRACT

This review summarizes the latest developments for the treatment of patients with early-stage breast cancer. Most of the clinically relevant changes were the result of using immune checkpoint inhibitors to treat patients with triple-negative breast cancer (TNBC) and CDK4/6 inhibitors to treat patients with hormone receptor-positive, HER2-negative (HRpos/HER2neg) tumors and a high risk of recurrence. Recent studies are presenting more and more data with long follow-up times and integrating translational analyses to evaluate new biomarkers such as circulating tumor DNA (ctDNA). This review article summarizes the latest developments published in recent months and puts the findings in context.

ZUSAMMENFASSUNG

Diese Übersichtsarbeit fasst die aktuellen Entwicklungen zur Behandlung von Patientinnen mit Frühstadien des Mammakarzinoms zusammen. Die meisten klinisch relevanten Veränderungen sind durch die Einführung der Immuncheckpoint-Inhibitoren bei Patientinnen mit triple-negativem Brusktrebs (TNBC) und der CDK4/6-Inhibitoren bei Patientinnen mit Hormonrezeptor-positiven, HER2-negativen (HRpos/HER2neg) Tumoren und hohem Rückfallrisiko vollzogen worden. Hier entstehen zunehmend Daten mit einer längeren Nachbeobachtungszeit und Integration von translationalen Analysen, die neue Biomarker wie zirkulierende Tumor-DNA (ctDNA) bewerten. In dieser Übersichtsarbeit werden die neuesten Entwicklungen der letzten Monate zusammengefasst und in den jeweiligen Kontext eingeordnet.

Introduction

This review article summarizes the latest publications and conference presentations on the treatment of patients with early-stage breast cancer.

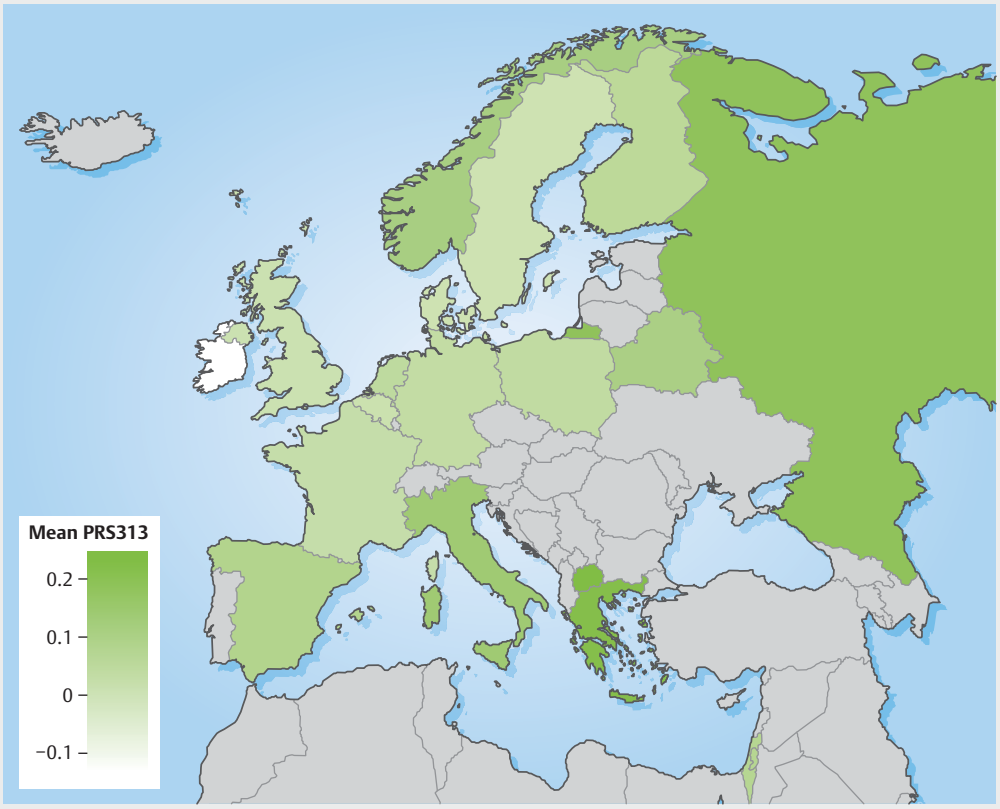
As the knowledge about breast cancer risks has increased, early screening and primary prevention has become increasingly individualized. New findings from preventive studies are now available. Despite numerous studies on immune therapy for patients with early-stage triple-negative breast cancer (TNBC), there is no recognizable pattern which would help to identify which patient populations would particularly benefit from or be badly affected by immune therapy. New findings are now also available for adjuvant therapy with avelumab. The use of circulating tumor DNA (ctDNA) is becoming increasingly established as a molecular marker based on multiple diagnostic studies. The findings of prospective studies such as the monarchE and PENELOPE-B studies are now feeding into prospective randomized study projects such as the SURVIVE trial.

Prevention and Hereditary Breast Cancer

Although individual studies on the prevention of breast cancer have increased our understanding of risk factors and pathogenesis, translating these insights into practice is still a slow process. This is due, on the one hand, to the need for large case numbers when carrying out randomized studies and, on the other hand, to a lack of individualized, personally relevant information about the risk of breast cancer. But some new findings should nevertheless be mentioned.

Distribution of the genetic risk of breast cancer in Europe and impact on prognosis

It is well known that mutations of certain genes represent a moderate or high life-time risk and can affect prognosis. A number of studies of patients with germline *BRCA1* or *BRCA2* mutation have investigated the prognosis of patients with early-stage and advanced breast cancer. Some publications found that prognosis for these mutations was poor [1, 2], other publications suggested



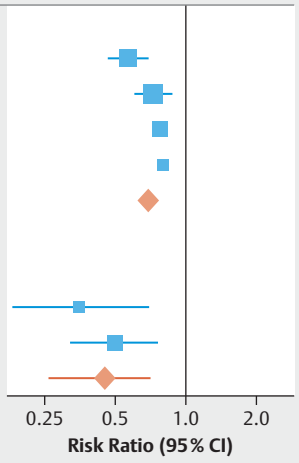
▶ **Fig. 1** Map showing the distribution of polygenic risk scores (PRS). Darker areas indicate a higher genetic risk of breast cancer in the local population (image based on data from [32]).

a slightly better prognosis [3 – 5], and others found that the mutations had no impact on prognosis [3, 6 – 11]. There are some indications for *PALB2* that mutations of this gene are associated with a poorer prognosis [12]. There is less data available on low penetrance genes, even though, taken together, they make up the greater part of familial breast cancer risks [13 – 20] and have a significant effect on the histopathological properties of the resulting breast cancers [21 – 29]. Many known low-penetrance genetic loci have been summarized into a polygenic risk score (PRS) which can be used in clinical practice. The most comprehensive score to date integrated 313 gene loci [30] und can differentiate between women with a lifetime risk of more than 30 percent (highest percentile) and women with a lifetime risk of less than 3 percent (lowest percentile) [31]. There are significant differences in the geographic distribution of risk scores (▶ **Fig. 1**), even though this does not appear to have a significant impact on the incidence of breast cancer in different regions [32]. In view of the effect of risk variants on the histopathology of breast cancer it can be assumed that they also affect prognosis. This was recently investigated in a large patient population [33]. No independent effect on prognosis was found in patients with disease. Notwithstanding the above, breast cancer mortality rates were higher in groups of healthy women with a high PRS, simply because of the higher incidence in this group [33].

Tamoxifen doses of 5 mg per day already effective in the TAM-01 trial

Some preventive studies have shown that tamoxifen can reduce the risk of breast cancer compared to placebo. A meta-analysis by the U. S. Preventive Task Force Services Group found a relative risk of 0.69 (95 % confidence interval [CI]: 0.59–0.84) [34] (▶ **Fig. 2**). From previous studies on the effectiveness of tamoxifen to treat breast cancer it has long been suspected that a dose of 20 mg may not be necessary to achieve an anti-tumor effect. One review article [35] concluded that 5 mg tamoxifen could already result in anti-tumor activity which could be sufficient to treat breast cancer. However, there are currently no randomized studies in the adjuvant setting which support this approach with a better side-effects profile [35]. When considering strategies for the prevention of breast cancer, it is important to mention the TAM-01 trial. The results of the trial were first published in 2019. In this study, tamoxifen at a dose of 5 mg/day was administered over 3 years and compared with placebo in 500 women with high-risk lesions including lobular and ductal carcinoma in situ. A recent 10-year follow-up study showed a sustained benefit for the 5 mg tamoxifen group compared to the placebo group: a 42 % reduction in the incidence of breast cancer and 64 % decrease in contralateral lesions, especially ductal carcinoma in situ [36]. As

Trials	Participants: Treatment	Participants: Placebo	Duration (years): Intended treatment	Duration (years): Total follow-up	Invasive breast cancer: Treatment N	Invasive breast cancer: Placebo N	Risk ratio (95% CI)
Tamoxifen							
NSABP-1	6681	6707	5	6.1	145	250	0.57 (0.46–0.70)
IBIS-I	3579	3575	5	16.0	214	289	0.73 (0.61–0.87)
Marsden	1238	1233	5	13.2	82	104	0.78 (0.58–1.04)
Italian	2700	2708	4	11.2	53	66	0.80 (0.56–1.15)
Combined (test of heterogeneity: Q = 4.9, I^2 = 38.7%; df = 3, p = 0.180)							0.69 (0.59–0.84)
Aromatase inhibitor							
MAP.3	2285	2275	5	2.9	11	32	0.35 (0.18–0.70)
IBIS-II	1920	1944	5	5	32	64	0.50 (0.32–0.76)
Combined (test of heterogeneity: Q = 0.8, I^2 = 0.0%; df = 1, p = 0.385)							0.45 (0.26–0.70)



▶ **Fig. 2** Breast cancer prevention studies investigating full-dose tamoxifen and aromatase inhibitors (image based on data from [34]). IBIS-I = International Breast Cancer Intervention Study [81]; MAP.3 = Mammary Prevention.3 trial [82]; NSABP-1 = National Surgical Adjuvant Breast and Bowel Project P-1 study [83]; Marsden = Royal Marsden Breast Cancer Prevention Trial [84]; Italian = Italian Breast Cancer Prevention Trial [85].

tamoxifen is not available in 5 mg doses in Germany, 10 mg can be administered every two days.

The 5 mg tamoxifen group experienced a slight increase in hot flashes but there was no significant increase in other typical side effects. When the study reviewed the number of serious undesirable events in both groups, there was one case with stage I endometrial carcinoma (0.4% of patients) and 20 cases with uterine polyps (5%) in the 5 mg tamoxifen group compared to 13 cases with uterine polyps in the placebo group. There were no significant differences with regards to thrombosis, cataracts, bone fractures, or other serious events.

One question currently being discussed is whether the 5 mg dose is adequate for all patients. It may not be sufficient, especially for so-called poor metabolizers who been characterized in various adjuvant studies [13, 37–39]. Tamoxifen has been mentioned in some national and international guidelines as a possible option for chemoprevention [40] and a few countries already offer chemoprevention as a standard option [41].

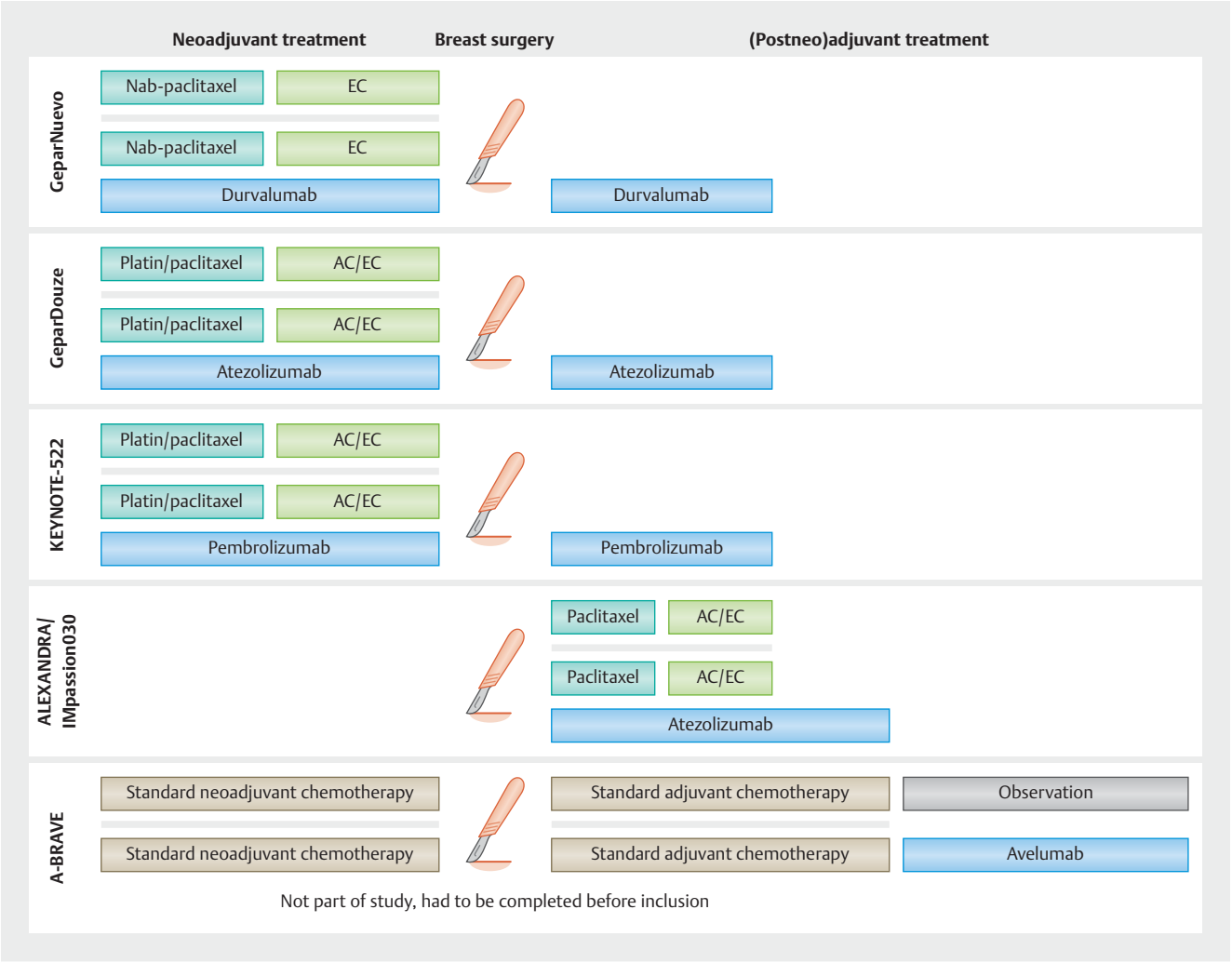
Prediction of individual chemoprevention success

This is the context in which studies to identify predictors for the effectiveness of chemoprevention are being carried out. In the IBIS-II study, a recent evaluation of the ratio between estradiol concentrations and sexual hormone-binding globulin (SHBG) concentrations was recently carried out, based on a preplanned analysis of data from the International Breast Cancer Intervention Study II (IBIS-II) [42]. IBIS-II is a randomized phase 3 trial which examines the effectiveness of anastrozole compared to placebo to prevent breast cancer developing in high-risk postmenopausal women. Overall, the study showed a decrease in the development of invasive estrogen receptor-positive breast cancer in the anastrozole group compared to the placebo group (hazard ratio = 0.46 [95% CI: 0.33–0.65]). The current analysis involved 628 participants: 212 (72 cases, 140 controls) from the anastrozole group and 416 (142 cases, 274 controls) from the placebo group. Analysis found an increase in the risk of breast cancer was associated with an increase in the ratio between estradiol and SHBG in the placebo group but not in the anastrozole group. This shows that the greatest benefit of anastrozole was in patients with higher estradiol-SHBG ratios, although a relative benefit from anastrozole was found in quartile 2 (0.55 [95% CI: 0.13–0.78]), quartile 3 (0.54 [95% CI: 0.22–0.74]) and quartile 4 (0.56 [95% CI: 0.23–0.76]) of the estradiol-SHBG ratios but not in quartile 1 (0.18 [95% CI: −0.60–0.59]). These data indicate that one quarter of patients who were identified as high-risk patients based on a conventional clinical risk prediction model may not benefit from preventive treatment with aromatase inhibitors and that therefore this therapy must be offered to fewer women, an approach which should be welcomed as it reflects the concept of *primum nil nocere*. Future studies will be needed to show how these findings can be translated into medical practice.

Immuno-oncological Treatment in Patients with Early-stage Breast Cancer

Immune checkpoint inhibitors in patients with TNBC

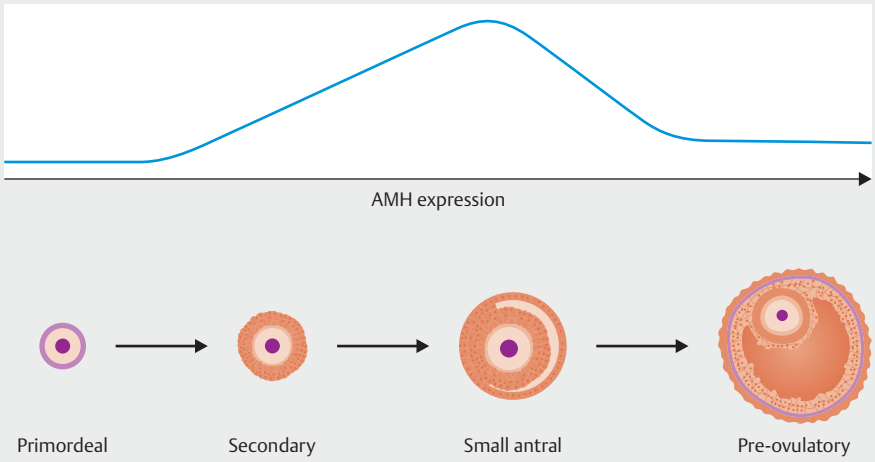
With the investigation of pembrolizumab in the KEYNOTE-522 trial, the first immune checkpoint inhibitor was introduced as a standard treatment option for patients with early-stage TNBC [43–46]. The neoadjuvant and adjuvant addition of pembrolizumab



▶ **Fig. 3** Overview of current studies investigating immune checkpoint inhibitors in patients with early-stage triple negative breast cancer. Recruitment into the studies is largely complete. EC: epirubicin + cyclophosphamide; AC: anthracyclines.

to carboplatin-based standard chemotherapy was able to improve the eventfree survival of patients with and without pathological complete remission (pCR). A recent study has now also demonstrated that the addition of pembrolizumab resulted in an overall survival benefit [47]. Similar data have also been reported for the GeparNuevo study, which added durvalumab in the neoadjuvant setting combined with chemotherapy but not as maintenance therapy after surgery as was done in the KEYNOTE-522 study. An improvement was found for invasive recurrence-free survival with a hazard ratio of 0.48 (95 % CI: 0.24–0.97) and for overall survival with a hazard ratio of 0.24 (95 % CI: 0,08–0.72) [48]. This shows that there is more and more evidence that immune checkpoint inhibitor therapy can improve the overall survival of patients with early-stage TNBC. Both studies (KEYNOTE-522 and GeparNuevo) used the immune checkpoint inhibitor at least in the neoadjuvant setting. The ALEXANDRA/IMpassion030 trial evaluated atezolizumab in the adjuvant setting in patients with stage II and III TNBC. After including almost 2200 randomized patients, the phase III trial was discontinued after it was found that atezolizumab was unlikely to improve invasive disease-free survival with a hazard ratio of 1.12 (95 % CI: 0.87–1.45), which crossed the prespecified futility boundary [49]. In view of these findings for atezolizumab, the data of the A-BRAVE trial, another immune checkpoint inhibitor study in the adjuvant setting, were awaited with interest [50].

The A-BRAVE trial included patients with TNBC who had concluded standard treatment consisting of chemotherapy and surgery. Some of the patients included in the study had also concluded neoadjuvant or adjuvant chemotherapy. A high risk of recurrence was required for both scenarios. This was defined as no pCR for the cases who received neoadjuvant therapy and as a large tumor and/or lymph node involvement for the patients who received adjuvant treatment [50]. Patients were randomized either to receive avelumab for one year or to observation. A total of 477 patients were randomized. The median follow-up time was 52.1 months. Disease-free survival (DFS) was higher with avelumab (hazard ratio = 0.81; 95 % CI: 0.61–1.09) but did not achieve statistical significance (p = 0.172). However, a statistically significant difference (p = 0.035) was observed for overall survival (sec-



▶ **Fig. 4** Fluctuations of anti-Müllerian hormone (AMH) levels during the cycle. (Source: Moolhuijsen LME, Visser JA. Anti-Müllerian Hormone and Ovarian Reserve: Update on Assessing Ovarian Function. J Clin Endocrinol Metab 2020; 105 [11]: 3361–3373. DOI: 10.1210/clinem/dgaa513. PMID: 32770239; PMCID: PMC7486884. © Endocrine Society 2020. Licensed under a Creative Commons Attribution 4.0 International License [https://creativecommons.org/licenses/by/4.0/]. Adapted.)

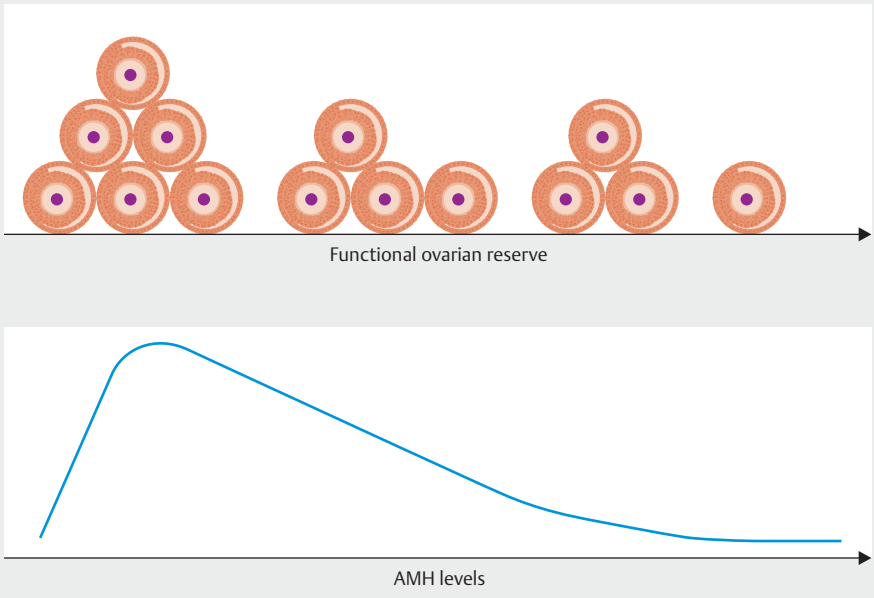
ondary study endpoint) with a hazard ratio of 0.66 (95% CI: 0.45–0.97). The side-effects profile was similar to that of other immune checkpoint inhibitor trials [50].

Following the negative results of the IMpassion030 trial, it was conjectured that the primary tumor may need to be present for immune therapy to achieve sufficient T-cell activation. The A-BRAVE study has now provided results for a different checkpoint inhibitor which do not support this hypothesis. Although many different studies have recently been published, the diversity of the results means that it is still not possible to identify clear patterns showing which groups of patients will specifically benefit from checkpoint inhibitor therapy. For the time being, pembrolizumab remains the standard approach approved for neoadjuvant/adjuvant therapy in high-risk patients with TNBC. The results of the GeparDouze study, another large study of patients with early-stage TNBC, are not yet available. ▶ **Fig. 3** provides an overview of the study designs of studies carried out to date which are testing immune checkpoint inhibitor therapy in patients with early-stage TNBC.

Treatment of Patients with Early-stage HRpos/HER2neg Breast Cancer

Chemotherapy in premenopausal patients

When treating patients with hormone receptor-positive, HER2-negative (HRpos/HER2neg) breast cancer, great efforts were made in the last two decades to avoid potential overtreatment with regards to chemotherapy. Several studies with large numbers of patients have evaluated multigene tests for their ability to define prognostic groups for patients who do not require chemotherapy (MINDACT, TailorX, RxPONDER, ADAPT) [51–53]. While the study findings for postmenopausal patients uniformly show that chemotherapy does not need to be administered to patients with a low or moderate risk of recurrence, all studies showed that this was not the case for premenopausal patients and that chemotherapy had an additional favorable effect on prognosis, while the ADAPT study found that dynamic determination of Ki-67 expression was able to identify a subgroup in the group of premenopausal patients who had a favorable prognosis even without chemotherapy [54]. However, a number of additional analyses have postulated that the main effect of chemotherapy in premenopausal patients could be due to the damage to ovarian function [55]. A biomarker which could specifically identify patients who would additionally benefit or not benefit from chemotherapy would be useful. Anti-Müllerian hormone (AMH), which is produced by the granulosa cells of early developing follicles, could be such a biomarker. Serum AMH correlates strongly with the number of developing follicles and is therefore considered a biomarker of ovarian reserve over time (▶ **Figs. 4** and **5**) [56]. It has also been linked to the effect of chemotherapy on ovarian function and varies from patient to patient [57–59]. The RxPONDER trial looked at this biomarker in more detail by examining whether a group of clinically premenopausal women could be identified for whom chemotherapy was not necessary. 21% out of more than 1000 premenopausal patients in the RxPONDER trial had postmenopausal AMH levels. When tested for interactions, the biomarker AMH showed that it was able to differentiate between premenopausal women who would benefit from chemotherapy (high AMH) and those who would not benefit from chemotherapy (low AMH) and the differentiation was statistically significant [60]. The hazard ratio for patients with low AMH levels was 1.2 (95% CI: 0.60–2.43), while the hazard ratio showing a benefit for patients with high AMH levels was 0.48 (95% CI: 0.33–0.69) [60]. Future studies will be required to investigate and confirm how this biomarker can be reliably implemented in routine clinical practice. The data also do



▶ **Fig. 5** Changes in anti-Müllerian hormone (AMH) levels with increasing age and decreasing ovarian reserve. (Source: Moolhuijsen LME, Visser JA. Anti-Müllerian Hormone and Ovarian Reserve: Update on Assessing Ovarian Function. J Clin Endocrinol Metab 2020; 105 [11]: 3361–3373. DOI: 10.1210/clinem/dgaa513. PMID: 32770239; PMCID: PMC7486884. © Endocrine Society 2020. Licensed under a Creative Commons Attribution 4.0 International License [https://creativecommons.org/licenses/by/4.0/]. Adapted.)

not answer the question whether clearly premenopausal patients (clinically premenopausal with high AMH levels) with sufficient suppression of ovarian function (OFS) can forego chemotherapy. It will still be necessary to discuss the benefit of chemotherapy with this group of patients.

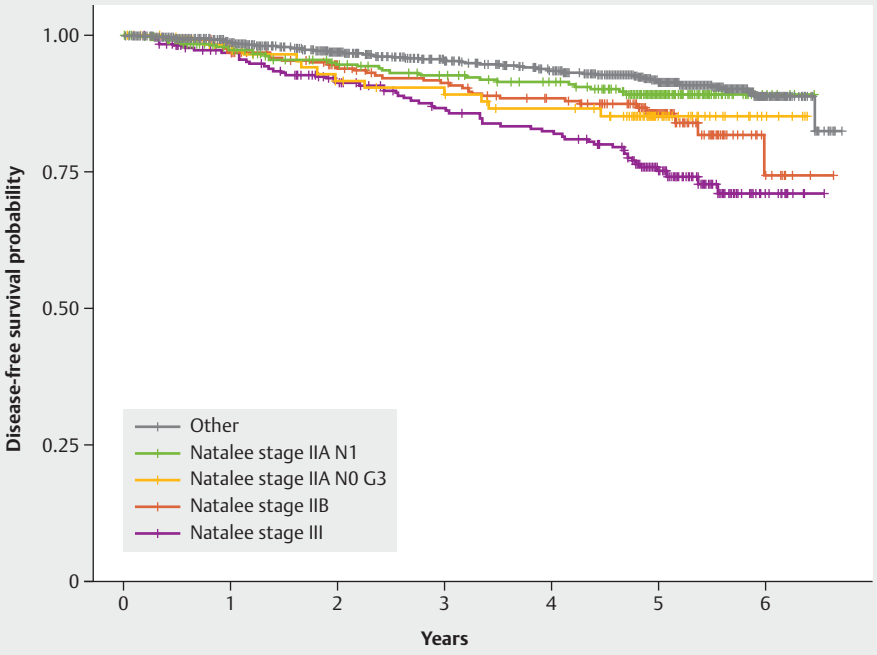
CDK4/6 inhibitors in the adjuvant setting – expansion to include node-negative patients

Abemaciclib has already been approved for the adjuvant treatment of patients with HRpos/HER2neg tumors and a higher risk of recurrence, based on the data of the monarchE trial [61–63]. Based on data from the NATALEE trial,ribociclib has now also been approved for adjuvant therapy [64]. The two studies differ in that the monarchE trial included patients with a significantly higher risk of recurrence while the NATALEE trial also included patients with a moderate risk of recurrence. Two studies from Germany estimated the percentage of patients with HRpos/HER2neg breast cancer who could be treated in accordance with the monarchE criteria as 13–18% and the percentage of patients, who could be treated in accordance with the NATALEE criteria as 32–43% [65, 66]. The prognostic effect of the inclusion and exclusion criteria on a postmenopausal HRpos/HER2neg population uniformly treated with upfront letrozole (PreFace study, [67]) is shown in ▶ **Fig. 6** and **7** [65]. The graphs show that node-positive groups can have a numerically better prognosis than, for example, patients who are node-negative but have a grade 3 tumor. This makes the recently published data focusing on this node-negative group of NATALEE patients especially interesting.

Patients who were node-negative needed additional poor prognostic criteria to be included in the NATALEE trial. The majority of the 613 node-negative patients in the NATALEE trial were patients with a tumor with a diameter of 2–5 cm (61%), a grade 3 tumor or Ki-67 ≥ 20% [68]. Inclusion based on a high genomic risk was rare [68]. The absolute difference with regards to invasive recurrence-free survival in the node-negative population after 3 years was 2.6% and the hazard ratio was 0.72 (95% CI: 0.41–1.27) [68]. The hazard ratio for the secondary endpoint "distant recurrence-free survival" (DRFS; for the current STEEP criteria see [69]) was 0.58 (95% CI: 0.29–1.17) [68]. Data with longer follow-up times should provide further information about the benefit of this treatment in this patient cohort with an intermediate risk of recurrence.

Circulating tumor DNA in the monarchE study

The monarchE study, a large, adjuvant therapy trial, was published some years ago, but more and more data on biomarkers and their clinical relevance are now becoming available. An analysis of ctDNA [70] in study participants was recently published. This biomarker was determined in 910 patients enrolled in the monarchE trial. This makes the monarchE trial the largest study investigating ctDNA in patients with HRpos/HER2neg breast cancer. An personalized assay was used to test for ctDNA in every patient, based on whole exome sequencing of the primary tumor. The aim was to confirm whether the individual tumor of a patient demonstrated an individual genomic pattern in blood [70]. ctDNA was detected in some patients over the course of the study, and the study population was divided into 4 groups accordingly:



Number at risk

1 959	1 778	1 608	1 513	1 453	895	97
296	262	239	225	213	124	7
95	86	75	72	65	32	6
262	235	207	194	181	106	11
261	235	205	184	174	103	15

▶ **Fig. 6** Prognosis of postmenopausal patients with hormone receptor-positive/HER2-negative breast cancer treated with upfront letrozole, stratified according to the inclusion criteria of the NATALEE trial. Data from the PreFace study. (Source: Fasching, Peter A. et al. Prognostic impact of selection criteria of current adjuvant endocrine therapy trials NATALEE and monarchE in postmenopausal HRpos/HER2neg breast cancer patients treated with upfront letrozole. Eur J Cancer 2024 Sep; 209: 114239. DOI: 10.1016/j.ejca.2024.114239. Epub 2024 Jul 21. © 2024 The Authors. Published by Elsevier Ltd. License: Creative Commons Attribution [CC BY 4.0] [https://creativecommons.org/licenses/by/4.0/]. Adapted.)

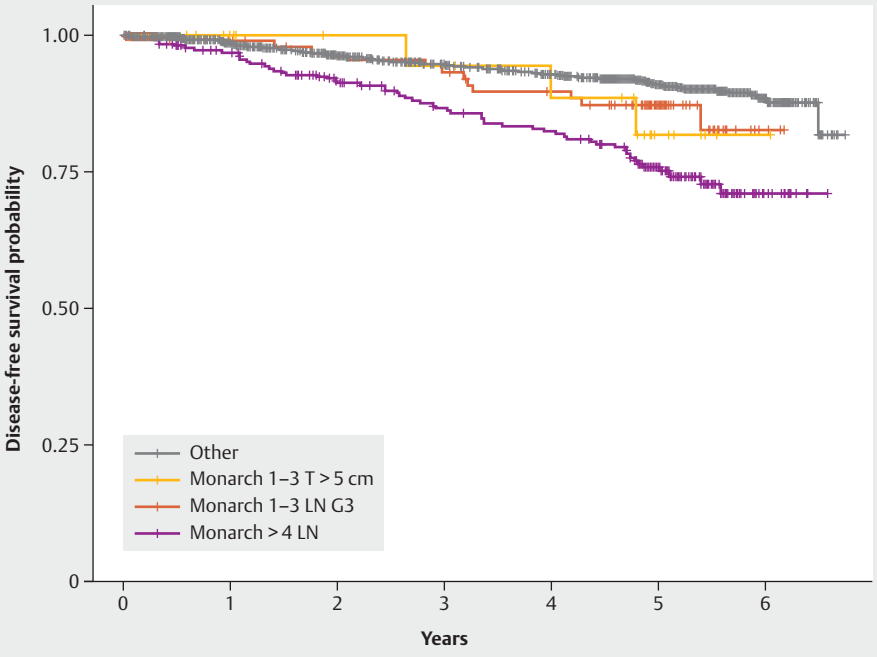
- negative at baseline and negative at follow-up (n = 749)
- negative at baseline and positive at follow-up (n = 82)
- positive at baseline and negative at follow-up (n = 24)
- positive at baseline and positive at follow-up (n = 34)

▶ **Table 1** shows the 4-year iDFS rates for the 4 groups. Evidence of individual ctDNA was an indication of metastasis and was adversely prognostic, even without clinical evidence of correlation. The time from ctDNA positivity to clinically evident metastasis was 7–15 months [70].

The figures are important because they are clinically relevant and should trigger a therapeutic response because of their effect size. Corresponding studies are already being carried out. The SURVIVE trial [71] investigated this approach in a randomized study. Patients were enrolled in the study if they had no metastasis and had concluded primary therapy, although patients receiving adjuvant non-chemotherapy could also be included in the study (for example, therapy with trastuzumab emtansine, pembrolizumab, abemaciclib, letrozole). HRpos/HER2neg patients could even be included up to 5 years after conclusion of primary therapy. However, these patients had to demonstrate a higher risk of recurrence (e.g., status post chemotherapy, tumor > 5 cm, lymph node involvement or grade 3 tumor). Intensified molecular screening for metastasis using individualized ctDNA and tumor marker testing was done in the intervention arm. Based on data from the monarchE trial, the assumption is that a positive ctDNA

▶ **Table 1** 4-year invasive disease-free survival (iDFS) rates of circulating tumor DNA (ctDNA) groups (from [70]). CI: confidence interval.

Group ctDNA at baseline	Group ctDNA at follow-up	N	4-year iDFS rate (95% CI)
Negative	Negative	749	87.5 (85.1–89.9)
Positive	Negative	24	58.3 (41.6–81.8)
Negative	**Positive**	82	11.0 (5.9–20.3)
Positive	**Positive**	34	0



Number at risk

2491	2254	2033	1912	1828	1114	117
26	21	18	17	15	6	1
97	91	83	80	74	41	3
261	235	205	184	174	103	15

▶ **Fig. 7** Prognosis of postmenopausal patients with hormone receptor-positive/HER2-negative breast cancer treated with upfront letrozole, stratified according to the inclusion criteria of the monarchE trial. Data from the PreFace study. (Source: Fasching, Peter A. et al. Prognostic impact of selection criteria of current adjuvant endocrine therapy trials NATALEE and monarchE in postmenopausal HRpos/HER2neg breast cancer patients treated with upfront letrozole. Eur J Cancer 2024 Sep; 209: 114239. DOI: 10.1016/j.ejca.2024.114239. Epub 2024 Jul 21. © 2024 The Authors. Published by Elsevier Ltd. License: Creative Commons Attribution [CC BY 4.0] [https://creativecommons.org/licenses/by/4.0/]. Adapted.)

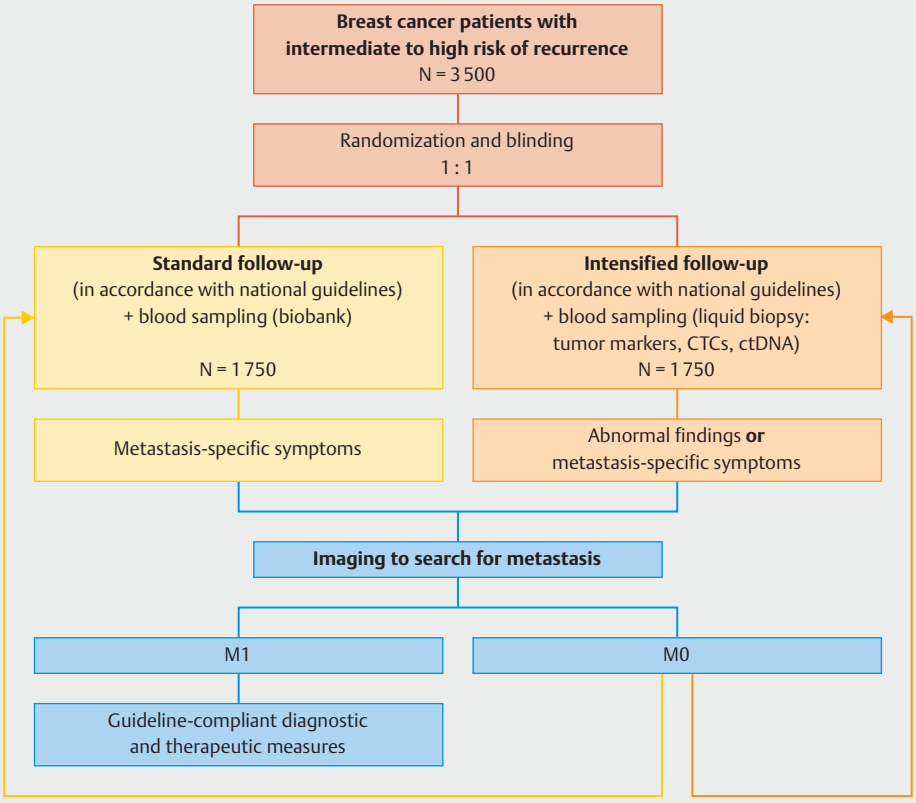
test will be followed by metastasis. The study is working on the hypothesis that after a positive ctDNA test, early administration of new drugs which have demonstrated an overall survival benefit in the metastatic setting (trastuzumab deruxtecan, sacituzumab govitecan, CDK4/6 inhibitors, capivasertib [72–80]) could improve overall prognosis. The study design is shown in ▶ **Fig. 8**.

The SURVIVE-HERoes study which is expected to start at the end of April 2025 is an example of how the setting can be used to investigate new therapeutic concepts (▶ **Fig. 9**). The SURVIVE-HERoes study includes patients from the SURVIVE trial with HER2 overexpression or HER2-low expression who tested positive for ctDNA in the SURVIVE study. These patients are then randomized to receive either treatment with trastuzumab deruxtecan or standard therapy.

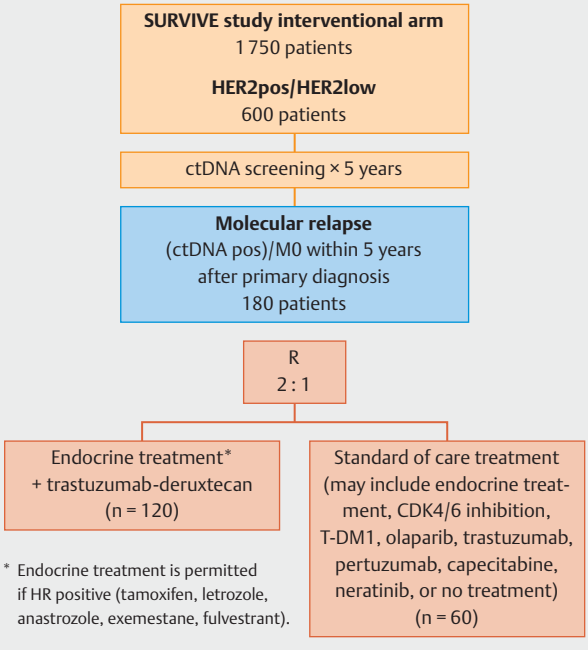
Outlook

The therapeutic landscape of patients with early-stage TNBC has changed significantly following the introduction of immune checkpoint inhibitors despite the related side effects. As the KEYNOTE-522 study has confirmed an overall survival benefit, the use of pembrolizumab will become more established in the therapeutic setting. Two CDK4/6 inhibitors have been approved for use in the adjuvant setting: abemaciclib and ribociclib. As 32–43% of HRpos/HER2neg patients could, in principle, be candidates for CDK4/6 inhibitor therapy with ribociclib, treatment centers and cancer specialists will be facing a challenge to provide these patients with the required medical care.

In addition to multigene tests, there is a growing body of data on ctDNA as a clear prognostic factor. New study concepts such as that of the SURVIVE trial will lead the way and show how ctDNA can be integrated into routine clinical practice.



▶ **Fig. 8** Study design of the SURVIVE study [71]. ctDNA: circulating tumor DNA; CTC: circulating tumor cells.



▶ **Fig. 9** Study design of the SURVIVE-HERoes study which is investigating selected patients from the SURVIVE study. ctDNA: circulating tumor DNA.

The results of studies which evaluated trastuzumab deruxtecan (Destiny-B05 trial) and sacituzumab govitecan (SASCIA trial) in the post-neoadjuvant setting or giredestrant (lidERA study) in the adjuvant setting will be published in the near future. Further studies are planned to evaluate new combinations of antibody-drug conjugates and immune therapeutic agents. These drugs, which have been successfully tested in the metastatic setting, are now moving into the neoadjuvant and adjuvant setting. The number of studies in these settings is expected to increase over the next few years.

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Conflict of Interest

B. A. received honoria and travel grants from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Genomic Health, Gilead, GSK, Lilly, Medtronic, MSD, Novartis, Onkowissen, Pfizer, Roche, Seagen, Stemline, TESARO.
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