

Update Breast Cancer 2023 Part 1 – Early Stage Breast Cancer

Update Mammakarzinom 2023 Teil 1 – Brustkrebs in frühen Krankheitsstadien



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ABSTRACT

With abemaciclib (monarchE study) and olaparib (Olympia study) gaining approval in the adjuvant treatment setting, a significant change in the standard of care for patients with early stage breast cancer has been established for some time

now. Accordingly, some diverse developments are slowly being transferred from the metastatic to the adjuvant treatment setting. Recently, there have also been positive reports of the NATALEE study.

Other clinical studies are currently investigating substances that are already established in the metastatic setting. These include, for example, the DESTINY Breast05 study with trastuzumab deruxtecan and the SASCIA study with sacituzumab govitecan.

In this review paper, we summarize and place in context the latest developments over the past months.

ZUSAMMENFASSUNG

Mit den Zulassungen von Abemaciclib (monarchE-Studie) und Olaparib (Olympia-Studie) in der adjuvanten Therapiesituation haben sich die Therapiestandards bei der Behandlung von Patientinnen mit Mammakarzinom in Frühstadien seit Langem deutlich verändert. Somit übertragen sich einige vielfältige Entwicklungen aus der metastasierten Therapiesituation langsam in die adjuvante. Kürzlich ist auch die NATALEE-Studie als positiv berichtet worden.

Weitere Therapiestudien mit Substanzen, die in der metastasierten Situation etabliert sind, werden zurzeit durchgeführt. Dies sind z. B. die DESTINY Breast05-Studie mit Trastuzumab-Deruxtecan und die SASCIA-Studie mit Sacituzumab Govitecan.

In dieser Übersichtsarbeit werden die neuesten Entwicklungen der letzten Monate zusammengefasst und in den jeweiligen Kontext eingeordnet.

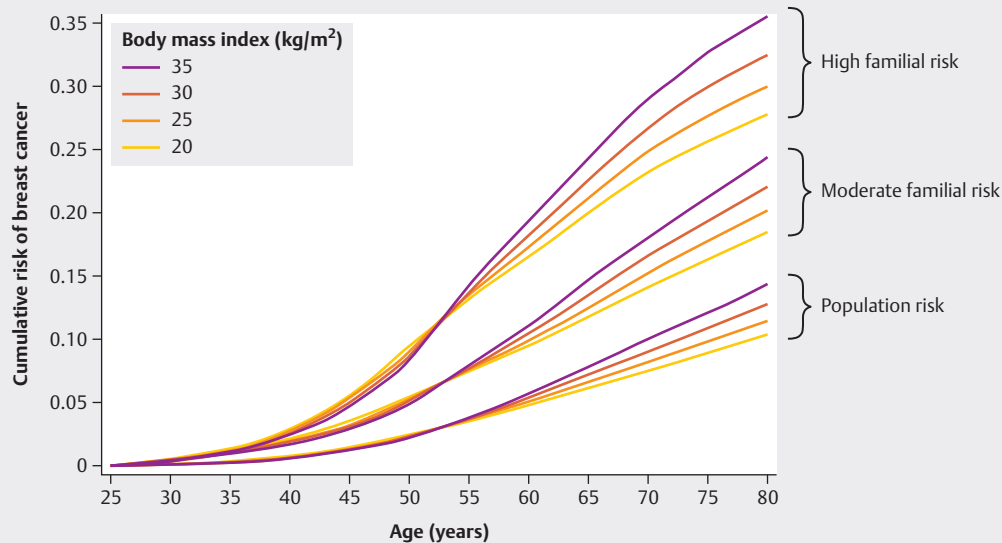
Prevention

Excess weight and risk of breast cancer – new insights

Over the past two decades, many risk factors have been independently associated with the risk of developing breast cancer. Genetic risk factors can explain up to 40% of the inherited breast cancer risk (defined as a doubled familial breast cancer risk) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. This is contrasted with risk factors that are not associated with genetic risk, which include, for example, reproductive health parameters, weight, or lifestyle factors [27]. Some risk factors, such as breast density, are partly determined by genetic factors and partly by other risk factors [8, 14, 15, 23, 28, 29, 30]. With this in mind, breast density plays a central role in determining the risk of breast cancer. Only now are we gradually starting to understand the interactions between the different risk factors [4, 31, 32, 33].

Recently, new findings have come to light in connection with body mass index (BMI) as a risk factor. It was already known that a higher body mass index tends to have a protective effect in premenopausal patients, while a higher BMI in postmenopausal patients is associated with an increased risk of disease [34, 35, 36,

37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47]. Moreover, a prospective cohort study was also able to show an association between familial risk and BMI (► Fig. 1) [48]. In ► Fig. 1 it can be seen that the impact of BMI on breast cancer risk is reversed in the period after menopause [48]. One explanation for this interaction between familial risk and BMI may lie in the relationship between homologous recombination and body mass index, and the associated accumulation of DNA damage [49]. It has been demonstrated that DNA damage in the breast epithelium of women with a BRCA mutation has a positive correlation to BMI. It was also found that blockades of estrogen biosynthesis led to a lower level of DNA damage [49]. Hormones such as insulin and leptin, which are also present in increased levels in obese patients, led to increased DNA damage in the mammary gland tissue. This, in turn, could be prevented by inhibition of PI3K or leptin [49]. While these correlations have been investigated in healthy epithelia in the context of breast cancer prevention, it is also conceivable that such correlations might potentially play a role in the prognosis and treatment of breast cancer. With endocrine resistance in particular, the homologous recombination signaling pathway has been identified as one of the important elements [50]. In this context, it is also significant that a high BMI is associated with reduced efficacy of endocrine



► **Fig. 1** Age-specific breast cancer risk by body mass index and familial risk. (Source: Hopper JL, Dite GS, MacInnis RJ et al. Age-specific breast cancer risk by body mass index and familial risk: prospective family study cohort (Prof-SC). *Breast Cancer Res* 2018; 20: 132. doi:10.1186/s13058-018-1056-1, Creative Commons Attribution 4.0 International License, <http://creativecommons.org/licenses/by/4.0/>)

breast cancer therapies [51]. In future, these interactions are likely to be an important field of research for the prevention and treatment of breast cancer.

Risk of contralateral breast cancer quantified in a large-scale study

In the context of treating breast cancer patients with a germline mutation, the risk of contralateral breast cancer is a question that often arises. This is important, firstly so that the risk can be taken into account on an individual basis when planning surgery, and secondly for the planning of follow-up care or screening. On this topic, very extensive data from over 14400 breast cancer patients have been presented as part of the CARRIERS study [52]. For all patients, it was a prerequisite that the contralateral breast had not been removed during primary care and that follow-up treatment could take place for at least one year. A total of 5 genes were investigated for their germline mutation status. The mutation rates were 0.9% (*BRCA1*), 1.1% (*BRCA2*), 0.9% (*CHEK2*), 0.6% (*PALB2*), and 0.7% (*ATM*) [52]. The median follow-up observation period was 11 years. Both *BRCA1* and *BRCA2* genes were shown to be associated with approximately three times the risk of contralateral cancer. This was the case regardless of whether the primary cancer was hormone receptor-positive or -negative. *CHEK2* was found to be associated with approximately twice the risk, mainly in patients with hormone receptor-positive primary cancer. An increased risk could also be demonstrated for *PALB2*, although the approximately three-fold increase in risk was limited to patients who had hormone receptor-negative primary cancer. This is consistent with data indicating that *PALB2* tends to have more of a risk-increasing effect in the case of triple-negative breast cancer (TNBC) [53, 54]. In the CARRIERS study, the absolute rates for developing contralateral breast carcinoma within 10 years were 4.3% for patients with

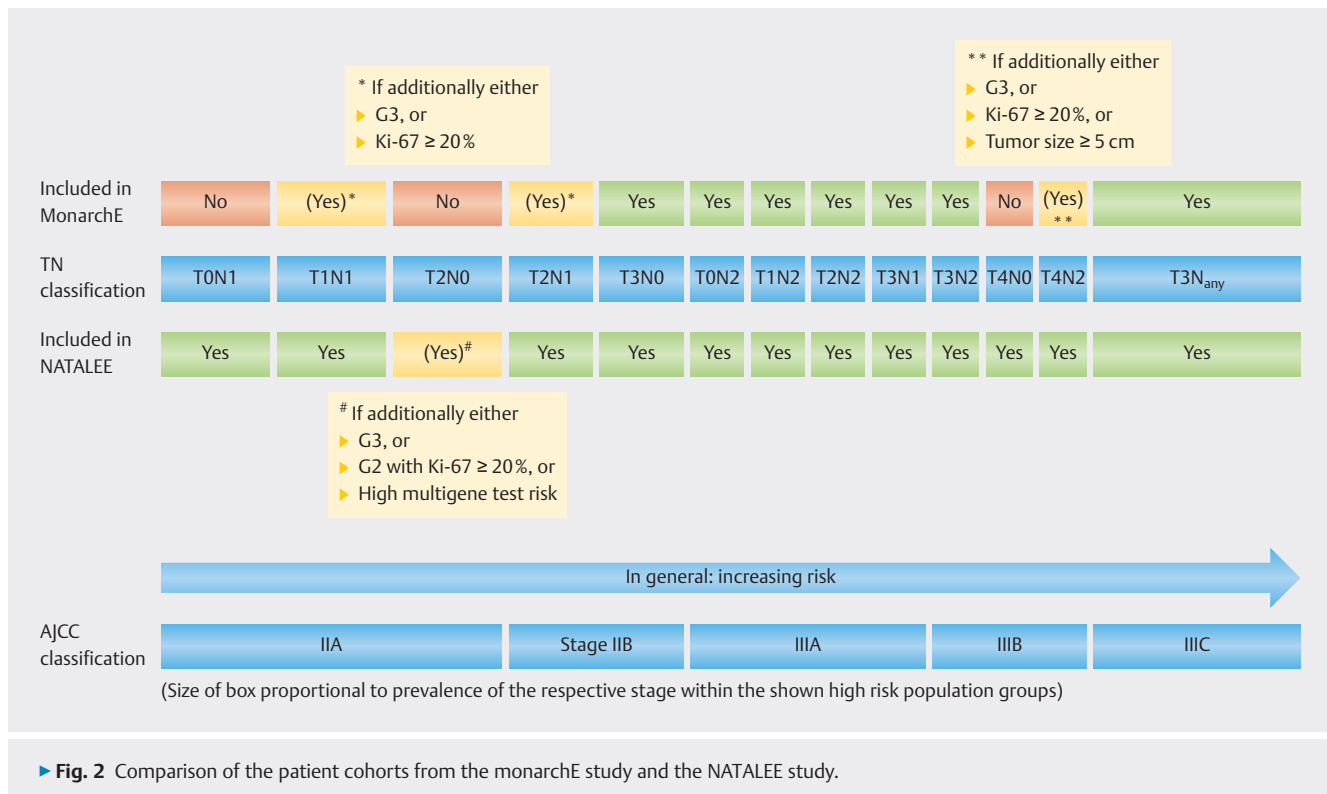
no germline mutation, 23% for *BRCA1* mutation carriers, 17% for *BRCA2* mutation carriers, and 8% for *CHEK2* mutation. With regard to the increased risk with a hormone receptor-negative primary tumor, the 10-year risk for developing contralateral cancer was 5.4%. In the case of the *PALB2* mutation, this risk was 19.7% [52].

These analyzes should help clinicians to better advise patients on surgical planning and to provide individualized follow-up care and screening.

Adjuvant Endocrine Therapies

CDK4/6 inhibitors in the adjuvant setting

Following the monarchE study, abemaciclib could be approved as an adjuvant treatment for HRpos/HER2neg patients at increased risk of recurrence [55, 56, 57]. Based on cohort 1 of the monarchE study, increased risk of recurrence is defined as either more than 3 affected lymph nodes, or 1–3 affected lymph nodes plus an additional tumor grading of 3, or a tumor size of at least 5 cm. In the USA, approval was first granted for patients with Ki-67 \geq 20%; however, the approval has recently been amended in the USA and is now in line with the European approval [58]. This means it is no longer necessary to determine the Ki-67 level of patients in the USA. The study had already received a positive evaluation in the first interim analysis due to a large difference between the randomization arms (endocrine standard therapy versus endocrine standard therapy + 2 years of abemaciclib) [56]. However, given that 73.6% of patients were still receiving treatment at the time of this evaluation, there were frequent calls for more sound data with a longer follow-up observation period [55, 57]. An evaluation has recently been published with a median follow-up observation period of 42 months, the longest follow-up to date [59]. In this analysis, 99.2% of patients were no longer receiving treatment, and there



had been 835 events in total (compared to 323 in the first interim analysis). The hazard ratio when comparing the randomization arms for invasive disease-free survival was 0.664 (95% CI: 0.578–0.762). The absolute difference was 6.8% after 4 years (79.4% in the standard endocrine arm versus 85.8% in the standard endocrine therapy + 2 years abemaciclib arm) [57]. In terms of overall survival, no benefit has yet been seen. The hazard ratio for overall survival was 0.92 (95% CI: 0.74–1.15) with a total of 330 fatal events. It can therefore be concluded that the results of the monarchE study for invasive disease-free survival have been consolidated, and that the therapeutic effect continues into the post-treatment period.

Although the results of the NATALEE/TRIO-033 study have not yet been definitively published, they have already been mentioned in a press release [60, 61, 62]. Compared to the monarchE study, the NATALEE/TRIO-033 study also included patients at low risk of recurrence, in particular patients with a negative lymph node status but with a tumor size greater than 2 cm, and patients with a T1 tumor, but with affected lymph nodes (► **Fig. 2**). Patients in the NATALEE/TRIO-033 study received either standard endocrine adjuvant therapy or additional treatment with ribociclib 400 mg over 3 years. The press release reported that ribociclib reduced the risk of recurrence in patients with AJCC stage II and stage III disease, regardless of lymph node involvement, with a consistent benefit [60, 63].

So far, abemaciclib remains the only drug approved in the adjuvant setting; however, it can be assumed that further approval will be sought based on the results of the NATALEE/TRIO-033 study.

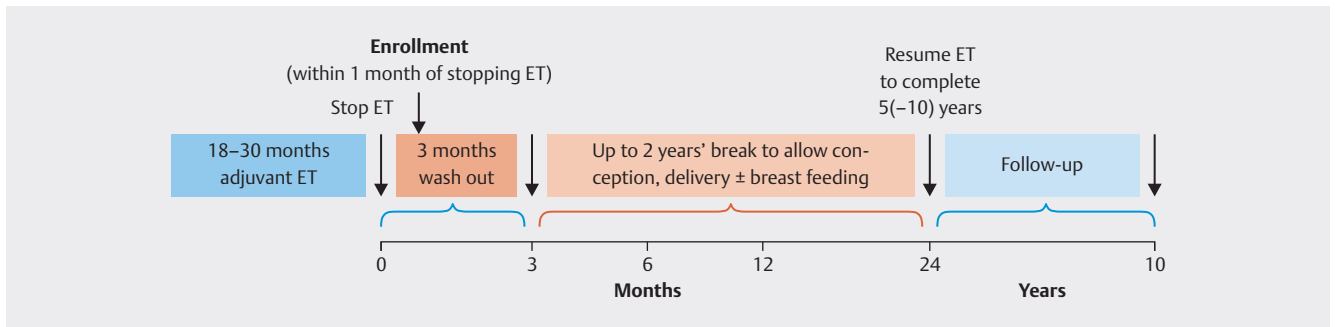
Pregnancy in patients following hormone receptor-positive disease

Although the occurrence of breast cancer in young women is rare [64, 65], the question of pregnancy often arises for patients who are still planning to have a family. Endocrine therapies take 5–10 years to complete depending on the risk of recurrence. Thus, in many cases, a decision must be made to interrupt the endocrine therapy so as not to jeopardize the fertility of older patients. This issue is investigated in the POSITIVE study [66]. The study participants were patients aged 42 or younger who started adjuvant endocrine therapy 18 to 30 months prior to enrolment in the study. Prior chemotherapy was explicitly permitted. The design of the POSITIVE study is shown in ► **Fig. 3**.

The primary study objective was breast cancer-free survival. The study was not randomized, and the data should be compared to data from the SOFT/TEXT studies. The POSITIVE study included 516 patients who could be examined for the primary endpoint. The median age of the study participants was 37, and 75% of them had not yet carried a pregnancy to term and given birth. 62% of the study participants had undergone chemotherapy prior to enrolment in the study [66].

With a median follow-up period of 41 months, a total of 44 events occurred relating to breast cancer-free survival. When compared with external data from the SOFT and TEXT studies, this figure appeared to be comparable in both studies. The aim was for the patients to resume endocrine therapy after the 2-year interval that was scheduled for conception and pregnancy. This did happen for 79% of the patients.

Although the authors conclude that oncological safety was not jeopardized during the reported follow-up period and that pa-



► Fig. 3 Design of the POSITIVE study (PARTRIGE).

tients should be offered this kind of treatment option [66], the interpretation of this study is not straightforward. The study was not a randomized trial, and the number of patients, at 500, was somewhat small for the adjuvant setting. The comparison group (SOFT/TEXT) was recruited more than 10 years prior to the POSITIVE study [67]. During this time the treatment has changed, which may make it difficult in some circumstances to draw comparisons between the studies. Furthermore, there were subgroups in which the 3-year incidence of recurrences was relatively high, such as patients with more than 3 affected lymph nodes (18.7% recurrence rate) or patients with a tumor larger than 5 cm (21.1% recurrence rate) [66]. Even though the case numbers were small and no attempt was made to draw comparisons with the SOFT/TEXT study, in future the POSITIVE study should focus, over a longer follow-up observation period, on the subgroups that demonstrated a high risk of recurrence.

Neoadjuvant Treatment

Olaparib in neoadjuvant treatment – long-term data from the GeparOLA study

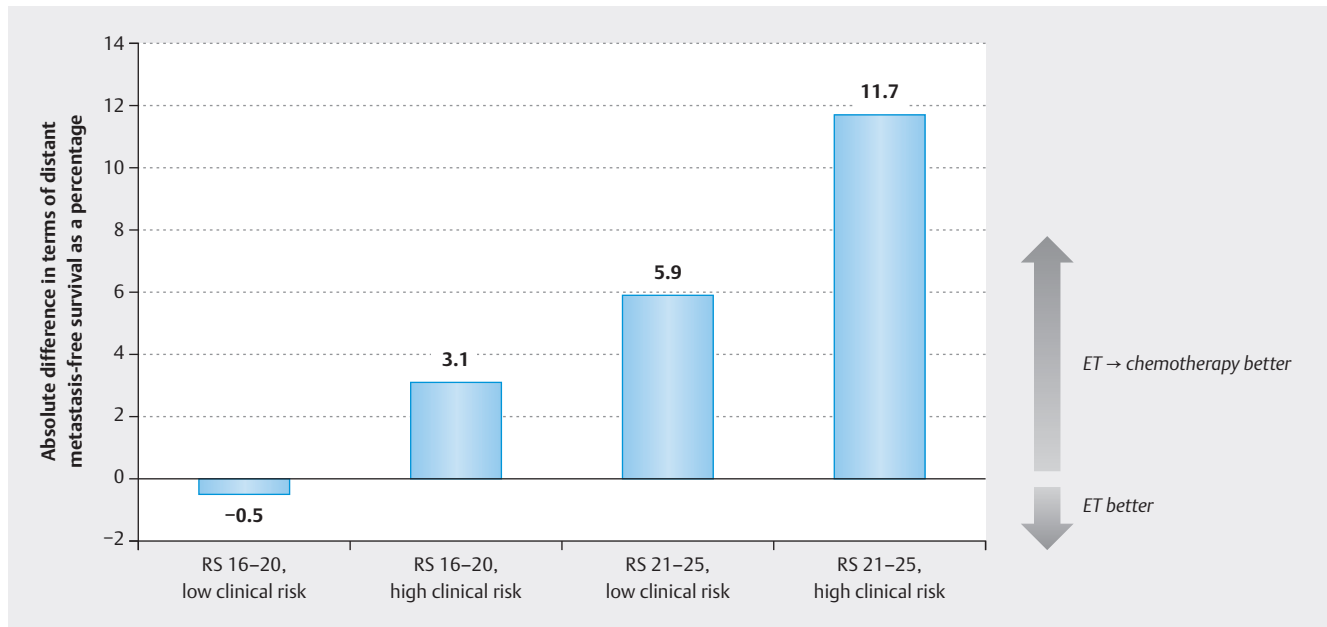
In the adjuvant setting, olaparib is approved for HER2-negative patients at high risk of recurrence. In this context, overall survival can be improved by 3.4% in absolute terms, from 86.4% to 89.8% according to a four-year follow-up observation period [68]. This indication is linked to the presence of a *BRCA1/2* mutation in the germline. However, due to the mechanism of action, it is hypothesized that other homologous recombination defects may also be associated with the efficacy of olaparib. In the metastatic context, some efficacy was also demonstrated in patients with a *PALB2* mutation, even though the number of cases was small [69]. In ovarian cancer, for some PARP inhibitors, the indication for PARP inhibitor therapy has occasionally been linked to a test for certain molecular patterns of homologous recombination in tumor DNA (HRD score) [70]. In the case of breast cancer, one of the studies looking into this question is the GeparOLA study [71]. In this neoadjuvant study, olaparib (at a dose of 100 mg twice daily) combined with paclitaxel (PO arm) was compared with carboplatin and paclitaxel (PCb arm), each followed by epirubicin/cyclophosphamide. The pCR rate was 55.1% in the PO arm and 48.6% in the PCb arm [71]. Long-term survival data for this study have now also been published [72]. In this analysis, the evaluations of the subgroups ac-

ording to *BRCA* mutation status and HRD score were of particular interest. Approximately half of the patients had a *BRCA1/2* mutation and a high HRD score, and the other half had a high HRD score without a *BRCA1/2* mutation. In the group of patients with a *BRCA1/2* mutation, the two therapies appeared to be similarly effective. However, for the group of patients with no *BRCA1/2* mutation who were included on the basis of a high HRD score, those in the PO arm had poorer invasive disease-free survival. The authors concluded that for patients with a *BRCA1/2* mutation, olaparib could replace platinum therapy because of its much better side effect profile [72]. However, it is important to note that patients without a *BRCA1/2* mutation (with a high HRD score) do not benefit as clearly from receiving olaparib treatment compared to carboplatin. However, in view of the Olympia study which showed an overall survival advantage, the results of the GeparOLA study are not of clinical relevance. Currently, olaparib is used postoperatively as monotherapy or in combination with standard endocrine therapy in patients who are at high risk of recurrence after completing standard therapy.

Biomarkers

Long-term follow-up data from the TailorX study

The TailorX study is the largest study to date to investigate the oncotype multigene test in a clinical trial setting so as to answer the question of whether chemotherapy is necessary in patients with early stage nodal-negative, hormone receptor-positive breast cancer, given their moderately increased risk of recurrence. For this purpose, patients with a recurrence score of 11–25 were randomized to treatment arms with regular adjuvant endocrine therapy, or with regular adjuvant endocrine therapy after adjuvant chemotherapy. The primary analysis was published after a median follow-up period of 7.5 years; for postmenopausal patients in particular, undergoing chemotherapy did not demonstrate any benefit. In premenopausal patients, undergoing chemotherapy did demonstrate a benefit [73, 74]. Many of the discussions about these results in premenopausal patients have focused on whether the greater part of this effect might be mediated by chemotherapy due to its effect on ovarian function. After standard chemotherapy, up to 70% of premenopausal patients developed chemotherapy-induced, permanent amenorrhea [75, 76]. It was also shown that patients who developed amenorrhea after adjuvant



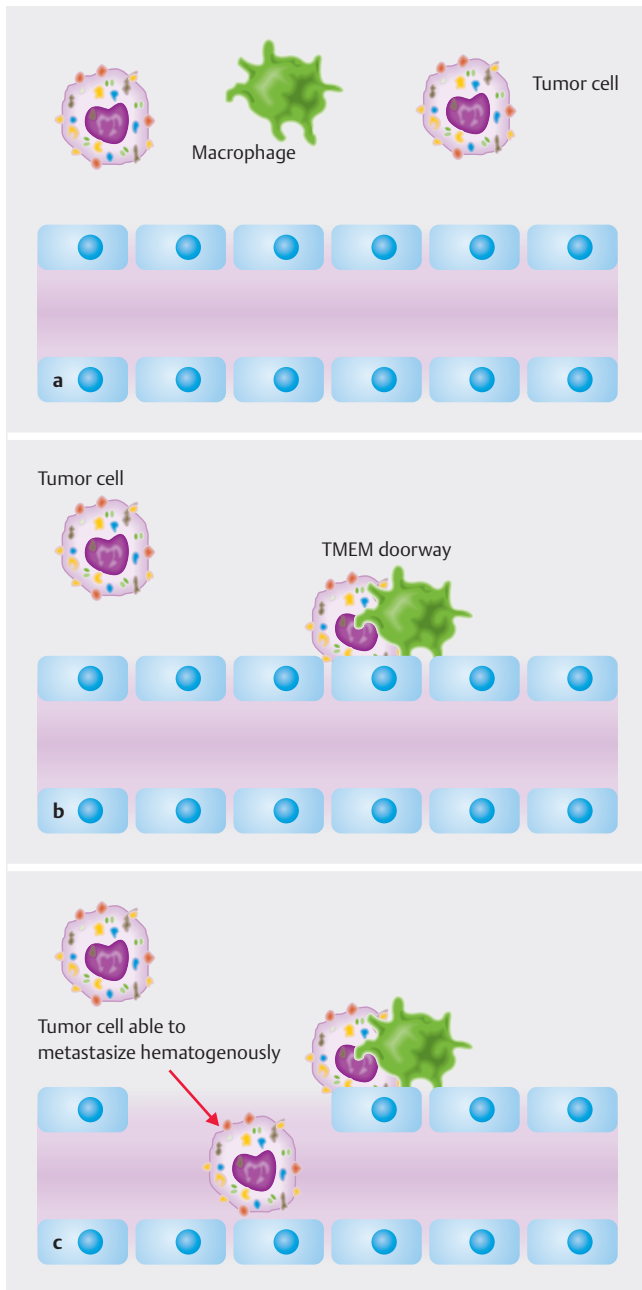
► **Fig. 4** Absolute difference in terms of distant metastasis-free survival in patients in the TailorX study, as a percentage. Subgroup of patients aged ≤ 50 with an RS of 16–25.

chemotherapy had a better prognosis [77, 78, 79]. Against this background, it is important to understand the mechanisms by which chemotherapy affects the prognosis in premenopausal HRpos/HER2neg patients. An analysis of the TailorX study, comprising additional analyzes which also addressed this question, has now been published with a median follow-up period of 11.0 years [80]. The data on annual event rates illustrate why this kind of long-term follow-up is so important. While 1.55% of patients had an invasive disease-free survival (iDFS) event each year at years 1–5, this rate was 2.66% at years 6–12. Thus, in the TailorX population, more iDFS recurrences occurred after 5 years than in the first 5 years after diagnosis [80]. Considering that the annual recurrence rates in patients with hormone receptor-positive breast cancer remain similarly high over many years, and the treatment for patients at increased risk can take up to 10 years, this additional analysis could provide substantial insights into the unanswered questions relating to the use of oncotypes in this patient population. The 12-year iDFS rates in the randomized patients (recurrence score 11–25) were 76.8% in patients who had received endocrine therapy, and 77.4% in patients who had additionally undergone chemotherapy [80]. Accordingly, the study did not show any overall advantage from undergoing chemotherapy. However, in the group of patients aged ≤ 50 , especially for patients with a high clinical risk of recurrence, an absolute difference between the randomization arms in terms of distant metastasis-free survival did indicate a benefit from undergoing chemotherapy ► **Fig. 4**. A benefit from undergoing chemotherapy can clearly be seen in patients aged ≤ 50 with a high risk of recurrence based on clinical parameters, and with a high recurrence score of 21–25 [80]. However, in patients with a low clinical risk of recurrence, the effect of undergoing chemotherapy appears to be significantly smaller.

Doorways formed from a tumor cell, a macrophage, and an endothelial cell could be the origin of hematogenous metastasis

In a study on neoadjuvant chemotherapy, researchers investigated a complex histological biomarker, as well as the influence of white or black ethnic origin of patients on the efficacy of neoadjuvant chemotherapy [81]. This biomarker has been known in the scientific community for some time, but so far has not acquired any particular clinical relevance. It is thought to reflect whether a tumor has a high or low probability of forming metastases. The passage of a tumor cell through the endothelium has been described as occurring in the location where a macrophage, a tumor cell, and an endothelial cell come into direct contact with each other (► **Fig. 5**) [82, 83, 84]. This meeting of the three cell types is also called a tumor microenvironment of metastasis (TMEM) doorway. In some studies the occurrence of these TMEM doorways has been associated with a higher risk of metastasis [85, 86, 87, 88, 89], possibly or especially after neoadjuvant chemotherapy [89, 90].

The study presented here included 183 patients with a residual tumor of at least 5 mm after neoadjuvant chemotherapy. 96 of the patients were black and 87 were white [81]. Firstly, a lower density of TMEM doorways was observed in TNBC patients compared to HRpos/HER2neg patients, who had a higher density of TMEM doorways in the tumor. Secondly, a significantly lower density of TMEM doorways was observed in white patients compared to black patients. In the overall patient cohort, the score for TMEM doorways was a clear prognostic factor. The hazard ratio for distant metastasis-free survival was 2.01 (95% CI: 1.17–3.44) when comparing patients with high versus moderate to low TMEM scores [81]. This paper shows that the molecular behavior of tumors differs markedly between different ethnic groups, and there is a need for further research on this topic. These ethnic differ-



► **Fig. 5** The structure known as a tumor microenvironment of metastasis (TMEM) doorway is created when three specific cells, a tumor cell, a macrophage, and an endothelial cell (a), form a spatially close connection (b). This structure serves as a doorway through which tumor cells can enter the blood vessels, and thus metastasize (c). Tumors with a high density of TMEM doorways have a higher probability of metastasis than tumors with a low TMEM density.

ences may play a major role, not only for drug development, but also for our understanding of molecular properties that could be used in prognostic models.

Outlook

This year, the treatment scenario for HRpos/HER2neg patients was supplemented with data from the NATALEE study. Looking at all of these data together will help us to determine which patients should be treated with abemaciclib, and which should be treated with ribociclib. Even though ribociclib has not yet been approved in the adjuvant setting, the NATALEE study included a significantly broader patient population with a lower risk of recurrence.

Currently, the available studies investigating treatment decisions in premenopausal patients with early stage HRpos/HER2neg cancer are the subject of intense analysis. The choice of adjuvant endocrine therapy, the integration of CDK4/6 inhibitors, and the use of multigene assays and other biomarkers, such as dynamic Ki-67, must be placed in a meaningful context so that chemotherapy is only performed when it can be expected to produce a benefit. The choice of endocrine therapy also needs to be investigated in this context. One study collecting data on endocrine therapy in premenopausal patients here in Germany is the CLEAR-B study (<http://www.clear-b.de/>).

Future studies will also soon clarify whether the new antibody-drug conjugates, trastuzumab deruxtecan and sacituzumab govitecan, are also of value in treating early stage cancers.

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Conflict of Interest

B. A. received honoraria and travel grants from AstraZeneca, Gilead, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo and Pfizer.
 M. B.-P. received honoraria for lectures and advisory role from Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkowissen, Seagen, Eisai, AstraZeneca, Amgen, Samsung, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Pintuition, Pierre Fabre, and study support from Mammothome, Endomag and Merit Medical.
 E. B. received honoraria from Gilead, Ipsen, Sanofi, Sandoz, SunPharma, AstraZeneca, Novartis, Hexal, BMS, Lilly, Pfizer, Roche, MSD, B Braun and onkowissen.de for clinical research management and/or medical education activities.
 N. D. has received honoraria from MSD, Roche, AstraZeneca, Teva, Pfizer, Novartis, Seagen, Gilead, MCI Healthcare.
 P. A. F. reports personal fees from Novartis, grants from BioNTech, personal fees from Pfizer, personal fees from Daiichi Sankyo, personal fees from AstraZeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from SeaGen, personal fees from Roche, personal fees from Hexal, personal fees from Agendia, personal fees from Gilead.
 T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.

A. D. H. received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer.

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References/Literatur

- [1] Lopes Cardozo JMN, Andrulis IL, Bojesen SE et al. Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival. *J Clin Oncol* 2023; 41: 1849–1863. doi:10.1200/JCO.22.01978
- [2] DeVries AA, Dennis J, Tyrer JP et al. Copy Number Variants Are Ovarian Cancer Risk Alleles at Known and Novel Risk Loci. *J Natl Cancer Inst* 2022; 114: 1533–1544. doi:10.1093/jnci/djac160
- [3] Ruth KS, Day FR, Hussain J et al. Genetic insights into biological mechanisms governing human ovarian ageing. *Nature* 2021; 596: 393–397. doi:10.1038/s41586-021-03779-7
- [4] Kapoor PM, Mavaddat N, Choudhury PP et al. Combined Associations of a Polygenic Risk Score and Classical Risk Factors With Breast Cancer Risk. *J Natl Cancer Inst* 2021; 113: 329–337. doi:10.1093/jnci/djaa056
- [5] Breast Cancer Association Consortium, Dorling L, Carvalho S, Allen J et al. Breast Cancer Risk Genes – Association Analysis in More than 113,000 Women. *N Engl J Med* 2021; 384: 428–439. doi:10.1056/NEJMoa1913948
- [6] Fachal L, Aschard H, Beesley J et al. Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes. *Nat Genet* 2020. doi:10.1038/s41588-019-0537-1
- [7] Dorling L, Carvalho S, Allen J et al. Breast cancer risks associated with missense variants in breast cancer susceptibility genes. *Genome Med* 2022; 14: 51. doi:10.1186/s13073-022-01052-8
- [8] Vachon CM, Scott CG, Tamimi RM et al. Joint association of mammographic density adjusted for age and body mass index and polygenic risk score with breast cancer risk. *Breast Cancer Res* 2019; 21: 68. doi:10.1186/s13058-019-1138-8
- [9] 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; 50: 968–978. doi:10.1038/s41588-018-0132-x

- [10] Mavaddat N, Michailidou K, Dennis J et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2019; 104: 21–34. doi:10.1016/j.ajhg.2018.11.002
- [11] 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. doi:10.1038/ng.3785
- [12] Michailidou K, Lindstrom S, Dennis J et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017; 551: 92–94. doi:10.1038/nature24284
- [13] Day FR, Thompson DJ, Helgason H et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat Genet* 2017; 49: 834–841. doi:10.1038/ng.3841
- [14] 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; 107: dju397. doi:10.1093/jnci/dju397
- [15] 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. doi:10.1186/s13058-015-0625-9
- [16] 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. doi:10.1038/ng.3242
- [17] 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; 107: djv036. doi:10.1093/jnci/djv036
- [18] Day FR, Ruth KS, Thompson DJ et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. *Nat Genet* 2015; 47: 1294–1303. doi:10.1038/ng.3412
- [19] Pharoah PD, Tsai YY, Ramus SJ et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet* 2013; 45: 362–370. doi:10.1038/ng.2564
- [20] 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. doi:10.1038/ng.2563
- [21] 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. doi:10.1038/ng.2561
- [22] Bojesen SE, Pooley KA, Johnatty SE et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet* 2013; 45: 371–384. doi:10.1038/ng.2566
- [23] 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. doi:10.1158/1055-9965.EPI-12-0066
- [24] 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. doi:10.1038/ng.1049
- [25] Haiman CA, Chen GK, Vachon CM et al. A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet* 2011; 43: 1210–1214. doi:10.1038/ng.985
- [26] Antoniou AC, Wang X, Fredericksen ZS et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet* 2010; 42: 885–892. doi:10.1038/ng.669
- [27] 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. *Geburtshilfe Frauenheilkd* 2018; 78: 481–492. doi:10.1055/a-0603-4350
- [28] Chen H, Fan S, Stone J et al. Genome-wide and transcriptome-wide association studies of mammographic density phenotypes reveal novel loci. *Breast Cancer Res* 2022; 24: 27. doi:10.1186/s13058-022-01524-0
- [29] Lindstrom S, Thompson DJ, Paterson AD et al. Genome-wide association study identifies multiple loci associated with both mammographic density and breast cancer risk. *Nat Commun* 2014; 5: 5303. doi:10.1038/ncomms6303
- [30] Lindstrom S, Thompson DJ, Paterson AD et al. Corrigendum: genome-wide association study identifies multiple loci associated with both mammographic density and breast cancer risk. *Nat Commun* 2015; 6: 8358. doi:10.1038/ncomms9358
- [31] Rudolph A, Song M, Brook MN et al. Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int J Epidemiol* 2018; 47: 526–536. doi:10.1093/ije/dyx242
- [32] Brouckaert O, Rudolph A, Laenen A et al. Reproductive profiles and risk of breast cancer subtypes: a multi-center case-only study. *Breast Cancer Res* 2017; 19: 119. doi:10.1186/s13058-017-0909-3
- [33] 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. doi:10.1002/ijc.30859
- [34] Ye ZF, Li S, Dite GS et al. Weight is More Informative than Body Mass Index for Predicting Postmenopausal Breast Cancer Risk: Prospective Family Study Cohort (Prof-SC). *Cancer Prev Res* 2022; 15: 8. doi:10.1158/1940-6207.Capr-21-0164
- [35] Pegington M, Harkness EF, Howell A et al. Magnitude and attributed reasons for adult weight gain amongst women at increased risk of breast cancer. *BMC Womens Health* 2022; 22: 11. doi:10.1186/s12905-022-02037-w
- [36] Niehoff NM, Terry MB, Bookwalter DB et al. Air Pollution and Breast Cancer: An Examination of Modification By Underlying Familial Breast Cancer Risk. *Cancer Epidemiol Biomarkers Prev* 2022; 31: 422–429. doi:10.1158/1055-9965.Epi-21-1140
- [37] Naaman SC, Shen S, Zeytinoglu M et al. Obesity and Breast Cancer Risk: The Oncogenic Implications of Metabolic Dysregulation. *J Clin Endocrinol Metab* 2022; 107: 2154–2166. doi:10.1210/clinem/dgac241
- [38] Kresovich JK, Xu ZL, O'Brien KM et al. Blood DNA methylation profiles improve breast cancer prediction. *Mol Oncol* 2022; 16: 42–53. doi:10.1002/1878-0261.13087
- [39] Geldhof V, de Rooij L, Sokol L et al. Single cell atlas identifies lipid-processing and immunomodulatory endothelial cells in healthy and malignant breast. *Nat Commun* 2022; 13: 19. doi:10.1038/s41467-022-33052-y
- [40] Smith SG, Sestak I, Morris MA et al. The impact of body mass index on breast cancer incidence among women at increased risk: an observational study from the International Breast Intervention Studies. *Breast Cancer Res Tr* 2021; 188: 215–223. doi:10.1007/s10549-021-06141-7
- [41] Oh H, Wild RA, Manson JE et al. Obesity, Height, and Serum Androgen Metabolism among Postmenopausal Women in the Women's Health Initiative Observational Study. *Cancer Epidemiol Biomarkers Prev* 2021; 30: 2018–2029. doi:10.1158/1055-9965.Epi-21-0604
- [42] Mubarik S, Liu XX, Malik SS et al. Evaluation of lifestyle risk factor differences in global patterns of breast cancer mortality and DALYs during 1990–2017 using hierarchical age-period-cohort analysis. *Environ Sci Pollut Res* 2021; 28: 49864–49876. doi:10.1007/s11356-021-14165-1
- [43] Masala G, Palli D, Ermini I et al. The DAMA25 Study: Feasibility of a Lifestyle Intervention Programme for Cancer Risk Reduction in Young Italian Women with Breast Cancer Family History. *Int J Environ Res Public Health* 2021; 18: 13. doi:10.3390/ijerph182312287
- [44] Lukasiewicz S, Czelewski M, Forma A et al. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers* 2021; 13: 30. doi:10.3390/cancers13174287

- [45] Kapoor PM, Mavaddat N, Choudhury PP et al. Combined Associations of a Polygenic Risk Score and Classical Risk Factors With Breast Cancer Risk. *J Natl Cancer Inst* 2021; 113: 329–337. doi:10.1093/jnci/djaa056
- [46] Houghton LC, Howland RE, Wei Y et al. The Steroid Metabolome and Breast Cancer Risk in Women with a Family History of Breast Cancer: The Novel Role of Adrenal Androgens and Glucocorticoids. *Cancer Epidemiol Biomarkers Prev* 2021; 30: 89–96. doi:10.1158/1055-9965.Epi-20-0471
- [47] Daly AA, Rolph R, Cutress RI et al. A Review of Modifiable Risk Factors in Young Women for the Prevention of Breast Cancer. *Breast Cancer* (Dove Med Press) 2021; 13: 241–257. doi:10.2147/BCTT.S268401
- [48] Hopper JL, Dite GS, MacInnis RJ et al. Age-specific breast cancer risk by body mass index and familial risk: prospective family study cohort (ProF-SC). *Breast Cancer Res* 2018; 20: 132. doi:10.1186/s13058-018-1056-1
- [49] Bhardwaj P, Iyengar NM, Zahid H et al. Obesity promotes breast epithelium DNA damage in women carrying a germline mutation in BRCA1 or BRCA2. *Sci Transl Med* 2023; 15: eade1857. doi:10.1126/scitranslmed.a de1857
- [50] Marra A, Gazzo A, Gupta A et al. Mutational signature analysis reveals patterns of genomic instability linked to resistance to endocrine therapy (ET) +/- CDK 4/6 inhibition (CDK4/6i) in estrogen receptor-positive/HER2-negative (ER+/HER2-) metastatic breast cancer (MBC). *Ann Oncol* 2022; 33 (Suppl 7): S88–S121. doi:10.1016/annonc/annonc1089
- [51] Barone I, Caruso A, Gelsomino L et al. Obesity and endocrine therapy resistance in breast cancer: Mechanistic insights and perspectives. *Obes Rev* 2022; 23: e13358. doi:10.1111/obr.13358
- [52] Yadav S, Boddicker NJ, Na J et al. Abstract GS4–04: Population-based estimates of contralateral breast cancer risk among carriers of germline pathogenic variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2. *San Antonio Breast Cancer Symposium 2022. Cancer Res* 2023; 83 (Suppl 5): GS4–04. doi:10.1158/1538-7445.SABCS22-GS4-04
- [53] Shimelis H, LaDuca H, Hu C et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. *J Natl Cancer Inst* 2018; 110: 855–862. doi:10.1093/jnci/djy106
- [54] Hoyer J, Vasileiou G, Uebe S et al. Addition of triple negativity of breast cancer as an indicator for germline mutations in predisposing genes increases sensitivity of clinical selection criteria. *BMC Cancer* 2018; 18: 926. doi:10.1186/s12885-018-4821-8
- [55] Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol* 2021; 32: 1571–1581. doi:10.1016/j.annonc.2021.09.015
- [56] Johnston SRD, Harbeck N, Hegg R et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol* 2020; 38: 3987–3998. doi:10.1200/JCO.20.02514
- [57] Johnston SRD, Toi M, O'Shaughnessy J et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023; 24: 77–90. doi:10.1016/S1470-2045(22)00694-5
- [58] United States Food and Drug Administration (FDA). FDA expands early breast cancer indication for abemaciclib with endocrine therapy. 2023. Accessed April 03, 2023 at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-early-breast-cancer-indication-abemaciclib-endocrine-therapy>
- [59] Johnston SRD, Andre V. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk, early breast cancer – Authors' reply. *Lancet Oncol* 2023; 24: e104. doi:10.1016/S1470-2045(23)00065-7
- [60] Translational Research in Oncology. NATALEE (TRIO033) Phase III trial demonstrates ribociclib significantly reduces the risk of recurrence for patients with early breast cancer, at interim analysis. 2023. Accessed April 05, 2023 at: <https://www.trioncology.org/news/natalee-trio033-phase-iii-trial-demonstrates-ribociclib-significantly-reduces-the-risk-of-recurrence-for-patients-with-early-breast-cancer-at-interim-analysis/>
- [61] clinicaltrials.gov. NCT03701334. A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NATALEE). NIH US National Library of Medicine; 2018. Accessed November 07, 2020 at: <https://clinicaltrials.gov/ct2/show/NCT03701334>
- [62] Slamon DJ, Fasching PA, Patel R et al. NATALEE: Phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC). *J Clin Oncol* 2019; 37: TPS597. doi:10.1200/JCO.2019.37.15_suppl.TPS597
- [63] Novartis. Novartis Kisqali® Phase III NATALEE trial meets primary endpoint at interim analysis demonstrating clinically meaningful benefit in broad population of patients with early breast cancer. 2023. Accessed April 03, 2023 at: <https://www.novartis.com/news/media-releases/novartis-kisqali-phase-iii-natalee-trial-meets-primary-endpoint-interim-analysis-demonstrating-clinically-meaningful-benefit-broad-population-patients-early-breast-cancer>
- [64] Fasching PA. Breast cancer in young women: do BRCA1 or BRCA2 mutations matter? *Lancet Oncol* 2018; 19: 150–151. doi:10.1016/S1470-2045(18)30008-1
- [65] Copson ER, Maishman TC, Tapper WJ et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol* 2018; 19: 169–180. doi:10.1016/S1470-2045(17)30891-4
- [66] Partridge AH, Niman SM, Ruggeri M et al. Abstract GS4–09: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer: Primary Results from the POSITIVE Trial (IBCSG 48–14/BIG 8–13). *San Antonio Breast Cancer Symposium 2022. Cancer Res* 2023; 83 (Suppl 5): GS4–09. doi:10.1158/1538-7445.SABCS22-GS4-09
- [67] Pagani O, Walley BA, Fleming GF et al. Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials. *J Clin Oncol* 2023; 41: 1376–1382. doi:10.1200/JCO.22.01064
- [68] Geyer CE, Jr., Garber JE, Gelber RD et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* 2022; 33: 1250–1268. doi:10.1016/j.annonc.2022.09.159
- [69] Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol* 2020; 38: 4274–4282. doi:10.1200/JCO.20.02151
- [70] Ngoi NYL, Tan DSP. The role of homologous recombination deficiency testing in ovarian cancer and its clinical implications: do we need it? *ESMO Open* 2021; 6: 100144. doi:10.1016/j.esmoop.2021.100144
- [71] Fasching PA, Link T, Hauke J et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). *Ann Oncol* 2021; 32: 49–57. doi:10.1016/j.annonc.2020.10.471
- [72] Fasching PA, Schmatloch S, Hauke J et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative early breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study. *San Antonio Breast Cancer Symposium 2022. Cancer Res* 2023; 83 (Suppl 5): GS5–02. doi:10.1158/1538-7445.SABCS22-GS5-02
- [73] Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 2018; 379: 111–121. doi:10.1056/NEJMoa1804710

- [74] Sparano JA, Gray RJ, Makower DF et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 2015; 373: 2005–2014. doi:10.1056/NEJMoa1510764
- [75] Jonat W, Kaufmann M, Sauerbrei W et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; 20: 4628–4635. doi:10.1200/JCO.2002.05.042
- [76] Ruddy KJ, Schaid DJ, Partridge AH et al. Genetic predictors of chemotherapy-related amenorrhea in women with breast cancer. *Fertil Steril* 2019; 112: 731–739.e1. doi:10.1016/j.fertnstert.2019.05.018
- [77] Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; 24: 5769–5779. doi:10.1200/JCO.2006.07.2793
- [78] Pagani O, O'Neill A, Castiglione M et al. Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) Trial VI. *Eur J Cancer* 1998; 34: 632–640. doi:10.1016/s0959-8049(97)10036-3
- [79] Francis PA. Role of Ovarian Suppression in Early Premenopausal Breast Cancer. *Hematol Oncol Clin North Am* 2023; 37: 79–88. doi:10.1016/j.hoc.2022.08.006
- [80] Sparano J, Gray RJ, Makower D et al. Abstract GS1–05: Trial Assigning Individualized Options for Treatment (TAILORx): An update including 12-year event rates. San Antonio Breast Cancer Symposium 2022. *Cancer Res* 2023; 83 (Suppl 5): GS1–05. doi:10.1158/1538-7445.SABCS22-GS1-05
- [81] Karadal B, Kim G, Sharma V et al. Abstract GS1–02: Racial Disparity in Tumor Microenvironment and Outcomes in Residual Breast Cancer Treated with Neoadjuvant Chemotherapy. San Antonio Breast Cancer Symposium 2022. *Cancer Res* 2023; 83 (Suppl 5): GS1–02. doi:10.1158/1538-7445.SABCS22-GS1-02
- [82] Roh-Johnson M, Bravo-Cordero JJ, Patsialou A et al. Macrophage contact induces RhoA GTPase signaling to trigger tumor cell intravasation. *Oncogene* 2014; 33: 4203–4212. doi:10.1038/onc.2013.377
- [83] Wyckoff JB, Wang Y, Lin EY et al. Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. *Cancer Res* 2007; 67: 2649–2656. doi:10.1158/0008-5472.CAN-06-1823
- [84] Harney AS, Arwert EN, Entenberg D et al. Real-Time Imaging Reveals Local, Transient Vascular Permeability, and Tumor Cell Intravasation Stimulated by TIE2hi Macrophage-Derived VEGFA. *Cancer Discov* 2015; 5: 932–943. doi:10.1158/2159-8290.CD-15-0012
- [85] Robinson BD, Sica GL, Liu YF et al. Tumor microenvironment of metastasis in human breast carcinoma: a potential prognostic marker linked to hematogenous dissemination. *Clin Cancer Res* 2009; 15: 2433–2441. doi:10.1158/1078-0432.CCR-08-2179
- [86] Karagiannis GS, Condeelis JS, Oktay MH. Chemotherapy-induced metastasis: mechanisms and translational opportunities. *Clin Exp Metastasis* 2018; 35: 269–284. doi:10.1007/s10585-017-9870-x
- [87] Rohan TE, Xue X, Lin HM et al. Tumor microenvironment of metastasis and risk of distant metastasis of breast cancer. *J Natl Cancer Inst* 2014; 106: dju136. doi:10.1093/jnci/dju136
- [88] Sparano JA, Gray R, Oktay MH et al. A metastasis biomarker (MetaSite Breast Score) is associated with distant recurrence in hormone receptor-positive, HER2-negative early-stage breast cancer. *NPJ Breast Cancer* 2017; 3: 42. doi:10.1038/s41523-017-0043-5
- [89] Karagiannis GS, Pastoriza JM, Wang Y et al. Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism. *Sci Transl Med* 2017; 9: eaan0026. doi:10.1126/scitranslmed.aan0026
- [90] DeMichele A, Yee D, Esserman L. Mechanisms of Resistance to Neoadjuvant Chemotherapy in Breast Cancer. *N Engl J Med* 2017; 377: 2287–2289. doi:10.1056/NEJMcibr1711545