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# Update Breast Cancer 2022 Part 1 – Early Stage Breast Cancer

## Update Mammakarzinom 2022 Teil 1 – Brustkrebs in frühen Krankheitsstadien

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**ABSTRACT**

Evidence relating to the treatment of breast cancer patients with early-stage disease has increased significantly in the past year. Abemaciclib, olaparib, and pembrolizumab are new drugs with good efficacy in the relevant patient groups. However, some questions remain unanswered. In particular, it remains unclear which premenopausal patients with hormone receptor-positive breast cancer should be spared unnecessary treatment. The question of the degree to which chemotherapy exerts a direct cytotoxic effect on the tumor or reduces ovarian function through chemotherapy could be of key importance. This group of patients could potentially be spared chemotherapy. New, previously experimental biomarker analysis methods, such as spatial analysis of gene expression (spatial transcriptomics) are gradually finding their way into large randomized phase III trials, such as the NeoTRIP trial. This in turn leads to a better understanding of the predictive factors of new therapies, for example immunotherapy. This review summarizes the scientific innovations from recent congresses such as the San Antonio Breast Cancer Symposium 2021 but also from recent publications.

**ZUSAMMENFASSUNG**

Die Erkenntnisse über die Behandlung von Mammakarzinompatientinnen mit frühen Krankheitsstadien haben im letzten Jahr deutlich zugenommen. Abemaciclib, Olaparib und Pembrolizumab sind neue Medikamente mit einer guten Wirksamkeit bei den entsprechenden Patientinnengruppen. Jedoch sind einige Fragestellungen nach wie vor unbeantwortet. Insbesondere welchen Patientinnen unnötige Therapien erspart werden können, ist bei prämenopausalen Patientinnen mit einem hormonrezeptorpositiven Mammakarzinom weiterhin unklar. Die Frage, inwieweit eine Chemotherapie einen direkten zytotoxischen Effekt auf den Tumor hat oder eher dadurch wirkt, dass die Ovarfunktion durch die Chemotherapie reduziert wird, könnte wegweisend sein. Dieser Patientinnengruppe kann möglicherweise eine Chemotherapie erspart bleiben. Neue, bislang experimentelle Biomarker-Analysemethoden, wie die räumliche Analyse der Genexpression (spatial transcriptomics), halten nach und nach Einzug in die großen randomisierten Phase-III-Studien, wie die NeoTRIP-Studie. Dies führt wiederum zum besseren Verständnis der prädiktiven Faktoren neuer Therapien, zum Beispiel der Immuntherapie. Diese Übersichtsarbeit fasst die wissenschaftlichen Neuerungen der aktuellen Kongresse wie dem San Antonio Breast Cancer Symposium 2021, aber auch von kürzlich veröffentlichten Publikationen zusammen.

## Introduction

Recent scientific findings relating to the prevention and treatment of patients with early-stage breast cancer refer mainly to the recently introduced new drug classes of CDK4/6, PARP and immune checkpoint inhibitors. In addition, many studies address the question of whether treatment can be de-escalated without loss of efficacy. This includes both surgical trials, such as the INSEMA trial, and trials assessing the use of multigene testing of affected lymph nodes, as in the RxPONDER trial. Knowledge of prevention is improving, and about 40 % of heritable familial risk can be explained by genetics. There is a need to develop definitive new prevention strategies, also in the context of non-genetic modifiable risk factors. These and other issues are discussed below.

## Prevention, *BRCA1/2* and Germline Testing

### Prevention and germline gene variants

With the advent of PARP inhibitors in the treatment of patients with breast carcinoma in both early and metastatic disease [1–5], genetic testing for germline mutations in the *BRCA1/2* genes is now considered necessary in most national and international treatment recommendations [6–8]. Studies in subgroups of patients with a lower mutation frequency indicate that testing is also useful in these patient groups [1, 9–11]. In unselected patients with advanced breast cancer, it was not possible to identify relevant subgroups with mutation frequencies below 3 % [9]. Only patients over the age of 60 and patients with a G1 tumor had lower mutation frequencies, however these always exceeded 0.5 %, which is still considered a threshold for meaningful testing in lung cancer and a *BRAF* mutation.

The *PALB2* gene also has high penetrance and carries a lifetime risk of breast cancer similar to the risk of a *BRCA2* mutation. *PALB2* is among the panel genes that are commonly tested [12–14]. Preliminary evidence exists that olaparib would have clinically relevant activity in patients with a *PALB2* mutation [15].

### Prevention interventions

In recent years, more and more genetic causes associated with familial breast cancer risk have been discovered [16–22], and approximately 40 % of the twofold increase in familial breast cancer risk can be explained [23]. However, the majority of breast cancer cases cannot be explained by genetic factors. In recent years, little has changed in the recommendations for the prevention of this disease. The relevant studies and their effects have recently been summarized [24, 25]. It is important to note that the prevention trials with tamoxifen, anastrozole, and exemestane did not dem-

▶ **Table 1** Results of chemoprevention trial endpoints for breast cancer.

| Trial (n) | Intervention | Breast cancer incidence | | | Death from breast cancer | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | Placebo | Intervention | RR or HR[1] | Placebo | Intervention | HR[2] | |
| NSABP-P1 (n = 13 388) | Tamoxifen | 250 | 145 | 0.57 (0.46–0.70) | 11 | 12 | NR | [67] |
| Royal Marsden (n = 2494) | Tamoxifen | 104 | 82 | 0.78 (0.58–1.04) | 9 | 12 | NR | [68] |
| IBIS1 (n = 7154) | Tamoxifen | 350 | 251 | 0.70 (0.60–0.83) | 26 | 31 | NR | [69] |
| IBIS2 (n = 3864) | Anastrozole | 165 | 85 | 0.51 (0.39–0.66) | 3 | 2 | NR | [70] |
| MAP3 (n = 4560) | Exemestane | 32 | 11 | 0.35 (0.18–0.70) | 0 | 1 | NR | [71] |

[1] Relative risk (RR) for the Royal Marsden trial and hazard ratio (HR) for all other studies.

[2] Hazard ratios (HR) not reported. Note the low case numbers.

onstrate a reduction in mortality from breast cancer. Indeed, there were cumulatively more deaths (n = 58) in the anti-hormonal prevention groups than in the placebo arms (n = 49) (▶ **Table 1**). Although the numbers of deaths is very low, no trend can be identified. By contrast, the Womens Health Initiative (WHI) trial showed that breast cancer mortality was reduced in the group of women who had undergone hysterectomy. In the WHI trial, hysterectomized women were randomized to an estrogen monotherapy (n = 5310) arm and a placebo (n = 5429) arm [26]. In the estrogen monotherapy group, the incidence of breast cancer was reduced (hazard ratio [HR] = 0.78, 95% CI: 0.65–0.93), as was breast cancer-related mortality (HR = 0.60; 95% CI: 0.37–0.97) [24, 26]. It must be emphasized that in the group of women who had not undergone hysterectomy, who were randomized to either an estrogen + progesterone replacement group or a placebo group, the incidence of breast cancer was increased in the estrogen + progesterone group. Furthermore, there was an increase in breast cancer-related mortality and the incidence of cardiovascular disease [27]. This led to a dramatic decrease in the use of hormone replacement therapies after publication in 2002.

Nonetheless, in light of these studies with long-term follow-up, it should be noted that antiestrogenic medication did not reduce breast cancer mortality, whereas a trial with estrogen therapy showed a possible reduction in mortality. The corresponding results cannot be transferred into practice; they represent the current state of knowledge for pharmacological prevention.

### Vaccines as prevention

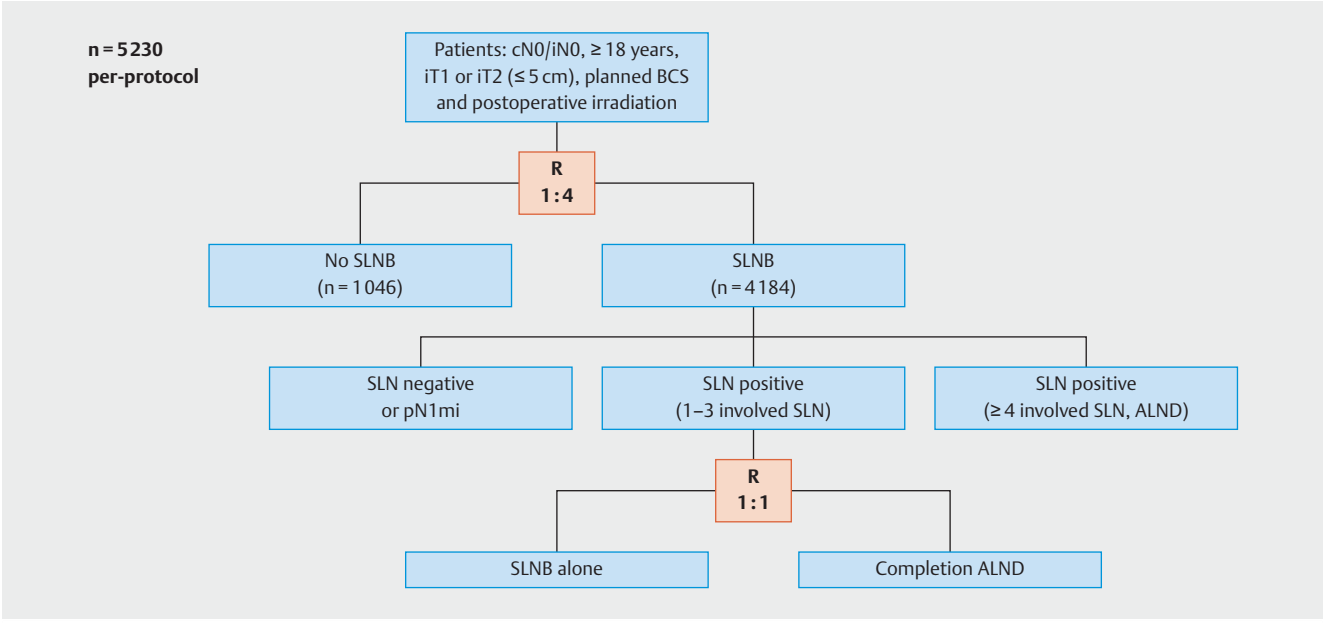
Another issue that is undoubtedly coming back into focus in light of vaccination in the COVID-19 pandemic is the attempt to prevent or treat breast cancer through vaccination. In this context, much of the discussion is based on antigens that are probably unique to breast cancer or on those that are measured individually (neo-antigens). These, in turn, are based on the genomic variants and aberrations that occur in the pathogenesis of the disease. It is known that a relevant proportion of breast cancers elicit an immune response that has an effect on treatment efficacy and prognosis [28–30]. Vaccines against SARS-CoV-2 have been developed extremely quickly. The platforms used for this purpose were initially developed, among other things, for the rapid production of cancer vaccines [31–33]. It is now hoped that the leap in development and the available data on the safety of such a vaccine can significantly advance this field of research. Indeed, several trials involving an mRNA approach are either in the planning stage or already under way [34]. Parallel efforts are being undertaken to identify tumor antigens or neo-antigens from cancers that may help identify targets for vaccination [35–37]. It remains to be seen how each type of cancer would respond to a modified immune system and whether such technology can be used for prevention.

## De-escalation of Axillary Surgery

Axillary lymph node dissection is one of the main causes of long-term sequelae such as edema or functional limitation of the arm on the operative side. However, some trials have already demonstrated good local and regional tumor control in the absence of axillary lymph node dissection [38, 39]. In the INSEMA trial from GBG, AGO-B and ABCSG, this question was assessed using a randomized study design (▶ **Fig. 1**). The quality of life data from this trial, which were collected using the EORTC-QLQ-C30 and BR23 questionnaires [38], have now been reported.

The INSEMA trial analyzed the consequences of omitting a surgical assessment of lymph node status by sentinel node biopsy (SLNB) in the cN0 group. Over 1000 patients had no axillary intervention and over 4000 patients underwent sentinel node biopsy (first randomization). The group of patients with a positive sentinel lymph node was subject to a second randomization (complete axillary dissection vs. no further treatment).

With respect to the first randomization, the omission of SLNB did not result in a clinically significant improvement in overall quality of life [38]. However, there were significant differences in terms of the arm symptom score on the EORTC-QLQ-BR23 questionnaire. In the long term, patients who did not undergo axillary




▶ **Fig. 1** Study design of the INSEMA trial.

surgery had a mean score of approximately 16. In contrast, patients who underwent surgery had a mean score of approximately 20 [38].

With respect to the second randomization, patients who underwent the less invasive procedure also fared significantly better in terms of their arm symptom score. Patients with SLNB alone had values of approximately 20–22, while patients who underwent complete axillary lymph node dissection had mean values of approximately 28–30 [38].

The benefits of a less invasive approach in terms of quality of life have thus been described. The extent to which this has an impact on prognosis will be determined by future analyses of the primary and secondary objectives of the INSEMA trial.

## Patients with Hormone Receptor-Positive Breast Cancer in Early Stages of Disease

### Aromatase inhibitors or tamoxifen with and without ovarian suppression in the context of adjuvant treatment in premenopausal patients

One issue that has puzzled scientists for more than a decade is which hormone receptor-positive premenopausal patients should receive ovarian function suppressor (OFS) treatment in the context of adjuvant treatment. Previous studies have shown that the addition of OFS to tamoxifen may improve disease-free survival and that treatment with aromatase inhibitors and OFS may have other advantages over treatment with tamoxifen and OFS. However, treatment escalation is associated with adverse effects and a reduction in quality of life. Therefore, OFS or treatment with aromatase inhibitors plus OFS is recommended only in patients at high risk of recurrence (e.g., after chemotherapy), whereas patients at lower risk of recurrence should preferably be treated with tamoxifen monotherapy. In patients at intermediate risk of recurrence, treatment with tamoxifen and OFS is recommended [6, 8]. However, it is often difficult to define risk categories with precision and it is up to the interdisciplinary tumor conference to determine the classification on an individual basis.

A meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) was recently published, comparing patients who were all treated with OFS and then randomized to treatment with either tamoxifen or aromatase inhibitors [40]. The analysis included 7030 patients enrolled in the following studies: ABCSG-12, SOFT, TEXT, HOBOE. The median follow-up period was 8.0 years. It was shown that the recurrence rate with OFS plus aromatase inhibitors versus OFS plus tamoxifen was reduced from 17.5 % to 14.7 % at 10 years (RR = 0.79; 95 % CI: 0.69–0.90). Although there was improvement in distant metastasis-free survival with a relative risk of 0.83 (95 % CI: 0.71–0.97), there was no improvement in terms of overall survival. The mortality rate at 10 years was 7.2 % with tamoxifen plus OFS and 6.8 % with aromatase inhibitors plus OFS (RR = 1.01; 95 % CI: 0.82–1.24).

Interestingly, the effect was observed only in years 2–4 after surgery and in patients with up to 3 affected lymph nodes. The effect was not detectable in patients with more than 4 affected lymph nodes (RR = 1.03; 95 % CI: 0.73–1.46) [40]. However, only 729 patients were assigned to this cohort, so no firm conclusions regarding risk subgroups should be made on the basis of this analysis.

Similarly, in the context of premenopausal patients with hormone receptor-positive breast cancer, a new analysis of the SOFT and TEXT trials was published. This analysis had an even longer follow-up period than previous publications. Essentially, two ques-

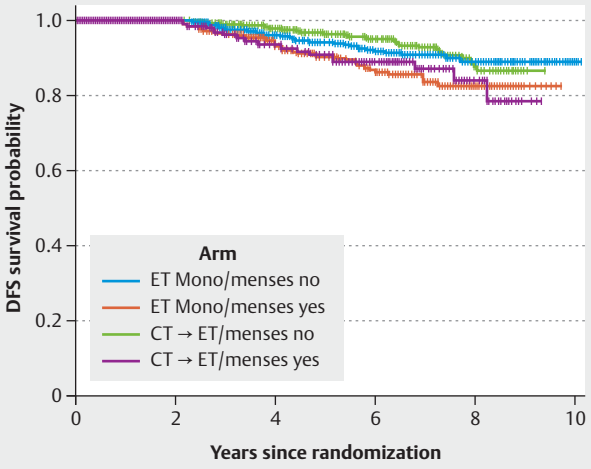
tions were addressed by the analyses of the SOFT and TEXT trials, the first being the addition of OFS to tamoxifen and the second being the analysis of tamoxifen vs. aromatase inhibitors. The median follow-up period was 12 years for the SOFT trial and 13 years for the TEXT trial [41]. This analysis further demonstrated that overall survival was improved with the addition of OFS. Subgroup analyses showed that this effect was greatest in the cohort at highest risk of recurrence (e.g., status after [neo]adjuvant chemotherapy, age < 35 years, more than 3 affected lymph nodes, grading 3) [41]. No difference was detected in patients at low risk of recurrence. It should be noted that these subgroup analyses are based in part on very low case numbers. Only 103, 103, and 126 deaths occurred in the tamoxifen alone, tamoxifen plus OFS, and exemestane plus OFS groups, respectively [41].

## Chemotherapy in premenopausal patients

Modern biomarker studies use multigene assays to investigate whether chemotherapy can be avoided in some patients with hormone receptor-positive breast cancer (MINDACT, TailorX, RxPONDER, ADAPT). They have all shown that in young patients < 50 years of age or in premenopausal patients, chemotherapy resulted in some improvement in prognosis even in terms of conventional cut-offs, whereas in postmenopausal patients with an appropriate risk score, there were no differences between patients who had received only antihormone treatment and those who had received additional chemotherapy [42–44].

The reasons for this finding are unknown. However, if it is due to the effect of chemotherapy on ovarian function (premature ovarian failure), another option would be to investigate whether ovarian suppression can be administered to premenopausal patients in order to spare them chemotherapy. Similarly, the results of the ADAPT trial showed that young women with up to 3 affected lymph nodes, a recurrence score ≤ 25, and a good response ($Ki67_{post}$ ≤ 10 %) to a short course of preoperative endocrine treatment had excellent 5-year metastasis-free survival. This suggests that chemotherapy could be omitted if the efficacy of endocrine treatment is optimal [45].

In an analysis of the German SUCCESS trials, 39 % of more than 1150 premenopausal patients under 45 years of age no longer had menstrual bleeding after chemotherapy [46]. The proportion of patients of approximately 40 % corresponds to the prognostic effect in the multigene studies, but this is only a hypothesis and remains to be proven. In this context, analyses such as those presented at the San Antonio Breast Cancer Symposium are of particular importance. In this regard, data from the RxPONDER trial have been analyzed in detail as a post-hoc analysis of the subgroup of premenopausal patients (n = 1654) [47]. In the recently published study, which had a median follow-up of 6.1 years (previously 5.3 years), the chemotherapy benefit for premenopausal patients in terms of disease-free survival (HR = 0.64; 95 % CI: 0.47–0.87) and distant metastasis-free survival (HR = 0.66; 95 % CI: 0.45–0.97) confirmed the benefit of chemotherapy plus endocrine treatment compared with endocrine treatment alone [47]. After chemotherapy, approximately 75 % of women in the chemotherapy arm and approximately 50 % in the endocrine monotherapy arm had no menstrual bleeding in the first 6 months after randomization. Although no formal analysis was carried out on this question, there appears to be no difference between patients receiving endocrine treatment alone vs. chemotherapy, especially in patients in whom menstrual bleeding persisted. In patients whose menstrual bleeding had stopped, there appeared to be a modest benefit in the chemotherapy group (▶ **Fig. 2**).




▶ **Fig. 2** Invasive disease-free survival in the RxPONDER trial in the premenopausal patient group. ET: endocrine treatment, CT → ET: Chemotherapy and endocrine treatment (data from [47]).

The question for future studies is how to identify the group of premenopausal patients in whom chemotherapy can be avoided without worsening the prognosis. Until then, chemotherapy in this group must be considered on a case-by-case basis, depending on patient and disease characteristics. In this regard, it may be helpful to determine the endocrine response by means of a short course of preoperative endocrine treatment, similar to the approach used in the ADAPT trials.

## CDK4/6 inhibitors in the adjuvant setting

Despite the negative outcome of the PALLAS trial, which investigated additional adjuvant therapy with 2 years of palbociclib [48], the final analysis of 469 events (previously 313) has now been reported [49]. There was no change with respect to the primary endpoint (invasive disease-free survival). The hazard ratio was 0.96 (95 % CI: 0.81–1.14). The subgroup analysis also failed to identify any group that demonstrated particularly high efficacy. Previously, it had been discussed that the risk profile in the study population may not have been set high enough to show a difference. Again, this could not be confirmed by the current subgroup analysis. Moreover, it appeared that patients with negative lymph nodes derived greater benefit from taking palbociclib (HR: 0.63; 95 % CI: 0.37–1.08) compared with patients with positive lymph nodes (hazard ratios ranging from 0.89 to 1.09) [49]. The adjuvant MonarchE trial had already yielded positive results, following which abemaciclib was approved for adjuvant treatment of high-risk patients in the United States [50]. The first, early analyses of the adjuvant ribociclib Natalee/TRIO-033 trial are expected in late

2022 [51]. In Germany, the ADAPT$^{cycle}$ and ADAPT$^{late}$ trials on the significance of CDK 4/6i in early breast cancer are still ongoing.

In Europe, regulatory approval of abemaciclib is expected in the near future (as of March 2022), as the EMA has already made a recommendation [52]. The recommendation for the appropriate indication is the combination of abemaciclib with endocrine treatment in HER2-negative, hormone receptor-positive breast cancer with positive lymph node status and high risk of recurrence. Thus, widespread adoption of abemaciclib in patients with early breast cancer is anticipated in the near future. In particular, if this treatment becomes more widely used, issues such as treatment adherence and the management of toxicity will undoubtedly become the focus of adjuvant endocrine-based treatment once again. A recent publication described discontinuation rates due to side effects in addition to quality of life. In the abemaciclib arm, discontinuation rates due to adverse events for abemaciclib were 18.5% [53]. Aromatase inhibitors are also known to be discontinued at a similar frequency in the context of adjuvant treatment [54]. The extent to which abemaciclib or the aromatase inhibitor contributes to this is a subject for future research.

### Selective estrogen receptor degraders

The selective estrogen receptor degraders (SERDs) are currently being investigated in many clinical trials in the metastatic setting and early disease stages [55, 56]. Since fulvestrant was not developed for adjuvant treatment [57], it is hoped that oral SERDs will further improve adjuvant endocrine treatment. Adjuvant trials such as liDERA/TRIO-045 or AMEERA-6 are already recruiting. Therefore, it is important to collect data to study the mode of action of SERDs in patients with early-stage disease. One such trial is the neoadjuvant coopERA trial, which compared the aromatase inhibitor anastrozole with the SERD giredestrant. Here, final analysis of Ki-67 reduction at 2 weeks showed that giredestrant resulted in a relative reduction of Ki-67 by 75% and anastrazole by 67%. This difference was statistically significant ($p = 0.043$) [58]. After the positive EMERALD trial [59] and the positive coopERA trial [58], there is a strong rationale for investigating SERDs in the early stages of the disease as well.

## Immunotherapy in Early-Stage Disease

### The latest biomarker analysis methods (spatial transcriptomics) have entered clinical trials

The NeoTRIP trial is a biomarker study that uses a methodological principle for biomarkers that will be used more and more in the years to come. For this reason, a brief description of the analysis is included here: When multiple genes are analyzed (as is the case in standard multigene assays), analytical methods have traditionally relied on lysing a portion of the tumor in its entirety and analyzing a sample of all the cells it contains. This can be optimized in terms of tumor content by dissecting different areas of the tumor, but ultimately it was not possible to exclude the presence of cells from the tumor environment in the analysis. With the development of new analytical methods, it is now possible to investigate a variety of markers in situ, in preserved tissue sections, or by spatial labeling of the biomaterial in a locally differentiated manner within the tumor [60, 61].

This makes it possible to assign expression signals to certain cell types, but also to investigate the spatial arrangement of certain cell types in relation to each other [60, 61]. These methods are referred to as “spatial genomics” or “spatial transcriptomics”. ▶ **Fig. 3** shows an example of how such techniques can be applied to a histological section in breast cancer.

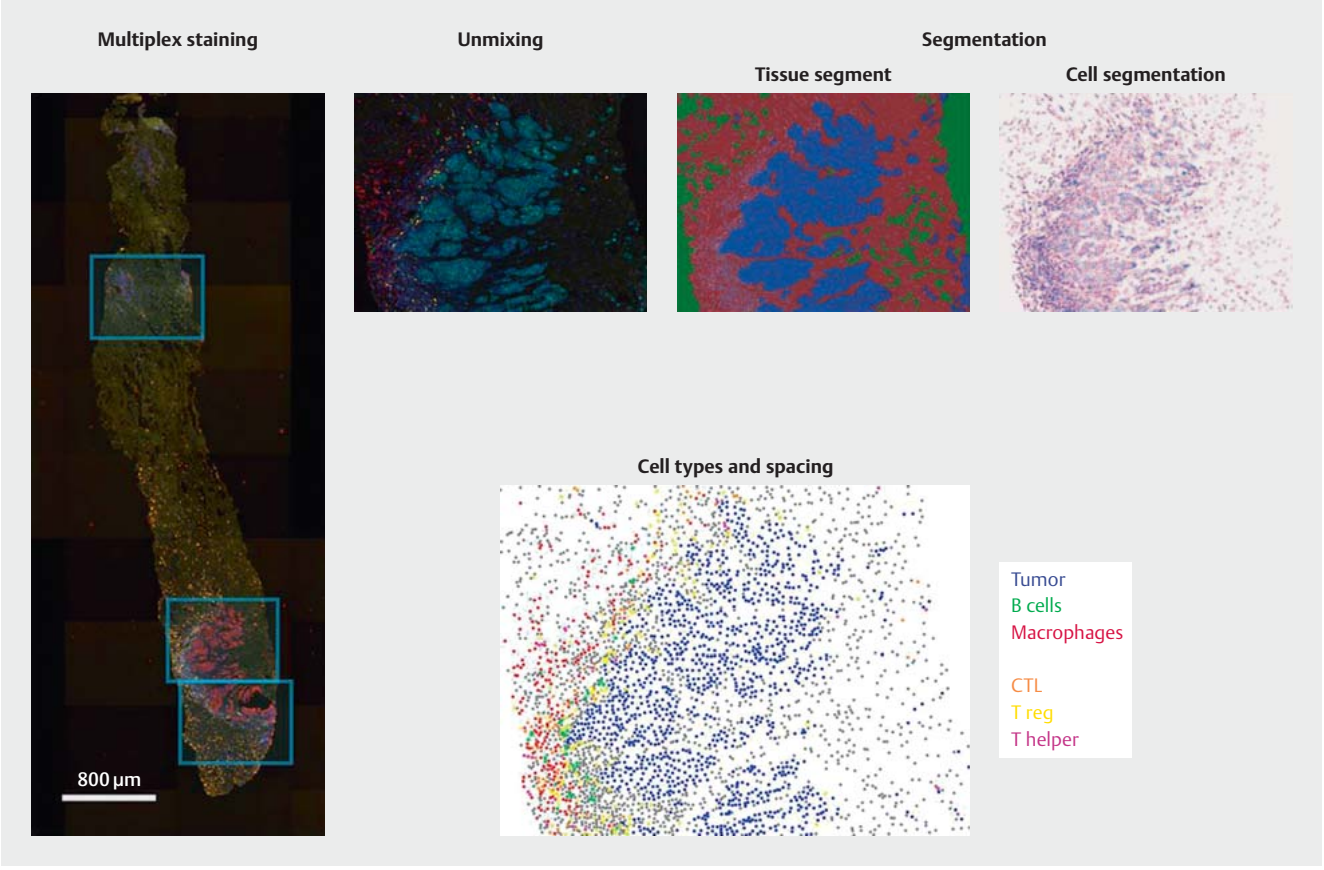
Such analyses have now been performed as part of the NeoTRIP trial, which compared a regimen of carboplatin and nab-paclitaxel with a regimen of carboplatin, nab-paclitaxel, and atezolizumab [62]. A total of 43 markers that can differentiate between immune cells and epithelial cells were assessed using an antibody- and mass spectroscopy-based system [63] in 237 of the 280 patients included. Indeed, two patterns could be identified that predicted a high pCR rate (approximately 65%) and a low pCR rate (approximately 25–35%) in patients treated with atezolizumab, whereas no predictive value was demonstrated for the spatial pattern in patients treated with chemotherapy alone [62].

This type of biomarker analysis will become more widely available in the years to come and will almost certainly provide new insights into tumor biology, particularly in terms of how certain cell types interact. In terms of understanding immune interactions between tumor cells and immune cells in the tumor and lymph nodes, these techniques will provide new, and hopefully clinically relevant, insights into tumor-microenvironment interactions.

### Sensitivity analyses to confirm the effects of immunotherapy

Pembrolizumab has already been approved in the United States for neoadjuvant/adjuvant treatment of patients with triple-negative breast cancer in the early stages of disease based on an analysis of event-free survival [64, 65]. There was an absolute increase of 7.7% in event-free survival at 3 years (from 76.8% with platinum-containing chemotherapy without pembrolizumab to 84.5% with the addition of pembrolizumab) [64]. This corresponded to a hazard ratio of 0.63 (95% CI: 0.48–0.82) [64]. Various sensitivity analyses have now been performed to test the robustness of this analysis. In addition to events such as local recurrence, distant metastases or death, secondary cancer events, initiation of therapy for metastases or positive incision margins at surgery were included. These sensitivity analyses showed no evidence of higher or lower efficacy of pembrolizumab. All hazard ratios ranged from 0.63 to 0.65 [66].

Subgroup analyses by tumor stage or nodal status also showed no relevant differences in terms of the efficacy of pembrolizumab. The hazard ratio in nodal-negative patients was 0.58 (95% CI: 0.37–0.91) and in nodal-positive patients was 0.65 (95% CI: 0.46–0.91). Stratification by AJCC disease stage showed a hazard ratio of 0.60 (95% CI: 0.42–0.86) in stage II and 0.68 (95% CI: 0.45–1.03) in stage III [66].




▶ **Fig. 3** Example of a multiplex analysis of several biomarkers and possible analysis methods for spatial arrangement (spatial proteomics, image courtesy of Barbara Seliger und Chiara Massa, Halle).

## Survival Analyses of the OlympiA Trial

### Adjuvant therapy with olaparib confers an overall survival benefit

The OlympiA trial was designed to investigate whether 12 months of adjuvant therapy with olaparib could improve invasive disease-free survival (iDFS) in patients at high risk of recurrence in the early stages of disease. In the initial publication in 2021, it was shown that iDFS was improved with a HR of 0.58 (95% CI: 0.41–0.82), with a median follow-up of 2.5 years and 1836 randomized patients [1]. Regarding overall survival, the interim analysis showed no statistically significant difference (HR: 0.68; 95% CI: 0.44–1.05; p = 0.02) [1]. The next interim analysis has now been published, with a median follow-up of 3.5 years [5]. The median PFS is now 0.63 (95% CI: 0.50–0.78). In terms of overall survival, this interim analysis has now reported statistical significance with a hazard ratio of 0.68 (95% CI: 0.47–0.97, p = 0.009) [5]. On the basis of these data, adjuvant therapy with olaparib was approved in the United States on March 11, 2022. It is certain to become established as a new therapeutic standard in Europe following approval.

## Future Perspectives

Some of the current issues are highly relevant because they have a direct effect on quality of life and the effectiveness of current treatments. There is an urgent need for clarity as to whether and which patients will benefit from chemotherapy, especially premenopausal patients with hormone receptor-positive breast cancer. This is where scientific efforts should be focused. In terms of new treatments, major adjuvant trials with SERDs are underway and other trials have been running for a long time. The question of whether trastuzumab-deruxtecan confers an advantage over T-DM1 in the HER2-positive post-neoadjuvant setting is currently being investigated as part of the DESTINY-B05/Trudy/AGO-B50 trial. The Astefania trial is investigating whether the effect of T-DM1 in this setting can be improved by immunotherapy with atezolizumab. Whether the anti-TROP2 ADC sacituzumab-govitecan is a good adjunct to the current regimen in triple-negative patients in the post-neoadjuvant setting is currently being investigated as part of the SASCIA trial. Individualized post-neoadjuvant therapies that are adapted to the genetic variants of resistant residual tumor tissue after neoadjuvant chemotherapy are also being investigated in innovative study designs with extensive translational support programs.

The next few years are expected to bring new discoveries that will improve treatment and, in some cases, reduce the need for unnecessary and toxic treatments that adversely impact quality of life.

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## Conflict of Interest

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