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Update Breast Cancer 2023 Part 3 – Expert Opinions of Early Stage Breast Cancer Therapies

Update Mammakarzinom 2023 Teil 3 – Expertenmeinungen zu Brustkrebs in frühen Krankheitsstadien

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ABSTRACT

The St. Gallen (SG) International Breast Cancer Conference is held every two years, previously in St. Gallen and now in Vienna. This year (2023) marks the eighteenth edition of this conference, which focuses on the treatment of patients with early-stage breast carcinoma. A panel discussion will be held at the end of this four-day event, during which a panel of experts will give their opinions on current controversial issues relating to the treatment of early-stage breast cancer patients. To this end, questions are generally formulated in such a way that clinically realistic cases are presented – often including poignant hypothetical modifications. This review reports on the outcome of these discussions and summarises the data associated with individual questions raised.

ZUSAMMENFASSUNG

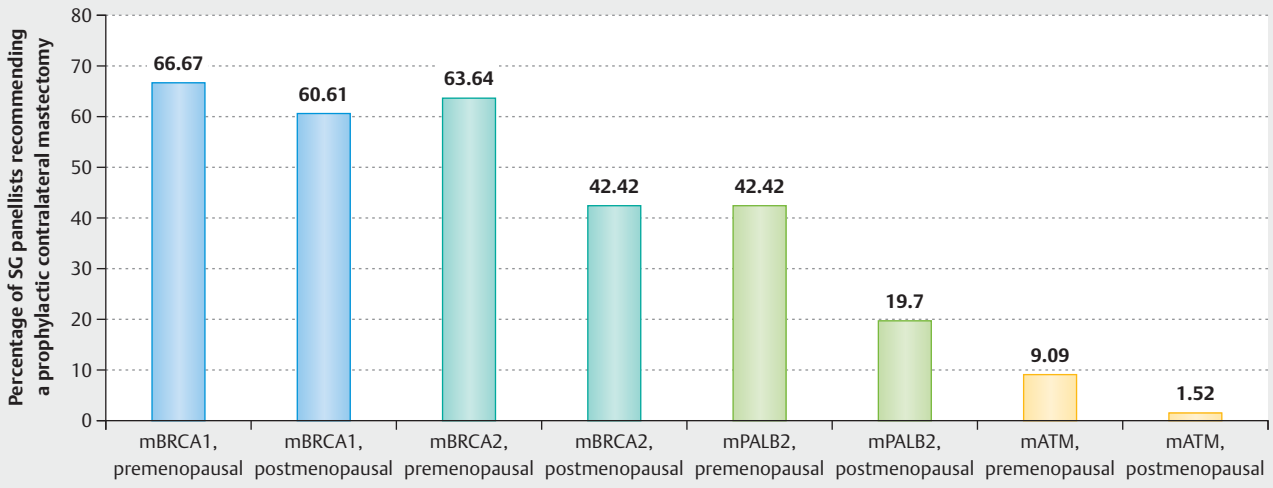
In einem 2-jährigen Rhythmus fand in St. Gallen in früheren Jahren und nun in Wien die „St. Gallen (SG) International Breast Cancer Conference“ statt. Dieses Jahr (2023) wurde diese Konferenz, die sich mit der Behandlung von Patientinnen in Frühstadien des Mammakarzinoms beschäftigt, zum 18. Mal durchgeführt. Am Ende dieser 4-tägigen Veranstaltung wird eine Panel-Abstimmung abgehalten, bei der ein Expertengremium über aktuelle kontroverse Themen bei der Behandlung von Brustkrebspatientinnen in Frühstadien abstimmt. Hierbei werden die Fragen meistens so formuliert, dass klinisch realistische Fälle – oft in verschiedenen Modifikationen – vorgestellt werden. Diese Übersichtsarbeit berichtet von den Abstimmungsergebnissen und fasst die mit den jeweiligen Fragen verbundene Datenlage zusammen.

Background

The St. Gallen International Breast Cancer Conference in Vienna focuses on the treatment of patients with early stages of breast carcinoma. After three days of predominantly review lectures on key topics, on day four, a panel discusses key topics on the treatment of patients with early-stage breast carcinoma. The questions and their responses are recorded in this paper (Supplementary Table **S1**), which were assessed by the St. Gallen panellists (SG panellists; Supplementary Table **S2**). Furthermore, a number of selected topics are presented in a research context, which provides more detailed background information for the assessment of the questions.

Quality of Life and Survivorship

One study that has been discussed since the Breast Cancer Conference in San Antonio in 2022 because of its clinical relevance to patients is the POSITIVE study. This study included young female patients on antihormone therapy who wanted to have children. The relapse rate was determined if endocrine therapy was interrupted for a maximum of two years. Out of the 516 patients included in the study, approximately 75% became pregnant and 44 had a relapse at a median follow-up of 41 months [1]. In Vienna/St. Gallen, two cases were presented, one of a premenopausal patient with more than three positive lymph nodes (high risk of relapse) and one of a still relatively young woman intending to preserve fertility after endocrine therapy (age 28). In both cases, the majority of SG panellists (approx. 78%) would not have opted to follow the POSITIVE study approach (Supplementary Table **S1; Questions 4 and 5**). Apparently, the high risk of relapse in the cases presented and the prospect of pregnancy after the end of regular endocrine therapy discouraged experts to opt to discontinue endocrine therapy. It remains to be determined how the data from the POSITIVE study will be assessed clinically based on a longer follow-up period.



▶ **Fig. 1** Presentation of results across multiple questions on how many SG panellists would recommend contralateral mastectomy in breast cancer patients in different situations and with different identified germline mutations (mBRCA1: BRCA1 germline mutation; mBRCA2: BRCA2 germline mutation; mPALB2: PALB2 germline mutation; mATM: ATM germline mutation).

Genetics

Although a number of breast cancer risk genes have been previously established [2–8] and approximately 40% of the family breast cancer risk can be explained [9], the mutation frequencies for most established breast cancer risk genes are low. After *BRCA1/2* mutations, *PALB2* mutations are among the most common germline mutations. However, the frequency among breast cancer patients is still very low at 0.5–2%, and in individuals without breast cancer, the mutation rate is approximately 0.1% [3]. Therefore, for most genes genotyped in panel testing [10], individual evidence for preventive and therapeutic interventions will be difficult to collect, simply because of low case numbers. Against this backdrop, the SG panel decisions were of particular interest. Here, the SG panel asked for opinions on contralateral prophylactic mastectomy for patients who received a new breast carcinoma diagnosis and a diagnosis of a mutation in different breast cancer risk genes. The panel decisions are shown in ▶ **Fig. 1**. It can be concluded that SG panellists are less likely to recommend contralateral mastectomy for lower lifetime risk and postmenopausal patients than for higher risk and younger patients. Particularly in the case of intermediate-risk constellations, opinions still differ considerably (e.g. in the case of *PALB2* mutations or in postmenopausal patients with *BRCA2* mutations). These results are consistent with the lifetime risk estimates published by the Breast Cancer Association Consortium (BCAC) (▶ **Fig. 2**) [3].

Adjuvant Endocrine Therapy and Chemotherapy Decisions in HRpos/HER2neg Patients

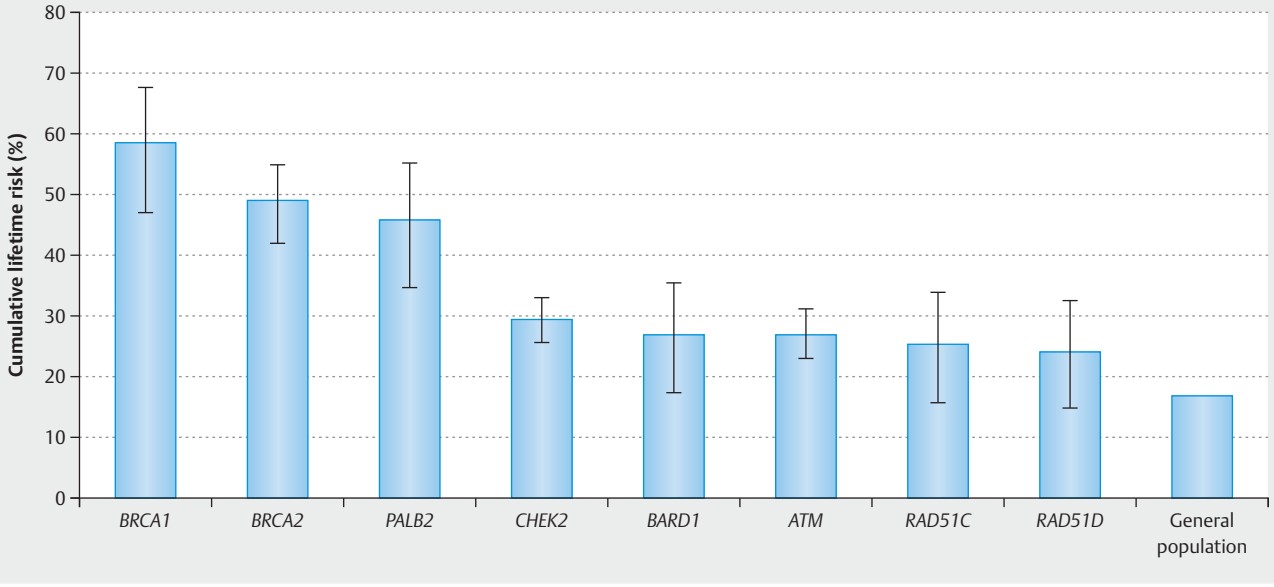
Endocrine therapies and abemaciclib

The main issues discussed in adjuvant endocrine therapy are:

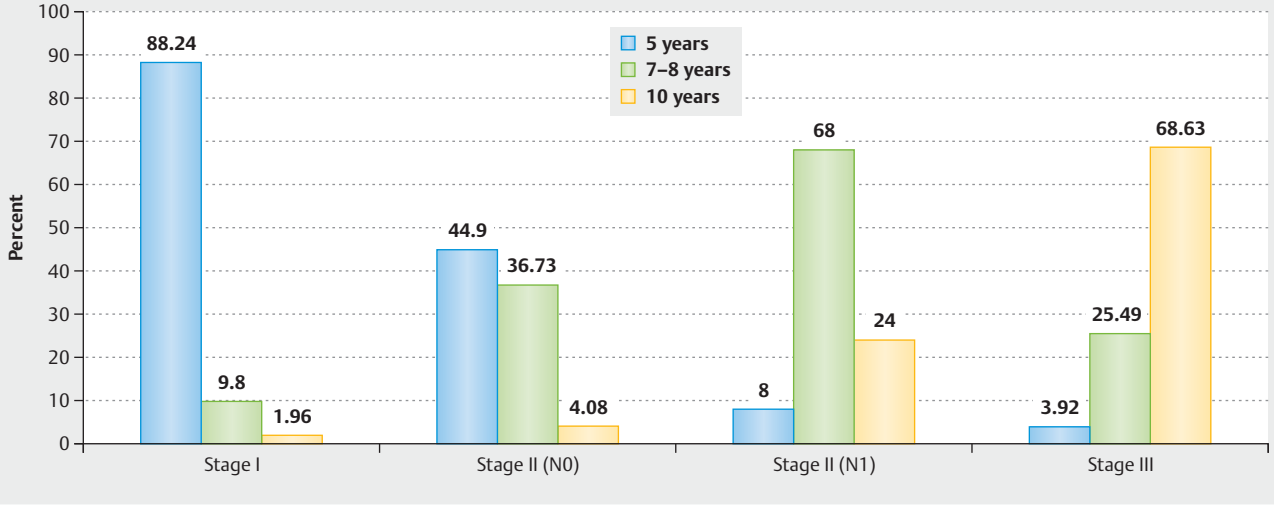
- the length of the adjuvant endocrine therapy,
- the use of CDK4/6 inhibitors (only abemaciclib has been approved to date),
- the use of aromatase inhibitors + ovarian function suppression (OFS) in premenopausal patients,
- the addition of OFS to tamoxifen therapy in premenopausal patients.

With regard to the indication for chemotherapy, different biomarkers have been established that can reliably identify patients with an excellent prognosis [11–14]. In premenopausal patients, the situation is more complex because, in principle, three different endocrine therapies (tamoxifen, tamoxifen + GnRH analogue and aromatase inhibitor + GnRH analogue) are available. Ovarian Function Suppression (OFS) with GnRH analogues is an effective medication to suppress ovary function. However, after chemotherapy, a large proportion of premenopausal patients have persistent chemotherapy-induced amenorrhea [15–17]. In the premenopausal setting, risk, indication for chemotherapy and implementation of endocrine therapy therefore influence each other.

With regard to the length of endocrine therapy, there is a clear trend among SG panellists to consider that the length of therapy is dependent on stage (▶ **Fig. 3**, **Questions 74 to 77**). Interestingly, a length of 7–8 years encompasses a pertinently large group of patients of all stages. The assessment of the benefit/risk ratio based on the large number of studies conducted appears to favour the duration of 7–8 years of general therapy [18–26]. A ge-



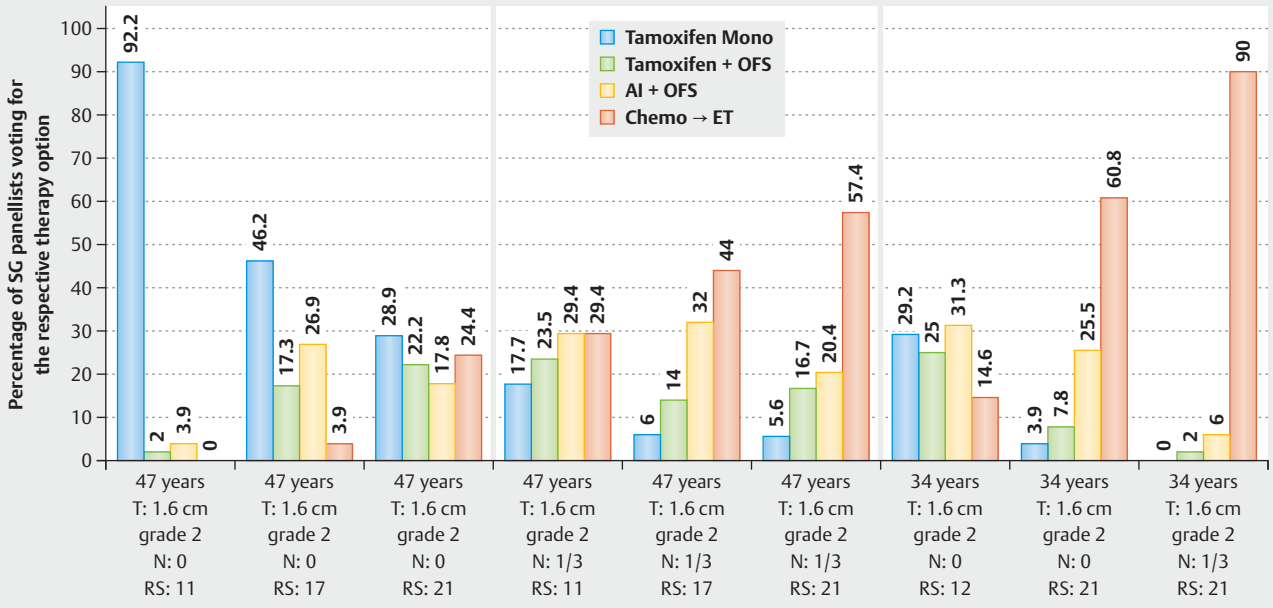
▶ **Fig. 2** Lifetime risk until the age of 80. The age of onset for the eight validated breast cancer risk genes [3] (Illustration from [65]).



▶ **Fig. 3** The panel decision for different stages of HRpos/HER2neg breast carcinoma in relation to the length of endocrine therapy.

nomic test does not appear to be necessary (**Questions 78 and 79**) to determine the duration of endocrine therapy.

To date, there are positive studies for two CDK4/6 inhibitors, the monarchE study [27–29] and the NATALEE/TRIO-033 study [30]. Abemaciclib is already approved for patients at high risk. In Europe, the approval is based on patients corresponding to cohort I. These were patients with at least 4 positive lymph nodes or 1–3 positive lymph nodes and additionally a tumour of at least 5 cm in size or a tumour grading of 3. In the USA, the use of abemaciclib was additionally dependent on the biomarker Ki-67. This has been repeatedly criticised by the research and clinical community [31, 32]. This was also the view of the majority of SG panellists (77.27%, **Question 80**). In fact, the US Food and Drug Administration (FDA) recently adjusted the indication so that the criteria in the US are now the same as in Europe [33]. In relation to the indication for abemaciclib, the exact prognosis of patients is expected to play an important role in the future. For example, determining the lymph node status in the context of the current clinical procedure is also important for axillary staging. It is not always feasible to remove four lymph nodes. For example, the SG panel dealt with the situation where only one lymph node was assessed as part of an axillary sentinel node biopsy and this lymph node contained tumour cells. With a grading of 2 and a tumour size of 2.3 cm, this hypothetical patient would have received adju-



▶ **Fig. 4** SG panellists therapy choices for different scenarios involving treatment of premenopausal patients with HRpos/HER2neg breast carcinoma (T: Tumour size; N: Nodal status; RS: Oncotype Recurrence Score).

vant chemotherapy. A considerable proportion of SG panellists (33.6%) would have extended the axillary resection to obtain all of the necessary information to support an indication amenable to abemaciclib (Supplementary Table **S1, Question 81**). Most colleagues would not have carried out any further therapy (44.4%). Some models are described in the literature that calculate the risk for further lymph nodes [34]. In the case presented in **Question 81**, the risk of additional positive lymph nodes is 15% [35] with the MSKCC calculator and 26% [36] with the MD Anderson calculator, assuming otherwise average patient and tumour characteristics. It is unclear whether SG panellists also assessed the risk in this way and the distribution of the answers given was based on this assumed risk, or whether a different risk was intuitively assumed.

Chemotherapy in HRpos/HER2neg patients

One of the most important clinical questions of our time is to identify which HRpos/HER2neg patients can be spared chemotherapy. Accordingly, a large block of the SG panellist discussions were devoted to this issue. Decisions were formulated for different scenarios. It became clear that the Recurrence Score played a major role in the treatment decision for or against chemotherapy, particularly in young patients (in this case a 34-year-old woman). In the case study of the 34-year-old patient, 90% of panellists opted for chemotherapy if at least one lymph node was involved and the Recurrence Score was 21. The same situation in a 47-year-old female patient, resulted in only 57% of panellists opting for chemotherapy (Supplementary Table **S1, Questions 86 and 92**). If necessary, SG panellists were guided by the recently presented subgroup analysis of the TailorX trial, which investigated the effect of chemotherapy in node-negative patients [37]. The analysis showed a benefit of chemotherapy especially in premenopausal patients who had a Recurrence Score of at least 21 and also a high clinical risk. In this group, the absolute difference for distant metastasis-free survival was 11.7% after 12 years, if chemotherapy had also been given before endocrine therapy [37].

On the other hand, SG panellists were only convinced of tamoxifen monotherapy without prior chemotherapy in 92.2% of cases if the patient was 47 years old, had no involved lymph nodes and the recurrence score was 11 or less. All panel decisions for the case variants are shown in ▶ **Fig. 4** and further questions on the topic can be found in the Supplementary Table **S1, Questions 83 to 103**.

Triple Negative Therapy and BRCA-associated Tumours

For patients with triple-negative breast carcinoma and increased risk of relapse, the two therapy options olaparib [38, 39] and pembrolizumab [40, 41] have been included in therapy management in recent years.

Pembrolizumab in the adjuvant situation

The design of the Keynote 522 study has raised specific questions that have been discussed more or less prominently in several countries [42]. The SG panellists also faced some of these controversies.

Obviously, the question is whether pembrolizumab therapy should be continued after pCR following neoadjuvant therapy. At just under 60%, the majority of SG panellists were in favour of continuing therapy in any case (Supplementary Table **S1, Ques-**

tion 107). In the Keynote 522 trial, no dose-dense chemotherapy was given in combination with pembrolizumab. This naturally leads to the question of whether dose-dense chemotherapy should be given in combination with pembrolizumab, as should be the standard of care for patients at increased risk of relapse [43]. This is countered by considerations that dose-dense therapy in combination with pembrolizumab has not been tested and the toxicity of this regimen is also unknown. Almost 30% of SG panellists indicated that they would opt for a dose-dense chemotherapy in this background, also in combination with pembrolizumab (**Question 106**). The remaining SG panellists would not support this or were unsure about this issue.

Even though the criteria for pembrolizumab therapy are set by the Keynote 522 study (tumour of at least 2 cm or at least one positive lymph node), the question was discussed whether patients with smaller tumours without positive lymph nodes should also receive neoadjuvant therapy with chemotherapy and pembrolizumab. This question was answered "yes" by only 4.6% of SG panellists (**Question 109**). Accordingly, most colleagues fall within the scope of the approval in this regard. There are data from small single-arm trials in which stage I patients were also treated with chemotherapy and pembrolizumab [44]. The pCR rates appeared to be comparable to those in the Keynote 522 study.

BRCA-associated tumours

In the case of a germline mutation in *BRCA1* or *BRCA2*, the additional question arises as to whether treatment with olaparib should be administered in addition to pembrolizumab after neoadjuvant therapy. Given the overall survival benefit of olaparib, the PARP inhibitor is a therapy recommended in most national and international treatment guidelines. SG panellists addressed this question in the context of a patient who had not achieved pCR after neoadjuvant therapy with chemotherapy and pembrolizumab (**Question 114**). The vast majority of SG panellists recommended the administration of olaparib (86% overall). A total of 62% of SG panellists would combine the therapies and 24% would prescribe them sequentially. SG panellists did not consider capecitabine if this hypothetical patient presented with a *BRCA1* mutation.

In the case of a patient with HRpos/HER2neg breast carcinoma, a germline mutation in *BRCA1* or *BRCA2* raises the question of combination or sequential abemaciclib treatment. A hypothetical patient with a *BRCA2* mutation and a high risk of relapse was considered to address this issue (**Question 115**). Just under half of SG panellists favoured a sequential treatment. Combination therapy is generally not supported for these types of cases and did not figure among the possible responses that could be selected by panellists. It is important to note that in the OlympiA trial, standard adjuvant endocrine therapy was given together with olaparib [39].

While in patients without a *BRCA1/2* mutation with stage II or III TNBC tumours, most of the SG panellists (78%) had opted for platinum-containing chemotherapy (**Question 104**), the question is slightly different in patients with a *BRCA1/2* mutation. In this case, only 37% of SG panellists clearly opted in favour of platinum-containing chemotherapy. This is for instance in line with the GeparSixto data. In this study, which randomised for or against platinum-containing chemotherapy, it turned out that patients with a *BRCA1/2* mutation also responded extremely well to platinum-free chemotherapy and it was rather the patients without a *BRCA1/2* mutation who benefited most from platinum therapy [45].

HER2-positive Disease

For patients with HER2-positive disease, three standard therapies are established with trastuzumab, pertuzumab [46–48] and T-DM1 [49]. Neratinib is also approved for the later therapy setting [50–52]. Innovations can be expected, for example, from the Destiny-Breast05 trial, which compares T-DM1 post-neoadjuvant with trastuzumab-deruxtecan [53]. This study is still recruiting.

Accordingly, no major controversies have to date arisen in this setting. The majority of SG panellists agreed that chemotherapy with paclitaxel monotherapy is an option for small tumours (**Question 111**) and that after neoadjuvant therapy with trastuzumab, pertuzumab, taxane and platinum which achieves pCR, pertuzumab does not need to be continued after surgery as an adjuvant (**Question 112**).

Oligometastatic Disease

The boundaries between palliative and curative therapy intentions are shifting

A number of retrospective studies have shown that patients with favourable advanced breast cancer prognoses achieve better overall survival (hazard ratios between 0.6 and 0.7) when they are treated locally like an early-stage patient (including surgery and radiotherapy) [54–58]. Against this background, this therapy strategy is accepted, but it can be argued that most patients will nevertheless die from their advanced tumour disease and that considerations regarding the side effects and adverse effects of the therapy should be paramount [58]. Data based on high-quality evidence on the topic are currently not available.

Three questions have been asked in this context (**Questions 118 to 120**). Three different cases of oligometastatic disease were presented, one triple negative patient and two HER2 positive patients (one hormone receptor positive and the other hormone receptor negative). For all cases, SG panellists voted for extensive therapy of the primary disease (57–68%) analogous to the situation of patients with early-stage disease. With the new therapy options with which an overall survival advantage could already be demonstrated in the metastatic situation (CDK4/6 inhibitors, trastuzumab-deruxtecan, sacituzumab-govitecan), this question will certainly gain further relevance.

Molecular Diagnostics

Analysis of ctDNA not yet clinical routine in patients with early-stage breast carcinoma

Several studies have shown the added prognostic value of determining circulating tumour DNA (ctDNA) for patients with early

stages of disease [59–61]. It is quite conceivable that circulating tumour DNA will make a significant contribution to prognosis and therapy planning for patients with early-stage breast cancer. It can also be assumed in further follow-up that an indication for active disease can be beneficial. With tumour markers and circulating tumour cells, it has already been shown that even 2 years after the primary diagnosis, a further classification into prognostic groups is possible [62,63].

It should be noted, however, that despite advances in ctDNA determinations in the early treatment setting, no studies have yet been conducted that have included ctDNA in a treatment or therapy management decision either at the time of primary diagnosis or in the further course of disease. The SG panellists' responses to these questions are therefore also relatively clear (**Questions 122 to 126**). Almost all SG panellists believed that ctDNA testing should not be performed as a routine test at this point in time (86%) and that prospective studies on the topic should be conducted first (89%). Also, results from clinical trials should not currently be used to support routine treatment decisions. The SURVIVE study (https://www.survive-studie.de) [64], which is currently recruiting in Germany, is looking at precisely this issue. The study design of the SURVIVE study is shown in ▶ **Fig. 5**. Patients who have a high risk of recurrence are included in this study. Primary therapy must not have been completed for more than two years. Patients will be randomised into an arm where intensified follow-up will take place based on regular examinations of individualised (informative) ctDNA determinations. For this purpose, the primary tumour is examined for mutations. This individual mutation profile is then examined in the blood sample in addition to established tumour markers and circulating tumour cells.

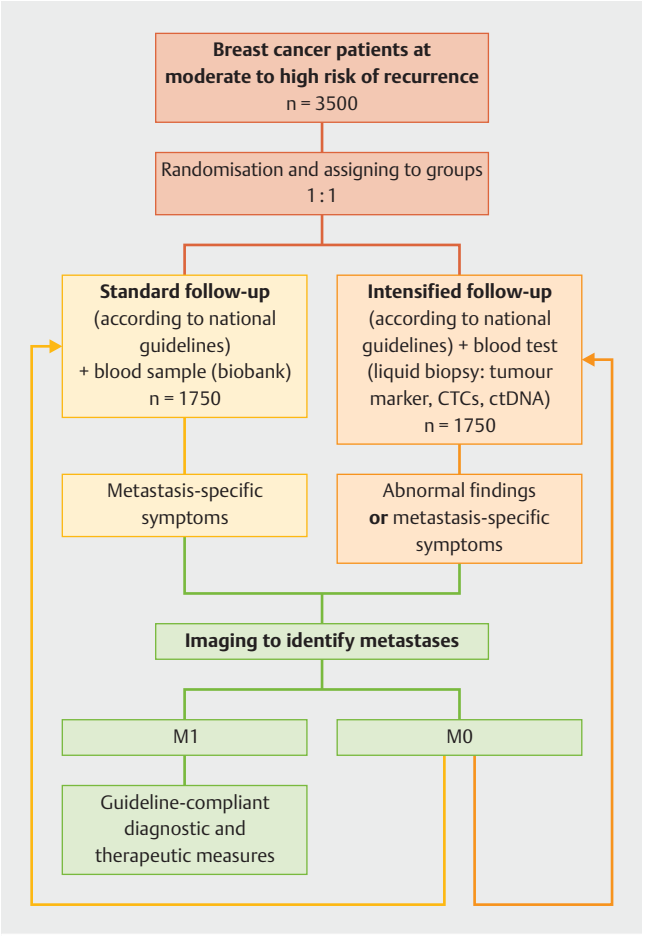
Available data on the interesting ctDNA biomarker is likely to increase significantly over the next few years. In addition to measuring tumour activity, ctDNA assays also provide insights on the genomic profile of tumour activity and could therefore influence treatment decisions in the case of a corresponding positive test.

Prospects

Further aspects on histopathological factors, ductal carcinoma in situ, male breast cancer, radiotherapy, surgical therapies and bone therapies are also included in Supplementary Table **S1**.

The decisions of the SG panel in Vienna represent a sentiment of many international colleagues (Supplementary Table **S2**) and therefore also take into account the preferences of different countries and health systems. It cannot be ruled out that this was also taken into account in the decisions and that SG panellists voted along these lines.

Since the implementation of oncology therapies is always an individual decision between the patient and the caregivers, the case variations are of particular value, because they shed light on the trends that cause slight changes in the disease constellation like no other conference. This should help the patients and the practitioners to better understand their situation and gain perspective.



▶ **Fig. 5** Study design of the SURVIVE study (Standard Surveillance vs. Intensive Surveillance in Early Breast Cancer Study).

Supplementary Data

- Supplementary Table **S1:**
  Polling questions among the St. Gallen panellists.
- Supplementary Table **S2:**
  Panellists of the St. Gallen Conference 2023 (after [66]).

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Conflict of Interest

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