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Update Breast Cancer 2021 Part 3 – Current Developments in the Treatment of Early Breast Cancer: Review and Assessment of Specialised Treatment Scenarios by an International Expert Panel

Update Mammakarzinom 2021 Teil 3 – aktuelle Entwicklungen bei der Behandlung von Brustkrebspatientinnen mit frühen Krankheitsstadien: Übersicht und Beurteilung von speziellen Therapiesituationen durch ein internationales Expertenpanel

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ABSTRACT

The continuous availability of findings from new studies repeatedly results in updated treatment recommendations and guidelines. In the case of breast carcinoma in particular, several studies have been published in the last few years that have transformed how early and advanced breast carcinoma is being treated. However, this by no means means implies that there is agreement among all experts on specific issues. It is precisely the diversity of interpretation of guidelines and study findings that reflects the constantly changing available data and its complexity, as well as the availability of new drugs. In recent years, new substances such as pertuzumab, T-DM1, neratinib and capecitabine have become available to treat patients with early stages of breast carcinoma. Furthermore, the first results on the use of CDK4/6 inhibitors for adjuvant treatment have now been published. Last but not least, the use of multigene tests to avoid the necessity of chemotherapy in certain patients is still under discussion. This review summarises the state of the data and publishes the results of the survey completed by experts at the 2021 St. Gallen Breast Cancer Conference on early-stage breast cancer.

ZUSAMMENFASSUNG

Kontinuierlich neue Studienergebnisse führen wiederholt zu aktualisierten Therapieempfehlungen und Leitlinien. Insbesondere beim Mammakarzinom wurden in den letzten Jahren einige Studien veröffentlicht, welche die Behandlung des frühen und fortgeschrittenen Mammakarzinoms deutlich verändert haben. Dies bedeutet jedoch nicht, dass die Meinungen aller Experten bei speziellen Fragen übereinstimmen. Gerade die Diversität bezüglich der Interpretation der Leitlinien und Studienergebnisse reflektiert die sich ständig ändernde Datenlage und ihre Komplexität sowie die Verfügbarkeit von neuen Medikamenten. Für die Therapie von Patientinnen mit frühen Stadien des Mammakarzinoms sind in den letzten Jahren neue Substanzen wie Pertuzumab, T-DM1, Neratinib, Capecitabin und weitere hinzugekommen. Des Weiteren gibt es erste Ergebnisse zum Einsatz von CDK4/6-Inhibitoren in der adjuvanten Situation. Nicht zuletzt wird nach wie vor diskutiert, wie Multigentests eingesetzt werden können, um den Einsatz von Chemotherapien bei bestimmten Patientinnen vermeiden zu können. Diese Übersichtsarbeit fasst den Datenstand zusammen und veröffentlicht die Abstimmungsergebnisse der St.-Gallen-Brustkrebskonferenz 2021 zum Mammakarzinom in frühen Krankheitsstadien.

Introduction

Every two years, following a multi-day conference in Vienna (formerly in St. Gallen), international experts complete a survey on current issues in clinical practice. The aim is to establish a snapshot of current opinion on national and international guidelines among an international panel of experts. The members of this year's panel are listed in ▶ **Table 1**. The questions were generally formulated in such a way as to apply to approximately 80 % of typical female patients with the corresponding characteristics. It was explicitly stated that in all scenarios exceptions exist and that the questions should be answered with the most common 80 % of concrete case studies in mind. The responses from this year's St. Gallen Meeting are listed in Supplementary Table **S1**. This review aims to present the current scientific background to selected sections of the survey.

Breast Cancer Risk and Genetics

One topic that is typically discussed by this international panel of experts is the risk of developing the disease and the associated genetic tests and preventive measures. Only recently, two groundbreaking papers were published describing the lifetime risk associated with "panel genes" [1, 2]. The publications confirmed that *ATM*, *BRCA1*, *BRCA2*, *CHEK2* and *PALB2* constitute risk genes. *BRCA1*, *BRCA2* and *PALB2* were also considered to be high-penetrance risk genes.

The SG-EBC Expert Panel did not advocate general testing of all breast cancer patients, despite the fact that almost a quarter of the experts were in favour of either offering panel testing to all breast cancer patients under 65 years of age or to all breast cancer patients regardless of age (Supplementary Table **S1**, question 1). Recent research suggests that approximately 5–10 % of all breast cancer cases involve a mutation in one of the known risk genes [1 – 5].

While clear clinical recommendations for preventive measures have been established in the case of *BRCA1* and *BRCA2* [6], no data are yet available for *PALB2*. Even though the described cumulative risk of disease associated with a confirmed *PALB2* mutation is approximately 40 % (similar to a *BRCA2* mutation) [1], it is unclear whether the measures employed in the case of a *BRCA2* mutation are equally safe and effective in patients with a confirmed *PALB2* mutation. Only (exactly) 50 % of the panellists agreed with this assessment with regard to prophylactic mastectomy (Supplementary Table **S1**, question 3).

The PARP inhibitors olaparib and talazoparib have already been approved for advanced breast cancer patients with germline mutations in *BRCA1/2* [7, 8]. In a press release dated 17 February

▶ **Table 1** Members of the 2021 St. Gallen Expert Panel.

Last name, first name, institute, country
Aebi Stefan, Tumorzentrum LUKS, Luzerner Kantonsspital, Lucerne, Switzerland
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Barrios Carlos, Centro de Pesquisa em Oncologia, Hospital São Lucas, PUCRS, Porto Alegre, Brazil
Bergh Jonas, Karolinska Institutet and University Hospital, Stockholm, Sweden
Bonnefoi Herve, University of Bordeaux 2, Bordeaux, France
Bretel Morales Denisse, Oncosalud, Lima, Peru
Brucker Sara, Universitäts-Frauenklinik Tübingen, Tübingen, Germany
Burstein Harold, Dana-Farber Cancer Institute, Boston, United States
Cameron David, The University of Edinburgh, Edinburgh, United Kingdom
Cardoso Fatima, Champalimaud Cancer Center, Lisbon, Portugal
Carey Lisa, UNC – Lineberger Comprehensive Cancer Center, Chapel Hill, United States
Chua Boon, Prince of Wales Hospital, Randwick, Australia
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Fitzal Florian, Medical University Vienna, Vienna, Austria
Francis Prudence, Peter McCallum Cancer Centre, Melbourne, Australia
Galimberti Viviana, European Institute of Oncology, Milano, Italy
Gamal Heba, National Cancer Institute, Cairo, Egypt
Garber Judy, Dana-Farber Cancer Institute, Boston, United States
Gnant Michael, Medical University Vienna, Vienna, Austria
Gradishar William, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, United States
Gulluoglu Bahadir, Marmara University School Of Medicine, Istanbul, Turkey
Harbeck Nadia, Frauenkliniken Maistrasse-Innenstadt und Großhadern, Munich, Germany
Huang Chiun-Sheng, National Taiwan University Hospital, Taipei, Taiwan
Huober Jens, Kantonsspital St. Gallen, St. Gallen, Switzerland
Ilbawi Andre, WHO Cancer Control Program, Switzerland
Jiang Zefei, 307 Hospital No. 8, Beijing, China
Johnston Steven, Royal Marsden Hospital, London, United Kingdom
Lee Eun Sook, National Cancer Center, Goyang-si, Korea
Loibl Sibylle, GBG Forschungs GmbH, Neu-Isenburg, Germany
Morrow Monica, Memorial Sloan-Kettering Cancer Center, New York, United States
Partridge Ann, Dana-Farber Cancer Institute, Boston, United States
Piccart Martine, Institut Jules Bordet, Brussels, Belgium
Poortmans Philip, Iridium Kankernetwerk & University of Antwerp, Antwerp, Belgium
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Regan Meredith, Dana-Farber Cancer Institute, Boston, United States
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Rugo Hope, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, United States
Rutgers Emiel, Netherlands Cancer Institute, Amsterdam, Netherlands
Sedlmayer Felix, Paracelsus Medical University, Salzburg, Austria
Semiglazov Vladimir, N. N.Petrov Research Institute of Oncology, St. Petersburg, Russian Federation
Shao Zhiming, Fudan University Cancer Hospital, Shanghai, China
Spanic Tanja, Europa Donna, Ljubljana, Slovenia
Tesarova Petra, Charles University Hospital and 1st medical faculty, Prague, Czech Republic
Thürlimann Beat, Kantonsspital St. Gallen, St. Gallen, Switzerland
Tjulandin Sergei, N. N. Blokhin Cancer Research Center, Moscow, Russian Federation
Toi Masakazu, Graduate School of Medicine Kyoto University, Kyoto City, Japan
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Turner Nicholas, The Royal Marsden Hospital, London, United Kingdom
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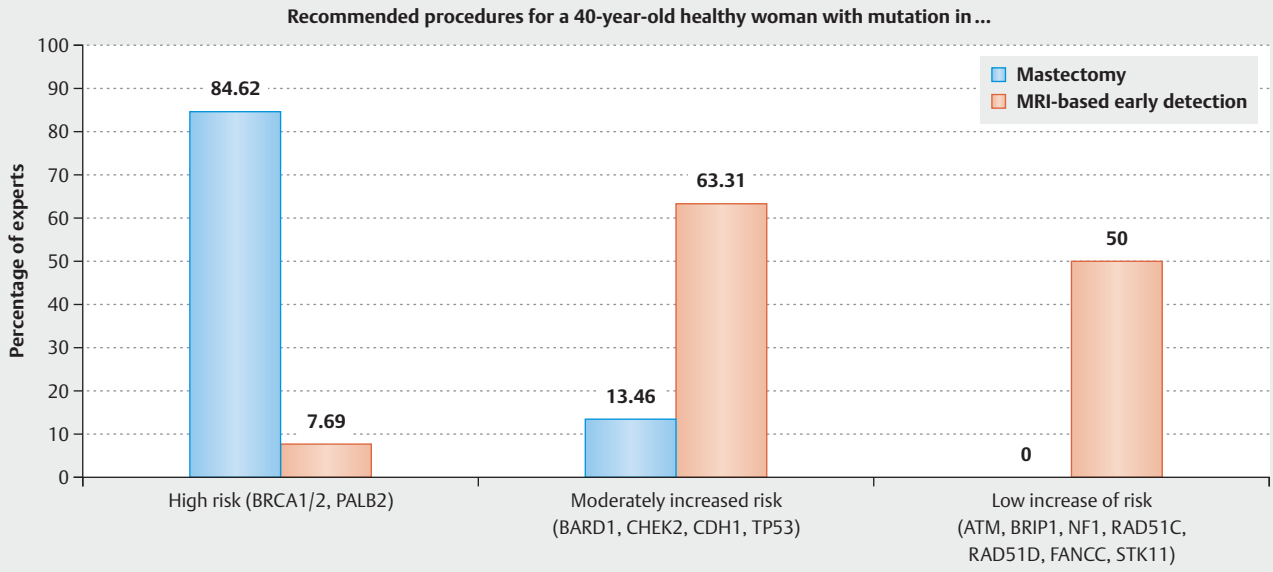
Winer Eric P., Dana-Farber Cancer Institute, Boston, United States
Xu Binghe, National Cancer Center, Beijing, China

2021, it was announced that the OlympiA trial had achieved its primary endpoint and that the findings of the study were positive [9]. Fifty per cent of the SG-EBC Expert Panel were in favour of testing in a scenario analogous to that of the OlympiA study (Supplementary Table **S1**, question 4). If therapy with PARP inhibitors becomes standard in adjuvant scenarios this will result in a significant increase in testing, and additional testing capacity will need to be created.

The risk associated with the various risk genes has now been relatively well established (high penetrance vs. medium penetrance vs. low penetrance). This raises the question of how measures such as prophylactic surgery or intensified early detection should be implemented for the various risk groups. The responses



▶ **Fig. 1** Recommended procedures (prophylactic or MRI-based screening) for healthy women with mutations in various risk genes.

of the panellists are summarised in ▶ **Fig. 1** and Supplementary Table **S1**, questions 5–10.

Ductal Carcinoma in Situ

The 2021 St. Gallen Consensus Conference survey involved only a small number of questions on DCIS, most of which related to radiation therapy. Most panellists did not agree that boost radiation should be routinely given to all patients with DCIS. However, a significant number were in favour of giving a boost in high-risk (larger DCIS lesions, close margins, presence of comedonecrosis) cases (Supplementary Table **S1**, questions 93–96). The merits of administering boost radiation therapy for DCIS need to be carefully weighed up. Improvements in local control are offset by the fact that giving a boost is detrimental to cosmetic outcomes and arm and shoulder functionality [10, 11].

There was, likewise, broad unanimity in the SG-EBC Expert Panel on the issue as to whether older patients and those with a lower risk of recurrence should undergo radiation therapy. The interesting finding here is that the panellists also considered a low biological or genomic risk, as established by a multigene assay, to be an indicator for not performing radiation therapy (Supplementary Table **S1**; questions 106–111). An analysis published this year likewise finds that the use of multigene assays is increasing and that this is reducing the number of patients at a low genomic risk undergoing radiotherapy for DCIS [12], even if this finding has not yet been established in a prospective study. Interestingly, a majority of panellists rejected the use of multigene signatures for the various radiation therapy scenarios to treat invasive carcinoma (Supplementary Table **S1**, questions 65–67).

The issue of hypofractionation in DCIS was not addressed in the 2021 St. Gallen survey. This is surprising, since up-to-date data on this issue have recently been published, and this is a highly relevant topic in clinical practice. In recently reported studies, moderate hypofractionation with a total treatment duration of three weeks yielded comparable results to conventional fractionation [11, 13].

DCIS and Endocrine Therapy

Asked whether endocrine therapy should be given to prevent DCIS recurrence and avoid radiation therapy, the response of the panellists was mixed. Only 16% responded that they would forego endocrine therapy altogether if radiation therapy was administered. The remaining panellists indicated that they would prescribe tamoxifen (5 or 20 mg) or an aromatase inhibitor. This is surprising, because to date no study investigating endocrine therapy as an alternative to radiation therapy has been published. Furthermore, no study on endocrine therapy in DCIS has yet demonstrated a survival benefit [14, 15], and the German Gynaecological Oncology Group (AGO), therefore, currently considers such treatment to be merely an option rather than a necessity (+/−).

Adjuvant radiation therapy

A majority of the St. Gallen panel generally considered moderate hypofractionation consisting of 15–16 doses over three weeks to be the standard of care for adjuvant radiation therapy for breast cancer (59%); this was true for breast-conserving therapy (72%) as well as for irradiation of the thoracic wall (90%) and of the regional lymphatic nodes (76%) following mastectomy (Supplementary Table **S1**, questions 60 and 97–99). Last year, the first data from the FAST and FAST-Forward trials on ultra-hypofractionated whole-breast irradiation given in 5 doses over 5 weeks or 1 week were published [16, 17]. Less than 10% of the St. Gallen

panel considered this to constitute a recommended regimen, a view reflected by the AGO grade of recommendation (+/−) and the recommendation of the German Society for Radio-oncology (DEGRO) [18].

Another subject that was addressed was the controversial question concerning the indication for regional node irradiation after neoadjuvant therapy. In the case of lymph node involvement prior to therapy and subsequent pCR, the majority of the panel recommended regional node irradiation in both triple-negative and HER2-positive disease, although a large majority did not consider it appropriate in patients with clinically unremarkable lymph nodes who had achieved pCR (Supplementary Table **S1**, questions 100–104). Prospective data have not yet been published, although clinical studies are underway.

An overwhelming majority of panellists were opposed to using commercially available gene expression profiles to inform decisions on adjuvant radiation therapy (neither in the case of BCS, nor in that of PMRT or RNI) (Supplementary Table **S1**, questions 65–67). Analogous to DCIS, panellists were asked whether radiation therapy should be reasonably omitted in older patients (> age 70) with a > 10 year life expectancy, after BCS for ER+ HER2− cancers). Nearly 90 % were in favour of foregoing radiation therapy in patients with a tumour size of < 2.5 cm and a low-int grade/low genomic score (G1–2). This was not felt to be the case in patients with tumours larger than 2.5 cm, in patients with a positive sentinel lymph node or in patients whose tumours displayed aggressive biological features (Supplementary Table **S1**, questions 106–111). The only long-term data available are from three studies, in each of which the risk of intra-mammary recurrence was significantly increased after a longer follow-up (approximately 10 % after 10 years), although this had no negative impact on survival rates [19 – 21].

Neoadjuvant Therapy in Triple-Negative Breast Cancer

Standard chemotherapy for triple-negative breast cancer (TNBC) is anthracycline/taxane-based. A dose-dense regimen of such therapy is more effective and is, therefore, preferable [22]. In contrast, there is no consensus on supplementary administration of carboplatin. Several meta-analyses and systemic reviews have now demonstrated that carboplatin supplementation is associated with significantly improved pCR rates [23 – 25]. Similarly, the GeparSixto trial has shown that carboplatin in addition to the standard regimen leads to an overall improved three-year disease-free survival (DFS) (86 vs. 76 %; HR = 0.56; 95 % CI: 0.34–0.93). Three-year overall survival, however, only demonstrated a trend (92 vs. 86 %; HR = 0.60; 95 % CI: 0.32–1.12) [26]. Interestingly, in this study, it was mainly the patients without a *BRCA1/2* mutation who benefited from supplementary carboplatin, both in terms of pCR rate and DFS [27]. For this reason, the decision on whether to administer carboplatin should not be based on *BRCA* mutation status. In general, employment of carboplatin is likely to result in a higher grade 3/4 haematotoxicity as well as higher rates of therapy discontinuation, and this should be discussed with the patient [28]. This is the reason why practitioners are ambivalent about routinely using carboplatin in neoadjuvant therapy for all patients with triple-negative breast carcinoma (Supplementary Table **S1**; question 39).

In metastatic breast cancer, immune checkpoint inhibitors (ICPi) are used in TNBC as first-line therapy [29, 30]. The results of studies on neoadjuvant treatment have now also been published. The phase 3 IMpassion031 study has revealed that the addition of atezolizumab to nab-paclitaxel followed by EC treatment led to a significant improvement in the pCR rate of 17 % [31]. The effect on pCR rate was independent of PD-L1 status. Similarly, the KEYNOTE-522 study on the ICPi pembrolizumab observed similar effects in both PDL1-positive and PD-L1-negative patients. Weekly supplementation of pembrolizumab to pacliatxel and carboplatin followed by EC treatment increased the overall pCR rate by 14 % [32]. Although in a later analysis involving more patients this difference was reduced to 7.5 % in the KEYNOTE-522 study [33], both studies demonstrated a trend towards improved event-free survival (EFS) [31 – 33]. However, data on overall survival have not yet been published. Furthermore, consideration must be given to the additional immunological side effects of ICPi (e.g. thyroiditis, hepatitis). Authorisation for pembrolizumab and atezolizumab in neoadjuvant treatment is currently pending in Germany. For this reason, ICPi should only be employed in the context of studies. The SG-EBC expert panellists took a similar view (Supplementary Table **S1**; question 40).

Neoadjuvant Therapy in HER2-positive Breast Cancer

Neoadjuvant therapy involving chemotherapy + trastuzumab + pertuzumab for HER2-positive breast carcinoma (N+ or NST) is an established approach due to its higher effectiveness [22, 34 – 36]. However, the role of anthracyclines in simultaneous chemotherapy is increasingly being viewed in a critical light. A total of five studies involving anthracycline-free regimens that instead employed carboplatin in combination with dual inhibition have now been published. Overall, these studies reveal pCR rates that are comparable to rates associated with the use of anthracyclines (64 % in TRYPHAENA and 68 % in TRAIN-2), as well as outcome data with a three-year DFS of between 90 % (TRYPHAENA) and 93.5 % (TRAIN-2), with significantly lower cardiotoxicity and avoidance of AML (1 % in the FEC arm of the TRAIN-2 study) [37, 38]. In St. Gallen, discussion on anthracycline-free treatment was conducted with reference to lymph node status. A large majority of the panel considered anthracyclines not to be necessary in node-negative patients, whereas a majority considered anthracyclines to be necessary in node-positive patients. The opinion of the experts in this area is not founded on objective data; 68 % of patients in the TRAIN-2 study, for instance, were node-positive. In summary, anthracycline-free, taxane-based chemotherapy with or without carboplatin in combination with dual inhibition with trastuzumab + pertuzumab is an effective alternative to an AT-based chemotherapy regimen and can be administered regardless of lymph node status (Supplementary Table **S1**, questions 35–38).

Surgery After Neoadjuvant Therapy

Axillary staging has become ever less radical in recent decades. After successful implementation of sentinel lymph node biopsy (SLNB) and increasing use of neoadjuvant systemic therapy (NAST), the question has arisen as to whether axillary dissection after neoadjuvant systemic therapy is beneficial and appropriate. It is, for example, the accepted standard that if the axilla is initially negative (cN0) and a macrometastasis (ycN1) is discovered in the sentinel node (SLN), an axillary lymph node dissection (ALND) is indicated. If a micrometastasis or isolated tumour cells are detected in the SLN, the SG-EBC expert panellists agree that axillary dissection is not mandatorily indicated (Supplementary Table **S1**; questions 43–45). Prior to NAST, a suspicious axillary lymph node should be clarified by means of a core needle biopsy (CNB) and clipped/marked. If complete clinical remission of the axillary lymph nodes occurs after NAST, a targeted axillary dissection (TAD) to remove both the SLN and the targeted lymph node (TLN) can be performed, regardless of subtype, to eliminate the need for an ALND. It is entirely possible that the SLN will correspond to the TLN. This was also the view of the SG-EBC panellists (Supplementary Table **S1**; question 55–57). Both the study by Caudle et al. [39] and the German SENTA study [40] attest to a false negative rate respectively of 1.4% and 4.3% for TAD. As survival data on TAD are still pending, participation in the ongoing AXSANA trial is recommended [41].

Post-neoadjuvant Therapy

Patients who do not achieve pathological complete remission (pCR) after neoadjuvant chemotherapy have a worse prognosis [42–46]. At the latest since the publication of the CreateX study, but especially now the results of the Katherine study have been presented, post-neoadjuvant systemic therapy has become established for treatment of early triple-negative or HER2-positive breast carcinoma [47,48]. As a result, the SG-EBC panellists discussed just a few, less contentious issues relating to this topic.

The first question incorporated two subordinate questions: whether (A) all patients who achieve pCR have a similar prognosis and whether (B) this also depends on the baseline clinical stage and the tumour subtype (Supplementary Table **S1**, question 73). The panellists were only able to answer "yes" or "no" once in response to both subordinate questions. Since the two questions are contradictory in nature, we do not consider the responses to be representative of the panel's opinion (⅔ of the panellists responded "yes"). At this point, it is worth considering the research on the prognostic relevance of the CPS-EG scoring system, which, in addition to post-therapeutic tumour burden, also takes into account baseline clinical tumour stage and tumour biology (ER status and grading). In this context, patients experience different recurrence rates, even within the group of patients who achieve a pCR [49,50]. There is a debate as to whether one specific biomarker – *BRCA1/2* status – might identify a group of patients who would not benefit from a pCR. Two studies have presented results supporting this hypothesis [51,52], while two others did not support this [27,53].

For the triple-negative breast carcinoma subgroup, the survey first asked to what extent patients with a pCR following neoadjuvant chemotherapy in combination with immunotherapy should receive adjuvant treatment with immuno-oncological substances/ICPi. As expected, the majority of panellists (85%) were not in favour of adjuvant immuno-oncological therapy (Supplementary Table **S1**, question 76). Only 9% favoured such treatment, while 6% favoured it depending on initial disease extent. Actually, such responses should be viewed in the light of the fact that (post-neo-)adjuvant therapy with ICPi has not yet been approved in Europe. Moreover, no data yet exist for a stratified approach based on the baseline stage or response to neoadjuvant (immuno)chemotherapy.

In addition, the panel was asked to what extent all patients with triple-negative breast carcinoma and residual tumour disease (i.e. non-pCR) should receive post-neoadjuvant chemotherapy with capecitabine after neoadjuvant chemotherapy (Supplementary Table **S1**, question 77). The majority of panellists were in favour of post-neoadjuvant therapy (88%), compared to only 12% who were not in favour. Indeed, the findings of the CREATE-X trial suggest there is no subgroup in which capecitabine therapy might not be expected to have an impact on disease-free survival [47]. However, an individualised approach taking into account the risk of recurrence and the expected spectrum of side effects is clearly justified.

With regard to patients with HER2-positive breast carcinoma who received neoadjuvant treatment, panellists were asked whether adjuvant HER2-targeted therapy should be continued after achieving a pCR (Supplementary Table **S1**, questions 74–75). Consistent with the six-year follow-up data of the APHINITY study [54], in the case of a clinically (i.e. pre-therapeutically) nodal-positive patient, 56% of panellists were in favour of blockade with trastuzumab + pertuzumab, while in the case of an initially nodal-negative patient, 70% were in favour of administration of trastuzumab alone [54,55]. In the presence of residual invasive tumour (non-pCR), 90% were in favour of the postneoadjuvant administration of trastuzumab-emtansine (T-DM1) in line with the data from the Katherine study [48]. In this regard, 77% were in favour of employing T-DM1 to treat patients with less than 5 mm of residual invasive cancer (Supplementary Table **S1**, question 79).

Questions on treatment after neoadjuvant endocrine therapy can be found in Supplementary Table **S1**, questions 81–85.

Adjuvant Therapy in HER2-positive Breast Cancer

Adjuvant treatment with trastuzumab and pertuzumab in patients with HER2/neu-positive breast carcinoma and affected axillary lymph nodes is standard and recommended by the Mamma commission of the AGO [22]. At present, the consensus is that node-negative breast cancer patients should not also be treated with the antibody therapy combination trastuzumab + pertuzumab. The APHINITY trial involving 4805 patients showed no benefit for patients with node-negative breast cancer after a median follow-up of 74 months [54]. The analysis to date considers inva-

sive recurrences and metastases, as data on overall survival is currently lacking. A subgroup analysis of patients with 1–3 affected lymph nodes (38% of the total population) and patients with more than 4 affected axillary lymph nodes (25% of the total population) is, as yet, not available [54].

Whether patients with HER2-positive breast cancer should receive adjuvant neratinib therapy following trastuzumab or trastuzumab + pertuzumab-based neoadjuvant or adjuvant therapy, or following post-neoadjuvant treatment with T-DM1, is a question that can be answered by the post-adjuvant ExteNET trial, the final results of which have recently been published [56]. In this trial, 2840 patients with HER2-positive breast cancer who had completed adjuvant therapy with trastuzumab were randomly assigned to receive one year of neratinib 240 mg/day or placebo. Neratinib was associated with a 5-year absolute benefit in invasive relapse-free survival compared to placebo of 5.1% and an 8-year absolute overall survival benefit of 2.1%. Thus, the numerical benefit in this trial was higher than in the APHINITY trial. Patients who had residual tumour after neoadjuvant therapy (non-pCR) had an absolute benefit of 7.4% in terms of invasive recurrence-free survival and an absolute benefit of 9.1% in terms of overall survival [56]. At the time of this study, supplementary treatment with pertuzumab was not standard. Similarly, post-neoadjuvant treatment of non-pCR patients with T-DM1, which is currently recommended, was also at the time non-standard, and, as such, it is impossible to definitively compare the risk reduction of adjuvant trastuzumab + pertuzumab with that of post-neoadjuvant T-DM1. However, the following conclusion by analogy can be assumed. In patients at very high risk of recurrence and metastasis in spite of treatment with trastuzumab + pertuzumab, for instance patients with more than four affected axillary lymph nodes, post-neoadjuvant therapy with neratinib may be considered in individual cases. Patients who have undergone post-neoadjuvant therapy with T-DM1 and who were diagnosed as high risk at the time of initial diagnosis, for instance those with a large primary tumour or multiple axillary lymph node involvement, may also benefit from post-T-DM1 treatment with neratinib. The European drug authorisation for neratinib places no restrictions on these treatment options. As such, this can be consciously discussed with patients at a very high risk of recurrence and metastases. This issue is addressed in Supplementary Table **S1**, question 143.

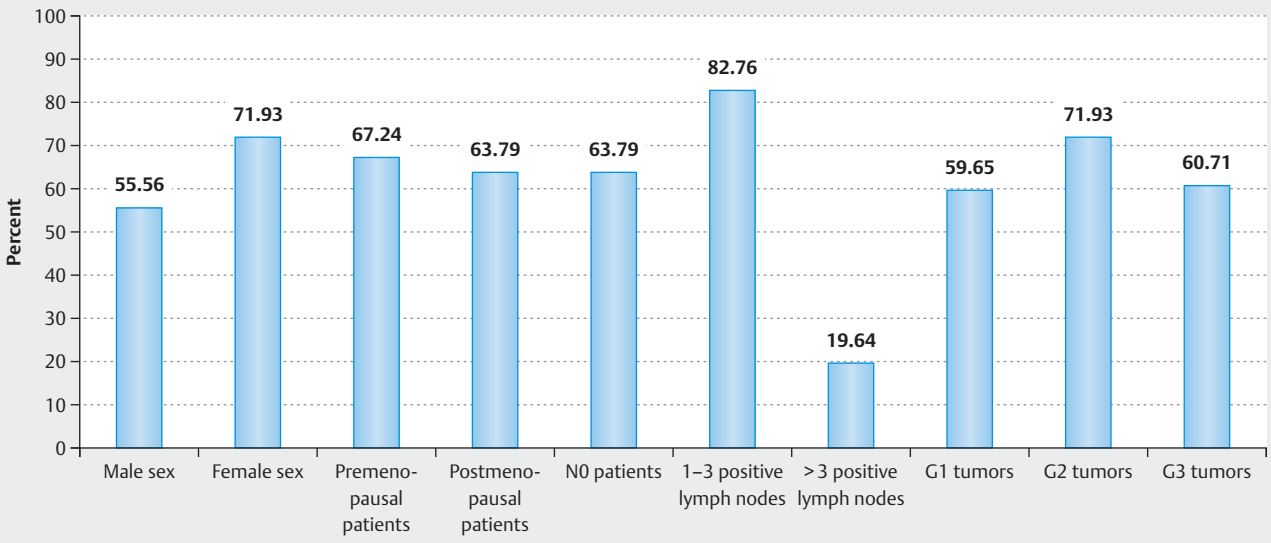
The question as to whether adjuvant, anthracycline-containing chemotherapy is required in patients with HER2-positive breast carcinoma is currently a subject of intense debate, both nationally and internationally. The large adjuvant trials NCCTG/NSABP, HERA and BCIRG with over 20 000 patients demonstrated a significant benefit for chemotherapy plus anti-HER2 therapy with trastuzumab compared to chemotherapy alone. The only study to directly compare anthracycline-containing chemotherapy with anthracycline-free chemotherapy in line with the TCH regimen (docetaxel, carboplatin, trastuzumab) was the BCIRG 006 study [57]. The outcome with respect to recurrence and metastases was not statistically dissimilar, while the short-term cardiac effects were slightly higher with the anthracycline-containing regimen than with the anthracycline-free regimens. All long-term data available to date show no additional cardiac events after 10–12 years of follow-up [58, 59]. The 10-year follow-up of the BCIRG 006 trial found five times as many cases of heart failure in the anthracycline-containing arms than in the anthracycline-free arm [60]. More recent studies, such as the TRAIN study with significantly fewer patients and pCR as the primary endpoint, reported similar results with regard to pCR, but revealed a different toxicity profile favouring anthracycline-free chemotherapy, especially in relation to cardiac events. However, such studies with well under 1000 patients are too small to establish a new anthracycline-free standard of treatment for patients with HER2-positive breast carcinoma, in particular because data on survival are unavailable for this study. The current AGO 2021 guideline supports this assessment [22]. Nevertheless, the risks of cardiac events suggest non-anthracycline therapy may be appropriate. This subject was picked up in question 144 (Supplementary Table **S1**).

Patients with a small (less than 2 cm), node-negative HER2-positive breast carcinoma are often treated with a combination of 12 weeks of paclitaxel weekly with 1 year of trastuzumab. Such therapy originated in a non-randomised phase II study [61, 62]. However, this study has clear weaknesses: 50 patients withdrew from the study, and no follow-up data are available for 69 patients. As such, only data from 406 patients can be analysed. Of these, just one third were under 50 years old. Most patients had a tumour 1–2 cm in size, while only 9% had a tumour 2–3 cm in size. 70% of the patients were hormone receptor-positive, while only 30% were hormone receptor-negative. All patients were histologically node negative. In view of these weaknesses, this study should be considered with extreme caution as a basis for making decisions on neoadjuvant and post-neoadjuvant therapy. In other words, neither the addition of carboplatin nor the general abandonment of anthracyclines is advisable – and certainly not the replacement of chemotherapy with T-DM1 as sole treatment for patients with HER2-positive breast carcinoma. Large prospective randomised trials would need to be conducted to replace the current standard with such treatment involving less chemotherapy. However, in individual cases and depending on the individual risk of the patient, an anthracycline-free therapy can be considered.

Pathology

In the field of breast pathology, the main topics of discussion are currently Ki-67, multigene tests, immune markers such as tumour-infiltrating lymphocytes (TILs) and PD-L1 expression. The SG-EBC Expert Panel voted on these areas.

Ki-67 is a strong pathological prognostic marker for patients with early stages of breast carcinoma [44, 63 – 65]. However, its clinical use and benefit is debated due to its inconsistent clinical assessment and variability. However, the International Ki67 in Breast Cancer Working Group (IKWG) found that for patients with a T1–2/N0–1 tumour stage, extreme thresholds of 5% and 30% could be employed to place patients relatively reliably into a group with a very good prognosis or a group with an unfavourable prognosis [66]. A majority of the SG-EBC Expert Panel likewise agreed with this for treatment of patients with an HER2-negative, hormone receptor-positive tumour (Supplementary Table **S1**, question 11). Approximately 63% of panellists considered a cut-off above 20% to be acceptable to indicate chemotherapy. In a



▶ **Fig. 2** Percentage of SG-EBC experts who would perform a multigene test in selected patients with a 1–3 cm HER2-negative, hormone receptor-positive tumour.

survey of 115 German decision-makers [67], 87% considered that chemotherapy would be indicated at a cut-off of 20%.

Prognosis is best determined not merely by means of a static Ki-67 value before the start of therapy, but also by its (non-)reduction during anti-endocrine therapy [68, 69]. This concept was also adopted in the German ADAPT trials and, along with a multigene assay, was able to identify patients with an excellent prognosis who did not require chemotherapy [70]. The SG-EBC Expert Panel responses can be found in Supplementary Table **S1**, questions 14 and 15.

The main benefit of multigene tests, which are designed to identify patients with an excellent prognosis [71 – 73], is to potentially eliminate the need for chemotherapy in this group of patients. In a (hypothetical) patient with an HER2-negative, hormone receptor-positive, 1–3 cm breast carcinoma, multigene tests seem most appropriate in the presence of 1–3 affected lymph nodes (▶ **Fig. 2**; Supplementary Table **S1**, questions 16–25).

Even though tumour-infiltrating lymphocytes (TILs) had been established as a prognostic parameter in breast carcinoma [74 – 76], they are not routinely evaluated and have, so far, not been used to inform treatment decisions. Likewise, PD-L1 has not been proven to be a predictive marker for anti-PD-1/PD-L1 therapy [32, 77]. Neither marker was recommended for routine use by the SG-EBC Expert Panel (Supplementary Table **S1**, questions 26–27).

Adjuvant Endocrine Therapy

One of the first issues raised by the survey concerned how to define hormone receptor positivity (Supplementary Table **S1**, question 113). 50% of panellists supported the concept that hormone receptor positive be defined as greater than or equal to 1%, while around 50% supported a figure of greater than or equal to 10%. This highlights the changing recommendations that have faced pathologists over the years [78]. More sensitive immunohistochemical staining techniques have resulted in increased positivity rates. Clinical analyses suggest that very weakly hormone receptor-positive tumours tend to behave similarly to triple-negative breast carcinomas [79]. The recommendations made by the Mamma commission of the AGO therefore refer to “questionably” endocrine-sensitive tumours within a range of 1–9% hormone receptor positivity [80].

A whole series of issues voted on by the panellists addressed the topic of optimal endocrine therapy for premenopausal patients. Much discussion and controversy on this subject focussed on the use of GnRH analogues and, where appropriate, their combination with aromatase inhibitors. There was clear consent on the question of whether women with an increased risk of recurrence who receive chemotherapy should also undergo ovarian suppression: 94.3% of panellists were in favour, while only 5.7% were not. Compelling evidence exists that ovarian suppression is beneficial in patients who have undergone chemotherapy. The ASTRRA study revealed that administration of GnRH analogues for 2 years in addition to tamoxifen confers a benefit for recurrence-free survival and also, potentially, for overall survival [81]: The estimated 5-year DFS rate was 91.1% in the TAM + OFS group and 87.5% in the TAM-only group (HR = 0.69; 95% CI: 0.48–0.97; p = 0.033). The estimated 5-year overall survival rate was 99.4% in the TAM + OFS group and 97.8% in the TAM group (HR = 0.31; 95% CI: 0.10–0.94; p = 0.029). A further analysis of the SOFT and TEXT studies revealed that patients who had received chemotherapy due to unclearly defined risk factors likewise benefited from ovarian suppression as an adjunct to endocrine therapy: in total, about 92% experienced a DRFI of 8 years (194 DRs), and the absolute benefit of Exemestan + OFS vs. TAM + OFS was 3%. In conclusion, use of Exemestan + OFS yielded an absolute benefit of 10–15% compared to TAM + OFS or TAM alone in 8-year DRFI in pre-

menopausal patients with hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence (as defined by clinicopathological features). The potential benefit from escalating endocrine therapy vs. tamoxifen alone is minimal in low-risk patients and, potentially, 4–5 % in intermediate-risk patients [82].

What is controversial, however, is whether chemotherapy is required in patients at an intermediate risk or whether ovarian suppression in addition to endocrine therapy is sufficient. The background to this discussion is the fact that in premenopausal patients chemotherapy triggers a loss of ovarian function, and hence at least part of the effectiveness of chemotherapy can be attributed to ovarian suppression. This hypothesis is supported by the fact that two earlier studies found that chemotherapy and ovarian suppression had a comparable effect in premenopausal patients [83, 84]. In the TailorX trial, women under 50 with an intermediate risk score were shown to have benefited from chemotherapy based on a reduction in recurrence rate [73, 85]. However, the patients in this study did not undergo ovarian suppression. The hypothesis that chemotherapy has an indirect effect in premenopausal women was also shared by a large majority of the panellists: only about 25 % of panellists considered that premenopausal and nodal-negative patients with an intermediate risk based on a gene expression test, e.g. Oncotype DX®, require chemotherapy; 22.5 % considered tamoxifen alone was sufficient, and 53 % preferred ovarian suppression plus endocrine therapy. On the question of the likely contribution of chemotherapy-induced ovarian suppression to the effectiveness of chemotherapy, around 56 % of the panellists stated they estimated this contribution to be 75 or 100 per cent. In light of these considerations, the 2021 AGO recommendations do not consider that an indication for ovarian suppression should be linked to administration of chemotherapy but, instead, to the finding of an intermediate or increased risk [80].

The St. Gallen Consensus 2021 only reached a general agreement on the optimal duration of adjuvant endocrine therapy for node-positive HR+/HER2− primary breast carcinoma: approximately 90 % of panellists were in favour of therapy lasting longer than 5 years, while approximately 50 % favoured 10 years. A consensus on therapy sequence and tolerability was not discussed. The AGO recommendations discuss prior therapy, sequence, risk and side effects in great detail in the corresponding chapter [80].

At the St. Gallen consensus meeting, the expert panel was very divided on the use of adjuvant abemaciclib in hormone receptor-positive, HER2-negative primary breast carcinoma: 54 % were not in favour of adjuvant abemaciclib in patients with 1–3 affected axillary lymph nodes, while the same number of experts were in favour of abemaciclib in patients with at least 4 affected axillary nodes (Supplementary Table **S1**; questions 121–122) [86]. Such survey findings are closely reflective of the AGO recommendation grade (+/−), which emphasizes a case-by-case approach and considers such therapy to be a viable option based on a consideration of all multifactorial decision criteria. In light of the negative findings of the PenelopeB and Pallas trials, neither St. Gallen nor the AGO recommend palbociclib use in primary breast cancer [80].

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