Article published online: 2023-09-12

Thieme

Treatment of Early Breast Cancer

The 18th St. Gallen International Breast Cancer Consensus Conference against the Background of Current German Treatment Recommendations

Behandlung des frühen Mammakarzinoms

18. Internationaler St.-Gallen-Konsens vor dem Hintergrund der aktuellen deutschen Therapieempfehlungen diskutiert

Authors

Michael Untch[1*], Maggie Banys-Paluchowski[2*], Sara Y. Brucker[3#], Wilfried Budach[4**], Carsten Denkert[5**#], Nina Ditsch[6*], Peter A. Fasching[7*], Renate Haidinger[8**], Jörg Heil[9,10**#], Christian Jackisch[11*], Wolfgang Janni[12*], Hans-Christian Kolberg[13**], David Krug[14*], Sibylle Loibl[15,16**#], Diana Lüftner[17,18*], Marion van Mackelenbergh[19**], Julia C. Radosa[20**], Toralf Reimer[21**], Manfred Welslau[22**], Rachel Würstlein[23**], Nadia Harbeck[23*#], Jens Huober[24*#]**

Affiliations

1 Klinik für Gynäkologie und Geburtshilfe, interdisziplinäres Brustzentrum, HELIOS Klinikum Berlin Buch, Berlin, Germany
2 Klinik für Frauenheilkunde und Geburtshilfe, Brustzentrum, Campus Lübeck, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany
3 Universitäts-Frauenklinik Tübingen, Tübingen, Germany
4 Klinik für Strahlentherapie und Radioonkologie, Universitätsklinikum Düsseldorf, Düsseldorf, Germany
5 Institut für Pathologie, Philipps-Universität Marburg und Universitätsklinikum Marburg (UKGM), Marburg, Germany
6 Klinik für Frauenheilkunde und Geburtshilfe, Brustzentrum, Universitätsklinikum Augsburg, Augsburg, Germany
7 Frauenklinik des Universitätsklinikums Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany
8 Brustkrebs Deutschland e. V., Hohenbrunn bei München, Germany
9 Brustzentrum Heidelberg, Klinik St. Elisabeth, Heidelberg, Germany
10 Medizinische Fakultät Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany
11 Klinik für Gynäkologie und Geburtshilfe, Sana-Klinikum Offenbach GmbH, Offenbach, Germany
12 Universitätsfrauenklinik Ulm, Ulm, Germany
13 Klinik für Gynäkologie und Geburtshilfe, Marienhospital Bottrop gGmbH, Bottrop, Germany
14 Klinik für Strahlentherapie (Radioonkologie), Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany
15 German Breast Group (GBG), Neu-Isenburg, Germany
16 Centrum für Hämatologie und Onkologie Bethanien, Frankfurt am Main, Germany
17 Immanuel Klinik Märkische Schweiz, Buckow, Germany
18 Immanuel Klinik Rüdersdorf, Medizinische Hochschule Brandenburg, Rüdersdorf bei Berlin, Germany
19 Gynäkologie und Geburtshilfe, Campus Kiel, Universitätsklinikum Schleswig-Holstein, Kiel, Germany
20 Klinik für Gynäkologie, Geburtshilfe und Reproduktionsmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany
21 Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Rostock, Germany
22 Onkologie Aschaffenburg, Hämato-Onkologische Schwerpunktpraxis am Klinikum Aschaffenburg-Alzenau, Aschaffenburg, Germany
23 Brustzentrum, Frauenklinik, LMU Klinikum München, München, Germany
24 Brustzentrum Kantonsspital St. Gallen, St. Gallen, Switzerland

Key words

St. Gallen Consensus 2023, early-onset breast cancer, genetics, pathology, surgery, radiotherapy, (neo)adjuvant systemic therapy

* Writing Committee
** Steering Committee
\# St. Gallen Panel Expert

Schlüsselwörter
St. Gallen Konsensus 2023, frühes Mammakarzinom, Genetik, Pathologie, Operation, Strahlentherapie, (neo)adjuvante Systemtherapie

received 25.4.2023
accepted 29.6.2023

Bibliography
Geburtsh Frauenheilk 2023; 83: 1102–1116
DOI 10.1055/a-2121-2495
ISSN 0016-5751

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Prof. Dr. med. Michael Untch
Klinik für Gynäkologie und Geburtshilfe, interdisziplinäres Brustzentrum, HELIOS Klinikum Berlin Buch
Schwanebecker Chaussee 50, 13125 Berlin, Germany
michael.untch@helios-gesundheit.de

Deutsche Version unter:
https://doi.org/10.1055/a-2121-2495

ABSTRACT

This year's 18th St. Gallen (SG) consensus conference on the treatment of early breast cancer (SGBCC: St. Gallen International Breast Cancer Conference) focused on practice-oriented questions. The individual situation and risk-benefit assessment were discussed in great detail. As in previous years, a German working group of leading breast cancer experts presented the results of the international SGBCC 2023 against the background of German treatment recommendations – especially the updated treatment recommendations of the Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) – for everyday clinical practice in Germany. The German treatment recommendations of AGO are based on the current evidence. The comparison with the clinical approach in Germany has proven useful, as the SGBCC panel consists of experts from different countries and disciplines. That is why country-specific characteristics can be incorporated into the SGBCC recommendations.

ZUSAMMENFASSUNG

Die diesjährige 18. St.-Gallen-(SG-)Konsensus-Konferenz zur Behandlung des frühen Mammakarzinoms (SGBCC: St. Gallen International Breast Cancer Conference) fokussierte auf praxisorientierte Fragestellungen. Die individuelle Krankheitssituation und Nutzen-Risiko-Abwägung wurden sehr detailliert diskutiert. Wie schon in den vergangenen Jahren hat auch dieses Jahr eine deutsche Arbeitsgruppe führender Brustkrebsexpertinnen und -experten die Ergebnisse der internationalen SGBCC 2023 vor dem Hintergrund der deutschen Therapieempfehlungen – speziell der aktualisierten Therapieempfehlungen der Kommission Mamma der Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) – für den Klinikalltag in Deutschland diskutiert. Die deutschen Therapieempfehlungen der AGO basieren auf der aktuellen Evidenz. Der Abgleich mit dem klinischen Vorgehen in Deutschland hat sich bewährt, da sich das SGBCC-Panel aus Expertinnen und Experten unterschiedlicher Länder und Fachdisziplinen zusammensetzt, weshalb länderspezifische Besonderheiten in die SGBCC-Empfehlungen einfließen können.

Introduction

This year's 18th St. Gallen (SG) consensus conference on the treatment of patients with early breast cancer (SGBCC: St. Gallen International Breast Cancer Conference) focused on practice-oriented questions and, in particular, on clinical situations that are controversial and difficult zu decide. One focus was to highlight the importance of individual treatment decisions and to clarify their clinical relevance using case studies with different clinical scenarios. This year's SGBCC panel consisted of 71 breast cancer experts from 27 countries, including five panel members from Germany (cf. ▶ **Table 1**). The SGBCC recommendations are based on a majority vote by the SGBCC panel. The aim is to establish an international consensus for everyday clinical practice. In parallel, we shall also work out which areas still have a low level of consensus in order to devise new study concepts.

The SGBCC panel consists of experts from different disciplines, coming from different countries with different health systems and resources. That's why a working group of German breast cancer experts has been commenting on the voting results of the SGBCC panel for several years. The German experts refer to the current treatment recommendations of the Mamma [breast] Commission of the Working Group for Gynecological Oncology e.V. (AGO) [1], that are updated every year and therefore are based on a high level of evidence and have a high degree of accuracy. In this manuscript we refer to the recommendations of AGO version 2023.1D [1, 2].

Follow-up Care in Early Breast Cancer

High body mass index

Patients with early invasive breast cancer have a chance of cure or long-term survival. The patient may support the long-term benefit of therapeutic interventions by additional measures, that affect lifestyle for example. It has been discussed whether a specific diet can help reduce the risk of recurrence in patients with a body mass index > 25 (BMI > 25). German experts agree with the majority vote of the SGBCC panel (73.21 %) that there is no *specific* diet to reduce the risk of recurrence. However, AGO recommends that

▶ **Table 1** International SGBCC Panel 2023.

- Stephan Aebi (Switzerland)
- Meteb Al-Foheidi (Kingdom of Saudi Arabia)
- Fabrice André (France)
- Mikola Anikusko (Ukraine)
- Rajendra Badwe (India)
- Andrea V. Barrio (USA)
- Carlos Barrios (Brazil)
- Jonas Bergh (Sweden)
- Hervé Bonnefoi (France)
- Denisse Bretel Morales (Peru)
- Sara Y. Brucker (Germany)
- Harold J. Burstein (USA)
- Carlos Caldas (GB)
- David Cameron (GB)
- Fatima Cardoso (Portugal)
- Maria Joao Cardoso (Portugal)
- Lisa Carey (USA)
- Steven Chia (Canada)
- Charlotte Coles (GB)
- Javier Cortes (Spain)
- Giuseppe Curigliano (Italy)
- Jana de Boniface (Sweden)
- Suzette Delaloge (France)
- Angela DeMichele (USA)
- Carsten Denkert (Germany)
- Gerd Fastner (Austria)
- Florian Fitzal (Austria)
- Prudence Francis (Australia)
- Heba Gamal (Egypt)
- Oreste Gentilini (Italy)
- Michael Gnant (Austria)
- William J. Gradishar (USA)
- Bahadir Gulluoglu (Turkey)
- Nadia Harbeck (Germany)
- Jörg Heil (Germany)
- Chiun-Sheng Huang (Taiwan)
- Jens Huober (Switzerland)
- Zefei Jiang (China)
- Orit Kaidar-Person (Israel)
- Marleen Kok (Netherlands)
- Eun-Sook Lee (Korea)
- Sherene Loi (Australia)
- Sibylle Loibl (Germany)
- Miguel Martin (Spain)
- Icro Meattini (Italy)
- Kathy D. Miller (USA)
- Monica Morrow (USA)
- Ann Patridge (USA)
- Frederique Penault-Llorca (France)
- Martine Piccart (Belgium)
- Lori Pierce (USA)
- Philip Poortmans (Belgium)
- Meredith Regan (USA)
- Jorge Reis-Filho (USA)
- Isabella Rubio (Spain)
- Hope Rugo (USA)
- Emiel J. T. Rutgers (Netherlands)
- Cristina Saura (Spain)
- Elzbieta Senkus (Poland)
- Zhiming Shao (VR China)
- Christian Singer (Austria)
- Beat Thürlimann (Switzerland)
- Masakazu Toi (Japan)
- Sara Tolaney (USA)
- Nicholas Turner (GB)
- Andrew Tutt (GB)
- Marie-Jeanne Vrancken-Peeters (Netherlands)
- Toru Watanabe (Japan)
- Walter Weber (Switzerland)
- Hans Wildiers (Belgium)
- Binghe Xu (VR China)

patients should be informed about modifiable risk factors, such as weight loss for high BMI (AGO chapter 16, slide 8: LoE [level of evidence] 2a, GR [grade] B, recommendation +) [1, 2].

Accordingly, we agree with the majority vote of the SGBCC panel (83.33 %) to motivate severely overweight patients (BMI > 30) to lose weight in order to reduce the risk of recurrence [1, 2].

The importance of acupuncture

According to the SGBCC panel, acupuncture is a standard method to relieve arthralgia-related symptoms during aromatase inhibitor (AI) therapy or chemotherapy-induced neuropathy and should be reimbursed by each healthcare system (majority vote: 69.64 %).

AGO recommends acupuncture as a complementary intervention not only for AI-induced arthralgias and chemotherapy-induced polyneuropathy (chapter 23, slide 10), but for a whole range of symptoms, including nausea/vomiting, depression, hot flashes, and sleep disorders (chapter 23, slides 6 + 10; chapter 24, slide 6). Reimbursement of costs is justified in these cases in the view of the German experts.

Interruption of endocrine treatment for pregnancy?

The first results of the POSITIVE study [3] indicate that young women with early hormone receptor-positive (HR+) breast cancer can temporarily pause therapy under certain conditions in order to conceive – after at least 18 months of adjuvant endocrine treatment. The SGBCC panel advises against interrupting endocrine treatment in women with HR+ breast cancer who have at least four positive axillary lymph nodes and who have been receiving tamoxifen plus OFS (ovarian functional suppression) for two years (majority vote: 78.57 %).

German experts point out the high risk of relapse in this scenario, with initially at least four positive lymph nodes, and agree with the SGBCC majority vote. In addition, the POSITIVE study [3] enrolled predominantly low-risk patients with only 6 % of patients (n = 31/516) that had stage III breast cancer. The situation mentioned above is not (adequately) reflected by the study results.

Due to the short follow-up of the POSITIVE trial the German experts do not advise to interrupt endocrine therapy after two years in patients with high risk. According to a meta-analysis by the "Early Breast Cancer Trialists' Collaborative Group" (EBCTCG), the annual recurrence and metastasis rates are up to 6 % in HR+ breast cancer over a period of up to 20 years – depending on the primary risk of the patient [4, 5]. The short follow-up of the POSITIVE study (median 41 months) does not yet allow evidence-based statements on the long-term course. However, this is an individual decision that must be discussed with the patient.

This also applies to young patients, who have time to become pregnant later. Here, again the German experts agree with the SGBCC majority vote (77.78 %).

Intravaginal estrogen administration

A postmenopausal woman receiving adjuvant AI for estrogen receptor (ER) positive (ER+) breast cancer may be treated intravaginally (topically) with estrogens if required for example in case of mucosal or vaginal dryness (majority vote: 57.58%). German experts add that vaginal estrogens are very likely safe in patients with ER+ breast cancer. There are no data to indicate that slightly elevated systemic estrogen levels negatively impact the efficacy of adjuvant AI treatment. It is important to use estriol instead of estradiol [1,2].

AGO recommends topical treatment with estriol on a case-by-case basis (2b B +/−), especially if non-hormonal interventions are insufficient (chapter 24, slide 3; chapter 24, slide 13) [1,2]. Whether vaginal dryness is a problem should be addressed proactively. German experts prefer intermittent administration of estriol.

Pathology

The role of tumor-infiltrating lymphocytes?

According to the SGBCC panel, detection of tumor-infiltrating lymphocytes in the stroma (sTILs) can be used as a criterion in favor of adjuvant chemotherapy in triple-negative breast cancer (TNBC). In a 43-year-old female patient with TNBC (primary tumor 1.6 cm; N0, grade 3, sTIL score 75%), the majority of SGBCC panel members voted for the use of adjuvant chemotherapy after tumor excision (87.93%). For a smaller primary tumor (T1b, 0.8 cm, sTIL score > 50%), 58.18% voted in favour of adjuvant chemotherapy.

According to the German experts, both votes are acceptable. According to AGO, chemotherapy should be considered for TNBC with a primary tumor with a size of at least 0.5 cm (chapter 11, slide 6) [1,2]. German experts point out that a high TIL score is not the sole criterion to avoid chemotherapy in TNBC (chapter 5, slide 15: 2b B +/−) [1,2]. The detection of TILs in the stroma can provide a prognostic information for therapy planning in individual cases. The predictive therapeutic significance, for example for immunotherapy or a de-escalating strategy, has not yet been evaluated in randomized trials. An important prerequisite is that there are standardized histological methods to determine and to measure TILs.

Genetics

Genetic counseling and testing

German experts agree with the SGBCC panel that patients with breast cancer must have access to genetic counseling (majority vote: 98.48%). The SGBCC panel voted on various clinical scenarios to determine if and when genetic testing is indicated in routine clinical practice. In each case, the results did not provide a clear recommendation for or against genetic testing in routine clinical practice. After all, almost 40% voted for all patients to be tested, i.e., also those without family predisposition. Almost 48% voted in favor of routine testing in everyday clinical practice for the therapy-relevant mutations in the *BRCA1/2* and the *PALB2* genes. This voting result reflects the diversity of international opinion on this topic. Therefore, without commenting on the individual voting results, German experts refer to the recommendations of AGO, which set out in detail the diagnostic and therapeutic indications for genetic testing ("companion diagnostic") (chapter 2, slides 4 + 6; chapter 2, slide 5) [1,2].

Genetic mutations

Based on different gene mutations *(BRCA1/2, PALB2, ATM, CHEK2)* and taking into account the menopausal status, the SGBCC panel voted whether prophylactic or risk-reducing contralateral mastectomy (CRRM) or intensified follow-up (mammography and MRI [magnetic resonance imaging]-based) should be recommended for patients with early breast cancer and evidence of a pathogenic mutation that increases the risk of breast cancer.

Two thirds of the panelists voted for CRRM if *BRCA1* mutations were detected in pre- or postmenopause and in a premenopausal patient. if *BRCA2* mutations were detected. Fewer panel members – about 42% – voted for CRRM when the *BRCA2* mutation is diagnosed in postmenopausal patients. Differences depending on menopausal status were also seen when a *PALB2* mutation was detected: If the *PALB2* mutation was diagnosed in premenopause, 42% of panel members voted for CRRM. If the patient was postmenopausal, 19% voted for CRRM. The remaining panelists voted in favor of intensified diagnostic imaging (▶ **Table 2**).

The voting results and different recommendations were intensively discussed in the German expert group. They reflect the known risks for contralateral breast cancer. In Germany, too, this topic is discussed intensively and controversially. The decision should be made in a "shared decision" process (participatory decision making). The patient should get detailed information on the current data, taking into account advantages and disadvantages (AGO: chapter 2, slide 25) [1,2].

The risk of contralateral breast cancer (CBC) is significantly increased in the presence of a pathogenic variant (PV) in *BRCA1, BRCA2*, and *CHEK2*. For a PV in *PALB2*, an increased risk is only considered for the ER-negative patients. In contrast, the *ATM*-PV carriers did not show a significantly increased risk of contralateral breast cancer [6,7].

We refer to current data: In premenopausal women, the cumulative 10-year incidence of CBC was estimated to be 33% for *BRCA1*-, 27% for *BRCA2*-, 13% for *CHEK2*-PV carriers with breast cancer, and 35% for *PALB2*-PV carriers with ER-negative breast cancer. The cumulative 10-year incidence of CBC among postmenopausal PV carriers was 12% for *BRCA1*, 9% for *BRCA2*, and 4% for *CHEK2* [7]. With the exception of *BRCA1/2* mutations, there are only limited data for other pathogenetic gene variants and therefore insufficient evidence in favor of CRRM for a risk reduction.

According to the German experts, a CRRM is plausible if a *BRCA1/2* mutation is demonstrated. In the case of pathogenic mutations in the *ATM* and *CHEK2* gene, intensified imaging during follow-up care is currently recommended. As part of participatory decision making, it is recommended that patients be informed of the potential benefits and respective risks, and that both options – prophylactic mastectomy or intensified follow-up – be discussed. Our patient representative on the German expert com-

▶ **Table 2** Risk-reducing mastectomy or intensified follow-up care – voting results of the SGBCC panel (2023) depending on the menopausal status and different gene mutations.

	Surgery	Intensive screening	Abstain
Gene: BRCA1, Menopausal Status: Pre	66.67%	13.63%	19.70%
Gene: BRCA1, Menopausal Status: Post	60.61%	16.67%	22.72%
Gene: BRCA2, Menopausal Status: Pre	63.64%	13.64%	22.72%
Gene: BRCA2, Menopausal Status: Post	42.42%	31.82%	25.76%
Gene: PALB2, Menopausal Status: Pre	42.42%	31.82%	25.76%
Gene: PALB2, Menopausal Status: Post	19.70%	53.03%	27.27%
Gene: ATM, Menopausal Status: Pre	9.09%	72.73%	18.18%
Gene: ATM, Menopausal Status: Post	1.52%	78.78%	19.70%
Gene: CHEK2, Menopausal Status: Pre	7.58%	71.21%	21.21%
Gene: CHEK2, Menopausal Status: Post	1.52%	78.78%	19.70%

mittee points out that, in these cases, CRRM should be covered by the statutory health insurance if the patient requests it.

Olaparib in patients with a *PALB2* mutation?

Opinion was also divided on whether patients with early breast cancer and *PALB2* mutations should be treated with olaparib in the adjuvant setting – in accordance with the criteria for adjuvant use of olaparib in patients with germline *BRCA1/2* mutation (*gBRCA1/2*mut). This is against the background that corresponding study data on *PALB2* are missing. A slight majority of panel members (53.45%) voted against, while 37.93% were in favor.

German experts point out the lack of data. Data on olaparib efficacy in *PALB2* mutations are only available for metastatic TNBC [8] with a "plus/minus" recommendation from AGO for the metastatic settting (chapter 2, slide 27) [1,2]. There are no adjuvant data on this question. Since this is a rare mutation, a randomized trial is unlikely to be done. The majority of German experts would draw an analogy in favor of adjuvant olaparib. There is agreement that this is an individual decision, taking into account the overall risk and the treatment alternatives. Unlike in the metastatic setting, a claim for reimbursement is required in the adjuvant setting.

Olaparib in patients with somatic *BRCA* mutation?

Controversy also surrounded the question of whether olaparib should be used in the adjuvant setting when a somatic mutation is detected in the *BRCA1* gene (*sBRCA1* mutation): Almost half of the panel members (48.28%) favor it, while almost as many (46.55%) are against.

The German experts also have different opinions. They point out that a germline *BRCA*-negative *(gBRCA)* but *sBRCA1*-positive breast cancer is very rare. Because the approval of olaparib relates to *gBRCA1/2* mutations, there is no formal indication for adjuvant olaparib use. It is not known whether a conclusion based on "biological criteria" is justifiable. There is agreement that a special testing for *sBRCA* mutations in breast cancer is currently not recommended. However, it may be useful to include *sBRCA* mutations in the context of comprehensive analyses in molecular tumor boards.

BRCA2 mutation in ER+ and HER2-positive (HER2+) breast cancer is also rare. If the inclusion criteria of the OlympiA study [9,10] are met with regard to the tumor stage, a slight majority of panel members (45.61% vs. 43.86%) would use olaparib in addition to standard adjuvant therapy. According to the German experts, this is *not* evidence-based. The adjuvant approval of olaparib does not include HER2+ breast cancer, but refers to HR+/HER2-negative (HER2−) breast cancer, taking into account the inclusion criteria of the OlympiA pivotal study [9,10].

Ductal Carcinoma in Situ (DCIS)

Vote for hypofractionation

The questions regarding ductal carcinoma in situ (DCIS) focused on adjuvant radiotherapy after breast-conserving surgery.

For low-risk patients with DCIS who undergo breast-conserving surgery, the SGBCC panel gave a clear vote in favor of moderate hypofractionated radiation regardless of menopausal status. For premenopausal women, the vote was even clearer than for postmenopausal women (majority vote: 50% and 33.85%), respectively). This may be a consequence of the fact that in postmenopause, radiotherapy indication in this constellation is rather rare, and 20% of SGBCC panel members recommend radiation therapy of the partial breast (5 fractions) for postmenopausal patients after breast-conserving surgery, but only for almost 5% of premenopausal patients. Regardless of menopausal status, no panel member voted for conventional fractionated radiation.

The German experts welcome the clear vote in favor of moderate hypofractionation. To date, AGO gives a "plus" recommendation (1a A + each) for both moderately hypofractionated and conventionally fractionated radiation therapy for those patients. Partial breast irradiation is also an alternative in Germany for postmenopausal patients with low-risk DCIS (AGO: chapter 7, slide 13) [1,2].

Indication for adjuvant radiotherapy

Using different clinical scenarios – depending on the age of onset (< 50 years, 50–65 years, > 70 years), tumor diameter (</>2 cm),

and/or evidence of comedonecroses (yes/no) – the SGBCC panel voted on which DCIS patients should receive adjuvant radiotherapy after breast-conserving surgery with a clear incision margin (> 2 mm).

German experts refrain from commenting on the individual – very detailed – scenarios and point out that postoperative radiation after breast-conserving surgery reduces the risk of ipsilateral local recurrence but has no effect on overall survival. It is therefore indicated when local control is the primary concern (AGO: chapter 7, slide 12). Fixed criteria for or against adjuvant radiotherapy do not exist, so the decision should be made individually in discussion with the patient. This also applies to patients receiving adjuvant endocrine therapy postoperatively because of ER+ DCIS – the reason being that the adjuvant radiation time window will have passed should adjuvant endocrine therapy be discontinued due to side effects.

The decision for or against radiation therapy after breast-conserving surgery cannot be broken down to one factor, but should take into account the overall constellation (benefit-risk). As a general rule, the following applies: According to the German experts, the more favorable the risk constellation and the lower the estimated life expectancy, the more likely it is that postoperative radiotherapy after breast-conserving surgery can be forgone.

A healthy postmenopausal woman who has received adjuvant radiotherapy after being diagnosed with ER+ DCIS and undergoing a breast-conserving operation is considering additional adjuvant endocrine therapy to reduce the risk of an "in-breast" relapse. Considering potential side effects and low effect of endocrine therapy, almost 40% (39.29%) of SGBCC panel members recommended low-dose tamoxifen (5 mg/day). Almost 30% (28.57%) would advise against endocrine therapy.

According to AGO, endocrine therapy is an option on a case-by-case basis as an addition to the adjuvant radiation therapy (chapter 7, slide 15) [1, 2]. For postmenopausal women with ER+ DCIS, tamoxifen (tamoxifen 20 mg/day, tamoxifen 5 mg/day) or the application of an AI are possible options [1]. The indication for endocrine therapy should be based on possible risk factors, potential side effects, and patient preference. Patients should be informed that additional endocrine therapy is not associated with an overall survival benefit and that the effect on local control in the ipsilateral breast is small [1]. The preventive effect concerns the contralateral side. There is no approval for this in Germany. The evidence for the benefit of low-dose tamoxifen (5 mg/day) is limited from the German point of view. However, low-dose tamoxifen appears to be better tolerated than standard-dose tamoxifen 20 mg/day [11].

Male Breast Cancer

A man with early invasive breast cancer without evidence of a *gBRCA1/2* mutation should undergo a conventional mastectomy according to the majority of SGBCC panel members (41.82%). 36.36% of the panel members expressed their support for breast-conserving surgery plus radiation therapy. Since men can undergo breast-conserving surgery in the same way as women, from the German point of view the majority vote (mastectomy) is not acceptable. The same surgical guidelines apply to men with early breast cancer as they do to women, in each case respecting the aesthetic/cosmetic considerations. The possibility of breast-conserving surgery exists regardless of *gBRCA1/2* status.

The preferred endocrine therapy in early male breast cancer, regardless of stage (I–III), is tamoxifen [1, 2]. The German experts agree with the majority vote of the SGBCC panel (stage I: 80%; stage III: 50.77%) for tamoxifen. Loss of libido can occur during endocrine therapy [12]. If AI is used, it must always be combined with a gonadotropin-releasing hormone agonist (GnRHa) in males. Nearly 30% of SGBCC panel members would use the AI/GnRHa combination in stage III.

Adjuvant Radiotherapy

Vote for moderate hypofractionation

Regarding the use of adjuvant radiotherapy in early invasive breast cancer, the SGBCC panel agreed on various clinical scenarios. A clear majority of participants was in favor of moderate hypofractionated radiotherapy (15–16 fractions over three weeks). Ultra-hypofractionated radiation therapy (5 fractions in one week) was not successful:

- Thoracic wall irradiation after mastectomy independent of radiation of the axillary lymph nodes: Moderate hypofractionation 64.06% (vs. 10.94% for ultra-hypofractionated radiotherapy [5 sessions/week])
- Whole-breast radiotherapy (WBRT) after breast-conserving surgery regardless of radiotherapy of the axillary lymph nodes: 60.94% (vs. 15.65% for ultra-hypofractionated radiotherapy [5 sessions/week])

The voting results are in line with the recommendations of AGO [1, 2]: Moderate hypofractionation is clearly the standard in Germany after breast-conserving surgery, whereas ultra-hypofractionation is currently an option in individual cases (AGO 1b B +/−). German experts point out that this year AGO has given a "plus" recommendation for the first time to moderate hypofractionation for locoregional irradiation of axillary lymph nodes (1b B +) (chapter 13, slide 26). However, conventional fractionation is still recommended (AGO 1a A ++) [1, 2]. The reason is that the evidence for moderate hypofractionation for the axillary nodes is somewhat weaker since relevant study data are not yet available as a full-length publication [13]. It is currently unclear whether tumor biology should influence the decision on fractionation.

Indication for "boost" radiotherapy

German experts agree with the majority vote (35.94%) of the SGBCC panel (with 34.38% abstentions) that, following a breast-conserving surgery of primary invasive breast cancer, there is an indication for "boost" radiotherapy to the primary tumor bed if one of the following prognostic factors is present: A poorly differentiated tumor (G 3), extensive intraductal component (EIC), TNBC or HER2+ subtype, and age < 50 years. The above mentioned "boost" criteria largely correspond to the German recommendations of AGO [1, 2].

German experts recommend intraoperative clip marking of the tumor bed if "boost" radiotherapy is indicated [1, 2]. They point

out that in Germany, "boost" radiotherapy is used very often in international comparison. The increased rate of side effects and increased risk of fibrosis should be considered when making treatment decisions [14, 15].

"Boost" radiotherapy after neoadjuvant systemic therapy?

There was a mixed vote on the question of whether "boost" radiotherapy could be waived if pathological complete remission (pCR) was achieved after neoadjuvant systemic therapy (NAST) with breast-conserving surgery. German experts point out that no data are available for this situation. This may be reflected in the fact that many SGBCC panel members (38.10%) did not vote.

German experts position themselves as follows: If there is an indication for "boost" radiotherapy based on prognostic factors, it is also recommended for patients with pCR, regardless of the underlying tumor biology.

Indication for whole-breast radiotherapy

The indication for adjuvant WBRT (after breast-conserving surgery) in a healthy postmenopausal woman with early luminal A-breast cancer (1.3 cm) without axillary lymph node involvement would be decided by the majority (41.30%) of SGBCC panel members based on life expectancy and the patient's age. The SGBCC panel members consider an indication for WBRT at a life expectancy of more than 15 years. An almost identical result emerged from the on-site vote among the audience (majority vote: 39%).

German experts agree with this. The focus on life expectancy corresponds to the recommendation of AGO, which, however, applies a life expectancy of 10 years [1, 2]. In the PRIME-II study, forgoing WBRT (after breast-conserving surgery) was associated with a significantly increased local ipsilateral risk of recurrence at 10 years ($p < 0.001$), but had no effect on overall survival (OS; $p = 0.68$) [16, 17]. The study included elderly patients (≥ 65 years) with HR+ early invasive breast cancer and low risk (pT1–2 < 3 cm, pN0, M0), who underwent breast-conserving surgery and adjuvant ET ± WBRT [16, 17]. The voting result of the SGBCC panel members suggests that the reduction of the local recurrence rate may be a good reason for WBRT – especially in the context of decreasing therapy duration as a consequence of hypofractionation and good tolerability.

The following vote substantiates this: Two thirds (63.46%) of SGBCC panel members considered the most important clinical outcome of the PRIME-II study to be the reduction of the "in-breast" recurrence rate, and only 26.92% would forgo adjuvant WBRT because of the lack of survival benefit. According to the German experts, the results of the PRIME-II study [16, 17] should be discussed with the patients in the sense of a "shared decision".

Indication for post-mastectomy radiation therapy

SGBCC panel members voted on the indication for post-mastectomy radiation therapy (PMRT) in postmenopausal patients based on several clinical scenarios – including lymph node involvement, tumor stage, tumor biology, and whether the type of reconstruction changes the indication (skin-sparing vs. conventional mastectomy). It seems worth mentioning that 25% of panel members recommended thoracic wall irradiation in a postmenopausal patient with an HR+ T2 tumor and a mastectomy with one positive lymph node. In contrast, with two positive lymph nodes, it was 54%, and with three positive lymph nodes, 94% suggested this intervention. German experts refer to the current recommendations of AGO (▶ **Fig. 1**) [1, 2].

According to the German experts, the decision for or against PMRT should be discussed in the interdisciplinary tumor board. The type of reconstruction does not affect the oncologic treatment decision. Surgical technique alone is not a reason for more extensive radiotherapy if the indication for nipple or skin-sparing mastectomy is correctly done. Conversely, if there is an indication for radiotherapy for oncological reasons, this should not be forgone – irrespective of any implant-based reconstruction that has already taken place.

Detection of a heterozygous *ATM* mutation

Detection of a heterozygous pathogenic mutation in the *ATM* gene is not a contraindication to adjuvant radiotherapy after breast-conserving surgery (SGBCC majority vote: 73.58%). These patients can undergo breast-conserving surgery and receive radiotherapy postoperatively. German experts agree with this. German experts add that this does not apply to patients with homozygous mutation in the *ATM* gene or when a *TP53* mutation is detected. In these two cases, radiotherapy should be viewed critically because of the increased risk of secondary malignancy, and ablative procedures should be considered first.

Breast and Axillary Surgery

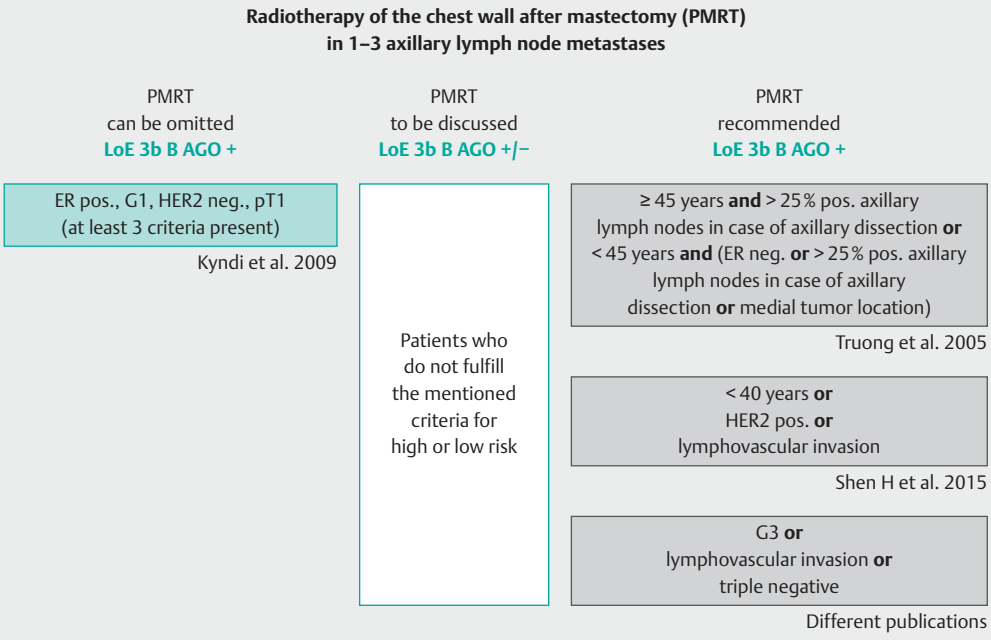
Axilla surgery

Surgery in the axilla after NAST has been debated for years. If the axilla is not tumor-free after NAST, the question arises about how patients are further treated in that area. In patients with TNBC and a residual tumor in the axilla (macrometastasis in 1/3 sentinel lymph nodes [SLN]) after anthracycline/taxane-based NAST, the majority (46.94%) of SGBCC panel members voted to complete axillary lymph node dissection (ALND). Just over 20% (20.41%) voted for radiation of the axilla and 28.57% would recommend ALND plus radiation. The audience vote yielded almost identical results.

The majority vote for ALND is in line with the AGO recommendation [1, 2]. German experts emphasize that in the case of macrometastatic SLN after NAST, the probability of other non-SLNs being affected is over 60% [18]. In Germany, no full-dose axilla radiation is recommended after ALND, as the risk of lymphedema increases significantly. There are currently insufficient data for axillary radiation alone. Here, the results of the AXSANA [19] and the TAXIS studies (NCT03513614) should be awaited.

According to the German experts, it seems important that AGO recommends a "targeted axillary dissection" (TAD) as an equivalent alternative to ALND in patients with clinical complete remission (ycN0) who initially had a nodal-positive disease prior to NAST, so that many patients with a good response to NAST can be spared ALND and its long-term effects.

German experts add that the decision for axillary treatment after NAST should be made in the interdisciplinary tumor board –



▶ **Fig. 1** Current recommendations of AGO for post-mastectomy radiation therapy (PMRT) in the axilla with 1–3 affected lymph nodes [1]. (Source: The Breast Cancer Commission of the Gynecological Oncology e. V. working group).

depending, among other things, on the extent of axillary lymph node involvement. In addition, there may be implications for subsequent systemic therapy, such as adjuvant use of olaparib [9, 10]. This applies not only to TNBC, but also to patients with HR+ breast cancer and a CPS-EG score ≥ 3.

Multifocal breast cancer

In light of the recent data from the ACOSOG-Z11102 study [20] on the surgical approach to multifocal breast cancer, the SGBCC panel recommended two tumor resections as the standard of care for two tumor lesions in the ipsilateral breast in low-risk patients, if technically feasible (majority vote: 68.18 %). The vote was based on the example of a postmenopausal patient with HR+/HER2− breast cancer without lymph node involvement and two ipsilateral tumors in two adjacent quadrants. German experts agree with this. In the ACOSOG-Z11102 study, previously published as an "abstract" and presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2022, patients had up to three ipsilateral tumors with a distance of ≥ 2 cm in a maximum of two affected quadrants. Patients with or without clinically abnormal axillary lymph nodes (cN0/cN1) were eligible for inclusion in the study. The cumulative incidence of local recurrence after five years was 3.1 % (95 % confidence interval [CI]: 1.3–6.4) [20].

Locoregional Recurrence

Indication for repeat radiotherapy

German experts agree with the majority vote of the SGBCC panel (58.18 %) to recommend breast-conserving surgery with adjuvant radiotherapy to a postmenopausal patient with ipsilateral recurrence (ER+/HER2−; cN0; lesion < 2 cm) again after nine years. At initial diagnosis, stage II was present without LN involvement. Radiotherapy was administered after lumpectomy. This was followed by adjuvant systemic therapy. German experts would like to add that it is necessary to clarify whether further radiotherapy is possible before the surgical intervention. This is the prerequisite for the indication of breast-conserving surgery. Partial breast radiotherapy (PBR) is preferable.

If the recurrence in the ipsilateral breast occurs after three years and adjuvant endocrine therapy was discontinued two years ago (for example, at the patient's request or due to side effects), a mastectomy is indicated according to the SGBCC panel (majority vote: 74.07 %). German experts also agree with this. Although there is no strict threshold for the relapse-free interval, the shorter it is, the less favorable the prognosis usually is, and the higher the cumulative toxicity risk under re-irradiation. In addition, if the recurrence interval is short, it is important to question how effective the initial radiotherapy was.

From the German expert opinion, the interval of three years is not an absolute contraindication to do another breast-conserving surgery plus radiotherapy, but the decision should be made with

caution. Mastectomy is a safe alternative to breast-conserving surgery plus radiotherapy.

Isolated local recurrence under endocrine treatment

If there is an isolated local recurrence during adjuvant AI therapy, which has been completely resected and submitted to definitive local therapy, the SGBCC panel members gave a heterogeneous opinion to continue endocrine treatment. Some (23.64%) chose to switch to tamoxifen. As many as 20% of SGBCC panel members had advocated for switching to fulvestrant plus CDK4/6 inhibitor, and 5.45% would combine a CDK4/inhibitor with an AI.

German experts believe that only switching to tamoxifen or switching from a non-steroidal AI to exemestane or vice versa is possible; both options are approved. There is no indication for switching to a CDK4/6 inhibitor plus fulvestrant or AI or to fulvestrant alone, neither of which has been studied or approved for this situation. German experts would recommend a preoperative therapy – taking into account the tumor size – to monitor the treatment response and to be able to adjust the therapy if necessary.

If the isolated local recurrence under AI therapy in the situation described above has a high ER expression (ER+/HER2−) and no adjuvant chemotherapy was initially given, the majority (62.94%) of SGBCC panel members would not recommend adjuvant chemotherapy even not in the case of a recurrence. German experts agree with this and recommend changing the endocrine therapy [1, 2].

In case of relapse under ongoing adjuvant ET, the decision for or against adjuvant chemotherapy cannot be made based on gene expression analysis. The majority (52.73%) of SGBCC panel members rightly point out that the clinical decision is made based on other factors such as grading, *Ki67* expression, HR status, or patient age. The gene signature thresholds have only been validated for the primary tumor, and not for the relapsed disease or the situation while ongoing adjuvant therapy [1, 2].

Adjuvant Endocrine Therapy

Uncertain endocrine sensitivity

Breast cancer with estrogen receptor (ER) expression of 1–10% is generally considered endocrine-positive (ER-low), but the endocrine sensitivity is uncertain. According to AGO recommendation, endocrine therapy is an option when endocrine sensitivity is questionable [1, 2]. Nevertheless, with very low ER expression and additional aggressive tumor biology, it cannot be ruled out that biologically and functionally the tumor behaves like TNBC and does not respond to endocrine therapy. In analogy to TNBC, chemotherapy – eventually with pembrolizumab – might be discussed. This should be considered in this special group of patients as part of an individualized therapy. Therefore, German experts cannot fully agree with the voting of the SGBCC panel members, since 57.38% recommend endocrine therapy at an ER expression of 1%. German experts add that in the abovementioned scenario – low ER expression – there is no evidence-based data using pembrolizumab.

Endocrine therapy duration

It is undisputed that patients with ER+/HER2− invasive stage I breast cancer should receive endocrine therapy for five years (majority vote: 88.24%). This is also true for stage II patients without axillary lymph node involvement (N0) (vote: 44.90%).

As many as 36.73% of SGBCC panel members would extend the endocrine therapy duration to 7–8 years in this situation (stage II, N0). German experts do not agree with this. Prolonged adjuvant ET in the sense of an extended endocrine adjuvant therapy (EAT) is indicated, according to the recommendation of AGO [1, 2], among other things, in nodal involvement (N+).

According to German experts, the duration of EAT depends not only on the initial tumor extent (nodal status, tumor size), but also on the initial ET. Recommended for the majority of patients is 7–8 years with AI therapy [21] and 10 years with tamoxifen [22–24]. In individual cases, a 10-year therapy can also be considered as an individual decision for patients with a very extensive primary tumor load, if the treatment is well tolerated and there are no osseous complications. The German experts agree with the other votes of the SGBCC panel members, well over 90% of whom recommend EAT in patients with ER+/HER2− invasive breast cancer stage II/N+ and III.

There is also consent that the decision in favor of EAT from stage II should be made taking into account established risk factors, such as stage, grading, treatment tolerability, and patient preference (majority vote: 96.97%). The German experts recommend a risk-benefit assessment. Individual deviations are reasonable and possible in individual cases (AGO chapter 10, slide 19) [1, 2].

The SGBCC panel members (majority vote: 60.61%) reject the use of gene expression analyses to determine the duration of endocrine therapy. The German experts agree, since the endocrine therapy duration can be reliably determined using established clinical criteria.

Adjuvant use of abemaciclib

The decision to treat patients with ER+/HER2− invasive breast cancer in the adjuvant setting additionally with abemaciclib is based on tumor stage and histology, and is independent of *Ki67* expression (majority vote: 77.27%). This is in line with the approval in Germany and the USA, which is based on the data from cohort 1 of the monarchE pivotal study [25–27].

Following this, the case of a patient with ER+/HER2− invasive stage II breast cancer (primary tumor 2.3 cm) and macrometastatic sentinel lymph nodes (SLN) was presented to the panel members for voting. The majority vote (44.44%) was that adjuvant chemotherapy plus endocrine therapy is adequate in this situation. Just over 35% would perform ALND to determine if additional lymph nodes are positive, and adjuvant treatment with abemaciclib is indicated. The audience vote yielded an almost identical result. According to German experts, it should be discussed in an interdisciplinary tumor board whether the number of positive lymph nodes should influence the decision on adjuvant systemic therapy. If this is the case and the likelihood of further lymph nodes being affected is high, ALND should be discussed considering the potential morbidity associated with ALND.

Neoadjuvant endocrine therapy

A simple majority (37.88 %) of SGBCC panel members would treat a 70-year-old patient with ER+/PR+ and HER2− invasive breast cancer (cT3N1) and a low risk – defined by gene expression and clinical criteria – with neoadjuvant endocrine therapy for approximately six months, followed by breast-conserving surgery. Another 34.85 % would give neoadjuvant ET until maximum response.

Neoadjuvant ET is very rarely performed in Germany – possibly as an option for elderly *and* comorbid patients, but not per se due to advanced age. However, it is generally an option when there is an indication for breast-conserving surgery for ER+ invasive breast cancer. If a neoadjuvant ET is used, German experts agree to administer the ET for a relatively long time. AGO recommends AI treatment for at least six months ("plus" recommendation) [1, 2].

Chemotherapy in ER-positive Breast Cancer

Therapy of choice in HR+/HER2− invasive breast cancer is endocrine treatment [1, 2]. If the risk of relapse is high, adjuvant chemotherapy is also indicated. The benefit in patients with genomic intermediate risk is questionable. SGBCC panel members voted on various clinical scenarios when chemotherapy should be recommended.

Short preoperative endocrine therapy

With a majority vote (69.70 %), SGBCC panel members recommend a short 2–4 week ET preoperatively to potentially identify those who do not require chemotherapy in addition to endocrine therapy in patients with HR+/HER2− early breast cancer and genomic intermediate risk. This procedure, which is based on the POETIC study [28] and the German ADAPT concept [29], got a "plus" rating from AGO [1, 2]. However, there is a lack of long-term data.

If endocrine sensitivity is checked preoperatively, German experts add that postmenopausal women should receive at least 2 weeks of treatment with an AI preoperatively, and premenopausal women should receive 4 weeks of ET plus OFS. The *Ki67* reduction is most effective when OFS and AI are combined. However, the opinion in the German expert panel is heterogeneous regarding the clinical consequences. Long-term data are lacking in premenopausal patients to determine whether this approach ensures that adjuvant chemotherapy is not needed. It should be noted that the gene expression test from the punch can be performed on the therapy-*naive* tumor.

Adjuvant therapy and multigene expression testing

According to subanalyses of the MINDACT, TAILORx, and RxPONDER studies [30 – 32], premenopausal patients with LN involvement benefit from chemotherapy and are not candidates for ET alone. However, the SGBCC panel rejected the question of whether gene expression testing can be omitted in premenopausal patients in stage I or II (majority vote: 76.60 %).

German experts agree with this. The multigene expression test allows pre-selection of premenopausal women with ER+ invasive stage I or II breast cancer for whom it may be appropriate to test for endocrine sensitivity (dynamic *Ki67*) preoperatively to omit additional chemotherapy. It should be noted that the clinical relevance of "dynamic *Ki67*" in premenopausal patients with intermediate genomic risk and 1–3 positive axillary LN has been intensively discussed in the German expert group. For some experts, further follow-up of the ADAPT study should be awaited.

Premenopausal women have the highest endocrine response probability with AI/GnRHa (~ 70–80 %). With tamoxifen, it is only about 40 % [29, 33]. If chemotherapy is not required, German experts refer to the recommendations of AGO on the risk-adapted application of adjuvant ET: For high-risk patients, AGO recommends the use of AI plus GnRHa (if chemotherapy is omitted), and for low-risk patients, tamoxifen plus GnRHa (chapter 10, slide 8) [1, 2].

Subsequent SGBCC panel votes addressed different clinical scenarios in pre- and postmenopausal patients with ER+/PR+ and HER2− invasive breast cancer and varying genomic risk. The question was, which adjuvant systemic therapy should be recommended.

German experts refrain from commenting on every single vote. According to German experts, it is important to note that tumor stage, tumor biology, *Ki67* score, possibly the endocrine response, and if indicated, gene expression testing in the context of menopausal status, are important factors for optimal adjuvant therapy in HR+/HER2− invasive breast cancer.

According to German experts, gene expression testing (independent of menopausal status) supports decision making in patients (HR+/HER2−) with intermediate clinical risk. High score values on gene expression tests increase the likelihood of chemotherapy being beneficial. For premenopausal patients (≤ 50 years), it should be noted that analogous to the data of the TAILORx and MINDACT studies, the benefit of chemotherapy is minimal with low genomic risk and high clinical risk at 12 and eight years (TAILORx and MINDACT, respectively). In contrast, the benefit of chemotherapy is clinically relevant in these patients with intermediate genomic risk [30, 32, 34]. Ongoing studies should clarify whether adjuvant therapy may be optimized in this patient group (chemotherapy "yes/no", CDK4/6 inhibitor plus endocrine therapy "yes/no").

Lobular cancer

The histology of breast cancer has no influence on chemotherapy indication. Therefore, even in patients with invasive lobular breast cancer (stage I–III, grade 1 or 2, clearly ER+ and HER2−, no pleomorphic features), chemotherapy may be indicated depending on individual risk. German experts agree with the majority vote of the SGBCC panel (60.0 %).

If a classic invasive lobular breast cancer (grade 1 or 2, clearly ER+/PR+, *Ki67* < 10 %, HER2-negative, no pleomorphic features) is present, and gene expression determination confirms low risk, the majority (63.46 %) of SGBCC panel members recommend no (neo)adjuvant chemotherapy for stages I–III. According to German experts, this can only be approved for stages I/II (patients with up to three positive LN). From stage III (≥ 4 positive LN), German experts recommend chemotherapy. In premenopausal patients with 1–3 positive LN, the tumor size and the *Ki67* expression

and a multigene assay should be considered for treatment decision.

Side effects of AI/GnRHa

If a 38-year-old amenorrheic patient with invasive ER+ stage II breast cancer develops menopausal symptoms under AI/GnRHa treatment, the SGBCC panel members (44.23%) recommend measuring estradiol levels every six months. The German experts only partially agree: Although menopausal symptoms may be a consequence of estrogen deprivation, elevated E2 levels may be present despite amenorrhea. Elevated E2 levels indicate that GnRHa therapy is not adequately downregulating ovarian function. This would have the consequence of taking another GnRHa and switching from a 3-monthly to a monthly administration or switching from AI to tamoxifen. Thus, controlling peripheral hormones may have therapeutic consequences for oncological therapy [35].

SGBCC panel members recommend switching to monthly GnRHa administration (majority vote: 64.62%) for a 39-year-old patient (stage II, ER+/HER2−) who had breakthrough bleeding under AI plus 3-monthly administration of GnRHa. More stringent monthly dosing may avoid escape phenomena that may occur under 3-monthly dosing. German experts share this opinion.

According to the majority vote of the SGBCC panel (35.38%), a premenopausal patient over the age of 40 with invasive ER+ stage III breast cancer after 5 years of treatment with AI/GnRHa should receive extended adjuvant endocrine therapy (EAT) and switch to tamoxifen. The patient developed not insignificant arthralgias under the treatment. German experts agree in both cases. Stage III warrants EAT because of the increased risk of recurrence. In the absence of data on AI/GnRHa therapy beyond five years, switching to tamoxifen is also warranted by indirect analogy.

Triple-negative Breast Cancer

Neoadjuvant use of platinum

Carboplatin is an integral component of neoadjuvant chemotherapy (NACT) with taxane/anthracycline and cyclophosphamide in early TNBC (stage II/III) when pembrolizumab is used in addition to chemotherapy. This is consistent with the KEYNOTE-(KN-)522 pivotal study of pembrolizumab (majority vote: 78.0%) [36, 37]. Pembrolizumab had been used in the neoadjuvant setting simultaneously to carboplatin/paclitaxel followed by doxorubicin/cyclophosphamide (AC), and was continued postoperatively as monotherapy.

In this situation, the SGBCC panel members recommend using carboplatin in addition to neoadjuvant taxane/anthracycline-based chemotherapy even if patients do not receive pembrolizumab (majority vote: 72.0%). This is in line with the “Plus” recommendation of AGO (chapter 12, slide 12) [1, 2].

Dose-dense chemotherapy plus pembrolizumab under discussion

In the KN-522 study [37], the AC regimen was administered every three weeks (q3W) as was pembrolizumab. Due to the lack of data, the majority of SGBCC panel members (38.46%) is unsure whether chemotherapy with AC can also be given 2-weekly (q2W) when pembrolizumab is used additionally. Just under 30% (29.23%) were in favor.

German experts discussed this issue intensively. In Germany, dose-dense chemotherapy is generally preferred for TNBC [1, 2]. Reference is made to the GeparNuevo and GeparDouze studies, both of which used dose-dense regimens together with immunotherapy [38, 39].

It is unclear whether the 2-weekly administration has unfavorable effects on the efficacy of immunotherapy. Despite the open questions, the German experts agree that dose-dense administration of the AC regimen in combination with pembrolizumab can be considered depending on risk and tolerability. But, it is important that pembrolizumab continues to be administered every three weeks, even in combination with the dose-dense AC regimen.

(Neo)adjuvant use of pembrolizumab

A premenopausal patient with TNBC who achieves pathological complete remission (pCR) under neoadjuvant chemotherapy with taxane/carboplatin followed by AC, plus additional pembrolizumab, should continue treatment with pembrolizumab (monotherapy) in the adjuvant setting despite pCR (majority vote: 58.49%). This is consistent with the pivotal study [37]. Only in individual cases, for example if pembrolizumab is very poorly tolerated, should adjuvant administration of pembrolizumab be omitted according to German experts. The absolute benefit in event-free survival (EFS) at three years was 2% in the pembrolizumab group compared with the control group [36].

German experts agree with the majority vote of the SGBCC panel that a 60-year-old patient with TNBC (cT2N0; 2–3 cm), who can undergo breast-conserving surgery, should be treated neoadjuvantly with chemotherapy plus pembrolizumab. The neoadjuvant approach is preferred in Germany and the neoadjuvant use of pembrolizumab is in accordance with the AGO recommendation [1, 2].

In contrast, neoadjuvant use of pembrolizumab-based chemotherapy in stage I TNBC (TNBC < 2 cm; cT1 cN0) [37] does not meet the approval. German experts support the SGBCC majority vote (46.15%) to forgo pembrolizumab in this situation.

Also not covered by the approval is the adjuvant use of pembrolizumab in a patient with primary surgery for stage II TNBC and positive lymph nodes (majority vote: 62.0%). The postoperative use of pembrolizumab is only approved together with neoadjuvant administration (plus chemotherapy). German experts point out once again that the neoadjuvant treatment is preferred for TNBC patients with a tumor size larger than 1 cm [1, 2].

HER2-positive Breast Cancer

Adjuvant trastuzumab administration

The preferred adjuvant regimen for patients with HER2-positive (HER2+) stage I breast cancer is the combination of paclitaxel/trastuzumab (TH) (majority vote: 84.62%). This is supported by the 10-year data from the APT study published this year [40], and the 5-year data from the ATEMPT study in the TH study arm [41].

Adjuvant administration of trastuzumab is the therapy of choice for patients with HER2+ breast cancer without clinically suspicious lymph nodes (cN0) who achieved pCR with neoadjuvant treatment with docetaxel/carboplatin plus trastuzumab/pertuzumab (TCHP) (majority vote: 63.27%). German experts agree. The 8-year data from the APHINITY study [42] showed no efficacy benefit for dual antibody blockade with trastuzumab/pertuzumab versus adjuvant trastuzumab administration in pN0 patients.

If residual tumor remains after neoadjuvant TCHP therapy and is HER2-negative by immunohistochemistry (IHC) and FISH analysis, the majority of SGBCC panel members recommend adjuvant treatment with trastuzumab emtansine (T-DM1) [43]. The German experts agree. However, it should be noted that retesting of the HER2 status on the residual tumor is not recommended by AGO; it is a decision made on a case-by-case basis [1, 2]. Currently, there is no evidence for retesting the receptor status on the residual tumor.

BRCA-associated Breast Cancer

Use PARP inhibition and checkpoint inhibition?

A 43-year-old female patient with a *gBRCA1* mutation and a stage II TNBC with lymph node involvement still had a residual tumor after neoadjuvant treatment according to the KN522 study (carboplatin/paclitaxel followed by AC, each plus pembrolizumab) [37]. In this situation, the majority (62.0%) of the SGBCC panel recommends using pembrolizumab and olaparib postoperatively. Just under a quarter of SGBCC panel members (24.0%) would administer both agents in sequence.

The German experts agree because PARP inhibition in this high-risk situation is an additional therapeutic approach with a potential efficacy benefit. However, this approach has not been evaluated in either pivotal study. Nevertheless, study data on the combination of checkpoint and PARP inhibition indicate that there are no safety concerns [44–46]. The potential benefit of additional olaparib administration should not be withheld from high-risk patients, as this therapy has a survival advantage. This is why the SGBCC majority vote is understandable from a German perspective. The current recommendations of AGO is in-line.

PARP inhibition and CDK4/6 inhibition?

For a *gBRCA2*-mutated patient with ER+/HER2− invasive stage III breast cancer, the SGBCC panel recommends olaparib and abemaciclib in sequence in the postneoadjuvant setting. This is in addition to standard endocrine therapy after neoadjuvant dose-dense therapy with AC/paclitaxel (majority vote: 48.02%). 37.25% would only use olaparib in addition to ET.

The post-neoadjuvant use of olaparib and abemaciclib is understandable in this patient as this is a high-risk scenario. Due to overlapping side effects, both substances should be given sequentially. The approval of both substances does not prevent sequential administration. German experts point out that the monarchE study [25] also had some patients who were included in the study only twelve months after primary diagnosis.

TNBC: Platinum or olaparib?

Detection of a *gBRCA1/2* mutation is not predictive of the benefit of platinum as part of (neo)adjuvant chemotherapy; therefore, *all* patients with *gBRCA1/2*-mutated invasive breast cancer should also receive platinum-based chemotherapy. This applies regardless of the availability of olaparib (majority vote: 50% and 60.87%, respectively [olaparib available]). German experts agree. The indication for platinum-based chemotherapy in TNBC is independent of the detection of a *gBRCA1/2* mutation (AGO chapter 12, slide 11) [1, 2]. In HR+ breast cancer, there is no indication for the use of platinum due to the absence of adequate study data.

Osteoprotective Therapy

According to AGO, adjuvant (osteoprotective) bisphosphonate use should be recommended for all postmenopausal patients [1, 2]. As with any treatment, a risk-benefit assessment is necessary. The majority vote of the SGBCC panel members (32.0%) that the use is an option only in postmenopausal women with ER+ invasive stage II/III breast cancer is not accepted. German experts point out that bisphosphonates act independently of receptor status. For denosumab, there are adjuvant study data showing benefit only for postmenopausal patients undergoing AI therapy [47].

Oligometastatic Disease

Chance of long-term survival?

Patients with oligometastatic disease may still have a chance of cure or long-term survival. Against this background, the SGBCC panel members (majority vote: 68.0%) recommend to resect and subsequently irradiate a patient with ER-negative/HER2-positive breast cancer (primary tumor 4 cm) plus axillary lymph node involvement (N+) and with isolated pulmonary metastases who achieved pCR during induction therapy with THP (taxane, trastuzumab, pertuzumab). The vote from the audience was almost identical. The SGBCC panel recommended this approach for said patient (4 cm, N+, isolated lung metastasis) regardless of tumor biology.

German experts agree that a curative treatment is sought. There are no study data for this clinical situation. Data on surgery for the primary tumor in the metastatic setting do not support this approach. According to German experts, these are individual decisions [1, 2].

If a patient with stage II invasive breast cancer in the contralateral axilla has isolated lymph node metastases, the SGBCC panel members (majority vote: 75.0%) recommend curative therapy with ALND on the contralateral side, plus radiation and adjuvant systemic standard therapy. The multidisciplinary approach is in line with the recommendation of AGO (chapter 21, slide 15) [1, 2]. Breast cancer patients with contralateral axilla metastasis usually have a good prognosis with the chance of long-term survival [48].

Molecular Diagnostics

Circulating tumor DNA is not yet standard

Molecular diagnostic methods are becoming increasingly common in oncology. They are accompanied by the hope of detecting recurrences earlier and improving prognosis through more targeted intervention. Numerous studies are investigating testing for circulating tumor cell DNA in the blood (ctDNA) to better predict the risk of recurrence in tumor patients. Currently, ctDNA testing is not a standard method and is reserved for clinical trials because it does not yet entail therapeutic consequences (majority vote: 89.3%).

Accordingly, the SGBCC panel members (majority vote: 86.0%) reject postoperative ctDNA testing in patients with early breast cancer in clinical practice. The German experts agree. In Germany, the SURVIVE study (Standard Surveillance versus Intensive Surveillance in Early Breast Cancer) is currently underway, the results of which are awaited (https://www.survive-studie.de/fuer-fachpersonal.html).

ctDNA without clinical consequences

SGBCC panel members disagreed on whether the result of a ctDNA testing performed as part of a translational research project of a study should be shared with the treating physician and/or the patient. According to German experts, there is no need to communicate the results – neither to the physician nor to the patient – as no therapeutic consequences can be derived from them. If the result is reported to the physician, it must also be reported to the patient.

With this in mind, a treatment switch should also be rejected if a patient achieves pCR in a clinical trial using neoadjuvant systemic therapy, and postoperative ctDNA testing in the trial detects ctDNA in the blood. German experts agree with the SGBCC panel (majority vote: 69.23%).

Study concept under discussion

A postmenopausal patient with ER+/HER2− stage III invasive breast cancer who has been successfully treated with standard endocrine therapy for five years will be enrolled in a clinical trial in which ctDNA testing will be used to determine further treatment. Patients whose ctDNA findings indicate an *ESR1* mutation are randomized and alternatively treated with AI or switched to fulvestrant. The question of whether this is a fair study was affirmed by a simple majority of SGBCC panel members (43.08% vs. 38.46% and 18.46% abstentions).

German experts do not have a uniform opinion either. There was consensus that stage III represents a high risk of recurrence, which is why further adjuvant treatment is reasonable. It is unclear whether the data on endocrine resistance, when an *ESR1* mutation is detected, originating from the metastatic situation can be transferred to the adjuvant situation. Since fulvestrant is only approved in the metastatic setting, some German experts support study participation to give patients the chance of adjuvant fulvestrant. Other German experts rejected the study concept to avoid the possibility of a patient with *ESR1* mutation being further treated with AI, and preferred a reimbursement claim for fulvestrant.

Acknowledgements

The post-SGBCC meeting of the German Breast Cancer Expert Group was organized and financially supported by onkowissen.de. The responsibility for manuscript preparation lies solely with the authors. The authors would like to thank Birgit-Kristin Pohlmann, Nordkirchen, for editorial support in the preparation of the manuscript.

Conflict of Interest

Prof. Michael Untch, MD: All remuneration to the AG/institution (referent and consultant activity): Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Lilly, MSD Merck, Myriad Genetics, Pfizer, Roche, Pierre Fabre, Novartis, Molecular Health, Agendia, GSK, Seagen, Gilead, Medac, Stemline Genzyme.
Maggie Banys-Paluchowski, MD, Associate Professor, received remuneration from: Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkowissen, Seagen, AstraZeneca, Eisai, Amgen, Samsung, Canon, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Pintuition, Pierre Fabre, ExactSciences, Syantra, Stemline, and study support from: EndoMag, Mammotome, MeritMedical, Gilead, Hologic, ExactSciences, Sirius Medical.
Prof. Sara Y. Brucker, MD, received remuneration from AstraZeneca, Roche, Novartis, Medtronic, Sanofi, Lilly, MSD, and Hologic. Prof. Wilfried Budach, MD, received remuneration from Merck, BMS, Jörg Eickeler Veranstaltungen, medpublico.
Prof. Carsten Denkert, MD, received remuneration from Novartis, Roche, MSD Oncology, Daiichi Sankyo, AstraZeneca, Merck, Molecular Health and study support from the European Commission, German Cancer Aid, BMBF, GBG, Myriad, and Roche. He is involved in patents for digital pathology (VMscope digital pathology software) and biomarker signatures (patents WO2015114146A1 and WO2010076322A1).
Prof. Nina Ditsch, MD, received remuneration from AstraZeneca, Daiichi Sankyo, Gilead Sciences, Lilly, Merit Medical, Molecular Health, MSD, Novartis, Onkowissen, Pfizer, pfm medical, Roche, Seagen, Teva.
Prof. Peter A. Fasching, MD, received grants from Biontech, Pfizer, Cepheid, and remuneration from Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, Esai, Merck Sharp & Dohme, Lilly, Pierre Fabre, SeaGen, Roche, Agendia, Sanofi Aventis, Gilead, Mylan, and Menarini.
Renate Haidinger has no conflicts of interest.
Prof. Dr. med. Jörg Heil has no conflicts of interest.
Prof. Dr. med. Christian Jackisch received remuneration from AstraZeneca, Lilly, Celgene, MSD; Eisai, Novartis, Pfizer, Gilead, Daiichi Sankyo, Medupdate, Streamed Up, Roche, and research support from Exact Sciences.
Prof. Dr. med. Wolfgang Janni received remuneration from AstraZeneca, Celgene, Chugai, Daiichi Sankyo, Eisai, ExactScience, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, Inivata.
Hans-Christian Kolberg, MD, Associate Professor, received remuneration from Pfizer, Novartis, Seagen, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, Teva, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lilly, SurgVision, Onkowissen, Gilead, Daiichi Sankyo, and MSD, as well as travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro, and owns shares in Theraclion SA and Phaon Scientific GmbH.
David Krug, MD, Associate Professor, received remuneration from Merck Sharp & Dohme, med update, onkowissen, and Pfizer, as well as research support from Merck KGaA.
Prof. Dr. med. Sibylle Loibl did not receive any remuneration. The following companies granted support and remuneration to the GBG: Abbvie, Amgen; AZ; Celgene/BMS, Daiichi Sankyo, Gilead, GSK, Incyte, Lilly, MSD, Merck KG, Medupdate, Streamedup, Novartis, Olema, Pfizer; Relay, Sanofi, Seagen, Roche.
Prof. Diana Lüftner, MD, received remuneration from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eli Lilly, Gilead, GSK, high5md, Loreal, Novartis, onkowissen, Pfizer, Roche, Teva.

Marion van Mackelenbergh, MD, Associate Professor, received remuneration from Amgen, AstraZeneca, Daiichi Sankyo, GenomicHealth, Gilead, GSK, Lilly, Molecular Health, MSD, Mylan, Novartis, Pfizer, Pierre-Fabre, Roche, Seagen, and travel fees from Daiichi Sankyo, Gilead, Lilly.
Prof. Julia Radosa, MD, received remuneration from Pfizer, Eisai, MSD, Medac GmbH, Roche, Novartis, Gedeon Richter, Lilly, Pierre Fabre, Daiichi Sankyo, Seagen, Theramex.
Prof. Toralf Reimer received remuneration from AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, Myriad, Novartis, Pfizer, and Roche.
Manfred Welslau, MD, received remuneration from Amgen, Astellas, AstraZeneca, Celgene, Gilead, Hexal, Janssen, Lilly, Novartis, Roche, Sanofi and has consulted and reviewed for Amgen, Bristol-Myers Squibb, Celgene, Gilead, Hexal, Janssen, Lilly, Medac, Novartis, Roche, Sanofi, AstraZeneca.
Rachel Würstlein, MD, Associate Professor, received remuneration from Agendia, Amgen, Aristo, Astra Zeneca, Celgene, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, GlaxoSmithKline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Mylan, Nanostring, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, PINK, PumaBiotechnology, Riemser, Roche, Sandoz/Hexal, Sanofi Genzyme, Seattle Genetics/Seagen, Stemline, Tesaro Bio, Teva, Veracyte, Viatris, FOMF, Aurikamed, Clinsol, Pomme Med, medconcept, MCI.
Prof. Nadia Harbeck, MD, received remuneration from Amgen, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Viatris, Zuelligpharma.
Prof. Jens Huober, MD, received research support from Celgene, Novartis, Hexal, and Lilly. Remuneration for lectures from Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Celgene, Eisai, Abbvie, Seagen, Gilead, and Daiichi Sankyo. Consultancy fees from Lilly, Novartis, Roche, Pfizer, Hexal, AstraZeneca, MSD, Celgene, Abbvie, Daiichi, Gilead. Travel fees from Roche, Pfizer, Novartis, Celgene, Daiichi Sankyo, and Gilead.

Reference

[1] AGO Kommission Mamma. Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome (März 2023). Stand: 15.04.2023. Accessed July 30, 2023 at: https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma

[2] Tjoung-Won PS, Müller V, Jackisch C et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer (EBC): Update 2023. Breast Care 2023. doi:10.1159/000531578

[3] Patridge AH, Niman SM, Ruggeri M et al. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. N Engl J Med 2023; 388: 1645–1656. doi:10.1056/NEJMoa2212856

[4] Pan H, Gray R, Braybrooke J et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017; 377: 1836–1846. doi:10.1056/NEJMoa1701830

[5] Nelson DR, Brown J, Morikawa A et al. Breast cancer-specific mortality in early breast cancer as defined by high-risk clinical and pathologic characteristics. PLoS One 2022; 17: e0264637. doi:10.1371/journal.pone.0264637

[6] Yadav S. Population-based Estimates of Contralateral Breast Cancer Risk among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2 and PALB2. San Antonio Breast Cancer Symposium 2022; Abstract No. GS4-04

[7] Yadav S, Hu C, Hart SN et al. Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer. J Clin Oncol 2020; 38: 1409–1418. doi:10.1200/JCO.19.02190

[8] Tung NM, Robson ME, Ventz S et al. TBCRC048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol 2020; 38: 4274–4282. doi:10.1200/JCO.20.02151

[9] Tutt A, Garber JE, Kaufman B et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. J Clin Oncol 2021; 39: LBA1. doi:10.1200/JCO.2021.39.15_suppl.LBA1

[10] Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med 2021; 384: 2394–2405. doi:10.1056/NEJMoa2105215

[11] de Censi A, Lazzeroni M, Puntoni M. 10-year results of a phase 3 trial of low-dose tamoxifen in non-invasive breast cancer. San Antonio Breast Cancer Symposium 2022; Abstract No. GS4-08

[12] Reinisch M, Seiler S, Hauzenberger T et al. Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial. JAMA Oncol 2021; 7: 565–572. doi:10.1001/jamaoncol.2020.7442

[13] Offersen B, Alsner J, Nielsen HM et al. OC-0102 DBCG phase III randomized trial of hypo- vs. standard fractionated RT in 2879 pN+ breast cancer pts. Radiotherapy and Oncology 2022; 170: S76–S77. doi:10.1016/s0167-8140(22)02478-1

[14] Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015; 16: 47–56. doi:10.1016/s1470-2045(14)71156-8

[15] Chua BH, Link EK, Kunkler IH et al. Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3–07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study. Lancet 2022; 400: 431–440. doi:10.1016/s0140-6736(22)01246-6

[16] Kunkler IH, Williams LJ, Jack WJL et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 2015; 16: 266–273. doi:10.1016/S1470-2045(14)71221-5

[17] Kunkler I, Williams LJ, Jack W et al. GS2-03. Prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): Wide local excision and adjuvant hormonal therapy ± whole breast irradiation in women =/> 65 years with early invasive breast cancer: 10 year results. San Antonio Breast Cancer Symposium 2020; Abstract No. GS2-03

[18] Moo T-A, Edelweiss M, Hajiyeva S et al. Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication for Axillary Dissection? Ann Surg Oncol 2018; 25: 1488–1494. doi:10.1245/s10434-018-6429-2

[19] Hartmann S, Kühn T, Hauptmann M et al. Axillary Staging after Neoadjuvant Chemotherapy for Initially Node-Positive Breast Carcinoma in Germany: Initial Data from the AXSANA study. Geburtshilfe Frauenheilkd 2022; 82: 932–940. doi:10.1055/a-1889-7883

[20] Boughey JC, Rosenkranz KM, Ballman KV. Impact of breast conservation therapy on local recurrence in patients with multiple ipsilateral breast cancer – Results from ACOSOG Z11102 (Alliance). San Antonio Breast Cancer Symposium 2022; Abstract No. GS4-01

[21] Gnant M, Fitzal F, Rinnerthaler G et al. Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer. N Engl J Med 2021; 385: 395–405. doi:10.1056/NEJMoa2104162

[22] Goss PE, Ingle JN, Pritchard KI et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med 2016; 375: 209–219. doi:10.1056/NEJMoa1604700

[23] Gray RG, Rea D, Handley K et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013; 31: 5. doi:10.1200/jco.2013.31.18_suppl.5

[24] Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381: 805–816. doi:10.1016/S0140-6736(12)61963-1

[25] Johnston SRD, Harbeck N, Hegg R et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020; 38: 3987–3998. doi:10.1200/JCO.20.02514

[26] Harbeck N, Rastogi P, Martin M et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021; 32: 1571–1581. doi:10.1016/j.annonc.2021.09.015

[27] O'Shaughnessy J, Rastogi P, Harbeck N. Adjuvant abemaciclib combined with endocrine therapy: Updated results from monarchE. ESMO Virtual Plenary Session, October 14, 2021

[28] Smith I, Robertson J, Kilburn L et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol 2020; 21: 1443–1454. doi:10.1016/S1470-2045(20)30458-7

[29] Nitz UA, Gluz O, Kümmel S et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol 2022; 40: 2557–2567. doi:10.1200/JCO.21.02759

[30] Piccart M, van 't Veer LJ, Poncet C et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 2021; 22: 476–488. doi:10.1016/S1470-2045(21)00007-3

[31] Sparano JA, Gray RJ, Ravdin PM et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. N Engl J Med 2019; 380: 2395–2405. doi:10.1056/NEJMoa1904819

[32] Kalinsky K, Barlow WE, Gralow JR et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med 2021; 385: 2336–2347. doi:10.1056/NEJMoa2108873

[33] Gluz O, Nitz U, Christgen M. Impact of age, recurrence score and ovarian function suppression on endocrine response to short preoperative endocrine therapy: Analysis of ADAPT and ADAPTcycle trials. Ann Oncol 2022; 33: S808–S869

[34] Sparano J, Gray RJ, Makower D. Trial Assigning Individualized Options for Treatment (TAILORx): An Update Including 12-Year Event Rates. San Antonio Breast Cancer Symposium 2022; Abstract No. GS1-05

[35] Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015; 372: 436–446. doi:10.1056/NEJMoa1412379

[36] Schmid P, Cortes J, Dent R et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med 2022; 386: 556–567. doi:10.1056/NEJMoa2112651

[37] Schmid P, Cortes J, Pusztai L et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020; 382: 810–821. doi:10.1056/NEJMoa1910549

[38] Loibl S, Schneeweiss A, Huober J et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. Ann Oncol 2022; 33: 1149–1158. doi:10.1016/j.annonc.2022.07.1940

[39] Loibl S, Jackisch C, Rastogi P et al. GeparDouze/NSABP B-59: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. Ann Oncol 2019; 30: iii38. doi:10.1093/annonc/mdz097.014

[40] Tolaney SM, Tarantino P, Graham N et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. Lancet Oncol 2023; 24: 273–285. doi:10.1016/S1470-2045(23)00051-7

[41] Tarantino P, Tayob N, Dang CT. Adjuvant Trastuzumab Emtansine versus Paclitaxel plus Trastuzumab for Stage I HER2+ breast cancer: 5-year results and correlative analyses from ATEMPT (TBCRC033). San Antonio Breast Cancer Symposium 2022; Abstract No. PD18-01

[42] Loibl S, Jassem J, Sonnenblick A et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. Ann Oncol 2022; 33: 986–987. doi:10.1016/j.annonc.2022.06.009

[43] Loibl S, Huang C-S, Mano MS et al. Adjuvant trastuzumab emtansine in HER2-positive breast cancer patients with HER2-negative residual invasive disease in KATHERINE. NPJ Breast Cancer 2022; 8: 106. doi:10.1038/s41523-022-00477-z

[44] Domchek SM, Postel-Vinay S, Im S-A et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol 2020; 21: 1155–1164. doi:10.1016/S1470-2045(20)30324-7

[45] Konstantinopoulos PA, Waggoner S, Vidal GA et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. JAMA Oncol 2019; 5: 1141–1149. doi:10.1001/jamaoncol.2019.1048

[46] Rugo HS, Llombart-Cussac A, Andre F et al. KEYLYNK-009: A phase II/III, open-label, randomized study of pembrolizumab (pembro) plus olaparib vs. pembro plus chemotherapy after induction with first-line pembro plus chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC). J Clin Oncol 2020; 38: TPS596. doi:10.1200/JCO.2020.38.15_suppl.TPS596

[47] Gnant M, Pfeiler G, Steger GG et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20: 339–351. doi:10.1016/S1470-2045(18)30862-3

[48] Díaz-Roldán J, Eguía-Larrea M, Rubio-Sánchez T et al. Systematic review of synchronous contralateral axillary metastases in breast cancer: really M1 disease? Breast Cancer 2022; 29: 9–18. doi:10.1007/s12282-021-01293-2