

## Treatment of patients with early breast cancer: 19th St. Gallen international breast cancer consensus discussed against the background of German treatment recommendations

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# Treatment of Patients with Early Breast Cancer

19th St. Gallen International Breast Cancer Consensus Discussed against the Background of German Treatment Recommendations

## Behandlung von Patientinnen mit frühem Mammakarzinom

19. Internationaler St.-Gallen-Konsens vor dem Hintergrund deutscher Therapieempfehlungen diskutiert



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St. Gallen Consensus 2025, early breast cancer, genetics, surgery, radiotherapy, (neo)adjuvant systemic therapy, survivorship

### Schlüsselwörter

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**ABSTRACT**

This year's 19th St. Gallen (SG) consensus conference on the treatment of patients with early breast cancer (SGBCC: St. Gallen Breast Cancer Conference) is based on numerous patient examples, each with different variables, to reflect the increasingly personalized treatment decision for early breast cancer. More than ever, not only breast cancer subtype, performance status, age and life expectancy are considered as individual factors, but various molecular and genetic variables are also part of the treatment decision. In this manuscript, the SGBCC voting results are discussed by a German group of breast cancer specialists in the context of the recently (2025) updated treatment recommendations of the Commission of the Gynecological Oncology Working Group (AGO Mamma). The German treatment recommendations are based on current evidence. As the international panel of the SGBCC consists of experts from different countries and disciplines, the votes represent an international cross-section of opinions.

Therefore, it is useful to discuss the voting results with respect to current German treatment guidelines.

**ZUSAMMENFASSUNG**

Die diesjährige 19. St.-Gallen-(SG-)Konsensus-Konferenz zur Behandlung von Patientinnen mit frühem Mammakarzinom (SGBCC: St. Gallen Breast Cancer Conference) basierte auf zahlreichen fiktiven Fallbeispielen mit jeweils unterschiedlichen Variablen, um der zunehmend personalisierten Therapieentscheidung beim primären – frühen – Mammakarzinom gerecht zu werden. Stärker denn je fließen nicht nur der Mammakarzinom-Subtyp, der Allgemeinzustand und das Lebensalter bzw. die Lebenserwartung als individuelle Faktoren in die Therapieentscheidung ein, sondern auch unterschiedliche molekulare und genetische Variablen. Wie schon in den vergangenen Jahren hat auch dieses Jahr eine deutsche Arbeitsgruppe führender Brustkrebsexpertinnen und -experten die Ergebnisse der internationalen SGBCC 2025 vor dem Hintergrund der deutschen Therapieempfehlungen – speziell der erst kürzlich (2025) aktualisierten Therapieempfehlungen der Kommission Mamma der Arbeitsgemeinschaft Gynäkologische Onkologie e. V. (AGO) – für den Klinikalltag in Deutschland diskutiert. Die deutschen Therapieempfehlungen der AGO Mamma 2025 basieren auf der aktuell vorhandenen Evidenz. Der Abgleich mit dem klinischen Vorgehen in Deutschland bewährt sich seit Jahren, da sich das SGBCC-Panel aus Expertinnen und Experten unterschiedlicher Länder und Fachdisziplinen zusammensetzt, weshalb länderspezifische Besonderheiten in die SGBCC-Empfehlungen einfließen können.

**Introduction**

The rationale behind the St. Gallen (SG) Breast Cancer Conference (SGBCC) on primary treatment of patients with early breast cancer is to develop an international consensus for routine clinical practice. The 19th SGBCC focused on multiple patient scenarios with varying clinical and/or genomic factors during its consensus voting to address possible treatment decisions for clinical practice. The goal was to explore the significance of variables such as age, patient performance status, tumor biology including molecular markers and genomic risk for individual treatment decisions.

The panel of international experts at the SGBCC Consensus 2025 consisted of 76 breast cancer specialists and included eight panel members from Germany (s. ► **Table 1**). The consensus is based on majority voting of the SGBCC panel. As the panel members work in different specialties and come from different countries with different health care systems and resources, a working group of German breast cancer specialists has commented on the voting results for many years in the context of the current treatment recommendations of the Mamma Commission of the Gynecological Working Group (AGO Mamma) [1]. The recommendations of AGO Mamma are updated every year and are based on a high level of evidence which incorporates current data [1, 2]. The comments of the German specialists in this article refer to the voting results of the SGBCC panel which were discussed

during the conference and are summarized and will be published elsewhere [3].

**Genetics: Focus on Pathogenic Variants**

According to AGO Mamma, patients with newly diagnosed primary breast cancer with no family history of breast cancer should be offered a genetic testing for pathogenic germline variants (pV) (known as panel testing) up to and including the age of 65 years. A slightly higher rate of VUS (variants of unclear significance) should be taken into account [1, 2]. Genetic testing for pV is highly recommended (Level of Evidence [LoE] 1b, GR [Grade] A, Recommendation ++) for the two breast cancer genes *BRCA1* and 2 in the germline (*gBRCA1/2*) and a simple recommendation for *gPALB2* (3a B +) (► **Fig. 1**) [1, 2].

The AGO recommendation basically corresponds to the majority vote of the SGBCC panel: more than two thirds of SGBCC panel members rejected the proposal to have routine testing for pV in all patients irrespective of age at first diagnosis (majority vote: 76.0%). Three quarters of panel members voted for genetic testing in patients with newly diagnosed breast cancer up to the age of 50 (majority vote: 77.3%). Routine testing at first diagnosis of early breast cancer up to the age of 70 was rejected (majority vote: 64.0%).

► **Table 1** International SGBCC panel 2025.

Chair: Harold Burstein (USA)		
<ul style="list-style-type: none"> <li>▪ Stephan Aebi (Switzerland)</li> <li>▪ Meteb Al-Foheidi (Kingdom of Saudi Arabia)</li> <li>▪ Zsuzsanna Bago-Horvath (Austria)</li> <li>▪ Francois-Clément Bidard (France)</li> <li>▪ Judy Boughey (USA)</li> <li>▪ Denisse Bretel Morales (Peru)</li> <li>▪ Sara Y. Brucker (Germany)</li> <li>▪ Harold J. Burstein (USA)</li> <li>▪ Maria Joao Cardoso (Portugal)</li> <li>▪ Lisa Carey (USA)</li> <li>▪ Steven Chia (Canada)</li> <li>▪ Charlotte Coles (GB)</li> <li>▪ Javier Cortes (Spain)</li> <li>▪ Giuseppe Curigliano (Italy)</li> <li>▪ Shaheena Dawood (United Arab Emirates)</li> <li>▪ Jana de Boniface (Sweden)</li> <li>▪ Angela De Michele (USA)</li> <li>▪ Carsten Denkert (Germany)</li> <li>▪ Gerd Fastner (Austria)</li> <li>▪ Prudence Francis (Australia)</li> <li>▪ Viviana Enrica Galimberti (Italy)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Heba Gamal (Egypt)</li> <li>▪ Armando Giuliano (USA)</li> <li>▪ Michael Gnant (Austria)</li> <li>▪ Bahadir Gulluoglu (Turkey)</li> <li>▪ Nadia Harbeck (Germany)</li> <li>▪ Chiun-Sheng Huang (Taiwan)</li> <li>▪ Jens Huober (Switzerland)</li> <li>▪ Wolfgang Janni (Germany)</li> <li>▪ Komal Jhaveri (USA)</li> <li>▪ Zefei Jiang (China)</li> <li>▪ Orit Kaidar-Person (Israel)</li> <li>▪ Virginia Kaklamani (USA)</li> <li>▪ Kevin Kalinsky (USA)</li> <li>▪ Daniela Kauer-Dorner (Austria)</li> <li>▪ Catherine M. Kelly (Ireland)</li> <li>▪ Sung Yong Kim (South Korea)</li> <li>▪ Marleen Kok (Netherlands)</li> <li>▪ Matteo Lambertini (Italy)</li> <li>▪ Sherene Loi (Australia)</li> <li>▪ Sibylle Loibl (Germany)</li> <li>▪ Terry Mamounas (USA)</li> <li>▪ Kelly Metcalfe (Canada)</li> <li>▪ Laura Michel (Germany)</li> <li>▪ Monica Morrow (USA)</li> <li>▪ Anusheel Munshi (India)</li> <li>▪ Mafalda Oliveira (Spain)</li> <li>▪ Shani Paluch-Shimon (Israel)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Martine Piccart (Belgium)</li> <li>▪ Shelley Potter (GB)</li> <li>▪ Meredith Regan (USA)</li> <li>▪ Isabel Rubio (Spain)</li> <li>▪ Hope S. Rugo (USA)</li> <li>▪ Shigehira Saji (Japan)</li> <li>▪ Cristina Saura Manich (Spain)</li> <li>▪ Elzbieta Senkus-Konefka (Poland)</li> <li>▪ Zhiming Shao (China)</li> <li>▪ Christian Singer (Austria)</li> <li>▪ Christine Solbach (Germany)</li> <li>▪ Christoph Tausch (Switzerland)</li> <li>▪ Beat Thürlimann (Switzerland)</li> <li>▪ Eriko Tokunaga (Japan)</li> <li>▪ Nicholas Turner (GB)</li> <li>▪ Andrew Tutt (GB)</li> <li>▪ Cicero Urban (Brazil)</li> <li>▪ Marcus Vetter (Switzerland)</li> <li>▪ Cynthia Villarreal-Garza (Mexico)</li> <li>▪ Marie-Jeanne Vranken-Peeters (Netherlands)</li> <li>▪ Walter Weber (Switzerland)</li> <li>▪ Hans Wildiers (Belgium)</li> <li>▪ Fraser Symmans William (USA)</li> <li>▪ Binghe Xu (VR China)</li> <li>▪ Yongmei Yin (China)</li> </ul>
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## Risk-adapted approach for identified pV

When a pV has been identified, the question is whether and which risk-reducing measures should be taken for the contralateral breast. In the case of a 45-year-old patient there was a clear majority vote of the SGBCC panel in favor of a risk-reducing mastectomy ± rekonstruktion if pV are detected in *gBRCA1* and/or *gBRCA2*. In the case of pV in *gBRCA2* the majority vote was for risk-reducing mastectomy irrespective of estrogen-receptor (ER) status. When a pV is identified in the *gPALB2* gene, 51.43% (majority vote) recommend risk-reducing mastectomy ± rekonstruktion, while just over 40% (minority vote: 41.43%) prefer intensified screening. If a pV is confirmed in moderate-risk genes (ATM, CHEK2 or CHEK2 del1100c), the majority of the SGBCC panel recommend intensified screening.

The different voting results also reflect current discussions in Germany and are in accordance with the recommendations of AGO guideline commission [1, 2]. Depending on the pV, the individual risk for the contralateral breast must be determined. The higher the risk, the more likely the recommendation for risk-reducing mastectomy (± rekonstruktion) (► Fig. 1). According to the German specialists, the aim is to get a maximum risk reduction for the patient. It is a multifactorial decision which also takes

family history, patient age, breast density and, of course, possible complications from the surgical procedure into account. The worse the prognosis, the more important is the focus on treating the current disease, with risk-reducing mastectomy becoming less important. The patient should be involved in decision-making (shared decision-making). If the focus is on screening, the national mammography screening program in Germany may be integrated into an intensified early screening program (► Fig. 2) [1].

## Age-dependent decisions

The recommendation of the SGBCC panel for mastectomy in patients with confirmed pV in high-risk genes is lower in older patients (≥ 65 years). The German specialists agree. The (still) remaining risk of dying from cancer is lower with advancing age. Counseling of patients should therefore be age-dependent. Patient age is another parameter in the context of multifactorial decision-making (see above).

When a patient with early breast cancer and confirmed pV in *gBRCA1* or *gBRCA2* genes undergoes risk-reducing bilateral mastectomy, the SGBCC panel recommends nipple-sparing mastectomy (NSM) with immediate reconstruction of the breast (majority vote: 65.2%). According to the SGBCC panel, this also applies

**Pathogenic gene variants associated with moderate to high risk of developing breast cancer**

	Oxford		
	LoE	GR	AGO
Risk of developing breast cancer			
▶ High and common: <i>BRCA1, BRCA2, PALB2</i>			
▶ High and rare: <i>CDH1, PTEN, TP53, STK11</i>			
▶ Moderate and common: <i>ATM, CHEK2</i>			
▶ Moderately increased: <i>BARD1, NF1, RAD51C, RAD51D</i>			
Clinical benefit* of genetic testing			
▶ <i>BRCA1, BRCA2</i>	1b	A	++**
▶ <i>PALB2</i>	3a	B	+**
▶ <i>CDH1, PTEN, TP53, STK11</i>	3b	B	+**
▶ <i>ATM, BARD1, CHEK2, RAD51C, RAD51D</i>	3a	B	+/-**

\* Clinical decisions must take the advantages of preventive interventions and concurrent risk of developing disease into account.

\*\* Participation in prospective trials and registry documentation is recommended.

▶ **Fig. 1** Current recommendations of AGO (version 2025.1) on pathogenic gene variants associated with a moderate/high risk of developing disease. Source: [1].

**Multimodal intensified screening and follow-up program (ISFP)**

	Oxford		
	LoE	GR	AGO
ISFP including MRI, breast sonography and mammography			++
▶ should be offered to <i>BRCA1/2</i> pV carriers			
▶ may be offered to pV carriers of other high-risk genes for breast cancer			
▶ may be offered to women with a family risk but without confirmed pV between the ages of 30 and 50 years with a breast cancer risk of $\geq 5\%$ in 10 years			
▶ may be offered to women who have developed breast cancer with a primary diagnosis before the age of 45, a familial risk, and no evidence of pV			
in the context of systematic quality assurance with evaluation of outcomes.			
▶ For early cancer detection	2b	B	++
▶ To improve metastasis-free survival	2b	B	+
▶ To reduce mortality	3a	C	+/-

Patients who had previous radiation therapy of the chest during childhood and adolescence (e.g., Hodgkin's disease, see S3-guideline on Hodgkin's disease) may be included in the ISFP.

▶ **Fig. 2** Current recommendation of AGO (version 2025.1) for an intensified multimodal early screening and follow-up program. Source: [1].

when a healthy woman with a pathogenic mutation requests bilateral risk-reducing mastectomy (majority vote: 78.8%).

The German specialists agree with both recommendations. NSM may be justified in a woman who has already developed disease but it is not obligatory. When deciding on the preferred surgical approach, individual circumstances should be considered. Surgery must be done by a highly trained and experienced surgeon. Less than 10% residual glandular tissue should remain postoperatively. It was once again pointed out that the decision should be based on shared decision-making.

## Ductal Carcinoma in Situ (DCIS)

The German specialists agree that estrogen receptor-positive (ER+) ductal carcinoma in situ (DCIS; grade 2) with microcalcifications should be resected irrespective of the patient's age and even if only limited microcalcifications are confirmed (< 1 cm). DCIS already constitutes a risk factor *per se* for invasive breast cancer. The German specialists emphasize that confirmation of microcalcifications with punch or vacuum biopsy is an unfavorable marker which additionally increases the risk and is therefore a further reason for surgery. Close annual monitoring alone is not an alternative to surgery [1, 2].

## Treatment decision after BCS depending on age

To treat a 40 or 55-year-old patient with ER+ DCIS (grade 2), the SGBCC panel recommends adjuvant radiation therapy after breast-conserving surgery (BCS), followed by endocrine therapy with either tamoxifen or an aromatase inhibitor (AI) (majority vote: 63.77% and 58.83%, respectively). For older (e.g., 70-year-old) patients, the SGBCC panel was considerably more cautious and preferred postoperatively either annual follow-up examinations (with interventions only carried out if required) or adjuvant radiation alone (respective vote: 36.23%).

According to the German guideline, adjuvant therapy should be discussed case-by-case based on a risk-benefit assessment [1, 2]. To date, no survival benefit has been shown for either adjuvant radiation or adjuvant endocrine therapy. Adjuvant radiation after BCS is one option (1a A +). Due to potential side effects, tamoxifen should be administered with caution (20 mg tamoxifen: 1a A +/-; 5 mg tamoxifen: 2b B +/-). Aromatase inhibitors may only be an option for postmenopausal women with ER+ DCIS (1b A +/-) [1, 2]. However, the possible prophylactic impact on the contralateral breast should also be taken into consideration.

With regard to older patients, the German specialists recommend, by analogy to invasive breast cancer, that older patients should be treated in the same way as younger patients. However, a geriatric assessment should be done. A risk-benefit assessment

is especially important for older patients. The patient's decision should be based on her overall physical condition, life expectancy, and taking into account that there is no proven evidence of a survival benefit. Counseling regarding adjuvant radiotherapy should be based on tumor stage and tumor biology, patient age, comorbidities and other therapeutic modalities, and should be open-ended. The German specialists are reluctant to give tamoxifen to elderly patients.

### Importance of the size of the DCIS lesion

The larger the DCIS lesion, the more SGBCC panel members recommend adjuvant radiation after breast-conserving surgery for ER+ DCIS (grade 2) in a non-elderly patient to prevent intramammary recurrence. According to the German guideline, the size of the DCIS lesion is a risk factor for ipsilateral recurrence, and the German specialists therefore agree with the panel [1, 2]. It was generally agreed that there is insufficient evidence to use gene expression testing for the treatment decision [4]. Genomic signatures are not indicated for DCIS.

## Breast and Axillary Surgery

### When is it possible to omit SLNB?

With regard to the INSEMA trial [5], the SGBCC panel voted on which patients with primary breast cancer could omit sentinel lymph node biopsy (SLNB). The voting was based on patient cases with different clinical variables.

The INSEMA trial [5] recruited patients with cT1/2 breast cancer ( $T \leq 5$  cm; G1–3), clinically node negative axilla (cN0), and breast-conserving surgery with planned radiation thereafter. However, more than 90% of patients had a tumor size of  $\leq 2$  cm. In more than 95% of cases, these women had luminal breast cancer (ER+/HER2-negative [HER2-]). Fewer than 5% had G3 tumors. 17% of SGBCC panel members would recommend SLNB for this study cohort.

In 2025 the German AGO guideline commission limited its recommendation to omit SLNB in patients with cT1, cN0, G1 or G2, HR+, HER2-negative breast cancer [1, 2]. Some of the panel members were more restrictive while a small minority of panel members would omit SLNB even in cases with tumor sizes of up to 3 cm. Ultimately, different factors play a role in every individual decision. The German experts underline that interdisciplinary logistics (especially skilled imaging of the axilla) in cancer centers is more important than ever.

For patients with HER2-positive (HER2+) or triple-negative early breast cancer (TNBC) it is agreed that, even in the cN0 situation, SLNB omission cannot be recommended. Very few of these patients were included in the INSEMA trial [5].

Almost two thirds of SGBCC panelists would *not* use the criteria of the INSEMA trial [5] to omit SLNB for patients with invasive lobular cancer (ILC) (majority vote: 59.7%). The German experts did *not* agree with this. The recommendation for SLNB does not differentiate between ductal breast cancer and ILC. This approach is supported by the forest plot analysis carried out in the INSEMA trial. More than 600 patients in the INSEMA trial had invasive ILC or

A patient with breast cancer has received neoadjuvant chemotherapy with clinical response, and after sentinel lymph node surgery she will receive radiation therapy to the breast. Which additional locoregional axillary therapy would you recommend?

	Number of positive sentinel lymph nodes	ITC	Micrometastatic residual disease	
		1 of 4 SLN	1 of 4 SLN	2 of 4 SLN
<b>ER positive, HER2 negative</b>	None	61%	30%	15%
	ALND	3%	15%	22%
	Nodal radiation	36%	48%	48%
	ALND + nodal radiation	0%	6%	15%
<b>triple negative</b>	None	35%	8%	5%
	ALND	6%	22%	28%
	Nodal radiation	55%	49%	38%
	ALND + nodal radiation	3%	22%	29%
<b>ER negative, HER2 positive</b>	None	45%	16%	8%
	ALND	5%	16%	23%
	Nodal radiation	46%	50%	40%
	ALND + nodal radiation	5%	19%	29%

► **Fig. 3** Patient who has shown a good clinical response to neoadjuvant chemotherapy. Which approach is recommended for the axilla in addition to adjuvant radiation therapy to the breast? Voting results of the SGBCC panel depending on the breast cancer subtype and axillary lymph node involvement.

ductal lobular breast cancer [5]. When dealing with rare cancers such as ILC, the German experts recommend collecting more data from real world.

### Axillary surgery after neoadjuvant systemic therapy

The German specialists agree with the majority vote of the SGBCC panel on the approach to axillary surgery (► **Fig. 3**): according to the SGBCC panel, patients with primary clinically node negative axilla (cN0) who respond to neoadjuvant systemic therapy (NAST) but still have isolated tumor cells (ITC) in a sentinel lymph node do not require ALND in addition to adjuvant radiation therapy, irrespective of the breast cancer subtype. If patients have micrometastases in one or two SLNs after NAST, the SGBCC panel additionally recommend radiation of the regional nodes ( $\pm$  ALND). Once again, the German specialists agree with the SGBCC panel [1, 2].

## Adjuvant Radiation Therapy

The votes of the SGBCC panel on adjuvant radiation focused on dosing and duration of radiation (fractionation) and the type of radiotherapy. Here again, most of the voting was based on patients with different clinical variables. From a German perspective, the proposed case scenarios were not always plausible because the information provided was too general.

## Radiation after mastectomy

Starting with the question about which type of adjuvant radiotherapy should be used in addition to systemic therapy in a patient with primary breast cancer after mastectomy, panel members voted on three different scenarios.

- In the case of a 43-year-old patient with triple-negative breast cancer (TNBC; G3, tumor size 2.9 cm; 2/3 positive sentinel lymph nodes [SLN]), almost all of the SGBCC panel members (majority vote: 94.1%) voted in favor of adjuvant radiation of the thoracic wall and the lymphatic pathways in addition to systemic therapy. The German specialists agree because of the higher risk of recurrence. What is notable about this situation is that a sentinel lymph node biopsy (SLNB) was carried out despite the increased risk while axillary lymph node dissection (ALND) was omitted. This vote is covered by the data from the SENOMAC trial [6] and corresponds to the AGO recommendation (mastectomy with planned adjuvant RT) [1, 2].
- The voting of SGBCC panel was significantly more heterogeneous in two patients with estrogen receptor-positive and HER2-negative primary breast cancer (ER+/HER2-; G2, tumor size 1.6 cm, 1/3 positive SLNs). The same clinical situation was discussed for a 66-year-old patient and for a 41-year-old patient.
  - (1) For the older patient (66 years old), a simple majority of the SGBCC panel (49.2%) recommended radiation of the chest wall and the regional nodes. 40.0% of the panel members did not see any indication for radiotherapy.
  - (2) When the identical clinical situation was considered for a 41-year-old patient with a low or intermediate multigene risk, 47% of SGBCC panel members voted respectively for either “no radiation therapy” or for “radiation of the chest wall plus the regional nodes.”

According to the German guidelines, both situations require individual discussion with the patient. With 1–3 positive lymph nodes, both patients had a moderate risk, but because they did not undergo ALND they did not meet the criteria of the SUPREMO study [7]. The options were either “no radiation therapy” or – as no ALND was carried out – radiation (alone) of the chest wall. The German specialists generally tended to favor the latter option. For both patients they would not generally recommend additional radiation of the regional nodes. From the German point of view the tumor location is missing, which is a relevant information. There is insufficient evidence for radiation of the lymphatic pathways alone.

### Which fractionation should be used following mastectomy?

In recent years, moderate hypofractionation has become more important and has largely replaced conventional (historical) fractionation [8]. This is supported by the current German guideline [1, 2] and was also apparent in the voting results of the SGBCC panel. The advantages of moderate hypofractionation include shorter radiation times and a lower risk of acute and sometimes late side effects with comparable safety.

The German specialists agree with the majority vote of the SGBCC panel that moderate hypofractionation is currently standard of care for post-mastectomy radiation ± breast reconstruction (allogeneic and autologous). This also applies in cases with a higher risk of recurrence. Moderate hypofractionation is the standard, irrespective of the number of involved lymph nodes [1, 2]. It was therefore remarkable that for higher risk situations (stage III, T3N2 and 8/11 involved lymph nodes), 42.1% of the panel members would prefer conventional fractionation. This is not supported by the data.

Moderate hypofractionation is also standard for patients after mastectomy (± implant breast reconstruction) who have had neoadjuvant chemotherapy. Although the data for this situation is limited, there is no reason why this group should not benefit from moderate hypofractionation. These patients have no prognostic benefit from longer radiation therapy. It was therefore surprising for the German specialists that in this situation only a narrow majority of the SGBCC panel (majority vote: 52.7%) voted for moderate hypofractionation and 47.3% were in favor of conventional fractionation.

### Which fractionation should be used after breast-conserving surgery?

If radiotherapy is indicated, the standard approach for patients with a small primary tumor (T1c pN0) who undergo breast-conserving surgery is also moderate hypofractionation, irrespective of the tumor subtype, the risk of recurrence, or the genomic risk [1, 2, 8]. This is supported by the voting results of the SGBCC panel.

- A 42-year-old patient with a small HR+/HER2- primary breast tumor (ER+/PR+, T1c, G2, pN0) and a high genomic risk who has breast-conserving surgery (BCS) would receive radiation therapy with moderate hypofractionation in addition to adjuvant chemotherapy plus endocrine therapy (majority vote: 70.9%). Almost 22% of the panel members already favor ultra-hypofractionated radiotherapy in five fractions.
- If the same patient is 10 years older (52 years old), postmenopausal, and has a G1 breast cancer (ER+/PR+; T1c pN0), 43% of the SGBCC panel would recommend ultra-hypofractionation in addition to adjuvant endocrine therapy (no chemotherapy because of the low risk), while 40% preferred moderate hypofractionated radiotherapy.
- If the 52-year-old patient described above has primary TNBC, grade 3 (T1c pN0, G3), there is agreement with the SGBCC panel that the standard treatment in addition to adjuvant chemotherapy is radiotherapy with moderate hypofractionation (majority vote: 63.6%).

The German experts currently recommend to wait for further results with regard to ultra-hypofractionation, even in low risk cases. The German specialists refer to the possibly increased risk of late toxicities [8]. It will be necessary to await further data from the FAST-FORWARD trial [9] which is expected to be available in 2026. The German specialists agree with the use of moderate hypofractionation.

## Partial breast radiation with ultra-hypofractionation

A somewhat different situation discussed by the SGBCC panel was that of a healthy older patient (69 years old) with a small primary ER+/PR+/HER2- breast tumor (T1c N0; G2) who had breast-conserving surgery and who would like to live to at least 86 years like her mother. In addition to adjuvant endocrine therapy, the SGBCC panel (majority vote: 41.1%) recommended adjuvant ultra-hypofractionated radiotherapy. 21.4% of the panel members preferred moderate hypofractionation and 35.7% favored partial breast radiation (PBI).

In the opinion of the German specialists, the best option in this setting is PBI which can be administered in the form of ultra-hypofractionation (5 × 5.2 Gy). This would achieve local control comparable to that of moderate hypofractionation but with lower toxicity. Omitting adjuvant radiation is not a primary option in the case of a healthy older patient who wishes to have therapy. This should also be considered with regard to the insufficient adherence to endocrine therapy and the higher risk of local recurrence. In older patients, the decision to omit adjuvant radiation therapy should depend on a geriatric assessment and the patient's assumed life expectancy.

## Radiotherapy of the axilla

For a postmenopausal female patient above the age of 60 years with a small primary breast tumor (T1c; cN0, no SLNB) and low risk, a simple majority (41%) of the SGBCC panel recommend whole breast radiation therapy (WBRT); 29% favored either PBI or SLNB followed by PBI respectively if the SLNB does not show any involvement.

The German specialists agree. Based on the INSEMA and SOUND trials [5, 6], WBRT is the recommended standard in this situation [10]. SLNB is not indicated in this case if the criteria of the INSEMA trial [5] are met. The precondition for PBI is usually pN0. After carefully weighing up the individual features and discussing them with the patient, PBI may be an option in individual cases, although study data are missing.

## Post-mastectomy radiation therapy after NAST

A 56-year-old patient with ER+/HER2- primary breast cancer (cT2 cN1; G3) who is ypT1b (0.9 cm) stage ypN0 after neoadjuvant chemotherapy (NACT) and mastectomy will receive endocrine standard therapy. Slightly more than half of the SGBCC panel (majority vote: 52.3%) recommended omitting post-mastectomy radiation therapy (PMRT) in this situation while 47.7% would recommend it.

From the perspective of the German specialists, this close vote indicates that the situation must be discussed with the patient weighing up the benefits and risks (shared decision-making). The German guideline recommends PMRT (radiation of the chest wall) if there is still residual tumor in the breast after NACT (1b B +) [1, 2]. In principle, the NSAPB B-51 trial [11] showed no benefit for adjuvant radiation if node conversion (cT1-3 cN1 → ypN0) occurs after NAST, but the overwhelming majority of patients had no residual tumor in the breast. In the group of patients with mastectomy, a benefit of PMRT continued to emerge.

If the above-described 56-year-old patient has HER2-positive (HER2+) primary breast cancer (cT2cN1; G3) after NACT which included anti-HER2 targeted therapy plus mastectomy with TAD (targeted axillary dissection) and is ypT0 ypN1a (0.4 cm residual tumor in one of two axillary lymph nodes), the SGBCC panel recommends PMRT in addition to established adjuvant systemic therapy (majority vote: 82.3%).

The German specialists critically note that the patient had not received ALND despite SLN involvement, which is standard in Germany [1, 2]. With regard to the question about surgery, the German specialists refer to the ongoing Alliance [12] and TAXIS trials (information available under: <https://www.gbg.de/studien/taxis> and/or <https://clinicaltrials.gov/study/NCT03513614>), which should provide further clarity. Irrespective of this, adjuvant radiation of the chest wall and the regional nodes is clearly indicated in patients with lymph node involvement after NAST.

The discussion further focused on two more case studies: a patient with ER+ (case 1) or HER2+ (case 2) breast cancer who had a clinical response to NAST but is stage ypN1a (3 mm in 1/4 SLN). With regard to the further approach in the axilla, the SGBCC panel recommended radiation therapy of the regional nodes (majority vote: 58% and 69%, respectively).

In the same situation (ypN+ after NACT), the German guideline recommends ALND with radiation of the regional nodes, including the supra- and infraclavicular lymph nodes and potentially the area of the internal mammary artery, irrespective of the breast cancer subtype (ER+ or HER2+) [1, 2]. With regard to the potential omission of ALND, we refer to the above-cited studies. If ALND is omitted, level I/II axillary lymph nodes should also be included in the target volume. Because of the increased risk of lymph edema, these should not be included if ALND is done.

## Should radiation therapy be omitted in elderly?

In the context of the EUROPA study [13], the SGBCC panel discussed which adjuvant therapy should be given to an older patient with a 1.3 cm primary breast tumor with high ER/PR expression (ER+/PR+ HER2 0 [IHC], G1-2) after BCS. The majority of the SGBCC panel recommended the current standard approach with adjuvant radiotherapy plus adjuvant endocrine therapy (majority vote: 59.0%). 27.9% would recommend endocrine therapy alone and 13.1% would recommend radiation therapy alone.

In principle, the German specialists agree with the majority vote of the SGBCC panel. It cannot be ruled out that there may be patients where it would be possible to omit one of the two options (radiotherapy or endocrine therapy). The decision must be made on a case-by-case basis. Omission of radiotherapy assumes that endocrine therapy was adhered to. If there are any doubts about the effectivity of endocrine therapy or if the focus is on local tumor control, radiotherapy alone, preferably in the form of PBI, may be an option. It should be noted that no invasive node stage was mentioned in the case vignette. WBRT would be recommended if treatment is analogous to that administered in the INSEMA trial [5].

## Drug Therapy for Primary Triple-negative Breast Cancer

With regard to the systemic treatment of primary triple-negative breast cancer (TNBC), the voting of the SGBCC panel focused on the use of the checkpoint inhibitor (CPI) pembrolizumab in neoadjuvant and post-neoadjuvant settings. Another issue discussed was the indication for anthracycline-based chemotherapy.

### Neoadjuvant concept preferred

The German guideline favors the neoadjuvant concept for the treatment of primary TNBC [1, 2]. Based on the KEYNOTE (KN)-522 trial [14], a combination therapy consisting of paclitaxel/carboplatin followed by anthracycline/cyclophosphamide, combined in each case with pembrolizumab (TCb/AC[EC]/pembrolizumab) is recommended as neoadjuvant therapy for tumor sizes of more than 2 cm or for cases with lymph node involvement (N+). The German specialists therefore agree with the SGBCC panel to use the KN-522 regimen as neoadjuvant therapy for tumor sizes of more than 2 cm in patients with clinically node negative axilla (cN0) (majority vote: 71.0%).

If the primary tumor size in a patient with high-grade TNBC (cN0) is 1.75 cm, the additional administration of pembrolizumab is not indicated. The German specialists add that this should be decided in the context of potential side effects of CPIs and based on a risk-benefit assessment. If necessary, there is the option to subsequently determine the tumor size in a breast cancer center. Only about half of the SGBCC panel recommended additional neoadjuvant use of pembrolizumab in this setting (majority vote: 53.7%). The German specialists add that this does not correspond to the inclusion criteria of the KN-522 trial and would represent an off-label use.

### Adjuvant therapy for primary TNBC

The German guideline commission of the AGO recommends primary surgery (++) for patients with a very small primary TNBC (cT1a, cN0). From stage cT1c (cN0) onwards, a neoadjuvant concept is recommended (cT1c/cN0: ++) [1, 2]. For cT1b/cN0, a neoadjuvant approach may be considered (cT1b/cN0: +). The value of chemotherapy is not clear in these cases and it is also not clear which patients would particularly benefit from chemotherapy. There are ongoing studies to answer this question (see GBG homepage).

The German experts therefore agree with the SGBCC panel that a patient with a small primary TNBC (cT1a/b) with axillary lymph node involvement (cN0) may have primary surgery. The indication for (neo)adjuvant chemotherapy increases with increasing tumor size. All panel members voted in favor of administering adjuvant chemotherapy when the tumor size was larger than 1 cm. This corresponds to the currently available data in which (neo)adjuvant chemotherapy is expected to benefit patients with tumor sizes of more than 1 cm [15, 16].

Adjuvant chemotherapy is also indicated for a TNBC patient treated with primary surgery who has stage 1 disease (tumor size 1.1 cm), a higher grade (G3), and axillary lymph node involvement. If the patient did not receive neoadjuvant treatment, then

the criteria of the KN-522 trial are not met. This applies irrespective of whether 1/3 SLN or 3/5 axillary lymph nodes are positive. The SGBCC panel prefers a TCb/AC regimen without pembrolizumab for both situations (majority vote: 39.71% for 1/3 SLN and 50.0% for 3/5 LN).

The German experts partially agree but, as recommended by the German guidelines, they prefer a dose-dense regimen with EC (epirubicin/cyclophosphamide, every two weeks) [1, 2].

### Treatment with or without anthracyclines?

There is no tumor size threshold above which an anthracycline-based regimen should be used. There is no special recommendation of the German guideline with regard to tumor size. The SGBCC panel agreed on a tumor size of 1 cm as the threshold (simple majority vote: 43.9%).

The German specialists point out that anthracycline/taxane-based regimens are standard for patients with axillary lymph node involvement [1, 2]. Six cycles of the TC regimen (taxane/cyclophosphamide) are an equieffective option for patients without axillary lymph node involvement. A German meta-analysis [17] of data from the PlanB and SUCCESS-C trials found a benefit for anthracyclines compared to the TC regimen if four or more axillary lymph nodes were positive. However, these were conventionally dosed anthracycline/taxane regimens.

### Focus on neoadjuvant systemic therapy

The discussions on NAST were based on a patient with primary TNBC stage 2 and axillary lymph node involvement (cN1), for whom neoadjuvant treatment would consist of TCb/AC plus pembrolizumab. The SGBCC panel proposed a chemotherapy regimen consisting of weekly administration of paclitaxel and carboplatin followed by administration of AC(EC) every three weeks (simple majority vote: 48.3%). This corresponds to the regimen of the KN-522 trial [14] and the recommendations of the German guideline [1, 2]. The German experts also suggest dose-dense AC or EC regimens as an option (every two weeks).

### Post-neoadjuvant approach with pCR

If the above-described patient (TNBC, stage 2, cN+) has a pathological complete remission (pCR) after NAST, the SGBCC panel recommends further post-neoadjuvant treatment with pembrolizumab in analogy to the KN-522 trial [14] (majority vote: 87.7%). This corresponds to the recommendation of the German guidelines (1b B +) [1, 2].

The further post-neoadjuvant treatment of patients with pCR is a topic of discussion. Potential side effects and late toxicities should be taken into consideration. In the KN-522 trial, it was the non-pCR patients who particularly benefited from further post-neoadjuvant treatment with pembrolizumab [14].

### Discussion of fertility preservation under pembrolizumab

There is currently an ongoing discussion relating to young female patients whether CPIs have a negative impact on fertility. The data on this are still unclear. Data on a combination of ipilimumab/nivolumab in malignant melanoma have shown an unfavorable effect on fertility. To date, this has not yet been confirmed for

pembrolizumab. According to drug prescription information, any potentially unfavorable effect is reversible within one year [18]. The majority of the German experts recommends, not to omit post-neoadjuvant administration of pembrolizumab. However, further data from ongoing clinical trials must be awaited.

For a 29-year-old patient with primary TNBC (tumor size 2.5 cm; cN0) who worries about preserving her fertility, the German specialists agree with the SGBCC panel (majority vote: 83.1%) that the patient should also receive pembrolizumab. Protective measures should be discussed with the patient in a fertility center. The German experts recommend proactively discussing the possible impact on fertility with young patients and offering them fertility-preserving options. Further information: FertiPROTEKT Netzwerk e. V. (<https://fertiprotekt.com>).

### Post-neoadjuvant approach for non-pCR

If the above-described patient (TNBC, stage 2, N+) does not achieve pCR, further post-neoadjuvant treatment with pembrolizumab is out of question. This also applies if the axilla are tumor-free and the residual tumor in the breast is < 1 cm. In this situation, in addition to post-adjuvant treatment with pembrolizumab the SGBCC panel recommends also administering capecitabine (majority vote: 75.8%). The German specialists agree. According to the German guidelines, this can be an option in individual cases if no pCR is achieved (5 D +/-) after neoadjuvant administration of pembrolizumab (plus platinum-based chemotherapy) [1, 2]. No scientific data has been published on this.

If the CPI (pembrolizumab) is contraindicated, it is generally agreed that a TCb/A[E]C regimen remains the chemotherapy of choice (SGBCC majority vote: 87.1%). The voting in the auditorium during the conference confirmed this (majority vote: 79%).

### Pathogenic variants in *BRCA1/2* genes

If the above-described patient (TNBC, stage 2, N+) additionally has a pathogenic variant (pV) in the breast cancer genes *BRCA1* or *BRCA2* and achieves pCR with TCb/A[E]C plus pembrolizumab, then there is no additional adjuvant indication for olaparib. Here too, the German specialists agree with the SGBCC panel (majority vote: 84.8%). These patients were not randomized in the OlympiA trial [19]. There are no further published data on this setting.

The situation is different if the patient has not achieved pCR and still has residual tumor in the axilla. In this case, both the German experts and the SGBCC panel (majority vote: 66.2%) agree that post-neoadjuvant pembrolizumab and olaparib are indicated. Reference is made to the OlympiA trial [19, 20] where the curves for disease-free survival started early to separate in favor of adjuvant administration of olaparib and resulted in a known overall survival benefit [20]. From the German perspective, olaparib should therefore be administered shortly after surgery and adjuvant radiation therapy. Whether capecitabine is additionally indicated is not clear. About 25% of SGBCC panel members voted in favor of it.

The German specialists add that *gBRCA1/2*-pV tumors are usually basal-like carcinomas for which olaparib is clearly indicated. Furthermore, reference is made to the safety data of the KEYLYNK-009 trial in which olaparib was successfully and safely combined with pembrolizumab [21, 22].

### TILs and ctDNA determination in TNBC?

In Germany, neither determination of tumor-infiltrating lymphocytes (TIL) nor testing of circulating tumor cell DNA in the blood (ctDNA testing) are recommended in routine clinical practice [1, 2]. To date, there is still insufficient clinical evidence that early therapeutic intervention can improve the patient's prognosis. Although detection of TILs and ctDNA is mentioned in the AGO recommendations, they are not yet used to guide treatment decision in Germany.

The German experts agree that adjuvant chemotherapy is indicated for a patient with a 1.2 cm primary TNBC (G3; pN0) and a high percentage of tumor-infiltrating lymphocytes (TILs > 50%). According to the SGBCC panel, adjuvant chemotherapy is indicated for both a 50-year-old (majority vote: 87.10%) and a 68-year-old patient (majority vote: 76.67%).

The German experts point out that postoperative chemotherapy is indicated for these patients irrespective of the percentage of TILs. The scientific data on TILs is not mature enough to be used for guiding treatment decision in daily clinical practice. TILs are therefore not routinely tested in Germany [23].

There is also no sufficient evidence to guide treatment decision by using ctDNA. The German specialists therefore agree with the SGBCC panel which rejected the use of tumor-specific assays in standard clinical practice when treating patients with early breast cancer (majority vote: 91.8%). Similarly, the ctDNA findings in a patient with a small primary TNBC (stage 1) who has achieved pCR after TCb/A[E]C therapy with negative imaging but positive ctDNA do not affect post-neoadjuvant therapy recommendations. The German view is that ctDNA testing should not be done outside of clinical studies. In Germany, the SURVIVE trial, which is supported by the Federal Ministry for Education and Research, is currently investigating this issue (information: <https://www.survive-studie.de/>). The recommendation of the SGBCC panel to omit post-neoadjuvant systemic therapy in this setting is correct (majority vote: 63.5%).

## Systemic Therapy for HER2-positive Primary Breast Cancer

When drug therapy for primary HER2-positive (HER2+) breast cancer was discussed, the initial focus was on a post-mastectomy patient diagnosed with extensive high-grade DCIS. Microinvasive ER-negative (ER-) and immunohistochemically HER2<sup>3+</sup> breast cancer was identified in the surgical specimen. The question was what the appropriate adjuvant systemic therapy for this patient should be. The SGBCC panel did not recommend adjuvant treatment with paclitaxel plus trastuzumab in this setting (majority vote: 54.7%). More than one quarter of panel members recommended adjuvant paclitaxel/trastuzumab in the case of 3–5 microinvasive lesions. For very small HER2+ invasive breast cancer without lymph node involvement (cT1a/b cN0), the SGBCC panel considered the threshold for adjuvant paclitaxel/trastuzumab is for tumors > 5 mm.

The German specialists agree. The German guideline recommends adjuvant chemotherapy including anti-HER2-targeted therapy for lesions of 6 mm and above (≥ T1b: 2b B + or T > 1 cm:

1a A ++). This should be decided on a case-by-case basis for cT1a breast cancer (2b B +/-) [1,2]. Study data have shown that patients with pT1a/b tumors tended to benefit from adjuvant chemotherapy plus trastuzumab. But this benefit was triggered in a significantly bigger cohort by patients with T1b tumors [24].

### Which (neo)adjuvant therapy should be recommended?

In Germany, a neoadjuvant therapy approach is preferred to treat HER2+ primary breast cancer. Individualized neoadjuvant and especially post-neoadjuvant treatment is possible with this approach, which has been shown to improve overall survival [25]. This especially applies to tumors which are larger than 2 cm [1, 2]. The vote of the SGBCC panel also supports this approach (majority vote: 91.30%).

The consensus for patients newly diagnosed with ER+/HER2+ breast cancer with a tumor size of more than 2 cm and clinically negative axilla is that antibody therapy with trastuzumab/pertuzumab (HP) is indicated in addition to neoadjuvant chemotherapy. The thinking behind this consensus is that it is not possible to absolutely exclude involvement of the axillary lymph nodes preoperatively.

The SGBCC panel prefers a TCb (taxane/carboplatin) regimen combined with HP for neoadjuvant chemotherapy. The German guideline also recommends this regimen (1b B ++). Chemotherapy with EC(AC)-taxane plus HP is also a standard regimen in Germany (1b B ++). The THP regimen (dose-dense taxane administration plus HP) is a “may be” option in Germany (2b B +) [1, 2].

If the above-described patient (ER+/HER2+, T > 2 cm) undergoes primary surgery and has a pN0 status postoperatively, the voting results of the SGBCC panel on the preferred adjuvant therapy recommendation were relatively diverse. In addition to chemotherapy (TCb or taxane monotherapy), the panel supported the administration of trastuzumab (without pertuzumab). A neoadjuvant approach would be preferred in Germany for such a patient (T > 2 cm).

If a patient with operable primary HER2+ breast cancer (stage 3) only has a suboptimal response to standard neoadjuvant chemotherapy plus anti-HER2 therapy, the SGBCC panel recommends surgery consisting of mastectomy plus ALND (majority vote: 88.9%). 6.3% preferred immediately switching to trastuzumab emtansin (T-DM1). The German specialists agree with the majority vote (surgery: mastectomy plus ALND) and additionally recommend switching to T-DM1 in the post-neoadjuvant setting [1, 2].

If a patient with ER-/HER2+ breast cancer (stage 2) has residual tumor and/or positive axillary lymph nodes after standard neoadjuvant therapy (TCbHP), the standard approach recommended by the SGBCC panel, based on two fictitious patients, is to switch to T-DM1 in the post-neoadjuvant setting. Immunohistochemical HER2 testing of the residual invasive tumor confirmed HER2<sup>2+</sup> status. FISH (fluorescence in situ hybridization) analysis was additionally carried out in one of the two cases, and the findings were negative.

The German experts agree with the SGBCC panel, as the indication for T-DM1 does not depend on the HER2 status of the residual tumor [26]. It should also be pointed out that FISH analysis

should always be carried out following immunohistochemical HER2<sup>2+</sup> testing.

### Importance of HER2DX testing

HER2DX is a genomic test which was developed for patients with early HER2+ breast cancer and has been tested in different retrospective clinical study cohorts in the USA. It consists of a pCR score and a score indicating the risk of recurrence (= risk score), which is based on information on immune status, luminal status, proliferation and HER2 status. Retrospective data showed that the HER2DX-pCR score correlates with the probability of achieving pCR after NAST. In some studies the risk score showed a correlation with patient survival [27, 28]. But because of the lack of prospective evidence for the therapeutic consequences, HER2DX is not recommended in Germany.

The majority of the SGBCC panel opposed using the HER2DX score in routine clinical practice to guide therapy. The German specialists agree with this for the above-mentioned reasons. The DEFINITIVE trial, supported by the European Union, is currently ongoing in Germany and aims to examine prospective evidence from HER2DX, focusing on therapy de-escalation (for more information: <https://www.thedefinitivetrial.eu/>).

### Standard regimen for stage 2/3 cancer and inflammatory carcinoma of the breast

For the SGBCC panel, the TCbHP regimen is the preferred neoadjuvant treatment regimen for locally advanced HER2+ breast cancer (stage 2 or 3) (majority vote: 74%). The vote in the auditorium at the conference supported the majority panel vote although the auditorium vote was slightly lower (majority vote: 54%). The German guideline recommends both the TCbHP and the EC(AC) paclitaxel/HP regimen (1b B ++) [1, 2].

The SGBCC panel also prefers the TCbHP regimen for the neoadjuvant treatment of ER-/HER2+ inflammatory breast cancer. The German experts do not agree and recommend a dose-dense anthracycline-based EC-paclitaxel/HP regimen. Patients with HER2+ inflammatory breast cancer have a poor prognosis, which is why an anthracycline-based regimen and dual antibody blockade is preferable.

### Systemic therapy for hormone receptor-positive primary breast cancer

The discussion on systemic therapy for hormone receptor-positive and HER2-negative (HR+/HER2-) primary breast cancer focused on chemotherapy indication, when or whether chemotherapy should contain anthracycline, the role of gene expression analysis, and when a CDK4/6 inhibitor should be administered in addition to endocrine therapy.

According to the SGBCC panel, chemotherapy should be recommended if there is an expected absolute benefit of at least 5% for distant recurrence-free survival (DRFS) (majority vote: 63%). 64% of attendees in the auditorium voted for this threshold. The German view is that this is an individual decision which must be taken together with the patient after providing the patient with

detailed information. The German specialists referenced two publications, one of them from Germany, which found that even a small expected benefit may lead to chemotherapy being recommended in clinical practice [29, 30].

### Use and value of multigene tests

In Germany, multigene tests are an option for intermediate risk patients with HR+/HER2- primary breast cancer to better assess the need for chemotherapy. Multigene tests are used in Germany if the risk cannot be defined with sufficient certainty based on clinical factors. The German guideline additionally recommends the use of dynamic Ki67 in some patients in accordance with the ADAPT concept but always in the context of multigene testing [1, 2, 31].

Patients with ER+/HER2- breast cancer (T ≤ 1 cm) without axillary lymph node involvement have a low risk of distant metastasis. It is generally agreed that multigene testing is not indicated for these patients (SGBCC majority vote: 61.9%). The German experts add that there is no evidence-based tumor size threshold above which multigene testing should be carried out. The decision depends on clinical and histopathological factors.

Determination of Ki67 expression cannot replace multigene testing in patients with HR+ breast cancer and intermediate risk [32]. The German specialists agree with the narrow majority vote (52.4%) of the SGBCC panel. They point out that Ki67 could be a factor in clinical scenarios to assess endocrine sensitivity based on dynamic Ki67 expression [1, 2]. A Ki67 expression of > 20% is one of the possible factors for the adjuvant use of endocrine combination therapy with a CDK4/6 inhibitor. In the NATALEE trial, for example, patients without axillary lymph node involvement and with G2 breast cancer were included if they either had Ki67 expression of > 20% or a multigene test showing that they are at high risk [33, 34].

### Neoadjuvant therapy recommendation

Neoadjuvant chemotherapy may be an option for patients with HR+/HER2- breast cancer and very low hormone expression. The tumor biology of these cancers is very similar to that of TNBC, which is why the treatment decision can be done based on the recommendations for TNBC [1, 2].

The German specialists therefore agree with the SGBCC panel (majority vote: 82%) and the voting from the auditorium at the conference (majority vote: 74%) that a 50-year-old patient with low ER and PR expression (ER: 5%, PR < 1%) and immunohistochemically HER2-negative breast cancer (T 3–4 cm; cN0; G3) should receive neoadjuvant treatment with the KN-522 regimen (AC-taxane + pembrolizumab).

NAST is not indicated in a 63-year-old patient with a clearly ER+/PR+ and HER2- primary cT3N1 breast cancer (G1) with a ductal and lobular histology. The German specialists agree with the simple majority vote of the SGBCC panel that the patient should have primary surgery (majority vote for mastectomy: 37.5%). If testing shows that this patient has a low genomic risk, the percentage of SGBCC panel members in favor of primary surgery (not: mastectomy) increased to 54.7%. The German specialists add that treatment decision in Germany is not based on the

results of multigene testing alone. Multigene testing may be used in addition to clinical factors if necessary [1, 2].

### Adjuvant olaparib therapy

One often discussed question is whether a patient with ER+/HER2- primary breast cancer and a confirmed pathogenic variant in the *PALB2* gene should additionally receive adjuvant treatment with olaparib. Unfortunately, these patients were not included in the OlympiA trial [19]. Clinical data for these patients is available in the metastatic setting [35]. The German specialists agree with the SGBCC panel which recommends adjuvant olaparib in addition to standard chemotherapy and/or endocrine therapy for a 49-year-old patient who meets the inclusion criteria of the OlympiA trial [19] (majority vote: 68.3%). In analogy to the metastatic setting, the German experts would aim for adjuvant administration of olaparib following an individual risk-benefit assessment carried out together with the patient after the health insurance company has agreed to cover the costs of treatment.

### Duration of adjuvant therapy

Standard endocrine therapy is administered for five years; this period can be extended to 7–8 years or even 10 years in patients with a higher clinical risk (extended endocrine therapy) [1, 2]. In the case of a patient with a 1.8 cm ER+/HER2- primary breast tumor (grade 2), three clinical scenarios were voted on.

- If the above-described patient has 1/4 positive SLN, extended endocrine therapy over 7–8 years is recommended.
- If the axilla are clinically unremarkable but the patient has a higher genomic risk, a simple majority of the SGBCC panel recommends endocrine therapy over a period of 7–8 years, while 37% would prefer 5 years. Given the N0 situation, the German specialists do not recommend further extended endocrine therapy. The clinical risk and the patient's preference should determine the duration of therapy. Multigene testing has not been validated for decisions on the duration of therapy.
- If 3/8 axillary lymph nodes are positive, the SGBCC panel favors extended endocrine therapy for a period of either 10 years (majority vote: 52.38%) or 7–8 years (vote: 46.03%). The German specialists are also in favor of extended endocrine therapy. The duration depends on the individual clinical risk.

### Adjuvant chemotherapy with/without anthracyclines?

Voting on adjuvant chemotherapy focused on which type of chemotherapy should be used and the importance of anthracyclines.

The starting point is a postmenopausal female patient with a ER+/PR+/HER2- 2.4 cm breast tumor without node involvement (T2N0; G2; high risk in multigene tests). The SGBCC panel recommends the anthracycline-free TC regimen (taxane/cyclophosphamide) as adjuvant chemotherapy (majority vote: 72.9%). An AC/taxane regimen is recommended if the above-described patient has a T2N1 tumor (G2) with 2/3 positive SLN (majority vote: 85.0%; TC regimen: 15%).

The German specialists confirm that adjuvant chemotherapy is indicated in both cases but emphasize that the type of chemotherapy does not depend on the results of multigene testing. Multigene testing has no predictive significance [1, 2, 36]. In the opin-

ion of the German specialists, the TC regimen is an acceptable option for patients without lymph node involvement. The higher the risk, the stronger the recommendations for an anthracycline-based regimen such as the AC(EC)/taxane regimen. In Germany, anthracyclines are preferably used to treat patients with lymph node involvement. The voting results of the SGBCC panel correspond to the recommendations of AGO Mamma [1,2].

If the above-described patient in the initial setting (T2N0) has a higher genomic risk, the SGBCC panel prefers an anthracycline-containing AC/taxane regimen in a pN0 setting (majority vote: 71.7%) compared to a TC regimen. The German specialists recommend both regimens are reasonable options. They point out again that the type of chemotherapy is based on clinical findings and not on the results of multigene testing.

If the primary breast tumor of the above-described patient is 1.8 cm (T1c N0) and has a higher grading (G3), the German specialists agree that an anthracycline-based AC(EC)/taxane regimen should be used in preference to the TC regimen because of the higher clinical risk (SGBCC majority vote: 66.1%).

### Adjuvant endocrine therapy?

The German experts agree that adjuvant endocrine therapy is an appropriate therapy for a postmenopausal patient (60 years old) with ER+/PR+/HER2- breast cancer (1–2 cm) and three positive axillary lymph nodes (T1cN1; 3/11 LN) as well as a low multigene risk and that this patient does not require adjuvant chemotherapy (majority vote: 71%). In Germany, a patient with three positive lymph nodes might receive a short endocrine induction therapy preoperatively to answer the question whether chemotherapy is indicated based on dynamic Ki67 and therefore define more accurately the tumor's endocrine sensitivity (ADAPT concept) [1,2,31]. In the trial, this subgroup of patients was very small and long-term data are missing, especially for patients with 3 positive axillary lymph nodes.

If the same patient has four positive lymph nodes (T1cN2; 4/11 LN; RS13), the German specialists point out that chemotherapy is definitely indicated and there is no indication for multigene testing. The German specialists recommend an AC/taxane regimen. About one third of the SGBCC panel respectively preferred an AC/taxane regimen, a TC regimen or omitting chemotherapy. From the German point of view the latter approach is not an option in this setting.

### Influence of multigene testing on therapy decisions

The influence of multigene testing on the treatment decision for ER+/PR+/HER2- primary breast cancer had a high priority in the SGBCC panel's voting. In Germany these tests are only used in addition to clinical and histopathological factors [1,2]. The Federal Joint Committee (G-BA) in Germany is currently reevaluating whether the cost of multigene testing should be reimbursed by health insurance companies or not, and if so, for which patients (N0, 1–3 positive lymph nodes, premenopausal versus postmenopausal patients).

Using the example of a fictitious premenopausal patient (42 years old) with ER+/HER2- primary breast cancer (T1c [1.4 cm] N0; G2) it became clear that the SGBCC panel's recom-

mendation for chemotherapy increased with higher genomic risk. If the multigene risk is low, the panel prefers adjuvant treatment with tamoxifen (majority vote: 63.93%) but favors adjuvant chemotherapy with subsequent endocrine therapy for patients with a moderate to high multigene risk (majority vote: 56.45%).

The German specialists again refer to the ADAPT concept based on dynamic Ki67 expression as an option for patients with a moderate multigene risk as this could provide useful information on whether it will be useful to omit chemotherapy [31]. If the patient shows a good response to endocrine therapy, it may be possible to omit chemotherapy if this is in line with all other risk factors.

According to the RxPonder trial [37], chemotherapy is indicated if the above-described premenopausal patient has one positive lymph node in the axilla. Here, too, the German specialists recommend using the ADAPT concept [31] with dynamic Ki67 response testing to omit chemotherapy if necessary. There is a clear statement, that Ki67 determination in the tumor biopsy and surgical specimen after endocrine treatment should only be used together with multigene testing for further therapy planning (especially on whether or not to recommend adjuvant chemotherapy). However, some of the German specialists are critical to this approach: the results of Ki67 determination in different specimens (biopsy or excised tumor specimen), possibly from different pathologies, could be contradictory, which is why caution is advised.

It is also important to be aware that the group of premenopausal patients with 1–3 positive axillary lymph nodes in the ADAPT study [31] was small with only 330 women compared to the RxPonder trial [37]. The RxPonder trial investigated 1665 patients (premenopausal, 1–3 positive lymph nodes) who achieved a relative risk reduction of about 50% with additional adjuvant chemotherapy. For these patients (N+), The German guideline recommends discussing the question of adjuvant chemotherapy on a case-by-case basis and to additionally administer optimal endocrine therapy, including GnRH analogs plus an aromatase inhibitor and CDK4/6 inhibitor [1,2]. The German specialists refer here to a meta-analysis [38] and the approval studies for abemaciclib and ribociclib [33,34,39].

Other variables of the above-described fictitious premenopausal patient related to the number of positive axillary lymph nodes and the multigene score. The voting results of the SGBCC panel show that as the risk increases – based on the number of positive lymph nodes and/or the multigene score – the recommendation for adjuvant chemotherapy followed by endocrine therapy plus a CDK4/6 inhibitor was getting stronger.

The German specialists agree with this opinion. From the German point of view it is important that the decision in favor of chemotherapy or endocrine-based therapy must be done independently of each other. The NATALEE trial [34] randomized both node-negative patients with additional risk factors (based on multigene testing, Ki67 expression, grading) and patients with positive axillary lymph nodes. The use of a CDK4/6 inhibitor in the context of endocrine-based treatment should be discussed with the patient even though currently no data is available on overall survival. However, meta-analyses in this setting (but with-

out the use of a CDK4/6 inhibitor) suggest that longer disease-free survival and distant disease-free survival (DFS and DDFS) after a longer follow-up translate into longer overall survival [40].

Another variable discussed in this case study was age. If the patient is 50 years old (instead of 42 years old) with a moderate multigene risk or, alternatively, a Ki67 expression of 20%, only a simple majority of the SGBCC panel favors adjuvant chemotherapy with subsequent endocrine therapy plus a CDK4/6 inhibitor. Support for endocrine therapy ± CDK4/6 inhibitor increased.

### Endocrine-based combination therapy

The post-neoadjuvant use of a CDK4/6 inhibitor must be guided by the preoperative clinical or surgical-pathological tumor stage. If a patient with ER+/HER2- primary breast cancer and lymph node involvement (T2N1, G2) is tumor-free in the axilla after NAST (ypN0) but still has residual tumor (1 cm) in the breast, additional administration of a CDK4/6 inhibitor in the post-neoadjuvant setting may be justified. With increasing risk, the indication for an additional CDK4/6-inhibitor is getting stronger from the German point of view [1,2]. The German specialists therefore agree with the SGBCC vote that treatment with a CDK4/6 inhibitor may also be indicated in the ypN0 setting if there has been preoperative lymph node involvement.

Adjuvant endocrine-based combination therapy with ribociclib is clearly indicated after chemotherapy for a postmenopausal patient with ER+/HER2- primary breast cancer without axillary lymph node involvement (T 2,1 cm; N0; G2) who has had primary surgery and has been found to be high risk with multigene testing. The recommendation for ribociclib in the German guideline includes the following settings: N+ or N0 T3/T4 or N0 T2 G3, or N0 T2 G2 and Ki67 ≥ 20% or high-risk multigene score [1,2]. In the NATALEE trial [34, 39] 1400 patients had no lymph node involvement. These patients had an absolute advantage of 5% with regard to disease-free survival compared to the control group without ribociclib [41].

The heterogeneous SGBCC vote makes it clear that this is a “borderline” situation: 41% of the panel recommend adjuvant use of an aromatase inhibitor (AI) and 38% the use of a CDK4/6 inhibitor in addition to an AI. Based on the currently available data, the German specialists support the use of AIs (including a CDK4/6 inhibitor).

### Luminal carcinoma in men

It is generally agreed that the additional use of a CDK4/6 inhibitor to men with ER+/HER2- primary breast cancer should be based on the same criteria as those used for women (majority vote: 91.7%). The German experts point out that too few men are currently receiving treatment in clinical studies as well as in approval studies.

The German specialists agree that patients with ER+/HER2- primary breast cancer should be followed up for as long as possible in clinical studies. A survival benefit is usually only apparent after 15 years or even later [40]. Long-term follow-up provides useful information for clinical progress and is a quality criterion for clinical studies.

## Survivorship – Follow-up of Early Breast Cancer

When discussing survivorship, the SGBCC panel focused on management and prevention of potential side effects and on follow-up care. The German specialists largely agree with the voting results.

### Polyneuropathy and gynecological symptoms

Nowadays, preventive measures such as cooling gloves or compression gloves are standard to reduce or, ideally, avoid the risk of polyneuropathy under taxane-based (neo)adjuvant systemic therapy. From a German perspective, it is unacceptable not to offer patients adequate preventive options. Successful prevention improves patients' quality of life and has a positive impact on treatment adherence [42]. The audience approved this in a spontaneous voting during the conference.

Sexual health during and after oncological treatment is a relevant issue for patients. The topic must be significantly expanded to also include gynecological symptoms and issues. It needs to be actively broached with the patient during follow-up at the latest. The clear SGBCC majority vote (93.1%) and the recommendations of the German guideline support this [1,2].

### Discussion of the follow-up interval

The SGBCC panel recommends annual mammography screening during follow-up for three years after BCS (majority vote 69.6%) for a low-risk patient with ER+/HER2- primary breast cancer. Just under one third of members suggested a follow-up interval of every two years. The results of the spontaneous auditorium vote were similar.

The German guideline also recommends annual intervals [1, 2]. Over the longer term, the German specialists could imagine the possibility of individualized follow-up intervals which would depend on the patient's oncological history, individual risk, and/or the biological aggressiveness of the tumor or the tumor type. For low-risk patients (e.g., ER+/low risk) the German specialists recommend follow-up (mammography) carried out at an interval of every two years. Individualized follow-up could possibly relieve the burden on both patients and radiological and oncological services (staff shortages/lack of appointments) without any disadvantages for patients.

### Duration of follow-up

Voting on the question of how long patients should be followed up by cancer specialists was mixed. The majority of the SGBCC panel voted for a period of 5 or 10 years (39% and 29% respectively). Just under one third (27%) did not commit to a specific time (“indefinite”). The question does not reflect clinical reality in Germany as follow-up in Germany is done by non-hospital-based gynecologists in private practice. The German guideline recommends a follow-up of (at least) five years, based on the duration of endocrine therapy [1,2]. In view of possible recurrences and long-term side effects, it would be useful if patient follow-up or support could continue for an indefinite period. Ultimately, the extent and duration of follow-up must be based on the individual situation. Ideally, follow-up will transform over time into screening.

## Treatment of Elderly Patients

The treatment of elderly patients in Germany is based on the treatment of younger women. But it is important to evaluate the physical and mental fitness of older women before starting treatment. A geriatric assessment should be done [1, 2]. The German specialists recommend basing the decision for therapy on shared decision-making with the patient.

## Approach for Locoregional Recurrence

Given the possibility that treatment may consist of repeated BCS and radiation in the form of PBI, the decision about the appropriate treatment for locoregional recurrence depends on the amount of time that has passed since the primary treatment. The longer the interval, the better the patient will tolerate repeated radiotherapy. Moreover, the interval between the primary disease and recurrence also represents a prognostic factor with regard to possible second locoregional recurrence.

The German guideline recommends an interval of at least five years to do a second BCS plus partial breast radiation [1, 2]. There is insufficient data about intervals of less than 5 years. In this respect, the German specialists agree with the SGBCC panel which favors an interval of at least five years.

The discussion focused on the fictitious case of a patient with primary TNBC (T1cN0) who has had breast-conserving surgery and presents with local recurrence in the breast (~ 1.5 cm) three years after adjuvant radiotherapy plus chemotherapy (AC/T). The SGBCC panel recommended mastectomy plus adjuvant chemotherapy with taxane/carboplatin (TCb) (majority vote: 37.7%). Just under 30% (27.5%) would additionally administer pembrolizumab.

The German specialists point out that in addition to a discussion by a multidisciplinary team or tumor board, a preoperative radiotherapy council should also be held to review the option of re-irradiation. Repeated radiotherapy in the form of PBI is not an appropriate therapy choice three years after primary treatment in a patient with unfavorable tumor biology. The German specialists also reject the option of mastectomy alone without adjuvant therapy. Pembrolizumab is not indicated for small TNBC (T1cN0).

The German specialists agree that multigene testing is not indicated for a patient with ER+/HER2- primary breast cancer and local recurrence under endocrine therapy with an aromatase inhibitor (SGBCC majority vote: 70.1%). There is no data available for this and therefore no evidence. Whether chemotherapy is indicated depends on the clinical situation.

## Primary oligometastatic disease

When deciding on the appropriate treatment for oligometastatic disease, the initial question must be whether there is a curative chance that could justify a more intensive treatment. This manuscript will not comment on all of the votes of the SGBCC panel on oligometastatic disease. Some of the fictitious case studies did not correspond to the guidelines used in Germany or the German specialists felt that important information was missing to answer the question.

## Is there a rationale for curative therapy for oligometastatic disease?

The question whether therapy with curative intent should be carried out or not was based on the example of a fictitious patient with ER-/HER2+ primary breast cancer (47 years old; T2N1) with solitary, histologically confirmed, bone metastasis. The case study was controversially discussed by the German experts. The patient responded well to induction therapy with TCbHP: the axillary lymph nodes were tumor-free. A small residual tumor remained in the breast with sclerosis of the only confirmed bone metastasis. The SGBCC panel recommended a surgical approach for breast and axilla with postoperative radiotherapy plus maintenance therapy with dual antibody blockade (majority vote: 76.5%).

- A curative treatment approach with BCS and SLNB is reasonable in the opinion of the German specialists as only a solitary metastasis has been confirmed and the patient has responded well to induction therapy. But the question about how long the patient should receive curative systemic therapy is unknown due to missing data.
- Some of the other German specialists would recommend treatment with curative intent and therefore avoid surgical intervention in breast and axilla as well as for the metastasis. Randomized studies in the metastatic setting have not shown that local breast therapy provides any survival benefit [43]. There is also no clear evidence which shows a benefit for local treatment of metastases [44]. Systemic maintenance therapy is preferred.

Both options should be discussed with the patient. Her preferences must be considered for decision-making.

In the case of an elderly patient (63 years old) with ER+/PR+/HER2- primary breast cancer (T2N1; 2.8 cm; 3/3 LK+, G2) and two bone metastases (lumbar spine, ribs), the German specialists agree that systemic treatment with an aromatase inhibitor plus a CDK4/6 inhibitor should be favored. In this case with a high-risk primary tumor, the focus is on the metastatic disease. Antiresorptive therapy should be additionally administered [1, 2]. Local radiation therapy is recommended if the patient is suffering from pain due to bone metastases and/or reduced stability. The German specialists discussed whether local radiotherapy of both metastases is appropriate, irrespective of the pain. This metastasis-targeting therapy is currently not common practice but is being investigated in ongoing clinical studies [44].

The German specialists do not agree with the majority vote of the SGBCC panel on the very general question whether locoregional therapeutic interventions should definitely be initiated when the metastatic burden is very limited and highly effective therapy options are available, and/or the patient has shown a very good initial response to therapy. A high percentage of SGBCC panelists and participants attending the conference in the auditorium voted in favor of locoregional therapy. In principle, the German guideline does not recommend this because the evidence for this approach is missing.

## Note

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## References

- [1] AGO Kommission Mamma. Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome. März 2025. Accessed June 14, 2025 at: [https://www.ago-online.de/fileadmin/ago-online/downloads/\\_leitlinien/kommission\\_mamma/2025/AGO\\_2025D\\_Gesamtdatei.pdf](https://www.ago-online.de/fileadmin/ago-online/downloads/_leitlinien/kommission_mamma/2025/AGO_2025D_Gesamtdatei.pdf)
- [2] Park-Simon T-W, Müller V, Albert U-S et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2025. *Breast Care (Basel)* 2025; 1–30. DOI: 10.1159/000545019
- [3] Ditsch N et al. Update Breast Cancer 2025 Part 1 – Expert Opinions of Early Stage Breast Cancer Therapies. *Geburtshilfe Frauenheilkd* 2025 (submitted)
- [4] Meattini I, Coles CE, Tramm T et al. Biomarker-Directed Radiotherapy in Breast Cancer: A Narrative Review. *JAMA Oncol* 2025; 11: 329–339. DOI: 10.1001/jamaoncol.2024.5780
- [5] Reimer T, Stachs A, Veselinovic K et al. Axillary Surgery in Breast Cancer – Primary Results of the INSEMA Trial. *N Engl J Med* 2025; 392: 1051–1064. DOI: 10.1056/NEJMoa2412063
- [6] de Boniface J, Filtenborg Tvedskov T, Rydén L et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. *N Engl J Med* 2024; 390: 1163–1175. DOI: 10.1056/NEJMoa2313487
- [7] Kunkler I. Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC randomized trial on behalf of the SUPREMO trial investigators. Texas/USA: San Antonio; 2024
- [8] Krug D, Baumann R, Combs SE et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. *Strahlenther Onkol* 2021; 197: 269–280. DOI: 10.1007/s00066-020-01744-3
- [9] Murray Brunt A, Haviland JS, Wheatley DA et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* 2020; 395: 1613–1626. DOI: 10.1016/S0140-6736(20)30932-6

- [10] Borm KJ, Hörner-Rieber J, Duma NM et al. De-escalation strategies in early breast cancer: implications of sentinel lymph node biopsy omission for adjuvant radiotherapy. *Strahlenther Onkol* 2025. DOI: 10.1007/s00066-025-02391-2
- [11] Mamounas EP, Bandos H, White JR et al. NRG Oncology/NSABP B-51/RT0G 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to whole breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence-free interval (IBCR-FI) in patients (pts) with pathologically positive axillary (PPAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). *JCO* 2019; 37: TPS600. DOI: 10.1200/JCO.2019.37.15\_suppl.TPS600
- [12] Boughey JC, Suman VJ, Mittendorf EA et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; 310: 1455–1461. DOI: 10.1001/jama.2013.278932
- [13] Meattini I. Exclusive endocrine therapy or radiation therapy in women aged 70+ years with luminal-like early breast cancer (EUROPA): pre-planned interim analysis of a randomized phase 3 trial [GS2-01]. *Texas/USA: San Antonio*; 2024
- [14] Schmid P, Cortes J, Dent R et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. *N Engl J Med* 2024; 391: 1981–1991. DOI: 10.1056/NEJMoa2409932
- [15] Tarantino P, Leone J, Vallejo CT et al. Prognosis and trends in chemotherapy use for patients with stage IA triple-negative breast cancer (TNBC): A population-based study. *JCO* 2023; 41: 510. DOI: 10.1200/JCO.2023.41.16\_suppl.510
- [16] Mukhtar RA, Hoskin TL, Habermann EB et al. Changes in Management Strategy and Impact of Neoadjuvant Therapy on Extent of Surgery in Invasive Lobular Carcinoma of the Breast: Analysis of the National Cancer Database (NCDB). *Ann Surg Oncol* 2021; 28: 5867–5877. DOI: 10.1245/s10434-021-09715-3
- [17] de Gregorio A, Janni W, Friedl TWP et al. The impact of anthracyclines in intermediate and high-risk HER2-negative early breast cancer—a pooled analysis of the randomised clinical trials PlanB and SUCCESS C. *Br J Cancer* 2022; 126: 1715–1724. DOI: 10.1038/s41416-021-01690-6
- [18] Gougis P, Hamy A-S, Jochum F et al. Immune Checkpoint Inhibitor Use During Pregnancy and Outcomes in Pregnant Individuals and Newborns. *JAMA Netw Open* 2024; 7: e245625. DOI: 10.1001/jamanetworkopen.2024.5625
- [19] 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. *JCO* 2021; 39: LBA1. DOI: 10.1200/JCO.2021.39.15\_suppl.LBA1
- [20] Garber JE. Pre-specified analyses of IDFS, DDFS and OS10 years from First Patient In (FPI) in the OlympiA trial of adjuvant olaparib in germline BRCA1/2 mutation-associated breast cancer [GS1-09]. *Texas/USA: San Antonio*; 2024
- [21] 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). *JCO* 2020; 38: TPS596. DOI: 10.1200/JCO.2020.38.15\_suppl.TPS596
- [22] Rugo H, Robson M, Im S-A et al. Abstract GS01-05: Pembrolizumab + Olaparib vs. Pembrolizumab + Chemotherapy After Induction With Pembrolizumab + Chemotherapy for Locally Recurrent Inoperable or Metastatic TNBC: Randomized Open-Label Phase 2 KEYLYNK-009 Study. *Cancer Research* 2024; 84: GS01-05. DOI: 10.1158/1538-7445.SABCS23-GS01-05
- [23] Nederlof I. Neoadjuvant nivolumab/relatlimab or nivolumab/ipilimumab in triple negative breast cancer with high tumor-infiltrating lymphocytes (TILs). *Barcelona/Spain*; 2024
- [24] 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
- [25] Geyer CE, Untch M, Huang C-S et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. *N Engl J Med* 2025; 392: 249–257. DOI: 10.1056/NEJMoa2406070
- [26] 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
- [27] Waks AG, Villacampa G, Brunet LP et al. 126MO HER2DX and pathological complete response in HER2-positive breast cancer: A combined analysis of 4 neoadjuvant studies. *ESMO Open* 2023; 8: 101465. DOI: 10.1016/j.esmoop.2023.101465
- [28] Villacampa G, Tung NM, Pernas S et al. Association of HER2DX with pathological complete response and survival outcomes in HER2-positive breast cancer. *Ann Oncol* 2023; 34: 783–795. DOI: 10.1016/j.annonc.2023.05.012
- [29] Coates AS, Winer EP, Goldhirsch A et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol* 2015; 26: 1533–1546. DOI: 10.1093/annonc/mdv221
- [30] Lux MP, Ciani O, Dunlop WCN et al. The Impasse on Overall Survival in Oncology Reimbursement Decision-Making: How Can We Resolve This? *Cancer Manag Res* 2021; 13: 8457–8471. DOI: 10.2147/CMAR.S328058
- [31] Harbeck N, Gluz O, Kuemmel S et al. Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0–3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. *Cancer Res* 2021; 81 (4\_Supplement): GS4-04. DOI: 10.1158/1538-7445.SABCS20-GS4-04
- [32] Mengel M, von Wasielewski R, Wiese B et al. Inter-laboratory and inter-observer reproducibility of immunohistochemical assessment of the Ki-67 labelling index in a large multi-centre trial. *J Pathol* 2002; 198: 292–299. DOI: 10.1002/path.1218
- [33] 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). *JCO* 2020; 38: 3987–3998. DOI: 10.1200/JCO.20.02514
- [34] Slamon D, Lipatov O, Nowecki Z et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. *N Engl J Med* 2024; 390: 1080–1091. DOI: 10.1056/NEJMoa2305488
- [35] Robson ME, Tung N, Conte P et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019; 30: 558–566. DOI: 10.1093/annonc/mdz012
- [36] Reimer T, Gluz O, Nitz U et al. Prospektive Phase-III PlanB-Studie: 5 Jahres Daten zum prognostischen Stellenwert von 21-Gen Recurrence-Score, zentralpathologischem Grading, ER, PR, Ki-67 Review beim frühem Hochrisiko HR+/HER2-negativen Mammakarzinom. *Senologie* 2016. DOI: 10.1055/s-0036-1583431
- [37] 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
- [38] Janni W, Untch M, Harbeck N et al. Systematic literature review and trial-level meta-analysis of aromatase inhibitors vs. tamoxifen in patients with HR+/HER2- early breast cancer. *Breast* 2025; 81: 104429. DOI: 10.1016/j.breast.2025.104429

- [39] Hortobagyi GN, Lacko A, Sohn J et al. A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. *Ann Oncol* 2025; 36: 149–157. DOI: 10.1016/j.annonc.2024.10.015
- [40] Untch M, Pérol D, Mayer EL et al. Disease-free survival as a surrogate for overall survival in HR+/HER2- early breast cancer: A correlation analysis. *Eur J Cancer* 2024; 202: 113977. DOI: 10.1016/j.ejca.2024.113977
- [41] Fasching PA, Stroyakovskiy D, Yardeley D et al. Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2- early breast cancer (EBC): 4-year outcomes from the NATALEE trial [LBA13]. *Ann Oncol* 2025; 35 (Suppl. 2): S1207
- [42] Michel LL, Schwarz D, Romar P et al. Efficacy of Hand Cooling and Compression in Preventing Taxane-Induced Neuropathy: The POLAR Randomized Clinical Trial. *JAMA Oncol* 2025. DOI: 10.1001/jamaoncol.2025.0001
- [43] Khan SA, Zhao F, Goldstein LJ et al. Early Local Therapy for the Primary Site in De Novo Stage IV Breast Cancer: Results of a Randomized Clinical Trial (EA2108). *JCO* 2022; 40: 978–987. DOI: 10.1200/jco.21.02006
- [44] Piroth MD, Krug D, Feyer P et al. Oligometastasis in breast cancer-current status and treatment options from a radiation oncology perspective. *Strahlenther Onkol* 2022; 198: 601–611. DOI: 10.1007/s00066-022-01938-x