

AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2025

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Keywords

Early breast cancer · (Post)(neo)adjuvant · Breast surgery · Reconstruction · Radiotherapy · Communication

Abstract

The Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group, AGO) presents the 2025 update of the evidence-based recommendations for the diagnosis and treatment of patients with early breast cancer. © 2025 The Author(s).
Published by S. Karger AG, Basel

Introduction

Optimal management of breast cancer requires a multidisciplinary strategy. Each year the interdisciplinary AGO Breast Committee provides updated state-of-the-art recommendations on the prevention, diagnosis, and treatment of breast cancer. This update follows a defined algorithm. The most recent and relevant publications are reviewed and the scientific validity is scored according to the Oxford Level of evidence (LoE). The strength of recommendation is determined by the Oxford Grades of recommendation (GR) and the AGO Grades of recommendation. The updated recommendations for early breast cancer (eBC) and metastatic breast cancer (mBC) of the AGO Breast Committee have been released in March 2025. This paper captures the updated recommendation of eBC. The updated slides with the annotated speeches and the patient forum are available

in the on-demand library (<https://www.ago.2025.de>). Chapters without relevant changes in content are not included in this manuscript.

Options for Primary Prevention and Lifestyle Factors

In a systematic review, the risk and incidence of transgender individuals were reported. Overall, FtM and MtF individuals have a higher risk of developing breast cancer compared to cisgender men but compared to cisgender women, their risk is lower [1]. In 6 cohort studies and 35 case reports, the risk of FtM individuals was higher than that of cisgender men (standardized incidence ratio [SIR] = 63.4; 95% CI, 32.2–124.9) but lower than that of cisgender women (SIR = 0.42; 95% CI, 0.07–2.41). MtF individuals also had a higher risk of developing breast cancer (SIR = 22.5; 95% CI, 5.54–91.8) compared to cisgender men; again, this risk was lower than that of cisgender women (SIR = 0.30; 95% CI, 0.22–0.42). These results highlight the fact that transgender individuals should undergo regular breast or chest examinations and imaging.

BC Risk, Genetics, and Prevention

Genetic germline testing is indicated in breast cancer patients due to a treatment indication for a PARP inhibitor in early (LoE1a/A/AGO++) or advanced disease as well as due to a family history (LoE2a/B/AGO++) or the patient's own medical history. With regard to the personal cancer

history, germline testing can be offered if a triple-negative breast cancer diagnosis was made before the 70th birthday [2], an ovarian cancer diagnosis was made before the 80th birthday or a man has breast cancer (LoE2b/B/AGO++). As the required 10% detection rate of pathogenic/likely pathogenic variants (PV) has not yet been proven for these three criteria, they are currently undergoing further validation and are therefore offered at the Centers of the German Consortium for Hereditary Breast and Ovarian Cancer Consortium (GC-HBOC). The analysis of PVs in the high-risk genes *BRCA1* and *BRCA2* is at the forefront of therapeutic germline testing in Her2-negative breast cancer patients with indication for PARPi. If a hereditary form of breast cancer is suspected, a panel analysis with other risk genes (e.g., *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, *PTEN*, *TP53*, *STK11*) is indicated (LoE 1b/B/AGO+). Low-risk variants that can have a multiplicative effect on the risk of breast cancer as a polygenic risk score (LoE 2b/B/AGO+) [3] and nongenetic variants that can have a multiplicative effect on the risk of breast cancer as a polygenic risk score (LoE 2b/B/AGO+) and nongenetic risk factors (e.g., breast tissue density, lifestyle factors) are of increasing clinical importance as they are included in the individualized calculation of breast cancer risk [4]. Women with an increased risk of breast cancer are offered a multimodal intensified surveillance/follow-up program (IFNP) including magnetic resonance imaging (MRI; AGO++). The examinations are offered to carriers of PVs in breast cancer risk genes as well as healthy women without evidence of a PV with a calculated breast cancer risk of 5% in 10 years (with certified software, e.g., CanRisk, AGO++) and breast cancer patients who fulfill the criteria for a genetic germline examination of the GC-HBOC and have developed breast cancer before their 46th birthday. Both, IFNP and risk-reducing unilateral or bilateral mastectomy can represent an individual prevention strategy but should not be offered without the presence of clearly defined genetic risk factors (LoE2a/B/AGO).

Early Detection and Diagnosis

In asymptomatic women, screening mammography (full-field digital mammography, FFDM) is highly recommended for women 50–75 years of age (LoE1a/A/AGO++). For women 45–50 of age, it is also recommended (LoE1a/A/AGO+), however, as long as legal regulations are pending, justifying indication is necessary. In the age group, 40–44 years with moderately enhanced risk or own history of breast cancer, individual shared decision-making is recommended (LoE 1b/B/AGO+/-).

It is suggested to estimate the risk by a modern version of the Tyrer-Cuzick model [5–8]. Outside the intensified program for early detection (IFNP), in women 40–44 years with “normal” risk and those younger than 40 years,

mammography screening is not recommended (LoE 1b/B/AGO-). Above 75 years of age, mammography screening can be offered to women in good health with a life expectancy of 10 years or longer (LoE 4/C/AGO+/-). Breast density is a known risk factor for breast cancer development and decreased FFDM sensitivity.

Though the European Commission Initiative on Breast Cancer already recommends digital breast tomosynthesis (DBT) for screening, AGO argues that a significant reduction in interval cancer rates has not been demonstrated so far (LoE1a/A/AGO+) [9, 10]. Synthetic 2D image reconstruction of the 3D dataset of DBT can significantly reduce radiation dose and is highly recommended instead of adding a FFDM (LoE1a/A/AGO++) [9, 10].

Although use of artificial intelligence as a second reader in FFDM could be beneficial regarding detection rate and workload optimization, it still needs further evaluation (LoE 1b/B/AGO+/-). Without standardization and no evidence for comparability of different systems, transfer into clinical routine is too early [11, 12].

Neither use of hand-held ultrasound (US) nor automated whole-breast US can be recommended as a sole modality for screening in women with normal or moderate risk (LoE 3a/C/AGO-) [9]. MRI screening in the extremely dense breast screening group with negative FFDM showed a significantly reduced interval cancer rate at the cost of slightly increased false-positive cases (LoE 1b/B/AGO+) [13, 14].

For patients with suspicious imaging (screening or diagnostic) or breast symptoms, clinical examination (LoE 3b/B/AGO++), FFDM (if not yet done; LoE 1b/A/AGO++), DBT (LoE 2a/B/AGO+) or contrast-enhanced mammography (CEM; LoE 1b/B/AGO+), US (LoE 2b/B/AGO++), and minimally invasive biopsies (LoE 1b/A/AGO++) should be performed. If FFDM, US and CNB/VAB do not allow clear diagnosis, MRI can also be helpful (LoE 2a/B/AGO+) [9, 15–17].

As part of surgical planning procedure, US of the breast (LoE 2b/B/AGO++) and the axilla is recommended (LoE 2a/B/AGO++). MRI can be performed in patients with reduced sensitivity of FFDM and US, nipple involvement, lobular invasive cancer, suspicion of multicentric disease, and/or high risk (LoE 1b/A/AGO+), provided that MRI-guided vacuum-assisted biopsy access is available in-house or among cooperating partners [18–20]. A recent study (RACER) shows, that CEM may have advantages over MRI and DBT, such that this method might have a future impact (LoE 2a/b/AGO+) [21].

In patients with clinically and/or sonographically suspicious axillary lymph nodes, core needle biopsy is recommended (LoE 2a/B/AGO++). If less than 3 nodes are suspicious or biopsy reveals lymph node involvement prior to neoadjuvant therapy, a clip should be inserted into the lymph node to allow targeted axillary dissection (TAD; at the time of surgery) (LoE 2b/B/AGO++) [22].

Imaging-based staging is recommended for candidates scheduled for (neo)adjuvant chemotherapy including CT scan of the chest, abdomen, and pelvis (LoE 2a/B/AGO++). In addition bone scan should be done (LoE 2a/B/AGO+), although some data suggest superiority of FDG-PET-Scan (LoE2a/B/AGO+/-) [23]. PET-CT as general staging tool should be reserved for individual cases with high-stage (III) cancer (LoE 2b/B/AGO +/-) [24].

Pathology

Prediction of endocrine responsiveness is of key importance for clinicians. The pathology report helps as follows.

1. Immunohistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue is a standard procedure. Hormone receptors are scored as percentage of positive tumor cell nuclei (estrogen receptor, ER is considered positive if $\geq 1\%$ with low positivity ranging from $\geq 1\%$ to 10% ; progesterone receptor, PR is considered positive if $\geq 10\%$ (LOE1a A, AGO ++)) [25].
2. Detection of endocrine responsiveness by Ki-67 decrease to $< 10\%$ in the surgical specimen or a repeat core biopsy after 3–4 weeks of preoperative endocrine therapy in early breast cancer [26] (LOE 1b A, AGO +). This endocrine induction therapy was established by several large phase III trials [27, 28].
3. Detection of secondary, i.e., acquired endocrine resistance by analysis of activating *ESR-1* mutations in liquid biopsy or metastatic tissue (LOE 1b A, AGO +). *ESR-1* mutations render ER constitutively active and thus confer resistance to aromatase inhibitors. In mBC with *ESR-1* mutation, there is usually strong immunohistochemical ER positivity. Consequently, in luminal mBC immunohistochemical ER analysis alone without testing of activating *ESR-1* mutation is not sufficient to establish endocrine sensitivity. The oral SERD elacestrant has shown activity in mBC for tumors harboring an *ESR-1* mutation [29].

With regard to the indication for checkpoint inhibitor therapy in breast cancer, PD-L1 testing is needed for the first line setting in metastatic triple-negative setting. A positive PD-L1 immune score (IC) of $> 1\%$ (cytoplasmic staining of the leukocyte stromal infiltrate [lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses] in relation to the tumor area) is needed for therapy with atezolizumab and nab-paclitaxel [30]. For therapy with pembrolizumab and chemotherapy, a Combined Positive Score (CPS, i.e., positive tumor cells + macrophages + lymphocytes divided by the number of tumor cells $\times 100$) of $> 10\%$ is the prerequisite [31]. Testing can be performed in the primary tumor or – if available – metastasis tissue (LOE 2 A, AGO ++)

using antibodies that are equivalent to those used in the respective registration trials (LOE 3 B, AGO +).

gBRCA 1 and 2 is tested for the indication of Olaparib in eBC and mBC or talazoparib in mBC; *PIK3CA* for indication of alpelisib in mBC, an alteration in the AKT1 – PTEN – *PIK3CA* pathway for indication of capivasertib [32]. Activating *ESR-1* alterations for testing of potential elacestrant effectivity in metastatic luminal BC is also recommended (++) , predominantly by liquid biopsy. Moreover, somatic BRCA mutation or gPALB2 mutation could also be determined in tumor tissue for evaluation of potential Olaparib responsiveness in mBC (AGO+) [33].

Prognostic and Predictive Factors

The determination of preoperative dynamic Ki67% levels after short-term induction endocrine therapy as a surrogate marker for endocrine responsiveness in combination with the 21-gene Recurrence Score represents a valuable decision-making tool (LoE 1b/B/AGO). The ADAPT trial showed convincingly that the predictive value for endocrine sensitivity in patients with an intermediate risk score between 12 and 25 and a Ki67 decrease below $\leq 10\%$ was excellent [28]. This strategy might also represent a practicable approach to guide escalation as well as de-escalation strategies, especially the identification of the subgroup of premenopausal patients in whom chemotherapy can be omitted.

CTCs and ctDNA are most commonly used for liquid biopsy. While the evidence on the clinical use of CTCs has not changed and CTCs are mainly used for predicting prognosis (LoE1a/A/AGO +) and early therapy response (LoE1a/A/AGO +) in the metastatic setting, the clinical significance of ctDNA has increased significantly due to new results from clinical studies in both early and metastatic breast cancer. In early breast cancer, the presence of ctDNA is associated with reduced disease-free and overall survival both before and after treatment, as shown in a large meta-analysis. Consequently, ctDNA can be used as a prognostic factor (pre-therapeutic LoE1a/A/AGO +/-; post-therapeutic LoE 1b/AGO +/-) [34]. Whether interventions based on post-therapeutic ctDNA positivity after definitive adjuvant treatment improve clinical outcomes is currently under investigation in ongoing trials (e.g., Artemis NCT04803539, PERSERVERE NCT04849364). Therefore, treatment decisions following (neo)adjuvant therapy should not be based on ctDNA positivity (LoE 5/D/AGO –) or mutations detected via ctDNA (LoE 5/D/AGO–) until clinical benefits from such strategies are demonstrated.

In the metastatic setting, ctDNA can be used to predict prognosis (LoE1a/A/AGO +) and monitor early treatment response (LoE 2/A/AGO +) [35]. However, treatment decisions based on ctDNA dynamics should not yet

be made, as more evidence is needed to support switching treatments upon rising ctDNA levels (LoE 5/D/AGO –).

ESR-1 mutations are associated with resistance to aromatase inhibitors (AIs). The role of *ESR1*-mutation tracking in hormone-receptor positive metastatic breast cancer patients receiving endocrine combination therapy with AI and CDK4/6i was evaluated by the PADA1-trial [36]. In the experimental arm, patients were switched from AI-palbociclib to fulvestrant-palbociclib upon detection of *ESR-1* mutations. Patients in the standard arm continued with AI until clinical progression. The early switch was associated with significant better progression-free survival (11.9 months vs. 5.7 months; HR 0.61 $p = 0.0040$). However, more evidence for this approach is needed, and therefore *ESR-1* mutation tracking is not routinely recommended (LoE 2b/B/AGO +/-).

To identify patients with *ESR-1* mutations for initiating treatment with the SERD elacestrant, ctDNA analysis is required based on the approval text (LoE1a/A/AGO ++). *PIK3CA* analysis for the indication of alpelisib can be performed using either tissue or liquid biopsy (LoE1a/A/AGO ++) [29].

Lesions of Uncertain Malignant Potential (B3)

Lesions of uncertain malignant potential (B3) are usually detected by mammography, US, or MRI and diagnosed by core or vacuum-assisted biopsy in asymptomatic women. Surgical treatment aims to identify potential upstaging to a more severe precursor (particularly DCIS) or even invasive lesions and to prevent a progression toward malignant disease during follow-up. Atypical ductal hyperplasia (ADH) has a particularly high risk of being associated with in situ or invasive breast cancer [37]. ADH has been treated with an open excision after histopathological confirmation in core-/vacuum needle biopsy (LoE3a/C/AGO++). Open excision may be omitted, if all following requirements apply: no mass-lesion radiologically, a small lesion (≤ 2 TDLU) in vacuum biopsy, and complete removal of imaging abnormality (LoE5/C/AGO+/-). However, in cases with ADH at margins in open biopsy specimens no further surgery is indicated, if incidental finding accompanies invasive or intraductal carcinoma (LoE3a/C/AGO+). In cases of biopsy of classical LIN/LCIS open excision can be avoided if no discordant imaging, especially no focal lesion is present (LoE2b/C/++) [38]. In contrast, high-risk variants of lobular neoplasia, which include pleomorphic and florid LCIS (pLCIS and fLCIS) are recommended for open biopsy, and preferably complete excision (LoE2b/C/AGO++). Flat epithelial atypia is upgraded to DCIS or invasive breast cancer in 5% of all cases. Open biopsy is recommended (LoE2b/B/AGO +) if vacuum biopsy could not remove $\geq 90\%$ of the

lesion [39]. The diagnosis of solitary or multiple papillomas on core biopsy might be associated with an increased risk of up to 30% (with atypia) for an invasive carcinoma or DCIS [40]. Therefore, in case of atypia or multiple lesions an open biopsy is mandatory (LoE3a/C/++), except for micropapillomas (< 2 mm) which are usually classified as B2 lesions. A radial scar (RS) may mimic carcinoma, mammographically because of its star-shaped appearance. Radial sclerosing lesions are only rarely associated with atypia or DCIS. When RS is associated with atypia (such as flat epithelial atypia, ADH, or classical LIN), management is similar to the previously mentioned lesions [41]. Medical prevention (e.g., low-dose tamoxifen [LoE1b/B/AGO+/-] or aromatase inhibitor [AI] [LoE1a/A/AGO+/-] for lesions with uncertain biological behavior may be performed only in very individual cases [42].

Ductal Carcinoma in situ

DCIS is a not life threatening preinvasive lesion that is considered to be a precursor of invasive breast cancer. It represents an extremely heterogeneous group of lesions with variable potential for progression to invasive disease, in which not all DCIS will progress to invasion [43]. Most DCIS cases are detected within the mammography screening. In addition to mammography, which is the main diagnostic tool, pre-therapeutic assessment in DCIS should also include breast and axillary US, especially to rule out an accompanying invasive solid part and lymph node involvement (LoE4/C/AGO++). Breast MRIs might be helpful for assessment of the extension and planning surgical procedure in DCIS (LoE1a/B/AGO+/-) but can lead to overestimations of the extension of the DCIS and by that to surgical overtreatment. Complete surgical excision remains the standard of care (LoE1a/A/AGO++). All guidelines recommend clear margins of 2 mm for DCIS lesions except below the skin and above the muscle. SNLB might be recommended in rare cases if the surgical procedure is not allowing a SLN in case of an upstaging to invasive cancer (e.g., cases of kind of mastectomy for large DCIS lesions, LoE 3b/B/AGO+). Radiotherapy (RT) is commonly recommended after BCS of DCIS (LoE1a/A/AGO+), whereas systemic endocrine treatment (tamoxifen 20 mg for 5 years or 5 mg for 3 years or anastrozol) is only recommended as an option (LoE1a-b/A-B/AGO+/-) [44]. Independent of DCIS grade adjuvant endocrine treatment and irradiation have no impact on survival (LoE1a). RT reduces the risk of ipsilateral (invasive and noninvasive) recurrences by 50%. The number needed to treat with RT (for ipsilateral breast recurrence) is 9. Adjuvant endocrine treatment has a moderate effect on ipsilateral invasive (HR 0.79; 95% CI, 0.62–1.01) and DCIS (HR 0.75; 95% CI, 0.61–0.92) recurrences and on contralateral invasive (RR

0.57; 95% CI, 0.39–0.83) and noninvasive cancer (RR 0.50; 95% CI, 0.28–0.87) (endocrine therapy, LoE1a). The number needed to treat to prevent any breast event is 15 (13 without RT and 17 with RT) [45]. A recently presented combined analysis from two prospective trials on RT has shown a substantial effect from tamoxifen on invasive relapse (HR = 0.49, 95% CI, 0.28–0.84, 15 year risk 19% vs. 11.4%) if no RT was performed in patients with low-risk DCIS (size ≤ 2.5 cm, grade 1–2, margin ≥ 3 mm) [46]. Additionally to established prognostic factors (size, differentiation, margin, histological type), the Oncotype DX DCIS Score [47] and DCISionRT [48] might be useful as prognostic factors for an ipsilateral recurrence after first diagnosis of a DCIS (LoE2b). The Oncotype DCIS Score is a multigene assay that has been independently validated in a prospective clinical trial and a population-based cohort. The score helps identify a subset of women >50 years old with unifocal disease that carries $<10\%$ risk of any local recurrence after breast-conserving surgery alone. DCISionRT provides information regarding the recommendations to add or omit RT. In the COMET trial women with low-risk DCIS (>40 yrs., HR+, G1 or 2) randomized to active monitoring every 6 months with mammography of the affected side, did not have a higher rate of invasive cancer at 2 years compared with those randomized to guideline-concordant care – median follow-up 36.9 months (the 2-year Kaplan-Meier cumulative rate of ipsilateral invasive cancer was 5.9% in the guideline-concordant care group vs. 4.2% in the active monitoring group) (LoE2a/B/AGO –) [49].

Oncological Aspects of BC Surgery

Surgery is a mandatory part of the multidisciplinary therapeutic approach in eBC. Treatment decisions should be made within a multidisciplinary conference after a careful pre-therapeutic assessment of the breast and axillary lymph nodes. Survival rates after BCS followed by radiation therapy are at least equivalent to those after mastectomy (LoE1a/A). Wire-marking and/or intra-operative US are highly recommended in non-palpable BC (LoE1a/A/AGO++). Probe-guided procedures like the use of MagSeed™ that has shown equivalency to needle localization in a prospective cohort study can be used as an alternative (LoE 1b/A/AGO+) [50]. Surgical clip marking of the tumor bed should be performed if boost or partial breast irradiation is indicated (LoE 2b/B/AGO+).

Two randomized trials (SOUND, INSEMA) have recently shown non-inferiority for the omission of sentinel lymph node biopsy (SLNB) for patients, who undergo primary surgery and present with negative lymph nodes on palpation and US [51, 52]. Although SLNB remains the standard of care for many patients with T1/T2 tumors (LoE 1b/A/AGO++), SLNB can be avoided in post-

menopausal patients (≥ 50 years with clinical T1 tumors and G1/2, ER/PR-positive, HER2-negative disease), who undergo breast-conserving therapy (LoE 1b/B/AGO+). Pre-treatment discussion of these patients in an interdisciplinary team is recommended.

In patients with pT1-3 cN0 tumors and ≤ 2 positive SLNs (including extracapsular extension), who undergo breast conservation or mastectomy, adequate irradiation and systemic treatment axillary lymph node dissection (ALND) should be omitted (LoE 1b/A/AGO–) [53]. For patients, with 1–2 positive sentinel lymph nodes after mastectomy without adjuvant chest wall irradiation the benefit of ALND is not clear (LoE 2b/B/AGO+/-). 99mTechnetium (Tc) colloid is the most frequently used technique for SLN marking. Indocyanine green and super paramagnetic iron oxide have shown similar detection rates and can be used as alternatives (LoE 2a/B/AGO+).

In patients, who undergo neoadjuvant chemotherapy (NACT) the tumor should be marked early in the course of systemic treatment. At surgery, the residual tumor or the post-therapeutic tumor bed (marked before treatment) should be removed within new margins (LoE 2b/C/AGO++). Patients who present initially with clinically negative lymph nodes should have SLNB after NACT (LoE 2b/B/AGO++). Patients with (CNB proven) positive axillary LN (pN+) at presentation, who convert to ycN0 should undergo either ALND or targeted axillary dissection (TAD; AGO+). TAD becomes increasingly popular in patients with 1–3 clinically positive nodes, although final outcome data are not yet available (LoE2b/B/AGO+) [54]. The accuracy of SLNB is lower compared to the adjuvant setting (LoE 2b/B/AGO +/-). In case of residual macrometastatic lymph node involvement (\geq ypN1a) after TAD, ALND is recommended (LoE 2b/B/AGO+), while the benefit from ALND is unclear for ypN1mi (LoE2b/B/AGO+/-) in case of adequate regional RT. In patients with ypN0(i+) stage after SLNB further axillary surgery should be omitted (LoE2b/B/AGO–).

Oncoplastic and Reconstructive Surgery

Oncoplastic surgical techniques are used to improve esthetic and quality of life outcomes without compromising oncological safety. In general, these are carried out before RT. In breast hypertrophy, tumor-adapted reduction before RT is associated with fewer complications than secondary reduction after RT; however, secondary reduction is still possible in terms of complication rate (major complications) (LoE 3a/B) [55]. Regarding the reconstruction options in case of mastectomy, heterologous, autologous, pedicled flap, and free flap reconstruction are recommended with the same level (LoE 2a/B/AGO +) depending on individual and tumor characteristics and patient wish. If reconstruction is performed

with an expander/implant after mastectomy and RT, prior autologous fat grafting can be considered (LoE 2b/B/AGO +/-). Furthermore, autologous fat grafting can be recommended after breast-conserving surgery (LoE 2a/B/AGO +), after autologous reconstruction (LoE 2a/B/AGO +) but also as the sole technique for breast reconstruction (LoE 1b/B/AGO +) [56].

Regarding implants, risk of capsular fibrosis is increased after RT. In case of need for radiation after mastectomy and reconstruction moderately hypofractionated RT (total dose approx. 40 Gy in approx. 15–16 fractions in approx. 3–5 weeks) should be preferred (LoE 1b/B/AGO ++) [57]. The prepectoral positioning of the implant will lead to a lower capsular fibrosis rate than the subpectoral position (OR, 0.57; 95% CI, 0.41–0.79) in case postmastectomy radiation was performed (LoE 2a/B/AGO +) [58].

A meta-analysis with 19,301 patients presented that prolonged prophylactic antibiotics could be better than only intraoperative antibiotics or antibiotics up to 24 h [59]. However, by the fact that several studies present limitations and potential bias, it was rated at least as an equivalent alternative (LoE 2a/B/+). Moreover, a prophylactic antibiotic (e.g., gentamicin) and/or antiseptic rinse intraoperatively is recommended (LoE 2a/B/+). A new and interesting strategy is to obtain a culture from the drainage after 7 days and to initiate targeted antibiotics based on the antibiogram. This can be considered on an individual basis (LoE 3a/C/+/-). Seromas are the cause of a higher infection rate and ultimately implant loss rate and it is important to avoid them. With the use of tranexamic acid (TXA) both intravenously/orally (LoE 2a/B/AGO +) [60] and topically (3 g TXA in 100 mL sodium chloride solution) in the sense of intraoperative irrigation of the implant cavity (LoE 1b/B/AGO +), the drainage volume and the rate of seromas can be significantly reduced. Contraindications to TXA should of course be taken into account.

Systemic Treatment of eBC – HR+/Her2– BC

One of the biggest challenges of HR+/Her2–BC in clinical practice is to distinguish patients who require both chemotherapy and endocrine therapy from those who are adequately treated by endocrine therapy alone. This is particularly true for patients with HR+/HER2–early breast cancer and 0–3 positive lymph nodes and otherwise favorable genomic and biological risk factors, especially in patients >50 years or in younger node-negative patients. Assessment of life expectancy, comorbidities and shared decision-making about the potential benefits of (neo)adjuvant therapy are fundamental principles of adjuvant therapy.

Tumors with ER >10% are defined as endocrine sensitive and in case of 1–10% (ER low) the tumor is considered questionably endocrine sensitive. There is growing evidence to suggest that ER low tumors behave clinically similar to TNBC and should be treated the same way. On the other hand, the impact of adjuvant endocrine therapy omission in patients with ER low BC is unknown. A retrospective study used data from the National Cancer Database and identified 354,378 patients with stage I to III ER-positive [61]. A total of 10,362 patients were classified ER low. The majority of the patients received chemotherapy. Adjuvant endocrine therapy was not used in 42% of them. The median follow-up was 3 years, the 2-year OS rate was 93.8%, and the 4-year OS rate was 87.1%. After controlling for various risk factors, omission of adjuvant endocrine therapy was associated with a 25% increased risk for death (HR 1.25, 95% CI [1.05, 1.48]; $p = 0.01$). However, information on the duration of treatment and adherence is not available in this retrospective study. The data suggest that a subset of patients with ER low BC may benefit from adjuvant endocrine therapy. Therefore, a careful discussion about the potential benefit of adjuvant endocrine therapy is recommended in patients with ER low BC (LoE2b/D/AGO+).

For patients with endocrine sensitive BC, endocrine therapy includes initial therapy (years 1–5), which may be combined with a CDK4/6i in the first 2 or 3 years if there is an increased risk of recurrence and extended adjuvant therapy (EAT, years 6–10+). Standard treatment duration is 5 years. A switch to a different, better tolerated endocrine treatment (TAM or AI), or a lower dose of TAM is better than discontinuing endocrine therapy completely (AGO++) [44]. In premenopausal women at low risk of recurrence, therapy with TAM for 5 years is recommended (AGO++). In high risk of recurrence, GnRHa plus TAM or AI should be used (LoE1a/A/AGO++). In postmenopausal patient, initial adjuvant endocrine therapy should be with an AI (LoE1a/A/AGO++) or with sequential therapy (LoE1a/A/AGO++) with AM (2–3 years) followed by AI or with an AI (2–3 years) followed by tamoxifen to complete 5 years. EAT can be recommended in patients with an increased risk of recurrence, e.g., positive lymph node status and/or T2/T3 tumors. In premenopausal women, TAM can be extended for up to 10 years (LoE1a/A/AGO++). EAT with 5 years of TAM should also be offered to those patients who were treated by ovarian suppression and TAM or AI during their initial treatment (LoE5/D/AGO+). If patients enter postmenopause in the first 5 years, endocrine therapy can be continued with 2.5–5 years of AI after 5 years of TAM (LoE1b/B/AGO+). In postmenopausal women at high risk of recurrence, extended therapy with 5 years of TAM (after 5 years of TAM) is possible (LoE1a/A/AGO+) but switching to an AI for 2–5 years should be preferred (LoE1a/A/AGO++). If patients at higher risk of

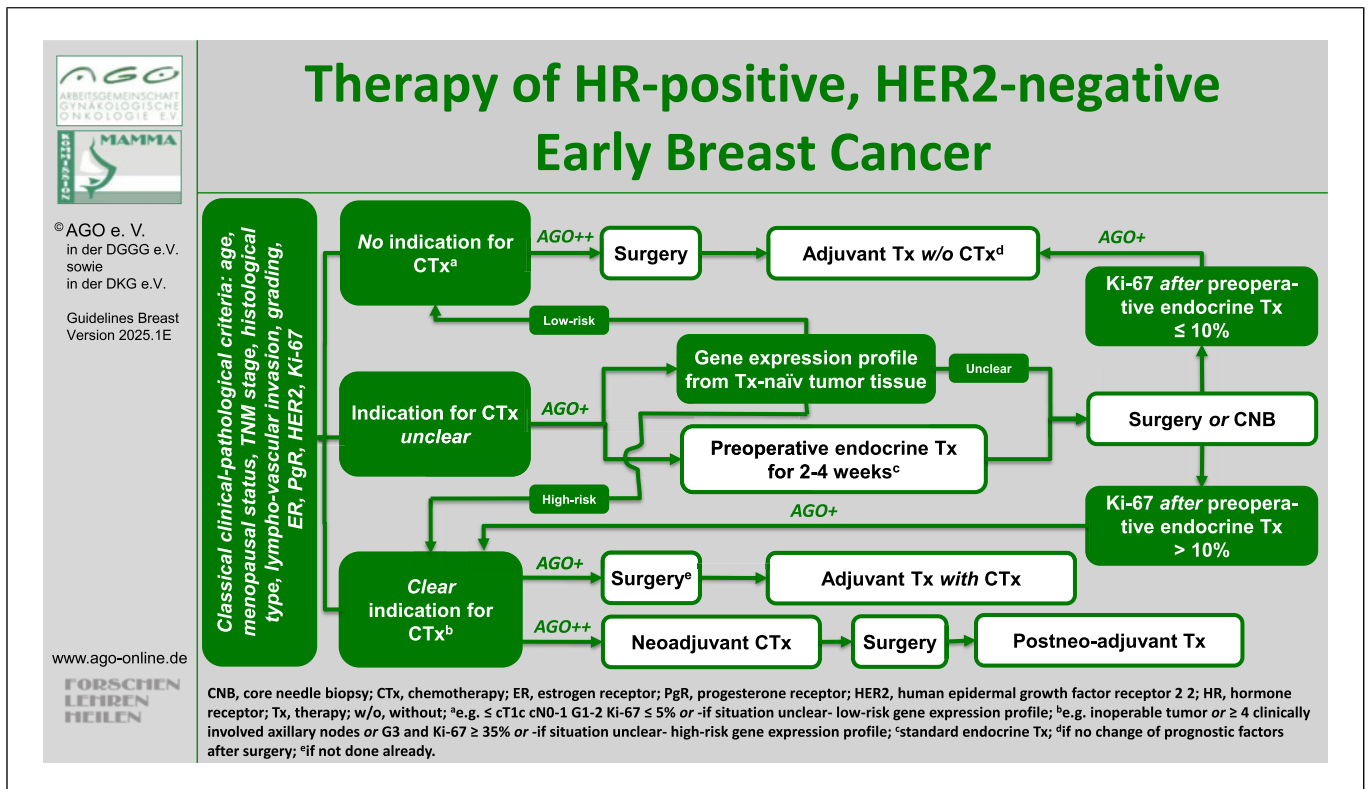


Fig. 1. Treatment algorithm for early HR+/HER2– BC.

recurrence have received an AI (upfront or switch), they should be offered 2–5 additional years of AI (LoE1a/A/AGO+). The duration of the endocrine therapy in postmenopausal women should not exceed 7–8 years, as no further benefits have been demonstrated [62].

A recent meta-analysis suggests that antiresorptive drugs have a protective effect on AI induced bone loss in postmenopausal patients receiving AIs for early BC [63]. Zoledronic acid might not only reduce vertebral fractures but also provide survival benefit [64]. Denosumab reduces the risk of clinical fractures by 50% in women on AI [65]. Antiresorptive therapy is recommended in all postmenopausal women (AGO++). It is important to note that all women who receive hormone ablation therapy for breast cancer are considered postmenopausal.

If chemotherapy is indicated, a dose-dense anthracycline-/taxane-based chemotherapy is the preferred regimen for either adjuvant or neoadjuvant chemotherapy (LoE1a/A/AGO++). A meta-analysis [66] showed that dose-dense regimens lead to significantly improved 10-year recurrence-free survival and overall survival compared to conventional schedules, irrespective of the molecular subtype. If the indication for chemotherapy is already clear preoperatively, NACT should be the preferred choice of treatment. The major advantages of NACT are improvement of operability and assessment of tumor-response. NACT allows individualized post-

neoadjuvant therapy with significant improvement in survival (LoE1b/A/+++).

In patients at increased risk of recurrence who fulfill the inclusion and exclusion criteria of the monarchE and/or NATALEE trial, an endocrine-based treatment should include an AI+/- GnRHa and either abemaciclib or ribociclib (LoE1b/B/+) [67–70]. The monarchE trial included patients with stage II and III HR+/Her2– BC at high risk of breast cancer recurrence (≥ 4 positive axillary lymph nodes or 1–3 positive axillary lymph nodes and either grade 3, tumor size ≥ 5 cm, or $Ki-67$ index $\geq 20\%$). The inclusion criteria of the NATALEE trial were much broader including all patients with axillary lymph node metastases and a group of patients with no nodal involvement. T1N0 was excluded, patients with $>T2N0$ were included as well as selected patients with T2N0. Patients with T2N0 were eligible if the tumor was at least grade 3 or grade 2 with either $Ki-67$ index of $>20\%$ and/or high genomic risk (Fig. 1).

Updated data of the monarchE trial demonstrated sustained benefit of abemaciclib with an absolute improvement in iDFS (HR, 0.680 [95% CI, 0.599–0.772]; $p < 0.001$) and DRFS (HR, 0.675 [95% CI, 0.588–0.774]; $p < 0.001$) rates of 7.6% and 6.7%, respectively, at a median follow-up of 54 months [69]. In an updated analysis of the NATALEE trial, the addition of ribociclib to endocrine therapy demonstrated a significant iDFS benefit (HR, 0.715; 95% CI, 0.609–0.840; $p < 0.0001$) with absolute

improvements of 2.7% at 3 years and 4.9% at 4 years. The benefit was observed irrespective of nodal involvement and tumor stage (absolute 4-year benefit: N0, 5.1%; N+, 5.0%) and stage (absolute 4-year benefit: stage II, 4.3%; stage III, 5.9%) [68, 70]. In both trials, statistical significance of overall survival was not reached in the interim analysis but the combination with CDK4/6i was more favorable. The toxicity profile and the duration of treatment are different for the two CDK4/6i. Safety remained consistent with previous reports.

Olaparib is recommended for patients with gBRCA1/2 mutation and high risk of recurrence according to the OlympiA study (LoE1b/A/++). Olaparib in combination with endocrine therapy is recommended for patients with HR+/Her2-BC, gBRCA1/2 mutation, and a CPS EG score ≥ 3 . The second interim analysis demonstrated a significant improvement of overall survival with olaparib compared to placebo (HR, 0.68; 98.5% CI, 0.47–0.97; $p = 0.009$) [71]. After a median follow-up 6.1 years, a sustained overall survival benefit was observed with an absolute improvement of 4.3% (HR: 0.72 [95% KI: 0.56; 0.93]) years [72].

In recent years, the combination of gene expression analysis and short preoperative endocrine therapy has become increasingly important. The ADAPT trial demonstrated excellent outcomes in patients with pN0-1 and HR+/HER2- BC with ET alone in both endocrine trial arms (RS0-11 control, RS12-25/ET response) [28]. The 5-year invasive DFS was 92.6% (95% CI, 90.80–94.0) in the experimental arm versus 93.9% (95% CI, 91.8–95.4) in the control arm. The 5-year distant DFS was 95.6% versus 96.3%, and the 5-year overall survival 97.3% versus 98%. These data suggest that endocrine response to short-course endocrine therapy can guide systemic treatment in early BC as is detailed in the AGO algorithm (Fig. 1).

Systemic Treatment of eBC – HER2+

In HER2-positive breast cancer, six cycles of an anthracycline-free regimen containing taxanes/carboplatin is an option (LoE1b/B/AGO++). Adjuvant trastuzumab is recommended for node-negative disease with tumors diameter >5 mm–10 mm if chemotherapy is recommended (LoE2b/B/AGO+) and highly recommended >10 mm (LoE1a/A/AGO++). For tumors <2 cm and node negative $12 \times$ paclitaxel weekly + trastuzumab for 12 months might be a good anthracycline-free option (LoE2b/B/AGO+) [73]. In tumors >2 cm and/or node-positive trastuzumab and pertuzumab is recommended as anthracycline-free combination with docetaxel and carboplatin (LoE1b/A/AGO+) or in the classical sequence AC/EC (q3wks or q2wks + G-CSF) followed by a taxane (LoE1a/A/AGO++). The data from the APHINITY-trial support adjuvant pertuzumab in addition to trastuzumab and chemotherapy in patients with node positive disease in HER2-positive

eBC (LoE1b/B/AGO++). At a median follow-up of 8.4 years, 8-year invasive DFS in node-positive patients was 86.1% for trastuzumab and pertuzumab versus 81.2% for trastuzumab alone (OS improvement by 2%). In the node-negative cohort, no additional clinical benefit was evident for the dual blockade (LoE1b/B/AGO+/-) [74]. Extended adjuvant treatment with neratinib in combination with standard endocrine therapy for 12 months showed a significant improvement in iDFS and OS of high risk (mostly stage II-III) HER2 and HR-positive patients who have completed 1 year of trastuzumab-based therapy (LoE1b/B/AGO+). Hence, no prospective data are available after pertuzumab and/or T-DM1 use, indication for this treatment remains unclear in this situation and may be decided on an individual basis.

In patients with HER2+ tumors, anthracycline-/taxane-based (AGO+) or anthracycline-free taxane-/carboplatin-based regimen (both AGO++) and trastuzumab (adding pertuzumab in nodal positive disease and/or tumors >2 cm at presentation [AGO++]) are recommended.

For patients with non-pCR after targeted therapy including dual inhibition for Her2-positive disease, T-DM1 is highly recommended (AGO++) due to a significant overall survival benefit [75]. In case of non-PCR, an additional extended anti-Her2 therapy after 1 year can be offered with neratinib after trastuzumab for HR-positive and high-risk (e.g., stage II-III) disease with LoE2b/B/AGO+.

Systemic Treatment of eBC – TNBC

Triple-negative breast cancer is one of the preferred indications for neoadjuvant therapy. Patients with node-negative disease and tumors of 2 cm or smaller are no candidates for pembrolizumab treatment. In general, it is recommended to use neoadjuvant for patients with tumors cT1c (LoE 2b/B/AGO++) but make a more individual decision for smaller tumors, i.e., cT1b neoadjuvant or adjuvant therapy LoE 2b/B/AGO+) and cT1a adjuvant chemotherapy (LoE 2b/B/AGO +/-).

The preferred chemotherapy regimen either given as adjuvant or as neoadjuvant have not changed. If there is no indication for pembrolizumab, either a carboplatinum containing regimen or pure dose-dense regimen can be chosen. In combination with weekly paclitaxel, carboplatinum can be given either weekly (AUC1.5) or every 3 weeks (AUC5) (LoE1b/B/AGO++) followed by dose-dens EC or AC. In case no carboplatinum is given in T1, N0, ddECx4 followed by weekly paclitaxel x12 remains the standard (LoE1b/b/AGO++). However, for adjuvant carboplatinum therapy we have limited data. Paclitaxel/carboplatinum for T1, N0 remains an option (LoE2b/B/AGO++). The PEARLY trial demonstrated in adjuvant and neoadjuvant treated patient also a benefit for Carboplatinum [76].

All patients with tumors larger than 2 cm or clinical nodal involvement should receive pembrolizumab as neoadjuvant therapy in addition to paclitaxel/carboplatinum followed by EC every 3 weeks and continue pembrolizumab for 9 cycles regardless of the response as adjuvant therapy [77]. The overall survival data demonstrated an improved overall survival with pembrolizumab (86.6% 5-y OS) over placebo (5-y OS 81.7%) (HR: 0.65; $p = 0.002$). GeparDOUze/NSABP B59 study using atezolizumab as checkpoint inhibitor (Cpi) did not meet the primary endpoint EFS [78]. The study will provide data of the combination of capecitabine with atezolizumab. Currently, there is no indication for a sole adjuvant Cpi treatment without a neoadjuvant pre-treatment with none of the currently available PD-1 or PD-L1 Cpi.

Capecitabine remains an option for postneoadjuvant therapy, especially in patients without Cpi treatment (LoE1a/A/AGO++). For patients with a germline BRCA1/2 mutation, the post-neoadjuvant treatment with olaparib is recommended in TNBC with non-pCR as well as in patients with stage IIa (AGO++) due to an overall survival benefit [71].

Adjuvant RT

After breast-conserving surgery, whole-breast irradiation with moderate hypofractionation (15 fractions) is considered standard of care (LoE1a/A/AGO++). Ultra-hypofractionation (5 fractions) can be considered in selected cases (LoE1b/B/AGO+/-). Boost irradiation is indicated for premenopausal patients (LoE1b/B/++) as well as for postmenopausal patients with risk factors (LoE2b/B/+). According to the results of IMPORT HIGH, RTOG 1005, and HYPOSIB [79], simultaneous-integrated boost is non-inferior to sequential boost delivery with moderate hypofractionation (LoE1b/B/++). Partial breast irradiation (PBI) is a viable alternative to whole-breast irradiation in patients with low-risk breast cancer: age ≥ 50 years, tumor size < 3 cm, pN0, ER/PgR pos., HER2 neg., G1-2, L0 R0, non-lobular histology, and no BRCA-mutation known (all conditions should be given). PBI may be considered on an individual basis in patients with either G3 or ER/PgR neg. tumors. Post-mastectomy RT (PMRT) may be omitted in patients with low-risk features (pT1-2, 1-2 involved LN, ER/PR pos., HER2 neg.) who had ALND according to the SUPREMO trial (LoE1b/AGO-) [80]. However, there is uncertainty for patients with 1-3 involved lymph nodes who had no ALND as well as for patients with pT3 pN0 (both LoE2b/B/AGO+/-). Moderate hypofractionation is considered standard of care for chest wall irradiation both with (LoE1b/B/AGO++) [81] and without reconstruction (LoE1a/A/AGO++). Also for regional nodal irradiation, moderate hypofractionation is strongly recommended due

to the results of the HypoG-01-trial demonstrating an overall survival benefit (LoE1b/B/AGO++) [82]. In patients with 1-2 involved sentinel lymph nodes (SLNs), the SENOMAC-trial demonstrated improved quality of life and comparable oncologic outcomes when ALND was omitted. Since RT to the axilla and supra-/infraclavicular lymph node regions was delivered in the overwhelming majority of patients in SENOMAC [83] as well as all patients in AMAROS and OTOASOR, irradiation of level I-IV is recommended in patients with 1-2 involved SLN (LoE1b/B/AGO+) in addition to treatment of the breast or chest wall. For a reduced field of irradiation to level I/II in these cases, evidence is lacking. Alternatively, RT to level I/II to 5 mm below the axillary vein can be considered if there is otherwise no indication for regional nodal irradiation (LoE2b/B/AGO+/-). In patients representative of the SOUND and INSEMA-trials who did not undergo SLN-biopsy, no intentional irradiation of level I/II is deemed necessary (LoE1b/B/AGO-).

BC: Special Situations

In general, treatment recommendations for elderly are the same as for the “younger patients” (AGO++), taking into account different biological, physical, psychological and treatment-related factors, the geriatric assessment and integrated into a collaborative decision-making process. Treatment options for frail patients [26].

- No breast surgery to prolong life if endocrine therapy is considered (LoE2b/C/AGO+). Breast surgery for local control (LoE1a/A/AGO+).
- No axillary clearing for cN0 (LoE2b/B/AGO+).
- Endocrine therapy alone without surgery/RT at first diagnosis (2b/B/+), renunciation of endocrine adjuvant therapy after BCS and RT (1b/A/+).
- No RT for pT1 (LoE1a/B/AGO+), pT2-3 (LoE 2b/B/AGO+/-) and pN0, R0, ER/PR positive, HER2-negative, if endocrine adjuvant therapy is considered.

For male, (neo-)adjuvant chemotherapy is the same as in women. For treatment of HR-positive male BC, TAM remains standard. AI have to be taken in combination with GnRH agonists (LoE4/C/AGO+). Inflammatory BC should be treated by neoadjuvant systemic treatment (2b/B/+++), mastectomy and RT of the chest wall and the regional lymph nodes, independent of response to NACT.

Tumor-infiltrated axillary lymph nodes without primary carcinoma (AxCUP) are most frequently resulting from occult breast cancer. Extensive histopathological examination is mandatory to exclude other origins. The treatment is performed similar to BCS in node-positive disease with NACT, TAD (if cCR) (LoE3b/C/AGO+/-) and RT of the regional nodes and the breast even if no primary has been detected (LoE 2 cB/AGO++).

Fibroepithelial lesions with rapid growth or size >3 cm should be excised (independently from the CNB result) (LoE 5 D/AGO ++). Only in malignant phyllodes tumors broad lesion-free margins are required and re-resection is recommended if the margin is less than 2 mm (LoE 2b B/AGO ++). Sentinel-node excision is recommended only in the case of mastectomy (2b/B/+) [84]. Adjuvant RT is indicated depending on size, biology, and pathological margin status (LoE 2b B/AGO +).

Outcome in secondary, radiation-associated angiosarcoma of the breast does not seem to be improved by more radical surgery. In case tumor-free margins can be achieved, breast-conserving surgery (wide excision) might be an option (3a/C/+/-). The decision for (neo) adjuvant cytotoxic treatment should be made based on individual risk factors (LoE3a/C/AGO+/-) since radiation-associated angiosarcoma of the breast does not respond well to chemotherapy. The individual case should be presented in a sarcoma board (5/D/++).

Metaplastic BC is relative chemoresistant and primary surgery, and axillary staging according to standard is recommended (LoE4/C/AGO++). Therapy highly depends on the subtype. In some metaplastic BC, NACT may be an option, if initially inoperable (5/D/+), in the case of TNBC if pembrolizumab is indicated (4/C/+/-), or in Her2+ tumors (4/C/+) [85].

Locoregional Recurrence

Basically, the local recurrence should always be confirmed histologically. This should include redetermination of estrogen, progesterone, and HER2-neu receptors. The receptor status is an indispensable predictive factor for therapeutic considerations (LoE 3b/B/AGO ++). A complete restaging should always be carried out using CT of thorax and abdomen and bone scintigraphy (LoE 2b/B/AGO ++). After a previous mastectomy, the aim should be a wide excision of the local recurrence with an R0 resection (LoE 3b/B/AGO ++). If prior breast-conserving therapy has been performed, mastectomy is the gold standard. Another breast-conserving therapy with R0 resection and, if necessary, partial breast irradiation should be discussed with the patient individually (LoE 2b/B/AGO +) [86, 87]. If the axilla is clinically suspicious, lymph node involvement should be confirmed histologically if possible and then an axillary lymphadenectomy should be performed. After R0 resection, systemic therapy should be based on the updated receptor status of the recurrence. This of course includes endocrine therapy for hormone-receptor positive recurrences (LoE 2b/B/AGO ++) as well as chemotherapy (LoE 2b/B/AGO +) [88, 89] or combined chemotherapy with anti-HER2 treatment (LoE 5/D/AGO +). Whole-breast RT is always indicated after previous breast-conserving surgery without further adjuvant RT. After mastectomy, the

thoracic wall should be irradiated, possibly including the lymphatic system, especially if adjuvant RT has not been performed before (LoE 2b/B/AGO +). A second irradiation can be carried out after the R1/R2 resection has been carried out (LoE 3b/B/AGO +/-), possibly also as brachytherapy. In the case of a thoracic wall recurrence after a mastectomy, the thoracic wall can be irradiated, possibly including the regional lymphatic drainage pathways. A second irradiation of the thoracic wall can be carried out with R1/R2 resection, if necessary as brachytherapy or with the addition of regional deep hyperthermia with R1/R2 resection. If adjuvant axillary radiation is not available, axillary radiation can be considered after R0 resection has been performed.

Osteoncology

Bisphosphonates and denosumab are key agents for managing skeletal-related events (SREs), hypercalcemia, and pain in metastatic breast cancer. Trials like CALGB 70604, OPTIMIZE-2, and REaCT-BTA demonstrate the efficacy of extended dosing intervals for zoledronic acid (e.g., every 12 weeks; LoE1a, GR A, AGO ++) compared to standard dosing (every 4 weeks), with no significant differences in outcomes for SREs or quality of life [90–92].

Radiation therapy for bone metastases is indicated particularly in the presence of a risk of fracture, restricted mobility, local pain, neurological complaints (LoE1a, GR A, AGO ++) and after surgical treatment (LoE 2b GR B, AGO ++). Techniques like single fraction RT (e.g., 8 Gy) and fractionated approaches (e.g., 5 × 4 Gy) are discussed, with considerations of patients' prognosis and symptoms [93, 94].

Stereotactic body RT offers higher doses and potential for better pain response and local control in select cases. Prophylactic RT is explored as an effective option for high-risk asymptomatic bone metastases (e.g., bone metastases ≥2 c; involvement of the hip/shoulder/sacroiliac joint or long bones, involvement of the junctional spine and/or posterior involvement), reducing SRE rates and improving survival [95].

Recurrent bone pain in previously irradiated areas of the skeleton can be re-irradiated using a single or fractionated irradiation. Surgical interventions, including vertebroplasty, kyphoplasty, and tumor resection, are recommended for specific cases such as spinal instability, fractures, or oligometastatic disease.

In the case of bone metastases in the spine and the presence of spinal compression syndrome or bony instability, surgical intervention should be considered (LoE 2b GR C AGO ++). Adjuvant bisphosphonates (e.g., zoledronate, clodronate) are reviewed for their survival benefits in early breast cancer, with varying dosing schedules can be recommended in postmenopausal or premenopausal patients with ovarian suppression (LoE1a GR A AGO +).

The effects of cancer treatments on bone density are discussed, along with therapies like denosumab, bisphosphonates, and hormonal agents to prevent fractures and maintain bone health. Findings from the FREEDOM trial highlight the risk of vertebral fractures post-discontinuation, underscoring the need for alternative management [96].

Complementary Therapy and Survivorship

In 2024, the actual guidelines in complementary medicine were published [38]. Included is a structured interview for patients to guide discussions with the medical team. All patients should be consulted as early as possible and in the course of the process repeatedly on the interest in information complementary medical measures and, if interested, reliable sources of information should be referred. Differentiation between effects on toxicity management and/or prevention or survival issues remains important. Physical exercise, mind-body medicine, additional complementary treatments (such as acupuncture), lifestyle interventions, nutrition, and dietary supplements are valid options in improving quality of life and physical and psychological symptoms. There is no data for use of whole body hyperthermia in BC patients (LoE 4 C -). We added research on the effects of mistletoe on survival in eBC and mBC (LoE 1b C -) and toxicity to reduce side effects (LoE 2a B +/-) [97]. Mistletoe (*Viscum album*) only should be applied as s.c. injection and not i.v. (LoE 2b B -).

Gynecological Issues, Pregnancy, and Reproduction

A real-world evaluation from the USA and Europe of physicians involved in breast cancer treatment reported that 31% of patients with menopausal symptoms do not receive any treatment. Additionally, 17% of patients receive systemic estrogens or progestones, despite the AGOs recommendation that systemic hormone replacement therapy (HRT) is contraindicated in patients with hormone-receptor positive disease (LoE1a/B/AGO-). According to a meta-analysis including 4,000 patients, in hormone-receptor-negative disease the risk for breast cancer recurrence under HRT was not elevated and HRT might therefore be used (LoE1a/B/AGO+/-). An alternative to treat menopausal symptoms is venlafaxine in a reduced dosage which does not interfere with tamoxifen metabolism and showed a reduction of 60% of hot flashes in BC patients [98]. A relatively new drug, which was approved last year for the treatment of hot flashes, is the neurokinin-3-receptor-antagonist fezolinetant. However, the EMA stated that patients with breast cancer were not included in the clinical trials and therefore, treatment decision should be based on an individual risk-benefit-evaluation (LoE5/D/AGO +/-) [99, 100].

The topical vaginal application of low-dose estriol is also an option for urogenital symptoms and might be continued after 3 months of treatment once or twice weekly (LoE4/D/AGO+/-). Two small randomized-controlled trials reported moderate effects of vaginal laser therapy to treat vaginal dryness in BC patients compared either with hyaluronic acid suppositories or sham laser (LoE1b/B/+/-) [101, 102].

Counseling on fertility preservation should be offered to all patients wishing to retain their fertility (AGO++). GnRH agonists, when administered for more than 2 weeks prior to chemotherapy, improve ovarian function recovery after 2 years, regardless of hormone receptor status (LoE1a/A/AGO+), and may moderately help preserve fertility (LoE2a/B/AGO+/-). New statements on the oncological safety of fertility preservation methods and assisted reproductive therapy highlight limited evidence due to study quality issues. Cryopreservation of ovarian tissue is oncologically safe but carries a risk of relapse due to potential tumor cells in the tissue (LoE 4D/AGO+). For BRCA1/2 breast cancer patients, transplanted ovarian tissue should be removed after pregnancy due to high ovarian cancer risk. Oocyte cryopreservation is another viable option, with no safety concerns (LoE 2 aC/AGO+). Interruption of endocrine therapy for up to 2 years after at least 18 months of treatment in women ≤ 42 years desiring children is unlikely to affect short-term survival (LoE2b/B/AGO+) [103]. BC prognosis during pregnancy is not worsened with adequate treatment (LoE3a), though poorer outcomes occur if BC develops during lactation or within the first year post-pregnancy. Chemotherapy with anthracyclines or taxanes after the first trimester may be safe (LoE2b/2a/AGO++), and platinum compounds can be considered based on genital cancer treatment experience (LoE4/AGO+/-). G-CSF use in dose-dense chemotherapy is debated (LoE4C/AGO+/-).

Breast Cancer Follow-Up

The goal of follow-up for BC patients is to detect curable recurrent disease (LoE1a/B/AGO++), to detect contralateral BC and to detect symptomatic metastatic disease (LoE3b/C/AGO+). So far, there is no evidence that early detection of circulating tumor cells or cfDNA and subsequent treatment lead to a better prognosis or can prevent metastatic disease (LoE 2a/D/-) [104]. The AGO recommends the participation in follow-up studies (e.g., SURVIVE-Study). Follow-up examinations in asymptomatic patients should not include tumor marker measurements and imaging of any kind.

Another important factor in the follow-up is to improve quality of life and to diagnose treatment-related side effects. We added endocrinopathies as important side effect which can occur in relation to immunooncological treatment.

Cardiologic work-up (echocardiography, BNP measurement in selected cases) is recommended in patients treated by anthracyclines/anti-HER2 and immunologic agents in the adjuvant situation 6, 12, 24 months and yearly up to 5 years after therapy and after the 5th year every 5 years and if the patient is symptomatic [105]. In addition, the improvement of treatment adherence is an essential part of follow-up care (LoE2b/B/AGO++).

Lifestyle modifications such as nicotine stop, reduction of alcohol intake below 6 gr per day, moderate physical intervention (minimum 150 min per week, twice weekly), weight change (to obtain normal BMI) might have an influence on quality of life but also BC prognosis.

For the detection of curable events, physical examination with mammography and adjunctive US are recommended. There is increasing data that newer methods like contrast-enhanced mammography might increase detection rates but are still not routinely performed [106]. For individuals at higher risk (e.g., women under 50, hormone receptor-negative breast cancer, or those with limited diagnostic access), MRI is recommended as an alternative or additional diagnostic tool. Chemotherapy increases the risk of hematologic malignancies, and RT to the breast or chest wall raises the risk of lung cancer. Patients and healthcare providers should be mindful of these risks. For women with premature ovarian failure or those undergoing aromatase inhibitor (AI) therapy, a DXA scan (for bone mineral density) should be performed at baseline and followed up according to individual risk.

This approach emphasizes a personalized, risk-based strategy for both cancer detection and the monitoring of potential long-term effects from cancer treatments.

Health Literacy and Communication

Health literacy is influenced both by individual abilities and skills (“personal health literacy”) and by the demands and complexity of the living environment and systems (“organizational health literacy”). Digital health literacy is the ability to search for, find, understand, and evaluate health-related information in relation to digital applications and digital information services and to apply the acquired knowledge to solve a health problem [107].

Healthy people as well as patients should be instructed and involved as “experts in their own affairs” during the process of preventing and treating cancer. The main focus is on enabling a self-determined decision on the basis of a sufficient healthy competence (LoE3a/AGO +) and improving shared decision-making, which depends on successful doctor-patient communication. In the era of increasing digitalization, the need for education and action with regard to digital health literacy of patients and health professionals is inevitable. Good communication skills are

a medical core competence and the basis for a trusting doctor-patient relationship. Qualified training measures can help promote communicative skills (LoE2a,b/AGO +). Successful communication and the development of a trustful doctor-patient relationship is an important cornerstone for patient participation in the shared decision-making process. The use of decision support in the physician-patient communication (AGO +) will improve knowledge, information and risk perception about treatment options, reduce the decision conflict, increase the feeling about clarity of personal values, encourage an active role in decision-making and improve the match between the chosen option and the patients’ values. Moreover, decision coaching based on evidence-based patient information can improve the decision-making process of patients. Decision coaching is able to improve the knowledge of patients (LoE2a/B/AGO +) and their active role in the process of decision-making (LoE2b/B/AGO +). Active involvement of caregivers and trusted persons should be integrated in decision processes (LoE4/C/AGO+). The use of eHealth (DiGA) can help improve quality of life during and after breast cancer treatment (LoE1b/B/AGO +), the PRO-based management can both reduce therapy associated side effects and improve the quality of life (LoE1b/A/AGO +) as well as PRO-based management can improve survival in metastatic breast cancer (LoE1b/B/AGO+/-) [108, 109].

Conclusion

The recommendations of the AGO Breast Committee presented here reflect the rapid development of diagnostic and therapeutic options for early breast carcinoma in recent months and years.

Conflict of Interest Statement

Prof. Dr. Tjoung-Won Park-Simon has received honoraria for lectures and/or consulting from Roche, AstraZeneca, GSK, Pfizer, Lilly, MSD, Exact Sciences, Daiichi Sankyo, Seagen, Novartis, Gilead Science, NCO, Onkowitz, Exact Sciences, Seagen, Stemline-Menarini and received travel compensation from Roche, AstraZeneca, Pfizer, Lilly, Daiichi Sankyo, Gilead, Pierre Fabre, Novartis. Prof. Dr. med. Volkmar Müller has received speaker honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowitz, high5 Oncology, Medscape, Gilead, Pierre Fabre, iMED Institut; consultancy honoraria from Roche, Pierre Fabre, PINK, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Seagen, Gilead, Stemline; and received institutional research support from Novartis, Roche, Seagen, Genentech, AstraZeneca; travel grants from AstraZeneca, Roche, Pfizer, Daiichi Sankyo, Gilead. Prof. Dr. med. Ute-Susann Albert has received honoraria for lectures from AstraZeneca GmbH, Lilly Deutschland GmbH, Menarini Stemline Deutschland GmbH, Novartis GmbH, Pfizer GmbH, PrimaVera Life GmbH. Prof. Dr. Maggie

Banys-Paluchowski M.B. has received honoraria for lectures and advisory from Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkowitz, Seagen, AstraZeneca, Eisai, Amgen, Stemline, Samsung, Canon, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Medical, Syantra, Pierre Fabre, Exact Sciences; received study support from EndoMag, Mammotome, MeritMedical, Gilead, Hologic, Exact Sciences; and received travel/congress support from Eli Lilly, Exact Sciences, Pierre Fabre, Pfizer, AstraZeneca, Daiichi Sankyo, and Roche. Prof. Dr. med. Rupert Bartsch received advisory role from AstraZeneca, Daiichi, Eisai, Eli Lilly, Gilead, Gruenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, Stemline; received lecture honoraria from Amgen, AstraZeneca, BMS, Daiichi, Eisai, Eli Lilly, Gilead, Gruenthal, MSD, MedMedia, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, Stemline; received travel support from AstraZeneca, Daiichi, MSD, Novartis; and received research support from Daiichi. Dr. med. Ingo Bauerfeind has received honorary for lectures from Lilly, Aurikamed, LMU München, Pfizer, Menarini Stemline. Prof. Dr. med. Vesna Bjelic-Radisic received honoraria for advisory boards from Pfizer, Roche, Lilly, Stemline, Pfm; received lecture honoraria from Pfizer, Lilly, Stemline, Pfm, mammotome; and received travel support from Pfizer. Prof. Dr. med. Jens-Uwe Blohmer has received honoraria for advisory boards and lectures from AstraZeneca, Daiichi Sankyo, Eisai, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Seagen. Prof. Dr. med. Wilfried Budach has received honoraria for lectures and advisory boards from Merck, BMS, Jörg Eickeler Veranstaltungen, med publico GmbH, BVDST. Prof. Dr. med. Peter Dall has received honoraria for lectures and advisory boards from Novartis, Pierre Fabre, MSD, Lilly, AstraZeneca, Gilead Sciences, Daiichi Sankyo, Eisai and Polytech. Prof. Dr. Nina Ditsch received honoraria for advisory boards from Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, Exact Sciences; received honoraria for lectures and speakers bureaus from AstraZeneca, Daiichi Sankyo, Exact Sciences, Pierre Fabre, I-Med-Institute, Meritmedical, pfm medical, Medi-Seminar GmbH, Roche, Lilly, Pfizer, Gilead, Novartis, Onkowitz, Jörg Eickeler Kongress, if-Kongress; received manuscript support from pfm medical ag; received trial funding from Gilead, BZKF. Prof. Dr. med. Eva Maria Fallenberg received research grant from DFG and received speaker honorarium from GE Healthcare, Bayer Healthcare, Guerbet, Siemens, BD, Roche, EUSOBI, ESOR, ESMO, B-Rayz. Prof. Dr. med. Peter A. Fasching participation on a Data Safety Monitoring Board or Advisory Board: Novartis, Pfizer, Roche, Daiichi Sankyo, AstraZeneca, Lilly, Eisai, Merck Sharp and Dohme, Pierre Fabre, SeaGen, Agendia, Sanofi Aventis, Gilead, Mylan; received honoraria for lecture, speakers bureaus, manuscript writing, or educational events from Novartis, Pfizer, Roche, Daiichi Sankyo, AstraZeneca, Lilly, Eisai, Merck Sharp and Dohme, Pierre Fabre, SeaGen, Agendia, Sanofi Aventis, Gilead, Mylan; received honoraria for consulting from Novartis, Pfizer, Roche, Daiichi Sankyo, AstraZeneca, Lilly, Eisai, Merck Sharp and Dohme, Pierre Fabre, SeaGen, Agendia, Sanofi Aventis, Gilead, Mylan; medical writing from Merck; honoraria paid to the institution Biontech, Cepheid, Pfizer. Prof. Dr. med. Tanja N. Fehm received honoraria from Onkowitz, MedCOnccept, FOMF; honoraria paid to the institution Roche, Novartis, Pfizer, MSD, AstraZeneca, Eisai, Lilly, Daiichi Sankyo, Prof. Dr. med. Michael Friedrich received honoraria for advisory board from Gilead Sciences and other honoraria from Roche, MSD. Prof. Dr. med. Bernd Gerber received travel support from Pfizer. PD Dr. med. Oleg Gluz received honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Gilead Science, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, Exact Sciences, Agendia, MedConcept, GynUpdate; re-

ceived minority shareholder from Westdeutsche Studiengruppe (WSG). Prof. Nadia Harbeck, MD has received honoraria for consulting and/or lectures from AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Viatrix, Zuelligpharma. Co-Director Westdeutsche Studiengruppe (WSG). Prof. Dr. med. Andreas Daniel Hartkopf has received honoraria for consulting and speaking engagements from AstraZeneca, Agendia, Amgen, Clovis, DaiichiSankyo, Eisai, ExactScience, Gilead, GSK, Hexal, Lilly, MSD, Novartis, Onkowitz, Pfizer, Roche, Pierre Fabre, Seagen, Stemline and Verazyte. Prof. Dr. med. Jörg Heil: None. Hörner-Rieber Juliane has received honoraria for lecture from Accuray International Sàrl, Pfizer Inc., AstraZeneca, Sanofi, and ViewRay Inc.; travel reimbursement from Varian Medical Systems; received research grants from IntraOP Medical and Varian Medical Systems, in each case “outside the submitted work”. Prof. Dr. med. Jens Huober has received honoraria for lectures from Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Seagen, Gilead, Daiichi; honoraria for consulting/advisory board from Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Daiichi, Gilead; and travel grants from Roche, Pfizer, Daiichi, Gilead. Prof. Dr. med. Hans-Heinrich Kreipe received honoraria for advisory board from Lilly; received lecture fees from AstraZeneca, Roche, Daiichi Sankyo, Pfizer. PD Dr. David Krug. D.K. received honoraria from AstraZeneca, best practice onkologie, ESO, ESMO, Gilead, med update, Merck Sharp and Dohme, Novartis, onkowitz, and Pfizer and received research funding from Stiftung Deutsche Krebshilfe and Merck KGaA. Prof. Dr. med. Thorsten Kühn has received from advisory board/lecture from Sysmex, Neodynamics, Pfizer, MSD, Merit Medical, Sirius Medical, Hologic, Endomag, Lilly and received trial funding from Merit Medical, Endomag, Mammotome. Prof. Dr. med. Sherko Kümmel has received lecture fees from Roche, Lilly, Exact Sciences, Novartis, Amgen, Daiichi Sankyo, AstraZeneca, MSD, Pfizer, Seagen, Gilead, Agendia; Hologic, PINK!; Stemline; received other honoraria from Roche, Daiichi Sankyo, Sonoscape; and received advisory board from Lilly, MSD, Roche, AstraZeneca, Stemline, Novartis, Daiichi Sankyo, MSD, Seagen, Gilead, Exact Science, Prof. Dr. med. Sibylle Loibl has received honoraria for advisory board, institutional from: Abbvie, Amgen, AstraZeneca, BMS, Celgene, DSI, Eirgenix, GSK, Gilead Science, Lilly, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Puma, Roche, Seagen, Stemline-Menarini; received honoraria for invited speaker, personal from Medscape; and received trial funding/others from: AstraZeneca, Abbvie, Celgene, Daiichi Sankyo, Greenwich Life Sciences, GSK, Immunomedics/Gilead, Molecular Health, Novartis, Pfizer, Roche, Stemline-Menarini, VM Scope GmbH. Prof. Dr. med. Diana Lüftner D.L. has received honoraria for advisory board activities and/or oral presentations from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, high5md, Loreal, MSD, Mundipharma, Novartis, onkowitz.de, Pfizer, Pierre Fabre, Roche and TEVA. Prof. Dr. med. Michael Patrick Lux. M.P.L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Hexal, Pfizer, Eisai, Gilead, Exact Sciences, Daiichi Sankyo, Agendia and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Hexal, Pfizer, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, AstraZeneca, and Eisai. He received travel expenses from AstraZeneca, Gilead, Pfizer and Daiichi Sankyo. Prof. Dr. med. Nicolai Maass has participated on advisory board from Amgen, AstraZeneca, Clovis, Daiichi Sankyo, GSK, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen and has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, GSK, Lilly, Novartis, Pfizer, Roche. Prof. Dr. med. Christoph Mundhenke has participated on advisory board from

AstraZeneca, Pfizer, Daiichi Sankyo, Seagen, Novartis and has received honoraria for lectures from Pfizer, Novartis, Prof. Dr. med. Toralf Reimer received honoraria for consulting and/or lectures from AstraZeneca, Daiichi Sankyo, Menarini, MSD, Novartis, Pfizer, Roche. PD Dr. med. Mattea Reinisch received honoraria and/or consultancy fee from AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, Streamed Up, and Somatex and received travel support from AstraZeneca, Daiichi Sankyo, Gilead, Lilly, Novartis, Pfizer, Roch. Prof. Dr. med. Kerstin Rhiem received honoraria for lectures from AstraZeneca, Pfizer, Novartis, streamed up GmbH. Prof. Dr. med. Achim Rody has participated on advisory board: AstraZeneca, Novartis, Roche, Exact Sciences, Pierre Fabre, Lilly, Seagen, Amgen, MSD, Gilead; has received honoraria for lectures from Pfizer, Celgene, Eisai; and received trial funding from Eisai. Prof. Dr. med. Marcus Schmidt M.S. reports personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, GILEAD, Lilly, Menarini Stemline, Molecular Health, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, and SeaGen; his institution has received research funding from AstraZeneca, BioNTech, Eisai, Genentech, German Breast Group, Novartis, Palleos, Pantarhei Bioscience, Pierre Fabre, and SeaGen. In addition, he has a patent for EP 2390370 B1 and a patent for EP 2951317 B1 issued. Prof. Dr. med. Andreas Schneeweiss received research grants from Celgene, Roche; received honoraria from Amgen, AstraZeneca, Aurikamed, Bayer, Celgene, ClinSol, Clovis Oncology, coma UroGyn, Connectmedica, Daiichi Sankyo, Gilead, GSK, if-kongress, I-MED, iOMEDICO, Lilly, MCI Deutschland, med publico, Metaplan, MSD, Mylan, NanoString Technologies, Novartis, onkowissen.de, Pfizer, Pierre Fabre, promedicis, Roche, Seagen, Streamed up, Tesaro and has received travel support from AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Pfizer, Roche. Prof. Dr. med. Florian Schütz received honoraria for lectures from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Lilly, MSD, Novartis, ClinSol, Pfizer, Roche Pharma; has participated on advisory board from Lilly, MSD, Gilead, Atheneum Partners, ClinSol. He received travel expenses from Lilly, Gilead. Prof. Dr. med. Hans-Peter Sinn has participated on advisory board from AstraZeneca, Exact Sciences, Daiichi Sankyo, Lecture: AstraZeneca, Diacentus and received trial funding from AstraZeneca. Prof. Dr. med. Christine Solbach received honoraria for lectures from DiaLog Service GmbH, Jörg Eickeler, Pfizer, Roche, AstraZeneca, MedConcept, I-Med, GBG, BVF Akademie, LÄK Hessen Akademie, Meet the Expert Academy and has participated on advisory board from MSD, Roche, Menarini Stemline Deutschland GmbH. Prof. Dr. med. Erich-Franz Solomayer received honoraria for lectures and/or consulting from Roche, Amgen, Celgen, Tesaro, AstraZeneca, Pfizer, Storz, Erbe, Gedeon Richter, Eisai, Medac, MSD, Vifor, Teva, Ethikon, Johnson Johnson, Daiichi Sankyo, Gilead, Exact Sciences, GSK, Pierre Fabre. Prof. Dr. med. Elmar Stickeler has participated on advisory board from Amgen, AstraZeneca, Gilead, Iomedico, Lilly, MSD, Novartis, Seagen, Roche and received honoraria for lectures from AstraZeneca, BSH Düsseldorf, Gilead, Iomedico, MSD, Novartis, Onkowissen, Pfizer, PharmaMar, Roche. Prof. Dr. med. Christoph Thomssen C.T. received honoraria as compensation for lectures and medical expertise from Rottalinn-Kliniken; Klinikum Basel; Onkowissen TV; ESMO, and BfArM (Federal Institute for Drugs and Medical Devices). Prof. Dr. med. Michael Untch M.U. has received honoraria to travel support, lectures and consulting or advisory role from AstraZeneca, Amgen, Daiichi Sankyo, Lilly, Roche, Pfizer, MSD Oncology, Pierre Fabre, Sanofi Aventis, Myriad, Seagen, Novartis, Gilead, Stemline, Genzyme, Agendia,

Onkowissen, Eisai and has received all honoraria and fees to the employer/institution. Prof. Dr. med. Marion Tina van Mackelenbergh has received honoraria to advisory role from Daiichi Sankyo, Exact Sciences, Gilead, Novartis, Pfizer, Pierre Fabre, Roche; received honoraria from AstraZeneca, Daiichi Sankyo, Elsevier, GSK, Jenapharm, Lilly, Menarini, Novartis, Pfizer, Seagen; received travel support from Daiichi Sankyo, Gilead. Prof. Dr. med. Isabell Witzel I.W. has received honoraria from AstraZeneca, Daiichi Sankyo, Gilead, GSK, Pfizer, MSD, Novartis, Roche, Seagen, Prof. Dr. med. Achim Wöckel has received honoraria as compensation for advisory boards, lectures, trial funding and has participated on advisory board from Amgen, AstraZeneca, Aurikamed, Celgene, Eisai, Lilly, Novartis, Pfizer, Roche, Tesaro, Sirtex, MSD, Exact Sciences, Pierre Fabre, Clovis, Organon, Daiji Sankyo, Seagen, Stemline, Gilead. PD. Dr. Rachel Würstlein served as advisor, consultant, speaker and travel grant: Agendia, Amgen, Apogepha, Aristo, AstraZeneca, Celgene, Clovis Oncology, Daiichi Sankyo, Eisai, Esteve, Exact Sciences, Gilead, Glaxo Smith Kline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Mylan, Nanostring, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, PINK, Puma-Biotechnology, Riemsler, Roche, Sandoz/Hexal, Sanofi Genzyme, Seattle Genetics/Seagen, Sidekick, Stemline, Tesaro Bio, Teva, Veracyte, Viatrix, Wiley, FOMF, Aurikamed, Clinsol, Pomme Med, medconcept, MCI, Medi-Seminar. Prof. Dr. med. Wolfgang Janni has received research grants and/or honoraria from AstraZeneca, Celgene, Chugai, Daiichi Sankyo, Eisai, ExactScience, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi Aventis, Roche, Pfizer, Seagen, Gilead, Inivata, Guardant Health. Prof. Dr. med. Marc Thill has participated on advisory board from Agendia, Amgen, AstraZeneca, Aurikamed, Becton/Dickinson, Biom'Up, ClearCut, Clovis, Daiichi Sankyo, Eisai, Exact Sciences, Gilead Science, Grünenthal, GSK, Lilly, MSD, Neodynamics, Novartis, Onkowissen, Organon, Pfizer, pfm Medical, Pierre Fabre, Roche, RTI Surgical, Seagen, Sirius Medical, Sysmex; received manuscript support from Amgen, ClearCut, Clovis, Organon, pfm medical, Roche, Servier; received travel expenses from Amgen, Art Tempi, AstraZeneca, Clearcut, Clovis, Connectmedica, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Hexal, I-Med-Institute, Lilly, MCI, MSD, Neodynamics, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, Seagen; received congress support from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Hexal, Lilly, Neodynamics, Novartis, Pfizer, Pierre Fabre, Roche, Sirius Medical; received honoraria for lectures from Amgen, Art Tempi, AstraZeneca, Clovis, Connect Medica, Eisai, Exact Sciences, Gedeon Richter, Gilead Science, GSK, Hexal, I-Med-Institute, Jörg Eickeler, Laborarztpraxis Walther et al. Lilly, MCI, Medscape, MSD, Medtronic, Novartis, Onkowissen, Pfizer, pfm medical, Roche, Seagen, Streamed Up, Stemline, Sysmex, Vifor, Viatrix, ZP Therapeutics; received trial funding from Endomag, Exact Sciences; and received trial honoraria from AstraZeneca, Biom'Up, Celgene, Clearcut, Neodynamics, Novartis, pfm medical, Roche, RTI Surgical.

Funding Sources

There was no funding for this paper.

Author Contributions

This manuscript is written by all authors.

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