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Review Article

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AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2025

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Abstract
The Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO; German Gynecological Oncology Group) presents the 2025 update of the evidence-based recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer (mBC).

Introduction

For the last 23 years, the Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO; German Gynecological Oncology Group) has been preparing and updating evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer. The AGO Breast Committee consists of gynecological oncologists specialized in breast cancer and interdisciplinary members specialized in pathology, radiologic diagnostics, medical oncology, and radiation oncology. This update has been performed according to a documented rule-fixed algorithm by thoroughly reviewing and scoring chapter by chapter the recent publications for their scientific validity (Oxford level of evidence [LoE], www.cebm.net) and clinical relevance (AGO grades of recommendation [GR]; Table 1). Here, we present the 2025 update on the diagnosis and treatment of patients with locally advanced and metastatic breast cancer, including algorithms; the full version of the updated slide set is available online as a PDF file in both English and German [1]. Moreover, a special version for patients is also available at www.ago-online.de.

Prognostic and Predictive Factors

CTCs and ctDNA are the 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 (LoE 1a/A/AGO+) and early therapy response (LoE 1a/A/AGO+) in the metastatic setting, the clinical significance of ct-DNA 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 LoE 1a/A/AGO+/−; post-therapeutic LoE 1b/AGO+/−) [2]. 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).

Table 1. AGO grades of recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restrictions, and should be performed
+	This investigation or therapeutic intervention is limited for patients and can be performed
+/−	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge, a general recommendation cannot be given
−	This investigation or therapeutic intervention can be of disadvantage to patients and might not be performed
−−	This investigation or therapeutic intervention is of clear disadvantage to patients and should be avoided or omitted in any case

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 (LoE 1a/A/AGO+) and monitor early treatment response (LoE 2/A/AGO+) [3]. 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−).

ESR1 mutations are associated with resistance to aromatase inhibitors (AI). 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 [4]. In the experimental arm, patients were switched from AI and palbociclib to fulvestrant and palbociclib upon detection of ESR1 mutations. Patients in the standard arm continued with AI until clinical progression. The early switch was associated with significantly better progression-free survival (11.9 months versus 5.7 months; HR 0.61 $p = 0.0040$). However, more evidence for this approach is needed, and therefore, ESR1 mutation tracking is not routinely recommended (LoE 2b/B/AGO+/−).

To identify patients with ESR1 mutations for initiating treatment with the SERD elacestrant, ctDNA analysis is required based on the approval text (LoE 1a/A/AGO++). PIK3CA analysis for the indication of alpelisib can be performed using either tissue or liquid biopsy (LoE 1a/A/AGO++) [5].

Endocrine and Targeted Therapy in Metastatic Breast Cancer

Endocrine-based therapy is the first treatment choice in advanced or metastatic, hormone receptor positive and HER2 low (HER2 1+ or 2+/FISH-) or negative breast cancer. Even in visceral crisis, endocrine-based therapy is often reasonable. Treatment decisions should be made after retrieval of fresh biopsies from metastatic sites to confirm endocrine responsiveness [LOE 2b/B/AGO++).

The combination of a CDK4/6 inhibitor with endocrine therapy (ET) is the recommended first-line treatment for HR+/HER2-mBC patients, as well as for later-line patients who have not yet received a CDK4/6 inhibitor. Premenopausal patients additionally need ovarian suppression (LoE 1a/A/AGO++). All studies evaluating the addition of a CDK4/6 inhibitor to ET successfully met their primary endpoint of progression-free survival (PFS). However, there are differences regarding the overall survival benefit. Thus, for postmenopausal women, ribociclib with AI or fulvestrant is recommended with AGO++, abemaciclib with AI with AGO+ and in combination with fulvestrant with AGO++, and palbociclib with AI or fulvestrant with AGO+ (LoE 1b/A).

In cases of early endocrine resistance and PIK3CA mutation, the INAVO 120 trial previously showed a highly significant PFS advantage for fulvestrant and palbociclib combined with inavolisib over fulvestrant and palbociclib (+placebo) [6]. So far AGO has not recommended this combination as inavolisib is commercially not available.

The optimal sequence upon progression on endocrine first-line treatment is not well defined, and different options depending on the detection of druggable mutations/alterations are possible. For those patients with ESR1 mutations and who have particularly experienced prolonged PFS on the prior line of ET and CDK4/6 inhibitors, the SERD elacestrant should be offered based on the data from the EMERALD trial (LoE 1b/B/+) [5]. Another SERD, imlunestrant, improved (EMBER-3 trial) PFS in combination with abemaciclib and could be an effective option in the future in endocrine 2nd line after approval of FDA and EMA [7].

The combination of the AKTi capivasertib and fulvestrant is an appropriate treatment option for those who have alterations/mutations in the PIK3CA/AKT1/PTEN pathway (LoE 1b/B/+) [8]. Currently, fulvestrant and alpelisib are also available for patients with activating PIK3CA mutations. However, alpelisib is associated with higher toxicities. All HR+ mBC patients should also be

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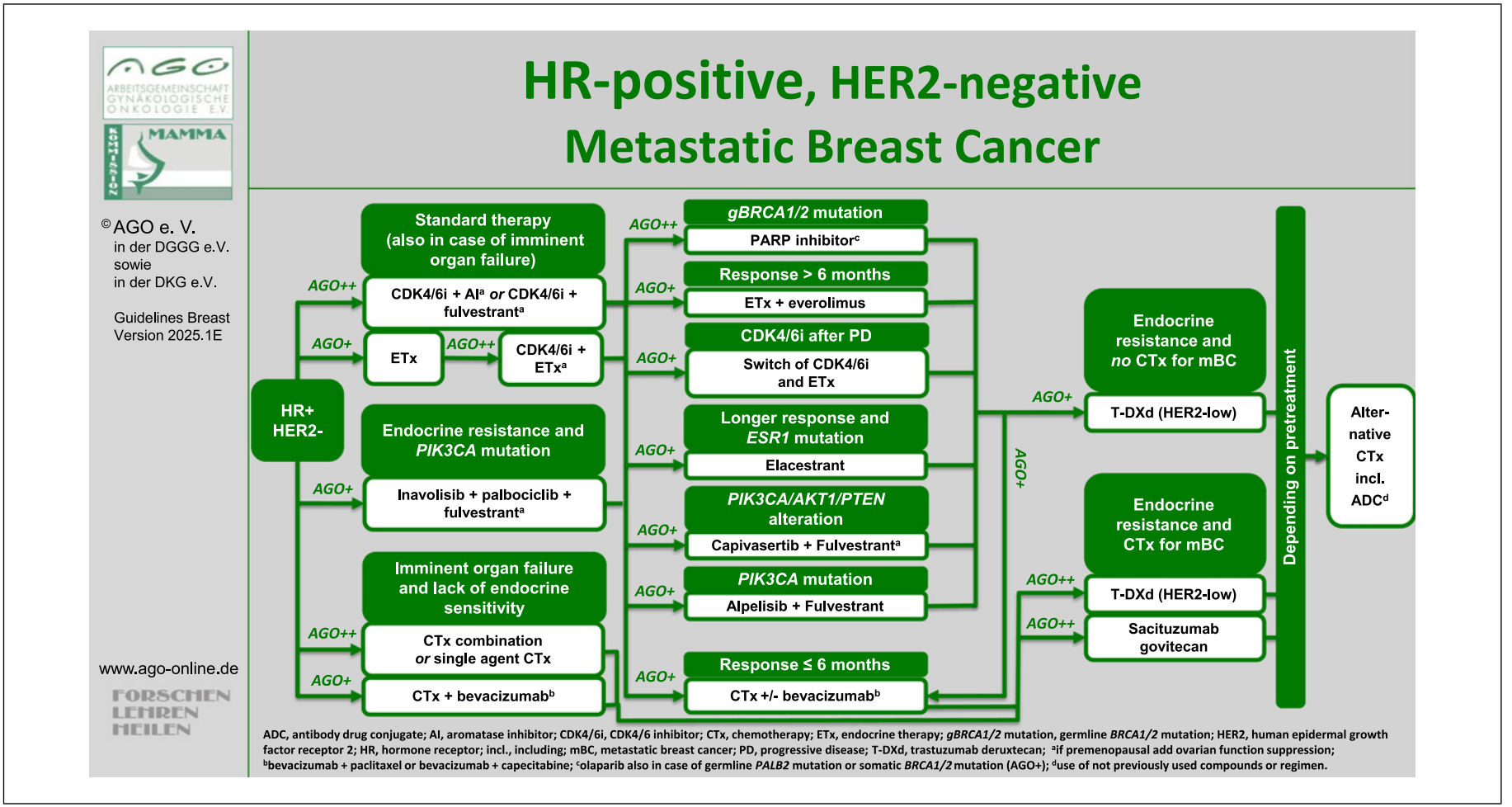

Fig. 1. Treatment algorithm for HR+/HER2-metastatic breast cancer.

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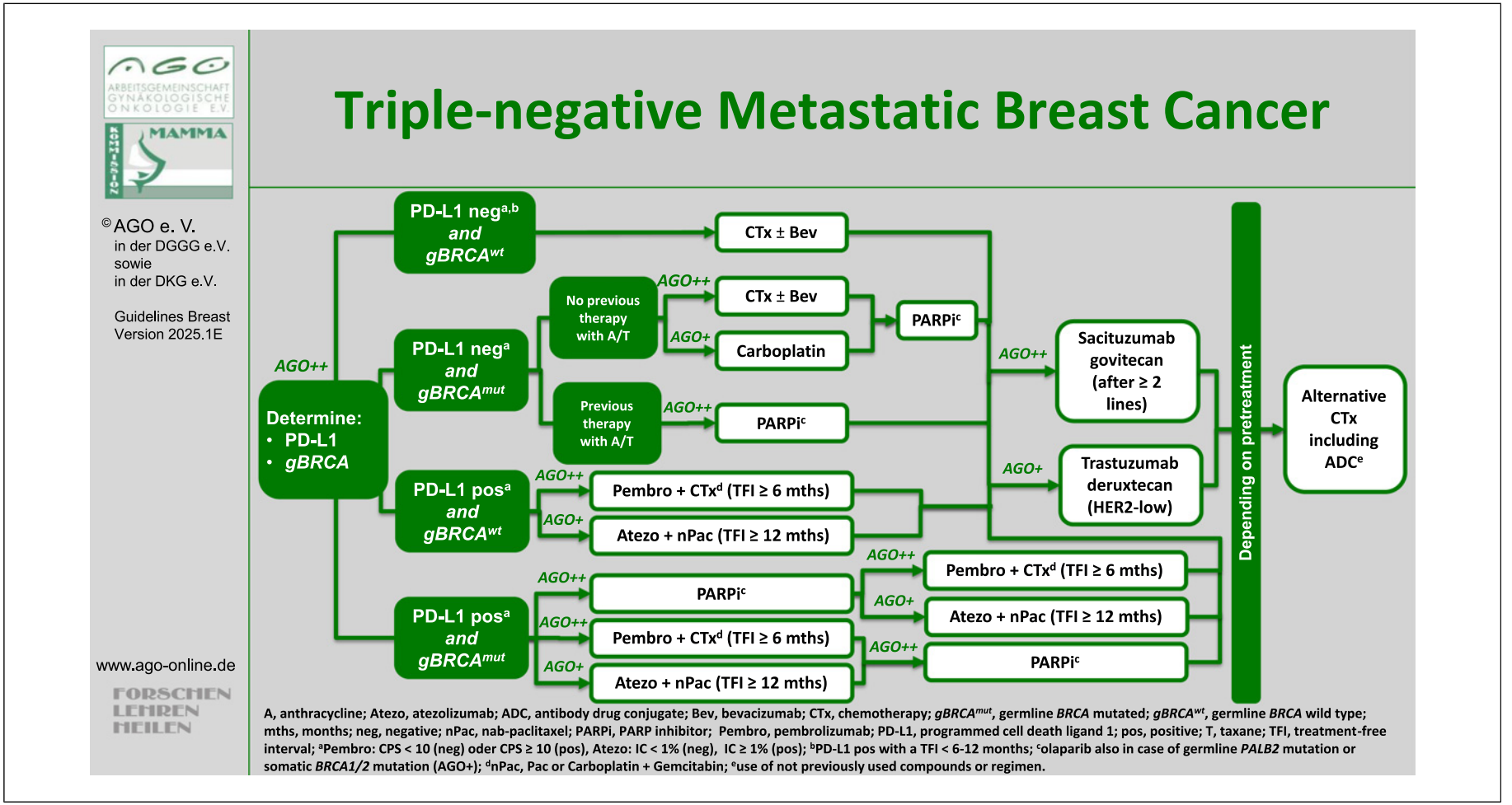

Fig. 2. Treatment algorithm for triple-negative metastatic breast cancer.

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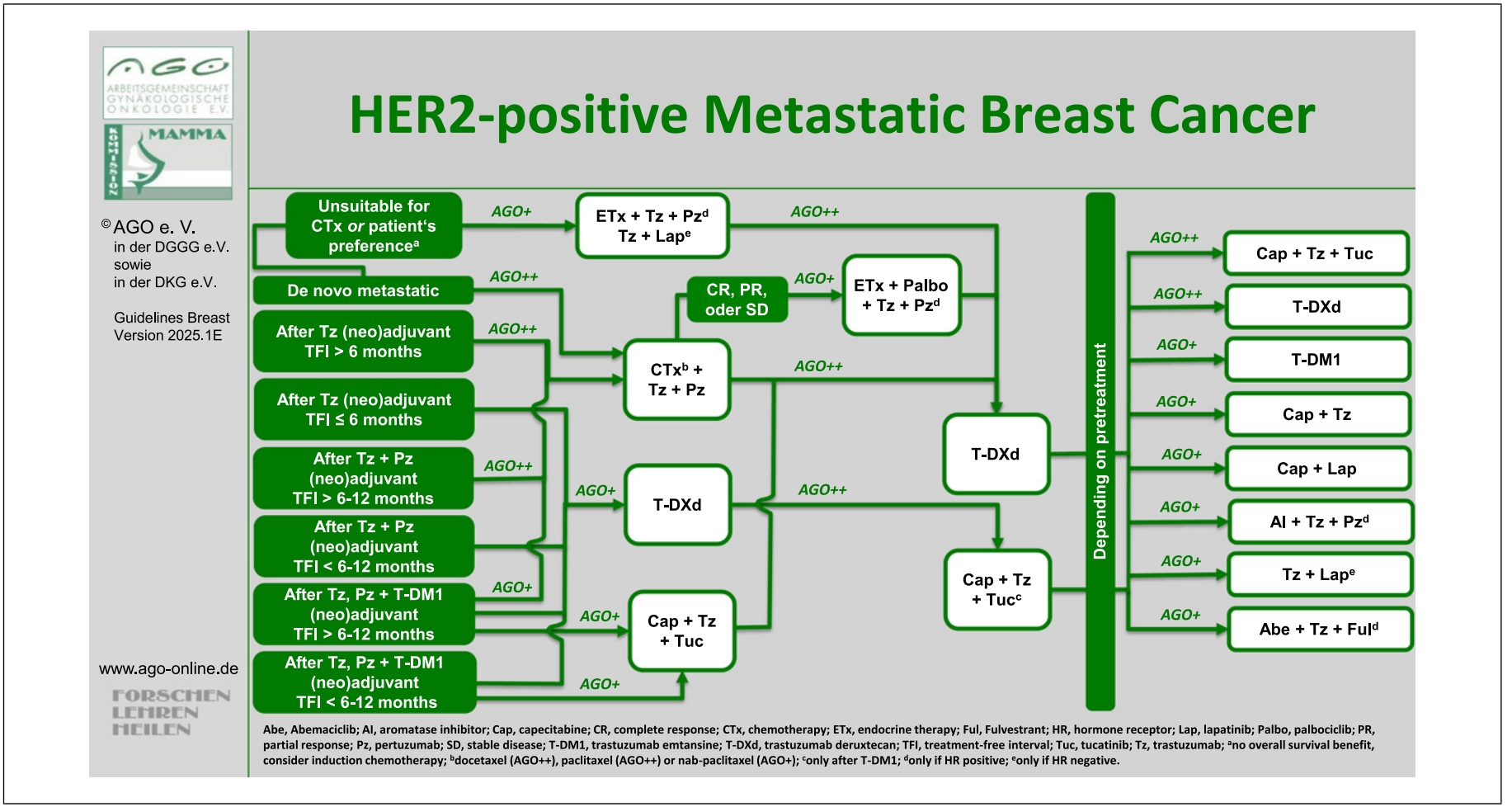

Fig. 3. Treatment algorithm for HER2-positive metastatic breast cancer.

assessed for gBRCA1/2 mutations regardless of family history since they may be eligible for PARPi therapy with either olaparib (LoE 1b/A/AGO++) or talazoparib (LoE 1b/A/AGO++). In patients with somatic mutations of BRCA1/-2 and/or germline mutations in PALB2, a PARP inhibitor therapy can be discussed (AGO LOE 3b/B/+/–). Here, the TBCRC 048 trial showed an 18-week clinical benefit rate of 53% and 83% for olaparib as a monotherapy [9]. Treatment options are summarized in the algorithm (Fig. 1).

Chemotherapy with or without Targeted Drugs in Metastatic Breast Cancer

In mBC, treatment selection is based on ER and/or PR, HER2 status, PD-L1, and several germline and somatic gene mutations/alterations (i.e., gBRCA/sBRCA, gPALB2, PIK3CA, PTEN, AKT, ESR1, and NTRK mutations). Here, next-generation sequencing should be strived for. For patients with HER2 low expression in the primary tumor or metastasis, treatment with the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) is highly recommended, especially for patients with HER2 low/HR+ disease after previous exposure to chemotherapy (LoE 1b/A/AGO++) [10]. Patients with HER2 low/HR+ (LoE 1b/B/AGO+) and even with an ultralow HER2 expression (expression between IHC scorings of 0 and 1 based on ASCO CAP guidelines; LoE 2b/B/AGO+/–) profited from T-DXd therapy right after endocrine therapy [11]. In later lines, sacituzumab govitecan is another good therapeutic option with overall survival benefit in patients with HR+, HER2– mBC after failure to CDK4/6 inhibitor-based therapy (LoE 1b/A/AGO++) [12]. Mono-chemotherapy is the treatment of choice if secondary resistance to ET arises and should be applied based on published protocols (LoE 1b/A/AGO++) (Fig. 1). In triple-negative breast cancer (TNBC) patients with PD-L1-positive metastatic disease and a treatment-free interval of more than 6 months, the combination of pembrolizumab with chemotherapy is recommended (LoE 1b/B/AGO++). The addition of atezolizumab to nab-paclitaxel has resulted in a nonsignificant, though clinically relevant improvement in OS. Therapy should be limited to this specific combination therapy (LoE 1b/B/AGO+) [13]. Sacituzumab govitecan (LoE 1b/A/AGO++) as well as T-DXd (LoE 2b/C/AGO+) are good options for patients with TNBC and relapse after >1 line of therapy. PARPi improved PFS in two trials (OlympiAD, EMBRACA) compared to any mono-chemotherapy as "physicians' best choice" in HER2– mBC with gBRCA1/2 mutation. Thus, olaparib (LoE 1b/B/AGO++) or talazoparib (LoE 1b/B/AGO++) are highly recommended in this setting [14]. Furthermore, olaparib showed activity in mTNBC with either somatic BRCA (LoE 2b/B/AGO+/–) or germline PALB2 (LoE 2b/B/AGO+) mutations [9] (Fig. 2). The role of CDK4/6 inhibitors is increasing in HER2+ ER+ (triple+) mBC. If no chemotherapy is possible, the outcome of the combination of ribociclib plus endocrine therapy plus trastuzumab and pertuzumab is excellent, leading to the same progression-free and overall survival times with and without induction chemotherapy (LoE 3b/C/AGO+/–) [15]. As maintenance after induction chemotherapy plus trastuzumab +/– pertuzumab, palbociclib plus endocrine therapy plus trastuzumab and pertuzumab improved progression-free survival to a clinically relevant extent (HR 0.74; CI 0.58–0.94) (LoE 1b/A/AGO+) [16]. Treatment options are summarized in the algorithm (Fig. 3).

Bone Metastasis

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; LoE 1a/A/AGO++) compared to standard dosing (every 4 weeks), with no significant differences in outcomes for SREs or quality of life.

Radiation therapy for bone metastases is indicated particularly in the presence of a risk of fracture, restricted mobility, local pain, neurological complaints (LoE 1a/A/AGO++), and after surgical treatment (LoE 2b/B/AGO++). Techniques like single fraction radiotherapy (e.g., 8 Gy) and fractionated approaches (e.g., 5 × 4 Gy) are discussed, with considerations of patients' prognosis and symptoms [17, 18].

Stereotactic body radiotherapy offers higher doses and the potential for better pain response and local control in select cases. Prophylactic radiotherapy is being explored as an effective option for high-risk asymptomatic bone metastases (e.g., bone met. ≥2 c; involvement of hip/shoulder/sacroiliac joint or long bones, involvement of junctional spine and/or posterior involvement) [19], reducing SRE rates and improving survival. 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/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 (LoE 1a/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 [20] highlight the risk of vertebral fractures post-discontinuation, underscoring the need for alternative management.

This comprehensive overview combines clinical trials, therapy recommendations, and practical considerations for optimizing bone health in oncology patients.

CNS Metastases

Brain metastasis (BM) and the optimal sequencing of local and systemic treatment remain a challenge in breast cancer treatment. Up to now, there is no evidence for screening in asymptomatic patients. Survival and symptom control in BM improved over time. Participation in the German registry study is recommended (BMBC, GBG-79). Interdisciplinary decisions should include expertise in medical oncology, radiation oncology, neurosurgery, and neuroradiology.

Local therapy can be offered as surgical resection with postoperative irradiation, stereotactic radiation (SRS or SRT), or whole brain radiotherapy (WBRT). Up to 4 BM should preferentially be managed by local treatments (SRS, SRT +/− surgery) without WBRT. 5–10 brain metastases can be treated with the same concept, if the total tumor burden is <15 mL or with WBRT preferably with hippocampal sparing. In cases with >10 metastases, WBRT with or without hippocampal sparing remains standard of care for most cases. Independent of the number of BM, additional systemic treatment is recommended. In specific cases, depending on extracranial disease and subtype, focusing on HER2 positivity medical treatment can be given first, in active or stable BM. Here, we upgraded both the combination of tucatinib/trastuzumab/capecitabine and T-DXd to LoE 1b/B/AGO+, with respect to actual data, reviews and meta-analysis [21]. We also added information of possibly increased risk of radionecrosis in the combination of ADCs and SRS or SRT accordingly. Leptomeningeal disease remains a clinical situation associated with a particularly poor prognosis and should combine the options of local and systemic treatment, including the best supportive care options. In addition to this year's AGO guidelines and for more details, we want to point to the DEGRO guidelines for personalized radiotherapy in BM, 2024 [22].

Specific Sites of Metastases

Individual local treatment for special metastases (e.g., pleural or peritoneal effusions or singular metastases) should also be seen in the context of effective systemic therapies available today (CDK4/6 inhibitors, SERDs, PIK 3 inhibitors, checkpoint inhibitors, PARP inhibitors, ADC s, novel antibodies, etc.). Therefore, systemic therapy remains the first approach in patients with stage IV breast cancer (LoE 2a/B/AGO++). Interventional regional procedures are an option, such as thermoablation for lung metastases (LoE 3b/C/AGO+/−) or interventional regional radiotherapy (SIRT/TARE) ((LoE 3a B/AGO+/−) and regional ablative procedures (RFA/MWA) for liver metastases (LoE 3b/C/AGO+/−). Local chemotherapy for ascites is not recommended (LoE 3b/D/AGO−) but could be an option to reduce dyspnea in pleural effusion (LoE 2b/C/AGO+/−). Whether radiation in addition to systemic therapy is beneficial remains unclear. Metastases should be biopsied before interventions to exclude secondary malignancies. The method of confirmation should be histology (LoE 3b/B/AGO++). Fine needle aspiration and cytology should remain exceptions (LoE 3b/B/AGO+).

There has been an ongoing debate about whether surgical removal of the primary tumor improves survival. To date, results of four randomized phase 3 trials have been reported [23–26]. Only in one of these trials did early local therapy of the primary breast tumor improve overall survival in patients with de novo metastatic disease after 10 years of follow-up in a very selected group of patients (i.e., those with HR+/HER2− breast cancer of less than 55 years of age and solitary bone-only metastasis). Despite better local control, surgery did not improve quality of life [23–25]. Consequently, primary tumor removal in stage IV breast cancer is not recommended with the expectation of survival improvement even in patients with bone-only disease (LoE 1b/B/AGO+/−) [23–28]. Nevertheless, surgery can help locally control the disease and, therefore, improve quality of live in individual cases.

For soft tissue and skin metastases, surgery can also help increase local control (skin, muscle, or nodal metastases (LOE 4, GR C, AGO+/−). Radiotherapy is recommended in case of paresis, spinal cord compression, or plexus infiltration (LOE 2b, GR C, AGO++). Additional regional hyperthermia with radiotherapy or electrochemotherapy can be recommended in single patients in centers with such expertise (LOE 4, GR C, AGO+/−).

Breast Cancer – Supportive Care and Side Effect Management

Optimal management of side effects and supportive care is essential for therapeutic success. Since the last update, no new agents in breast cancer treatment have been approved additionally. Elacestrant that was approved as the first oral approved SERD last year has an acceptable toxicity profile [29] including nausea, vomiting, elevated liver enzymes and pain as well as diarrhea and arthralgia. These side effects compare favorably with all other endocrine/endocrine-based therapies. However,

they might also require interdisciplinary management and patient coaching, particularly in the case of alteration of drug dosing and scheduling.

Side-effect management of immunotherapies (CPI) as well as ADC and their high variability of toxicity in various organs is still a challenge. Therefore, interdisciplinary management and patient coaching remain an important topic. Most importantly, early diagnosis of ILD and subsequent treatment with corticosteroids come into focus in ADCs, CPI, CDK4/6 inhibitors and other cancer agents.

ILD requires proactive management according to grade and causing agents. The diagnostic work-up starts with chest CT once symptoms arise. Corticosteroids (starting dose ≥0.5 mg/kg/d prednisolone-equivalent) need to be commenced early. It is important to note that still, re-challenge of T-DXd is only recommended in patients with grade 1 ILD/pneumonitis that resolves; in patients with grade ≥2 ILD/pneumonitis, T-DXd should be permanently discontinued. Recommendations for dose holds or therapy discontinuations are detailed in the respective product information. Proactive and successful side effect management requires a truly interprofessional approach by nursing staff and physicians as well as thorough patient education.

Specific "ImmunoTOX boards" in centers with high expertise might be helpful in emergency cases or challenging differential diagnosis. Investigators' brochures and adequate patient information are relevant for patient management and in any uncertain situation. We expect the final S3 guidelines in supportive management to support these strategies within 2025.

Patient-reported outcomes (PRO) are of high relevance in the preservation of quality of life and patient management (LoE 2b/B/+/–) [30]. eHealth and especially the introduction of breast cancer-specific DiGAs [31] show first promising results in support management and improving symptoms as well as adherence from patients side. These tools need to be monitored carefully; more data are needed.

Palliative Care

It is well accepted that mBC in an early phase is incurable but treatable. However, the late "palliative" phase must be differentiated as the focus is set on end-of-life care. Early introduction of palliative care concurrent with active treatment is important to improve symptoms and QoL. Furthermore, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. At that phase of MBC, advanced care planning should be routinely implemented in a multiprofessional approach. It is very important to point out that with the recent therapeutic progress with innovative and effective compounds; the patient's goals are differing in each phase. Meanwhile, we are in the position to prolong PFS and OS without increasing toxicity. The recent results of studies with targeted drugs and ADCs present with OS benefit. With such compounds, targeted and more individual treatment strategies take center stage. Patient-reported outcome data are crucial to estimate treatment success and course and balance this with patient preferences.

Conflict of Interest Statement

Prof. Dr. med. Marc Thill is in the advisory boards of Agendia, Amgen, AstraZeneca, AURIKAMED, Becton/Dickinson, Biom'Up, ClearCut, Clovis, Daiichi Sankyo, Eisai, Exact Sciences, Gilead Science, Grünenthal, GSK, Johnson & Johnson, Lilly, MSD, Neodynamics, Novartis, onkowissen, Organon, Pfizer, pfm Medical, Pierre Fabre, Roche, RTI Surgical, SamanTree, Seagen, Sirius Medical, and Sysmex and has received manuscript support from Amgen, CairnSurgical ClearCut, Clovis, Lilly, Organon, pfm medical, Roche, and Servier; travel expenses from Amgen, Art Tempi, AstraZeneca, Clearcut, Clovis, Connectmedica, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Hexal, I-MED Institute, Lilly, Menarini Stemline, MSD, Neodynamics, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, Seagen, and ZP Therapeutics; congress support from Amgen, AstraZeneca, Celgene, Daiichi Sanyko, Gilead, Hexal, Lilly, Menarini Stemline, Neodynamics, Novartis, Pfizer, pfm medical, Pierre Fabre, Roche, and Sirius Medical; lecture honoraria from Agendia, Amgen, Art Tempi, AstraZeneca, Clovis, Connectmedica, Eisai, Endomag, Exact Sciences, Gedeon Richter, Gilead Science, GSK, Hexal, I-MED Institute, Jörg Eickeler, Laborarztpraxis Walther et al. Lilly, Medscape, Menarini Stemline, MSD, Novartis, onkowissen, Pfizer, pfm medical, Roche, Seagen, Sirius Medical, STREAMED UP, Sysmex, Vifor, Viatris, and ZP Therapeutics; trial funding from Endomag and Exact Sciences; and trial honoraria (institutional) from AstraZeneca, Biom'Up, CairnSurgical, Clearcut, Neodynamics, Novartis, pfm medical, Roche, and RTI Surgical. Prof. Dr. med. Wolfgang Janni has received research grants and/or honoraria from AstraZeneca, Celgene, Chugai, Daiichi Sankyo, Eisai, Exact Sciences, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, Inivata, and Guardant Health. Prof. Dr. med. Ute-Susann Albert has received lectures from Pfizer, Novartis, and AstraZeneca and is in the advisory boards of Daiichi Sankyo and Pfizer. Prof. Dr. Maggie Banys-Paluchowski has received honoraria for lectures and advisory from Roche, Novartis, Pfizer, pfm, Eli Lilly, onkowissen, Seagen, AstraZeneca, Eisai, Amgen, Samsung, Canon, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Medical, Syantra, resitu, Pierre Fabre, and Exact Sciences; trial support from Korean Breast Cancer Society, EndoMag, Mammotome, Merit Medical, Sirius Medical, Gilead, Hologic, Exact Sciences, Claudia von Schilling Stiftung, Damp Stiftung, and Ehmann Stiftung Savognin; travel expenses and congress support from Eli Lilly, Exact Sciences, Pierre Fabre, Pfizer, Daiichi Sankyo, Roche, and Stemline. Prof. Dr. med. Rupert Bartsch has performed an advisory role at AstraZeneca, Daiichi, Eisai, Eli Lilly, Gilead, Grunenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, and Stemline; received lecture honoraria from Amgen, AstraZeneca, BMS, Daichi, Eisai, Eli Lilly, Gilead, Grunenthal, MSD, MedMedia, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, and Stemline; received travel support from AstraZeneca, Daiichi, MSD, and Novartis; research support from

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