AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2023

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Introduction

For the last 21 years, the Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group, AGO) has been preparing and updating evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer (mBC). The AGO Breast Committee consists of gynecological oncologists specialized in breast cancer (BC) 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; Table 1). Here, we present the 2023 update on diagnosis and treatment of patients with locally advanced and mBC; 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

Molecular pathology for classification of BC subtypes and prediction of targeted therapies is a key element in personalized oncology. In mBC, there are four gene mutations with therapeutical implications in routine practice. Poly(ADP-ribose)-polymerase inhibitor (PARPi) monotherapy is effective in patients with a BRCA1/2 germline mutation (gBRCA1/2mt) (LoE 1a/A/AGO++). Recently, it was demonstrated for somatic mutations as well. Although EMA approval is based on trial results from germline mutation carriers only, in selected cases, determination of BRCA status from tumor tissue is possible to evaluate potential sensitivity of tumor cells toward PARPi.

Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations indicate response to corresponding inhibitors such as alpelisib (LoE 1b/A/AGO++) [2]. PIK3CA is mutated in about 40% of BC, predominantly of luminal and human epidermal growth factor receptor 2 (HER2)-enriched type.

Activating mutations of the estrogen receptor gene (ESR1) (LoE 2b/B/AGO+/−) occur in 15–40% of hormone-treated BC patients, resulting in autocrine growth stimulation and endocrine resistance against aromatase inhibitors (AIs) and tamoxifen but not fulvestrant [3]. Due to the approval of the selective estrogen receptor degrader elacestrant the ESR1 mutation testing is necessary (AGO 1b/B/+/−) [4].

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 of 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 for patients and might not be performed
−−	This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case

Besides gene amplification and overexpression of the HER2, HER2 can gain transforming potential by activating gene mutation within the kinase domain. This alteration is particularly frequent in lobular cancer and results in effective growth blockade by tyrosine kinase inhibitors like tucatinib, lapatinib, or neratinib (LoE 4/C/AGO+/−) [5].

Expression of programmed cell death ligand 1 (PD-L1) by tumor-infiltrating leucocytes either in primary BC or metastatic disease is predictive of a response to checkpoint inhibitors such as atezolizumab or pembrolizumab (LoE 1b/B/AGO++). Regarding the rare subpopulation of secretory BC, NTRK gene fusions detected in tumor tissue are the target for TRK inhibitors such as larotrectinib and entrectinib (LoE 2a/B/AGO+) [6].

Circulating tumor cells represent interesting new candidates for early response evaluation (LoE 1b/B/AGO+) in the future, but treatment decision cannot be made on the base of the CTC count (LoE 1b/A/AGO−) and should not be used outside of a clinical trial [7]. Targetable mutation, like *ESR1* can be determined from circulating DNA in peripheral blood, but it must be kept in mind that about 30% of metastasizing tumors are "non-shedders" without detectable DNA delivery. Consequently, DNA analysis from primary tumor (*BRCA*, *PIK3CA*) or metastasis (*ESR1*, *HER2*) must be preferred.

At present, therapy-relevant mutational analysis for actionable genomic alterations in mBC represents an area of great interest. These new approaches include companion diagnostics for therapy options arising from other tumor entities (e.g., *BRAF*, *FGR1*) and large panel gene analysis to identify new treatment options in late line therapy (LoE 3a/C/AGO+/−). Use of next-generation sequencing tools should be limited to situations with tier 1 and 2 treatment options suggesting variants of strong and or potential clinical significance recommended by AMP, ACMG, and ASCO/CAP [8].

Endocrine and Targeted Therapy in mBC

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) as endocrine-based therapy are the treatment of choice in the first-line situation of patients with hormone receptor-positive (HR+)/HER2-negative (HER2−) mBC. In premenopausal patients, the combination of GnRHa plus AI plus ribociclib based on the results of the MONALEESA-7 study (LoE 1b/B/AGO++) or the combination of GnRHa + fulvestrant plus CDK4/6i (LoE 2b/B/AGO++) are recommended. In the prospective randomized phase 2 Right Choice trial, premenopausal patients with aggressive HR+/HER2− advanced or mBC were treated either with ribociclib plus endocrine therapy (ET) or with the treatment of physician's choice combination chemotherapy [9]. Aggressive disease characteristics were defined by rapid progression or symptomatic non-visceral disease or symptomatic visceral metastases; more than half of the patients had a so-called visceral crisis. Progression-free survival (PFS) was 24 months in the ribociclib arm versus 12.3 months in the chemotherapy arm. The result was highly significant with a hazard ratio (HR) of 0.54 (p = 0.0007). In patients with visceral crisis, the HR was 0.87 and in those patients without visceral was 0.34. The "dogma" of first-line chemotherapy, especially in patients with aggressive disease with visceral metastases is no longer valid in general, but we still have to wait for the full publication, the overall survival (OS) data, and additional data from other studies in postmenopausal patients.

While all studies with CDK4/6i met their primary endpoint of PFS, there are differences with regard to the secondary endpoint. With a median survival of 53.9 to 51.2 months, the PALOMA-2 study could not demonstrate a significant increase in OS (HR: 0.956; 95% CI: 0.777–1.777) [10]. In the context of PALOMA-3, a significant prolongation of the OS with palbociclib and fulvestrant compared to fulvestrant alone was only achieved in the exploratory analysis (HR: 0.787; 95% CI: 0.64–0.97) [11]. Even if the reasons for the lack of significance are partly unclear and much discussed and there is real-world evidence for palbociclib with an OS benefit, the current recommendations are strictly based on the results of the randomized clinical studies. Thus, 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).

According to the MAINTAIN study, CDK4/6i beyond progression with change of the ET partner can be considered individually (LoE 2b/C/AGO+/−). Since several studies with endocrine monotherapy after CDK4/6i have

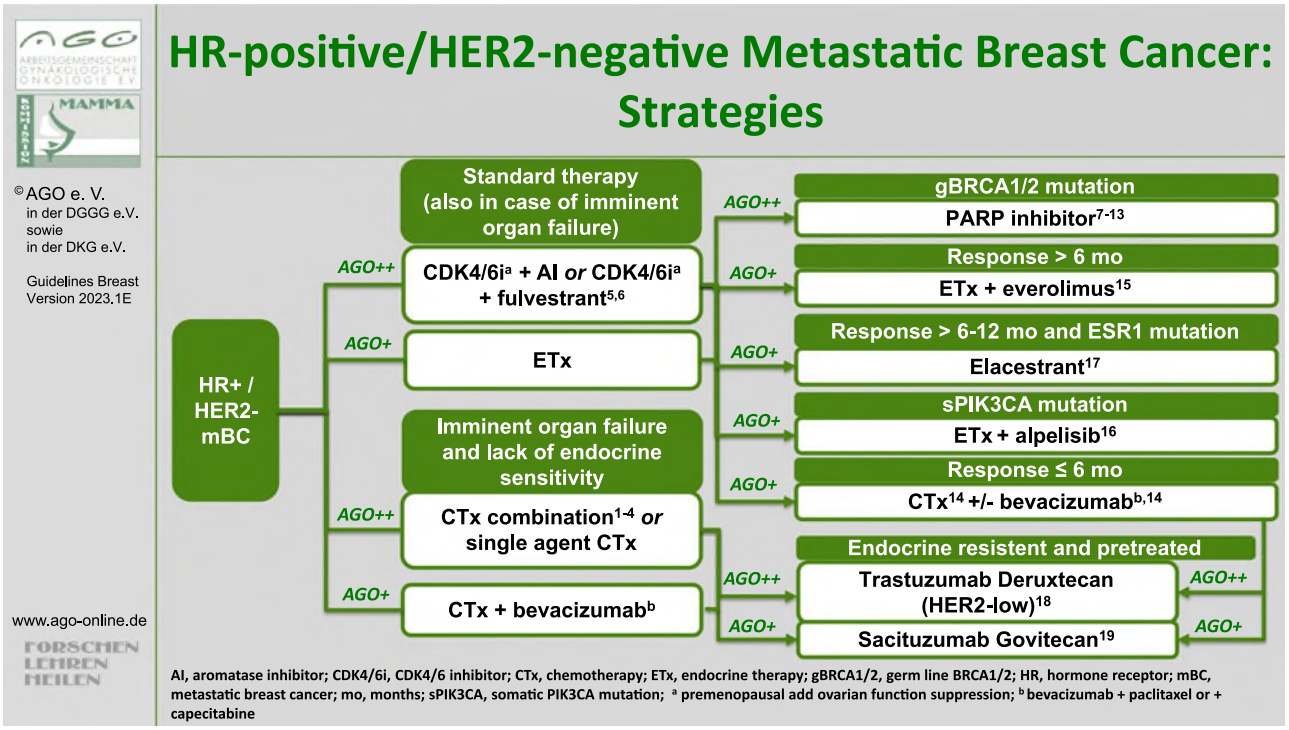

Fig. 1. Treatment algorithm for metastatic HR+/HER2– BC.

not presented any clinically relevant increase in PFS, it is only recommended on an individual basis (LoE 1b/B/AGO+/–).

However, the first approved selective estrogen receptor degrader elacestrant showed a clinically significant increased PFS, especially in the case of a longer response to a CDK4/6i, and a significantly prolonged OS with *ESR1*-mut. By this, elacestrant is recommended in the present constellation with AGO+ (LoE 2b/B) [4]. All treatment options are summarized in Figure 1.

In the case of a "triple-positive" BC (HR+/HER2+), different options are available in later lines, including chemotherapy-free regimens. Based on the data from the MonarcHER study, the combination of abemaciclib, trastuzumab, and fulvestrant was upgraded to AGO+ [12].

Chemotherapy with or without Targeted Drugs in mBC

In mBC, a good quality of life (QoL), as well as controlling any signs and symptoms resulting in an improved general health status are important (LoE 1a/A/AGO++). The first therapeutic choice in HR+ mBC is the combination of CDK4/6i with ET (please refer to the chapter on endocrine-based therapy for metastatic disease). If there is a decision for chemotherapy in the evolution of mBC, mono chemotherapy is the treatment of choice in slow-progressing disease or if secondary resistance to ET arises (LoE 1b/A/AGO++). In mBC, treatment selection is based on ER and/or PR, HER2-status, PD-L1, and several germline and somatic mutations such as g*BRCA*, *PIK3CA*, *AKT*, *PTEN*, *ESR1* mutation status best assessed in the most recent biopsy (LoE 1a/A/AGO++). For patients with HER2 low expression (HER2 1+ or 2+) in the primary tumor or metastasis, treatment with the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) is highly recommended, especially for patients with HER2 low/HR+ disease (LoE 1b/A/AGO++) [13]. The recommendation for patients with HR+, HER2– mBC after failure to CDK4/6i-based therapy, sacituzumab govitecan is another good therapeutic option [14].

In triple-negative breast cancer (TNBC) patients with PD-L1-positive tumor disease and a treatment-free interval (TFI) 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+) [15, 16]. Sacituzumab govitecan (LoE 1b/A/AGO++) as well as T-DXd (LoE 2b/C/AGO+/–) are very good options for patients with TNBC and relapse after 1st line therapy.

PARPi improved PFS in two trials (OlympiAD, EMBRACA) compared to any mono chemotherapy as "physicians' best choice" in HER2– mBC with g*BRCA1/2* mutation [17]. Thus, olaparib (LoE 1b/B/AGO++) or talazoparib (LoE 1b/B/AGO++) are treatment options in this setting. Furthermore, olaparib showed activity in mTNBC with either somatic *BRCA* (LoE 2b/B/AGO+/–) or germline *PALB2* (LoE 2b/B/AGO+/–) mutations [18].

Regarding the treatment of patients with HER2+ advanced BC, it is evident that the classic recommended sequence of taxane plus dual therapy in the first-line setting followed by T-DM1 followed by lapatinib/trastuzumab plus capecitabine can hardly be maintained for all patients, as already numerous patients have received these therapies in the (neo)adjuvant or post-neoadjuvant situation and several new therapy options are available. Accordingly, diversified algorithms have become necessary.

n the first-line setting, dual therapy with 3-weekly docetaxel (LoE 1b/A/AGO++) or weekly paclitaxel (LoE 2b/B/AGO++) is recommended for patients with primary metastatic disease after adjuvant trastuzumab therapy prior to a TFI of >6 months. Last year, the results of the DESTINY-Breast03 study comparing T-DM1 to T-DXd were presented. PFS and OS were improved significantly with HRs of 0.28 (95% CI: 0.22–0.37; $p = 7.8 \times 10–22$) and 0.56 (95% CI: 0.36–0.86; $p = 0.007172$), respectively [19]. Since T-DM1 was previously an approved option after early progression (TFI <6 months), it is now being replaced by T-DXd (LoE 4/D/AGO+/–). After dual HER2-targeted antibody-based therapy in the (neo)-adjuvant and a TFI of > 6–12 months, reinduction of dual blockade (LoE 4/D/AGO++) and in the case of a TFI of <6–12 months, T-DXd is recommended (LoE 5/D/AGO+/–). If patients have received both – dual therapy and T-DM1 – in the (neo-)adjuvant setting, beside the reinduction of the dual therapy with a taxane (TFI >6–12 months) and T-DXd, tucatinib in combination with capecitabine and trastuzumab has become available according to the published data from the HER2CLIMB study (LoE 5/D/AGO+) [20]. The low LoE indicates that those patients have not been recruited into the trials and treatment recommendations are extrapolations.

In second-line, therapy with T-DXd (LoE 1b/B/AGO++) or tucatinib and trastuzumab with capecitabine after prior therapy with T-DM1 (LoE 1b/B/AGO++) are recommended. Several options are available for third and later lines. The combination of tucatinib with capecitabine and trastuzumab has the highest grade of recommendation (LoE1b/B/AGO++). In further lines, combination of trastuzumab plus ET and abemaciclib can be an option (LoE 2b/B/AGO+).

Bone Metastasis

More than 65–70% of patients with advanced BC develop skeletal metastasis. Bisphosphonates and denosumab have been successfully used to reduce hypercalcemia (LoE 1a/A/AGO++), skeletal events/complications (LoE 1a/A/AGO++), bone pain (LoE 1a/A/AGO++), and prolong bone pain-free survival (bisphosphonates: LoE 1a/A/AGO++; denosumab: LoE 1b/A/AGO++) [21]. Based on a difference regarding the evidence for a de-escalation of denosumab, pamidronate, and zoledronic acid (i.e., every 12 weeks rather than every 3–4 weeks), de-escalation is only recommended in the case of zoledronate (LoE 1a/A/AGO++) but not in case of the other two bone-targeted agents (LoE 2b/B/AGO+/–) [22]. Severe side effects must be considered, and prevention of osteonecrosis of the jaw should be performed based on the ASORS (Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin) evaluation [23]. Planned sequential therapy with multiple bone-targeted agents should be approached with caution based on higher osteonecrosis of the jaw rates (LoE 2b/B/AGO+/–) [24]. In case of spinal cord compression, treatment should begin immediately (LoE 1c/D/AGO++) and steroids should be started at first symptoms (LoE 2a/C/AGO+) [25]. If radiotherapy is indicated, the choice of regimen (1 × 8–10 Gy vs. multiple fractions) depends on prognosis, performance status, and patient preference.

CNS Metastases

The incidence of brain metastases in patients with breast cancer (BMBC) is increasing due to improvements in imaging as well as improved survival related to advances in systemic therapy for extracranial disease. Recent data demonstrate that patients with inflammatory BC are at an increased risk for the development of BMBC [26]. For patients with oligometastatic BMBC (≤4 metastases or 5–10 metastases with cumulative volume <15 mL), stereotactic radiotherapy or surgery (if indicated) with postoperative radiotherapy of the resection cavity are recommended (LoE 1b/B/AGO++). If stereotactic radiotherapy is not feasible, whole-brain radiotherapy should be applied (LoE 1a/A/AGO++). In patients with favorable prognosis, hippocampal avoidance should be considered (LoE 1b/B/AGO+) to decrease the risk of neurocognitive sequelae.

Patients with new or progressive intracranial lesions should be discussed in a multidisciplinary tumor board (LoE 5/D/AGO++). Systemic treatment alone as primary treatment is not a standard (LoE 3a/D/AGO+/–). However, for patients with HER2+ BC and newly

diagnosed or progressive asymptomatic BMBC, systemic therapy alone may be an option if regimens with proven clinical activity in active BMBC are used (LoE 2b/C/AGO+). In case of stable extracranial metastatic disease and new or progressive intracranial lesions, the current systemic therapy may be continued if adequate local treatment of brain metastases is conducted (LoE 2c/C/AGO+). In HER2+ stable BMBC, tucatinib and T-DXd are recommended with an equally high LoE (LoE 2b/B/AGO+). However, the highest evidence for active BMBC is available for tucatinib in combination with capecitabine and trastuzumab based on the results from the HER2Climb trial [27]. The prognosis of patients with leptomeningeal metastases is still poor. Treatment options for those patients include radiotherapy, intrathecal, and systemic treatments. Recent data demonstrated improved PFS and OS with proton craniospinal irradiation in a phase 2 trial [28]. However, it is not clear whether these results can be reproduced with photon radiotherapy (LoE 2b/B/AGO+/−). Patients with HER2+ disease may benefit from intrathecal administration of trastuzumab based on recent studies demonstrating improved outcome (LoE 3a/C/AGO+/−) [29, 30].

Specific Sites of Metastases

Individual local treatment approaches based on special localizations of metastatic spread (e.g., pleural or peritoneal effusions or singular metastases) are stepping into the background due to more and more effective systemic therapies. Therefore, systemic therapy remains the mainstay of primary stage 4 BC (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 3b/C/AGO+/−) and regional ablative procedures (RFA/MWA) for liver metastases (LoE 3b/C/AGO+/−). Local forms of chemotherapy, like in the case of ascites, are not recommended (LoE 3b/D/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 [31–34]. Only in one of these trials early local therapy of the primary breast tumor improved OS 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− BC of less than 55 years of age and solitary bone-only metastasis) [34]. Despite better local control, surgery did not improve QoL [31–33]. Consequently, primary tumor removal in stage 4 BC is not recommended with the expectation of survival improvement even in patients with bone-only disease (LoE 1b/B/AGO+/−) [31–36].

Supportive Care and Side Effect Management

Optimal side effect management and supportive care are essential for therapeutic success. Before start of capecitabine therapy, dihydropyrimidin-dehydrogenase deficiency testing needs to be performed, preferably DPYD genotype testing (LoE 1a/A/AGO++). Even though DPYD variants (heterozygous or homozygous) are rare with about 4.1%, therapy-associated morbidity and mortality (2.3% vs. 0.1% w/o DPYD variants) are increased in patients with dihydropyrimidin-dehydrogenase deficiency under therapy with 5-fluorouracil and its derivates [37].

Two new antibody-drug conjugates have recently become available in Germany: main toxicities of T-DXd are interstitial lung disease (ILD), neutropenia, nausea, and alopecia [13], and those of sacituzumab govitecan are (febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia [38]. Neratinib is associated with high rates of G3 diarrhea; weekly dose escalation starting with 120 mg/d, then 160 mg/d, and the full dose of 240 mg/d after 2 weeks together with loperamide prophylaxis reduces G3 diarrhea substantially [39].

Abemaciclib is associated with an invasive disease-free survival benefit in the curative setting based on the monarchE results. Again, ILD is a rare side effect of CDK4/6i therapy; abemaciclib is associated with a 2.9% incidence (all grades) with only 0.4% > G3 events [40]. In monarchE, venous thrombotic events with abemaciclib were low with 2.3% in all grades (1.2% G3/4). The incidence is about twice as high with tamoxifen than with an AI as the endocrine backbone.

Interstitial lung disease (ILD) requires proactive management according to grade and causing agents. The diagnostic work-up starts with chest CT once symptoms arise (LoE 1a/B/AGO++). Corticosteroids (starting dose ≥0.5 mg/kg/d prednisolone-equivalent) need to be commenced early (LoE 1a/B/AGO++). It is important to note that currently, rechallenge 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 [41]. 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.

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 [42–44].

It is very important to point out that with the recent therapeutic progress with innovative and effective compounds, the patient goals are differing in each phase. Meanwhile, we are in the position to prolong PFS without increasing toxicity. The recent results of studies with CDK4/6i, checkpoint inhibitors, antibody-drug conjugates, and PARPi presented an 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.

Conclusion

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

Conflict of Interest Statement

The authors have the following conflicts of interest: Prof. Dr. Med. Marc Thill: MT received personal fees for consulting from Agendia, Amgen, AstraZeneca, Aurikamed, Becton/Dickinson, Biom'Up, ClearCut, Clovis, Daiichi Sankyo, Eisai, Exact Sciences, Gilead Science, Grünenthal, GSK, Lilly, MSD, Norgine, NeoDynamics, Novartis, Onkowissen, Organon, Pfizer, pfm Medical, Pierre Fabre, Roche, RTI Surgical, Seagen, Sirius Pintuition, and Sysmex; for manuscript support from Amgen, ClearCut, Clovis, pfm medical, Roche, and Servier; for travel expenses from Amgen, Art Tempi, AstraZeneca, ClearCut, Clovis, ConnectMedica, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Hexal, I-Med-Institute, Lilly, MCI, Medtronic, MSD, NeoDynamics, Norgine, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, and Seagen; for congress support Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Hexal, NeoDynamics, Novartis, Pfizer, Roche, and Sirius Medical; for lectures from Amgen, Art Tempi, AstraZeneca, Clovis, ConnectMedica, Eisai, Exact Sciences, Gedeon Richter, Gilead Science, GSK, Hexal, I-Med-Institute, Jörg Eickeler, Laborarztpraxis Walther, Lilly, MCI, Medscape, MSD, Medtronic, Novartis, Onkowissen, Pfizer, pfm medical, Roche, Seagen, STREAMED UP, Sysmex, Vifor, and Viatris; for trial funding from Endomag, Exact Sciences; and institutional fees from AstraZeneca, Biom'Up, Celgene, ClearCut, NeoDynamics, Novartis, pfm medical, Roche, and RTI Surgical.

Prof. Dr. Med. Ute-Susann Albert, lectures: Pfizer, Novartis, and AstraZeneca; advisory board: Daiichi Sankyo.

PD Dr. Malgorzata Banys-Paluchowski: M.B. 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 Pintuition, Pierre Fabre, and Exact Sciences; study support from Endomag, Mammotome, Merit Medical, Gilead, Hologic, and Exact Sciences; and travel/congress support from Eli Lilly, Exact Sciences, Pierre Fabre, Pfizer, Daiichi Sankyo, and Roche.

Dr. Med. Ingo Bauerfeind, honoraria for lectures: Pfizer, Roche, and Seagen.

Prof. Dr. Med. Jens-Uwe Blohmer, honoraria for advisory boards and lectures: AstraZeneca, Daiichi Sankyo, Eisai, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, and Seagen.

Prof. Dr. Med. Wilfried Budach, lecture: Merck, BMS, Jörg Eickeler Veranstaltungen, medpublico GmbH, and BVDST.

Prof. Dr. Med. Peter Dall, honoraria for lectures and advisory boards: Novartis, Pierre Fabre, Gilead, MSD, Daiichi Sankyo, Lilly, AstraZeneca, Pfizer, and Roche.

Prof. Dr. Nina Ditsch, advisory boards and speakers bureaus advisory boards and speakers bureaus: AstraZeneca, Aurikamed, BGGF, Daiichi Sankyo, Elsevier Verlag, ESO, Exact Sciences, Gilead, GSK, if-Kongress, KelCon, Leopoldina Schweinfurt, Lilly, Lukon, Molecular Health, MSD, Novartis, Onkowissen, Pfizer, RG-Ärztefortbildungen, Roche, and Seagen.

Prof. Dr. Med. Eva Maria Fallenberg, research grant: DFG; speaker honorarium: GE Healthcare, Bayer Healthcare, Guerbet, Siemens, BD, Roche, EUSOBI, ESOR, ESMO.

Prof. Dr. Med. Peter A. Fasching, advisory board: Pfizer, Novartis, Roche, Daiichi Sankyo, Eisai, AstraZeneca, Lilly, MSD, Seagen, Agendia, Pierre Fabre, Sanofi-Aventis, and Gilead Science; lecture: Pfizer, Novartis, Roche, Daiichi Sankyo, Eisai, AstraZeneca, Lilly, MSD, Seagen, and Gilead Sciences; and other: Onkowissen, art tempi.

Prof. Dr. Med. Tanja N. Fehm, Onkowissen.

Prof. Dr. Med. Michael Friedrich, advisory board: Gilead Sciences; other honoraria: Roche and MSD.

Prof. Dr. Med. Bernd Gerber, lecture honoraria: Roche, AstraZeneca, Seagen, Novartis, Pfizer, and MedConcept; and others: Pfizer.

PD Dr. Med. Oleg Gluz, honoraria for lectures and/or consulting: Amgen, AstraZeneca, Daiichi Sankyo, Gilead Science, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, Exact Sciences, and Agendia; and minority share holder: Westdeutsche Studiengruppe (WSG)mmc1.

Prof. Dr. Med. Nadia Harbeck, honoraria for lectures and/or consulting: Amgen, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Viatris, and Zuellig Pharma; minority share holder: Westdeutsche Studiengruppe (WSG).

Prof. Dr. Med. Andreas Hartkopf, honoraria for consulting and speaking engagements from AstraZeneca, Agendia, Amgen, Clovis, Daiichi Sankyo, Eisai, Exact Science, Gilead, GSK, Hexal, Lilly, MSD, Novartis, Onkowissen, Pfizer, Roche, Pierre Fabre, Seagen, Stemline, and Verazyte.

Prof. Dr. Med. Jörg Heil, none.

Prof. Dr. Med. Jens Huober, trial funding: Novartis and Lilly; honoraria for lectures: Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Celgene; AbbVie, Seagen, Gilead, and Daiichi; honoraria for consulting/advisory board: Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, AbbVie, Daiichi, and Gilead; and travel grants: Roche, Pfizer, Daiichi, and Gilead.

Prof. Dr. Med. Christian Jackisch, advisory board: AstraZeneca, Novartis, Lilly, Gilead, Exact Sciences, Pfizer, Roche, GSK, Pierre Fabre, Roche, and Seagen; lecture: Art tempi, AstraZeneca, Lilly, Novartis, Roche, Amgen, Pierre Fabre, Exact Sciences, MSD, Gyn Update, and STREAMED UP.

Prof. Dr. Med. Cornelia Kolberg-Liedtke, advisory board: SeaGen, Exact Sciences, Pfizer, Novartis, AstraZeneca, Lilly, SeaGen, Daiichi Sankyo, Agendia, Gilead, and Onkowissen; and lecture: Novartis Ireland, NOGGO, CECOG, PINK, Pfizer, Roche, AstraZeneca, Carl Zeiss Meditec, Lilly, SeaGen, and Daiichi Sankyo; other: Gilead Science and POMME; stockholding: Phaon Scientific and Theraclion SA; and trial Funding: Gilead Science.

Prof. Dr. Med. Hans-Heinrich Kreipe, advisory board: Lilly; lecture: AstraZeneca, Roche, Daiichi Sankyo, and Pfizer.

PD Dr. David Krug, lecture: Merck Sharp and Dohme, Onkowissen, and Pfizer; research funding: Merck KGaA; and advisory board: Gilead.

Prof. Dr. med. Thorsten Kühn, advisory board: Sysmex and NeoDynamics; trial funding: Merit Medical, Endomag, and Mammotome; and lecture: Pfizer.

Prof. Dr. Med. Sherko Kümmel, lecture: Roche, Lilly, Exact Sciences, Novartis, Amgen, Daiichi Sankyo, AstraZeneca, Somatex, MSD, Pfizer, pfm medical, Seagen, Gilead Science, and Agendia; other honoraria: Roche, Daiichi Sankyo, and Sonoscape; and advisory board: Lilly, MSD, and Roche.

Prof. Dr. Med. Sibylle Loibl, board, advisory board, institutional: AbbVie, Amgen, AstraZeneca, BMS, Celgene, DSI, EirGenix, GSK, Gilead Science, Lilly, Merck, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Puma, Roche, Samsung, Sanofi, and Seagen; invited speaker, institutional: AstraZeneca, DSI, Gilead, Novartis, Pfizer, Pierre Fabre, Roche, and Seagen; invited speaker, personal: Medscape and Stemline-Menarini; trial funding/others: AstraZeneca, AbbVie, Celgene, Daiichi Sankyo, Greenwich Life Sciences, Immunomedics/Gilead, Molecular Health, Novartis, Pfizer, Roche, Seagen, VM Scope Gmbp.

Prof. Dr. Med. Diana Lüftner, lecture: Lilly, Roche, MSD, Onkowissen, Novartis, Pfizer, Daiichi Sankyo, Gilead, AstraZeneca, Loreal, and high4md; advisory board: Lilly, Advisory board: Lilly, Roche, MSD, Novartis, Pfizer, Daiichi Sankyo, Gilead, and AstraZeneca; and other: Novartis.

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Prof. Dr. Med. Toralf Reimer; trial funding: German Cancer Aid and Else Kroener-Fresenius-Stiftung; advisory board: MSD, Novartis, and Myriad; and lecture: Pfizer, Novartis, Roche, and AstraZeneca.

Prof. Dr. Med. Kerstin Rhiem, lecture: AstraZeneca, Amgen, and Roche.

Prof. Dr. Med. Achim Rody, advisory board: AstraZeneca, Novartis, Roche, Exact Sciences, Pierre Fabre, Lilly, Seagen, Amgen, and MSD; lecture: Pfizer, Celgene, and Eisai; and trial funding: Eisai.

Prof. Dr. Med. Marcus Schmidt: MS reports personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Lilly, 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, lecture: Amgen, AstraZeneca, Aurikamed, Clinsol, ConnectMedica, Gilead Science, GSK, I-Med, Lilly, MSD, NanoString, Novartis, Onkowissen, Promedicis, Pfizer, Pierre Fabre, Roche, Seagen, and STREAMED UP; and other: Thieme.

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Prof. Dr. Med. Hans-Peter Sinn, advisory board: Exact Sciences and Daiichi Sankyo; lecture: AstraZeneca; and trial Funding: AstraZeneca.

Prof. Dr. Med. Christine Solbach, lecture: DiaLog Service GmbH, Jörg Eickeler, Pfizer, MedConcept, Medicultus, GBG, Dt. Röntgengesellschaft, BVF Akademie, LÄK Hessen Akademie, Meet the Expert Academy; advisory board: MSD and Roche.

Prof. Dr. Med. Erich-Franz Solomayer, Roche, Amgen, Celgen, Tesaro, AstraZeneca, Pfizer, Storz, Erbe, Gedeon Richter, Eisai, Medac, MSD, Vifor, Teva, Ethikon, Johnson & Johnson, Daiichi Sankyo, Gilead, Exact Sciences, GSK, and Pierre Fabre.

Prof. Dr. Med. Elmar Stickeler, advisory boards: Gilead, Iomedico, Lilly, MSD, and Seagen; and lecture: Pfizer, Bsh Düsseldorf, Gilead, Iomedico, PharmaMar, Onkowissen, and Roche.

Prof. Dr. Med. Christoph Thomssen, compensation for advisory boards, lectures or publications: Amgen, AstraZeneca, Aurikamed, Daiichi Sankyo, Forum Sanitas, Gilead, Jörg Eickeler, Hexal, Lilly, Medupdate, MSD, NanoString, Novartis, Onkowissen, Pfizer, Roche, Seagen, and Vifor.

Prof. Dr. Med. Michael Untch: M. U. has received honoraria for lectures and consulting or advisory role from AstraZeneca, Art tempi, Amgen, Daiichi Sankyo, Lilly, Roche, Pfizer, MSD Oncology, Pierre Fabre, Sanofi-Aventis, Myriad, Seagen, Novartis, Gilead, Stemline, Genzyme, Agendia, Onkowissen, Eisai; all honoraria and fees to the employer/institution.

Prof. Dr. Isabell Witzel, lecture: Daiichi Sankyo, Pfizer, Roche, MSD, Lilly, Seagen, AstraZeneca, and Gilead; other: Onkowissen.

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PD. Dr. Rachel Würstlein, Agendia, Amgen, Aristo, Astra Zeneca, Aurikamed, Celgene, Clinsol, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Sciences, FOMF, Gilead, Glaxo Smith Kline, Hexal, Lilly, MCI, medconcept, Medstrom Medical, MSD, Mundipharma, Mylan, NanoString, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, PINK, Pomme-med, Puma Biotechnology, Riemser, Roche, Sandoz/Hexal, Sanofi Genzyme, Seattle Genetics/Seagen, Stemline, Tesaro Bio, Teva, Veracyte, and Viatris.

Prof. Dr. Med. Volkmar Müller: VM received speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, MSD, Novartis, Roche, Teva, Seattle Genetics, Genomic Health, Hexal, Roche, Pierre Fabre, Clinsol, Daiichi Sankyo, Eisai, Lilly, Tesaro, Seattle Genetics, and Nektar; institutional research support from Novartis, Roche, Seattle Genetics, and Genentech; and travel grants: Roche, Pfizer, and Daiichi Sankyo.

Prof. Dr. Med. Wolfgang Janni, lecture: Amgen, AstraZeneca, Daiichi Sankyo, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, and Gilead Science; trial Funding: Amgen, AstraZeneca, Lilly, Novartis, and Roche.

Prof. Dr. Tjoung-Won Park-Simon, honoraria for lectures and/or consulting: Roche, AstraZeneca, GSK, Pfizer, Lilly, MSD, Exact Sciences, Daiichi Sankyo, Seagen, Novartis, Gilead Science, NCO, Onkowissen, Exact Sciences, and Seagen; and travel compensation: Roche, AstraZeneca, and Pfizer.

Funding Source

The authors received no financial support/funding for this review article.

Author Contributions

This paper was written by all members of the AGO Breast Committee.

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