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# AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2021

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## Introduction

For the last 19 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 and interdisciplinary members specialized in pathology, radiologic diagnostics, medical oncology, and radiation oncology. This update was 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) [1] and clinical relevance (AGO grades of recommendation) (Table 1). We herewith present the 2021 update of 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 [2]. Moreover, a special version for patients is also available at www.ago-online.de (Table 1).

## Prognostic and Predictive Factors

Molecular pathology for classification of tumors and for efficacy prediction of targeted therapies is a rapidly growing field.

In MBC there are four gene mutations with the potential to interfere with therapy. Poly(ADP-ribose)-polymerase (PARP) inhibitor monotherapy is effective in patients with a BRCA1/2 germline mutation (*gBRCA1/2 mt*) (LoE 1/A/AGO++) [3]. Recently, it could be shown that the same is true for somatic mutations (LoE 2b/B/AGO+/–) [4] and probably for *PALB2* mutations as well (LoE 2b/B/AGO+/–). Although EMA approval has been based on studies of germline mutation carriers only, in selected cases determination of BRCA status from tumor tissue is possible to evaluate the potential sensitivity of tumor cells towards PARP inhibition.

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

Activating mutations of the estrogen receptor gene ESR1 (LoE 2b/B/AGO+/–) occur in 15–40% of endocrine-treated breast cancer patients, leading to autocrine growth stimulation and endocrine resistance against aromatase inhibitors and tamoxifen but not fulvestrant [6].

Besides, gene amplification and overexpression of HER2 can gain transforming potential by activating gene mutation within the kinase domain. This alteration is particularly frequent in lobular cancer [7] and results in effective growth blockade by tyrosine kinase inhibitors like tucatinib, lapatinib, or neratinib (LoE 4/C/AGO+/–).

Expression of programmed death ligand 1 (PD-L1) by tumor-infiltrating leukocytes either in the primary tumor or the metastasis itself is predictive for the response to checkpoint inhibitors, such as atezolizumab (LoE 1b/B/AGO++) [8]. For prediction of atezolizumab efficacy in metastatic triple-negative breast cancer (mTNBC), immune-cell PD-L1 positivity seems essential (punch biopsies, resection specimens). At least 1% cytoplasmic staining of the leukocyte stromal infiltrate (lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses) is considered positive, for pembrolizumab if the combined positive score is at least 10% (LoE 1b/B/AGO++). Tumor staining should not be assessed. In IMpassion130, Ventana antibody SP142 with positive control (tonsil) was used [8]. Other antibodies are probably equivalent and different cutoffs may apply. Participation in the National Pathology Society QA program is obligatory and reference pathology is needed if a center is not yet qualified.

## Endocrine and Targeted Therapy in MBC

In women with hormone receptor (HR)-positive, HER2-negative MBC, endocrine-based therapy should be considered the first choice, irrespective of menopausal status. Premenopausal women rendered postmenopausal by either GnRH analogs or other means of ovarian function suppression should then be treated like postmenopausal women.

The majority of patients are candidates for a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combination

**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 benefit 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 |

therapy. The evidence concerning abemaciclib, palbociclib, and ribociclib has been completed with regard to a variety of patient populations according to therapy line, menopausal status, and endocrine combination partners. Those combination therapies are rated with LoE 1b/B/AGO++ for postmenopausal patients. For premenopausal patients the combination of a CDK4/6 inhibitor with GnRH analog plus fulvestrant is rated with LoE 2b/B/AGO++, for the combination with a GnRH analog plus an aromatase inhibitor the ratings are different. Due to a better evidence ribociclib is rated with LoE 1b/B/++ and palbociclib/abemaciclib with LoE 3b/C/AGO+ and LoE 5/C/AGO+, respectively. All three drugs have been thoroughly investigated in first and further therapy lines in endocrine-sensitive and -resistant MBC and have demonstrated a homogeneous improvement of progression-free survival (PFS) with hazard ratios between 0.42 and 0.58 (summarized in Thill and Schmidt [9]). Thus, no subgroup could be identified neither by clinical markers nor by biomarkers that does not benefit from using a CDK4/6 inhibitor in addition to endovascular therapy. Overall survival (OS) was shown in premenopausal patients in the MONALEESA-7 [10] study and in postmenopausal patients who had participated in the MONALEESA-3 [11] and MONARCH-2 study [12].

Patients with HR-positive breast cancer carrying a *gBRCA* mutation might be candidates for PARP inhibitors. Both the confirmatory studies OlympiAD with olaparib (LoE 1b/A/AGO++) [3] and EMBRACA with talazoparib (LoE 1b/B/AGO++) [13] included about 50% HR-positive breast cancers and showed a better PFS compared to standard of care monochemotherapies. The final OS analysis of the OlympiAD study showed a significant OS benefit for olaparib in patients without prior metastatic treatment. However, this analysis had a low patient number [3].

In PIK3Ca-mutated patients the PI3Kα-specific inhibitor alpelisib has shown a significant improvement in combination with fulvestrant when compared to fulvestrant alone after progress on an aromatase inhibitor (LoE 1b/B/AGO+) [5]. Therefore, another treatment option to overcome endocrine resistance exists, most likely to be effective after CDK4/6 inhibition.

## Chemotherapy with or without Targeted Drugs in MBC

In MBC, a good quality of life as well as controlling any signs and symptoms resulting in an improved general health status is important (A/AGO++). Monochemotherapy is the treatment of choice in slowly progressing disease or if secondary resistance to endocrine therapy arises (LoE 1b/A/AGO++). In contrast, combination chemotherapy is recommended in case of urgent remission or visceral crisis according to the ABC-5 definition.

In MBC treatment selection is based on ER and/or progesterone receptor and HER2 status either from the primary tumor or from the metastatic site (AGO++). In TNBC patients with PD-L1-IC-positive status, the combination of nab-paclitaxel and the PD-L1 inhibitor atezolizumab is a new option in the first-line therapy of MBC (LoE 1b/B/AGO+) [8]. However, the combination with paclitaxel is not recommended (LoE 1ba/B/AGO–) [13]. In addition, a combination of pembrolizumab and first-line chemotherapy (i.e., paclitaxel or nab-paclitaxel or carboplatin/gemcitabine) might be another option in PD-L1-positive tumors with a combined positive score ≥10 (LoE 1b/B/AGO+/–) [14].

PARP inhibitor improved PFS in two trials (OlympiAD, EMBRACA) compared to any chemotherapy as "doctors' best choice" in HER2-negative MBC with *gBRCA1/2* mutation [3, 15]. Thus, olaparib (LoE 1b/B/AGO++) or talazoparib (LoE 1b/B/AGO++) are new 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 [4] (Fig. 1).

In mTNBC independent of PD-L1 status and *gBRCA1/2* mutation, the antibody-drug conjugate sacituzumab govitecan showed promising activity (LoE 1ba/B/AGO+) [16].

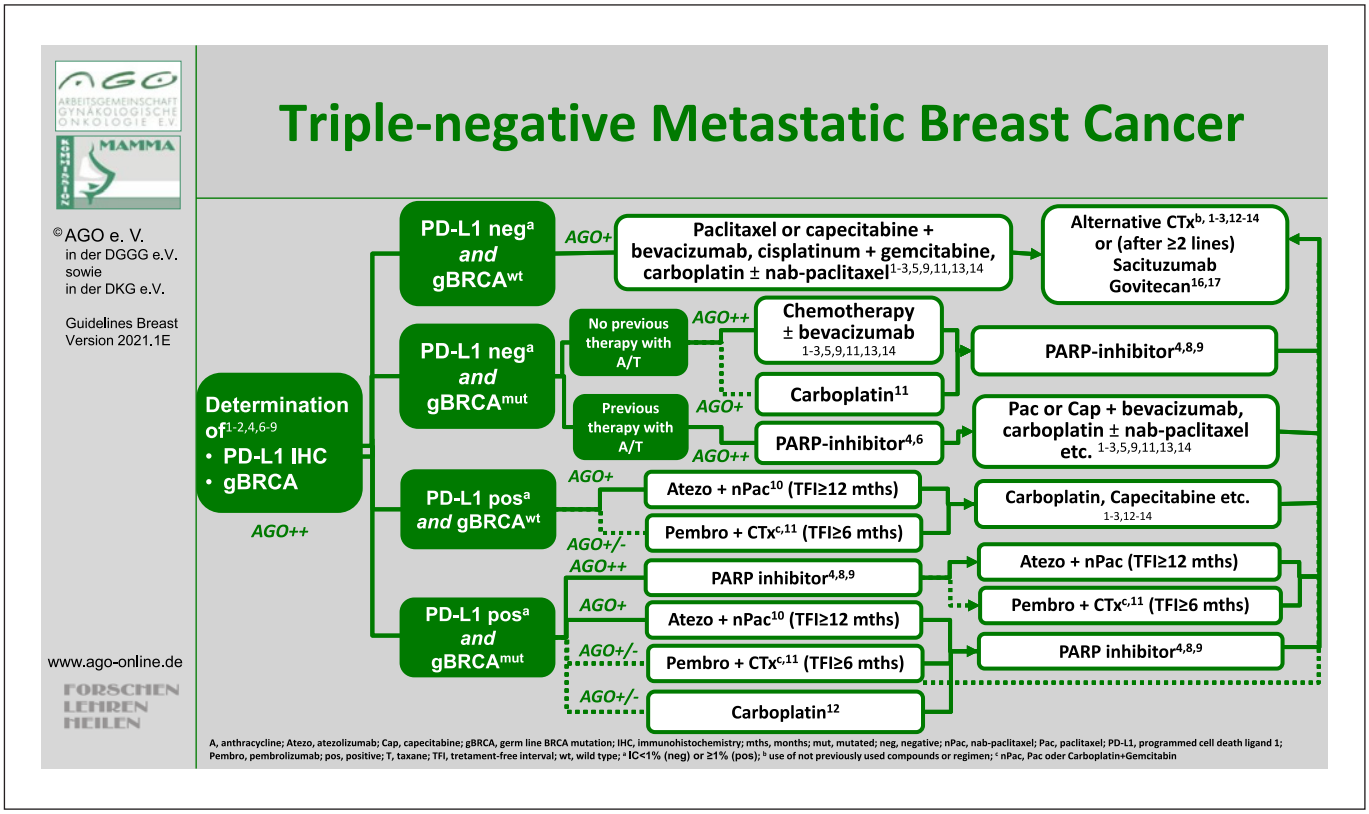


**Fig. 1.** Treatment algorithm of metastatic triple-negative breast cancer.

In HER2-positive MBC, taxane-based chemotherapy plus dual blockade of the HER2 receptor by trastuzumab and pertuzumab is recommended as first-line combination. Upon progression, T-DM1 is recommended for second-line therapy (LoE 1b/A/AGO++). In case of progression after two previous lines of anti-HER2 therapy, tucatinib combined with trastuzumab/capecitabine is a novel anti-HER2 therapy resulting in PFS and OS prolongation (LoE 1b/B/AGO++) [17]. Both trastuzumab deruxtecan (LoE 2b/B/AGO+) [18] and neratinib (LoE 1b/B/AGO+) [19] are additional new therapeutic options in heavily pretreated HER2-positive MBC.

## Bone Metastasis

Over 65–70% of patients with advanced breast cancer develop skeletal metastasis [19]. Bisphosphonates and denosumab have been successfully used to reduce hypercalcemia (LoE 1a/A/AGO++), skeletal events/complications (LoE 1a/A/AGO++), and bone pain (LoE 1a/A/AGO++), as well as to increase bone pain-free survival (bisphosphonates: LoE 1a/A/AGO++; denosumab: LoE 1b/A/AGO++) [20]. 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 case of zoledronate (LoE 1a/A/AGO++) but not in case of the other two bone-targeted agents (LoE 2b/B/AGO+/–) [21]. 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 [22]. 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+/–) [23]. 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+) [24]. If radiotherapy is indicated, the choice of regimen (1 × 8–10 Gy vs. multiple fractions) depends on prognosis, performance status, and patient preference.

## Central Nervous System Metastases

About one-third of all patients with MBC develop metastasis in the course of disease, the vast majority with parenchymal central nervous system metastasis. Overall, the cumulative incidence has risen from 10 to 40% due to

improvements in systemic therapy and diagnostic imaging.

In the presence of singular brain metastases up to a size of 4 cm, local therapy consisting of stereotactic radiation therapy or resection in combination with radiation of the tumor bed (without whole-brain radiation) should be given preference (LoE 1b/B/AGO++). Whole-brain irradiation alone, possibly in combination with boost irradiation, should be reserved to patients in poor general condition or with an unfavorable prognosis (LoE 2b/B/AGO+). Current data from a randomized phase 3 study suggest that sparing the hippocampus could be beneficial for the patient in view of the frequently observed neurocognitive impairment after whole-brain radiation. However, the clinical benefit is more likely to be classified as marginal (LoE 2b/B/AGO+/–).

The treatment of choice in the presence of multiple brain metastases, frequently in combination with a supportive corticosteroid therapy, is whole-brain irradiation. In particular, systemic therapy with corticosteroids (LoE 3a/B/AGO+/–) is usually aimed for previously irradiated patients who lack a radiation reserve.

With regard to the systemic treatment of brain metastases or the response to central nervous system metastases under palliative systemic therapy, the response data are particularly good for HER2-positive breast cancer. However, the study data must be assessed critically, since in many studies either asymptomatic only or stable, pretreated patients with brain metastases were allowed to be included. Unplanned, retrospective, exploratory subgroup analyses showed that T-DM1 [25, 26] and neratinib [27] are also effective in central nervous system metastases. Only tucatinib [18], lapatinib, and neratinib were investigated in prospective studies and showed good response rates and response duration. In the HER2-CLIMB trial the secondary endpoint of PFS in patients with brain metastases showed a significant reduction in the risk of progression or death by 52% in the tucatinib arm. In the presence of leptomeningeal metastases, intrathecal, systemic, and radiotherapeutic treatment are equally important.

### Specific Sites of Metastases

Systemic therapy remains the mainstay of primary stage IV breast cancer (LoE 2a/B/AGO++). There has been an ongoing debate whether surgical removal of the primary tumor improves survival. To date, four randomized phase 3 trials have been conducted [28–31]. In none of these trials did early local therapy of the primary breast tumor improve OS in patients with de novo metastatic disease. Despite better local control, surgery did not improve quality of life [30]. Based upon the available data we do not recommend primary tumor removal in stage IV breast cancer with the expectation of survival improvement (LoE 1b/B/AGO–) [28–31]. Results from the Japanese Clinical Oncology Group 1017 trial, a very large trial designed similarly to the ECOG-ACRIN 2108 trial, are pending. Recruitment to this trial is completed and results are expected to be published in 2022. However, in individual cases, e.g., in case of a symptomatic tumor (LoE 5/D/AGO+/–) or bone-only disease (LoE 2b/B/AGO+/–), surgery can be an option [28]. Only patients with limited or oligometastatic disease and a good response to systemic treatment should be considered for surgical procedures at the primary site as well as at the metastatic sites (LoE 2b/C/AGO+). In oligometastatic disease a surgical approach has to be considered as part of the whole, potentially curative treatment strategy [32]. Only few minor amendments were added to the AGO recommendation already presented in 2020. Approximately 10% of all MBC patients present with malignant pleural effusion, and about 17–30% of all patients with malignant pleural effusion have a MBC [33]. Malignant pleural effusion should be treated in symptomatic cases. To control malignant pleural effusion, video-assisted thoracoscopy with pleurodesis (LoE 1b/B/AGO++) or continuous pleural drainage with indwelling pleural catheters (LoE 2a/B/AGO++) are options. In patients with bone marrow infiltration, chemotherapy is usually the choice of treatment (LoE 4/D/AGO++). There have been some case series in patients with HR-positive bone marrow infiltration that reported responses to endocrine-based therapy (LoE 4/C/AGO+) [34].

### Breast Cancer: Supportive Care and Side Effect Management

Optimal side effect management and supportive care are major contributors to the overall risk/benefit balance associated with oncological therapies. This chapter of the AGO recommendations includes detailed aspects that are particularly relevant for the treatment of breast cancer patients and is based on the most recent version of the German S3 guidelines [35] and other international guidelines, such as those of the ESMO, wherever available.

Chemotherapy can lead to reactivation of hepatitis B in carriers [36]. Before the start of chemotherapy, screening for hepatitis B (HBsAG, anti-HBC) should therefore be performed in all patients (LOE 2c/B/AGO+). If one of the tests is positive, HBV DNA needs to be determined. In case of HBV DNA detection, virustatic therapy needs to be initiated and chemotherapy interrupted (LoE 1b/A/AGO++).

The essential drug management for antiemetic therapy has been revised (https://www.mascc.org/antiemetic-

guidelines). For patients in the acute and as well in the delayed emetic high-risk group, olanzapine on days 1–4 may be offered (LoE 1b/A/AGO+), particularly if nausea is a concern. As sedation and weight gain are side effects, dose reduction from 10 to 5 mg/day is a valid option [37, 38].

Chemotherapy-induced peripheral neuropathy is a common toxicity following taxane or subsequent T-DM1 therapy with an incidence of up to 50% grade 1–2 and up to 20% grade 3 and 4. Thus, besides continuing measures for neuropathy prevention such as tight surgical gloves and compression stockings (LoE 2b/B/AGO+), cooling gloves and stockings (LoE 2b/B/AGO+/–) and tactile stimulation (LoE 5/D/AGO+) are very important. While drug-based prevention and treatment options are limited (AGO+/–), non-drug-based therapy might be an option with functional treatment (LoE 2a/C/AGO+), physiotherapy (LoE 5/D/AGO+), and acupuncture (LoE 2b/B/AGO+).

Detailed and practical management information for new drugs such as CDK4/6 inhibitors or immunotherapy can be found in the respective package inserts which are regularly updated.

## Palliative Care

It is well accepted that MBC in the early phase is incurable but treatable. However, the late "palliative" phase has to 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 quality of life. Furthermore, discussions about patient preferences at the end of life should begin early in the course of metastatic disease [39–41].

It is very important to point out that with the recent therapeutic progress with innovative and effective compounds, patient goals are differing in each phase. Meanwhile, we are in a position to prolong PFS without increasing toxicity, and the very recent results of studies with CDK4/6 inhibitors, checkpoint inhibitors, and PARP inhibitors presented an OS benefit. With such compounds the targeted and more individual treatment strategies take center stage. Therefore, patients are not satisfied anymore to be treated with a palliative approach instead of being treated with a curable and life-prolonging approach. Thus, patient-reported outcome data are crucial to estimate treatment success and course.

## Conflict of Interest Statement

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