Thieme

AGO Algorithms for the Treatment of Breast Cancer: Update 2021

AGO-Algorithmen zur Behandlung von Brustkrebs: Update 2021

Authors

Andreas Schneeweiss[1], Peter A. Fasching[2], Tanja Fehm[3], Bernd Gerber[4], Christian Jackisch[5], Sibylle Loibl[6], Marcus Schmidt[7], Elmar Stickeler[8], Achim Wöckel[9], Wolfgang Janni[10], Volkmar Müller[11], on behalf of the AGO Kommission Mamma*

Affiliations

1 Nationales Centrum für Tumorerkrankungen, Universitätsklinikum Heidelberg, Heidelberg, Germany
2 Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany
3 Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany
4 Universitätsfrauenklinik und Poliklinik, Universität Rostock, Rostock, Germany
5 Obsterics and Gynecology, Klinikum Offenbach GmbH, Offenbach, Germany
6 German Breast Group, Neu-Isenburg, Germany
7 Geburtshilfe und Frauenerkrankungen, Johannes-Gutenberg-Universität, Mainz, Germany
8 Klinik für Gynäkologie und Geburtsmedizin, Universitätsklinikum Aachen, Aachen, Germany
9 Frauenklinik und Poliklinik Universitätsklinikum Würzburg, Würzburg, Germany
10 Frauenklinik, Klinikum der Universität Ulm, Ulm, Germany
11 Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

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Correspondence

Prof. Dr. Wolfgang Janni
Klinikum der Universität Ulm, Frauenklinik
Prittwitzstraße 43, 89075 Ulm, Germany
Wolfgang.Janni@uniklinik-ulm.de

* Prof. Dr. W. Janni, Ulm | Prof. Dr. V. Müller, Hamburg | Prof. Dr. U.-S. Albert, Würzburg | PD Dr. M. Banys-Paluchowski, Hamburg | Dr. I. Bauerfeind, Landshut | Prof. Dr. J.-U. Blohmer, Berlin | Prof. Dr. W. Budach, Düsseldorf | Prof. Dr. P. Dall, Lüneburg | Prof. Dr. N. Ditsch, Augsburg | PD Dr. E. Fallenberg, München | Prof. Dr. P. Fasching, Erlangen | Prof. Dr. T. Fehm, Düsseldorf | Prof. Dr. M. Friedrich, Krefeld | Prof. Dr. B. Gerber, Rostock | PD Dr. O. Gluz, Mönchengladbach | Prof. Dr. N. Harbeck, München | Prof. Dr. J. Heil, Heidelberg | Prof. Dr. J. Huober, St. Gallen/Ulm | Prof. Dr. C. Jackisch, Offenbach | Prof. Dr. C. Kolberg-Liedtke, Berlin | Prof. Dr. H. Kreipe, Hannover | Dr. D. Krug, Kiel | Prof. Dr. T. Kühn, Esslingen | Prof. Dr. S. Kümmel, Essen | Prof. Dr. S. Loibl, Neu-Isenburg | Prof. Dr. D. Lüftner, Berlin | Prof. Dr. M. Lux, Paderborn | Prof. Dr. N. Maass, Kiel | Prof. Dr. C. Mundhenke, Bayreuth | Prof. Dr. U. Nitz, Mönchengladbach | Prof. Dr. T.-W. Park-Simon, Hannover | Prof. Dr. T. Reimer, Rostock | PD Dr. K. Rhiem, Köln | Prof. Dr. A. Rody, Lübeck | Prof. Dr. M. Schmidt, Mainz | Prof. Dr. A. Schneeweiss, Heidelberg | Prof. Dr. F. Schütz, Speyer | Prof. Dr. H.-P. Sinn, Heidelberg | Prof. Dr. C. Solbach, Frankfurt | Prof. Dr. E. Solomayer, Homburg | Prof. Dr. E. Stickeler, Aachen | Prof. Dr. M. Thill, Frankfurt/Main | Prof. Dr. C. Thomssen, Halle/Saale | Prof. Dr. M. Untch, Berlin | Prof. Dr. I. Witzel, Hamburg | Prof. Dr. A. Wöckel, Würzburg

ABSTRACT

Therapy options shown in the algorithms are based on the current AGO recommendations, but cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, etc. must be taken into account for the actual treatment choice. In individual cases, other evidence-based treatment options may also be appropriate and justified. Regardless of approval status, the algorithms only take into account drugs that were available in Germany at the time the algorithm was last updated. Here we present the 2021 update of AGO treatment algorithms for early and metastatic breast cancer, which are intended to intensify structured treatment decision by providing reproducible and evidence-based treatment paths and may be helpful for a broad treatment landscape.

ZUSAMMENFASSUNG

Die in den Algorithmen aufgezeigten Behandlungsoptionen basieren zwar auf den aktuellen AGO-Empfehlungen, können aber nicht alle evidenzbasierten Behandlungsoptionen darstellen, da frühere Therapien, der Patientinnenstatus, Begleiterkrankungen, Patientinnenpräferenzen usw. bei der tatsächlichen Therapiewahl mitberücksichtigt werden müssen. Andere evidenzbasierte Behandlungsoptionen können in Einzelfällen auch angemessen und gerechtfertigt sein. Ungeachtet ihres Zulassungsstatus werden nur die Medikamente in den Algorithmen aufgenommen, die zum Zeitpunkt des letzten Algorithmus-Updates in Deutschland zugelassen waren. Die Aktualisierung der AGO-Behandlungsalgorithmen für die Therapie von frühen und metastasierten Brustkrebserkrankungen von 2021 wird hier vorgestellt. Diese Aktualisierung soll strukturierte Behandlungsentscheidungen durch die Darlegung reproduzierbarer, evidenzbasierter Therapiepfade verstärken und kann für eine breit angelegte Behandlungslandschaft nützlich sein.

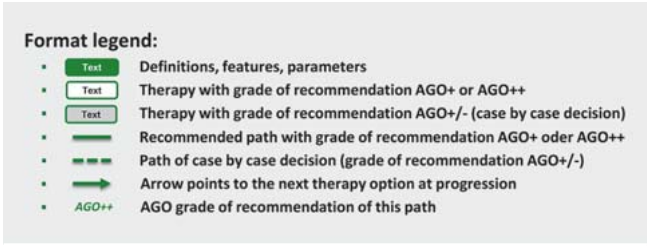
Introduction

The Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group, AGO) provides annual recommendations on prevention, diagnosis and treatment of early and metastatic breast cancer [1, 2]. The Committee is a multidisciplinary team of national experts.

Since 2020, this group also publishes algorithms to better illustrate the overall therapeutic concept. These algorithms are based on the current AGO recommendations, but obviously cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, etc. must be considered for the actual treatment choice. The recommendations are evidence-based but also reflect expert opinion, reflected by different grades of recommendation (▶ **Table 1**). In individual cases, other evidence-based treatment options (not listed here) may also be appropriate and justified. In some situations, e.g. positive Phase III data or U. S. Food and Drug Administration (FDA) approval, the algorithms also take into account drugs that are not approved in Germany at the time the algorithm was last updated. The general structure of the formatting is illustrated in ▶ **Fig. 1**.

▶ **Table 1** 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.

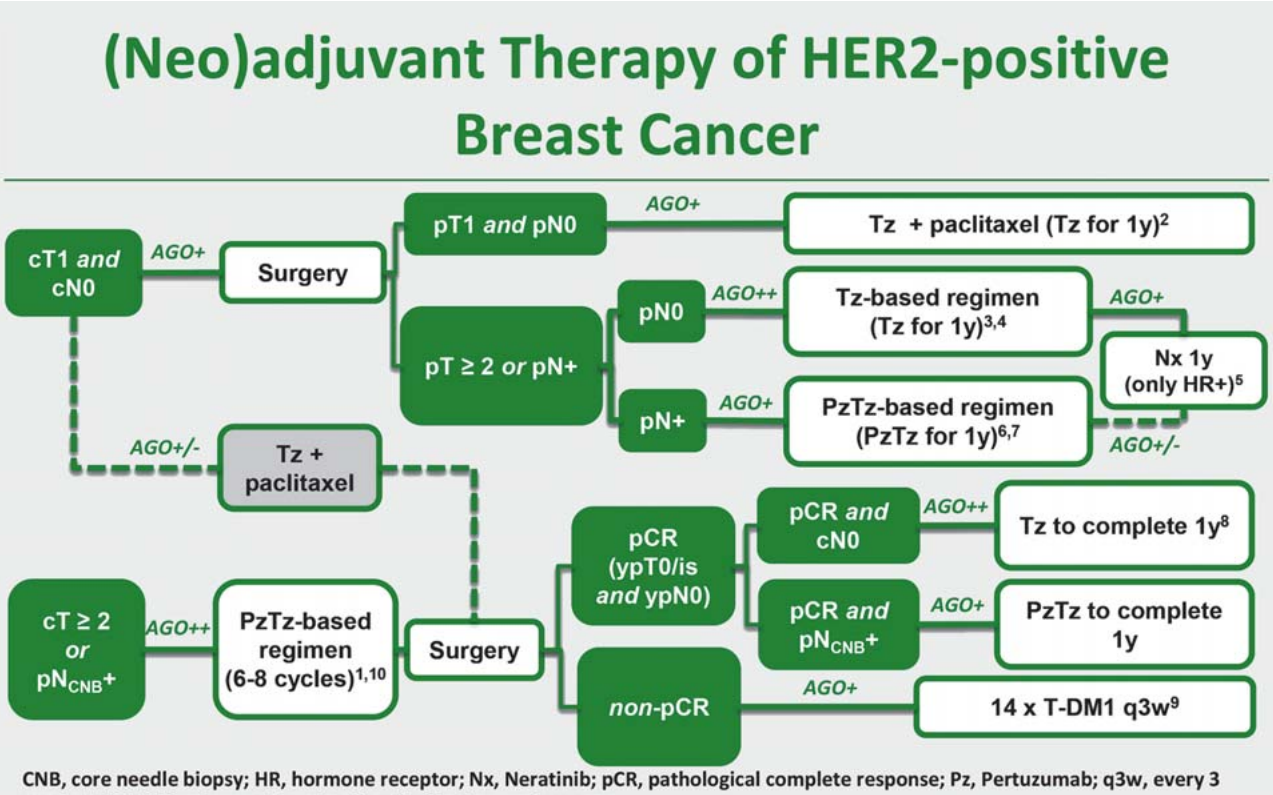


▶ **Fig. 1** Format legend for the AGO agorithms.

Algorithm (Neo)adjuvant Therapy of HER2-positive Breast Cancer (▶ **Fig. 2**)

Patients with HER2-positive cT1 cN0 breast cancer should undergo upfront surgery in order to confirm the low-risk situation (pT1 pN0), histologically. In this case, systemic treatment can be deescalated to 12 × paclitaxel qw and trastuzumab monotherapy completed for one year. In case of pT2 pN0 a taxane based polychemotherapy plus trastuzumab monotherapy is recommended which might be followed in case of a HR+ tumor by neratinib monotherapy for up to 1 year. For patients with confirmed positive lymph nodes (pN+) HER2 targeted therapy should be escalated to trastuzumab and pertuzumab for up to one year.

Patients with HER2-positive breast cancer ≥ 2 cm and/or clinically positive lymph nodes should be treated with a taxane based polychemotherapy and dual antibody blockade in the neoadju-



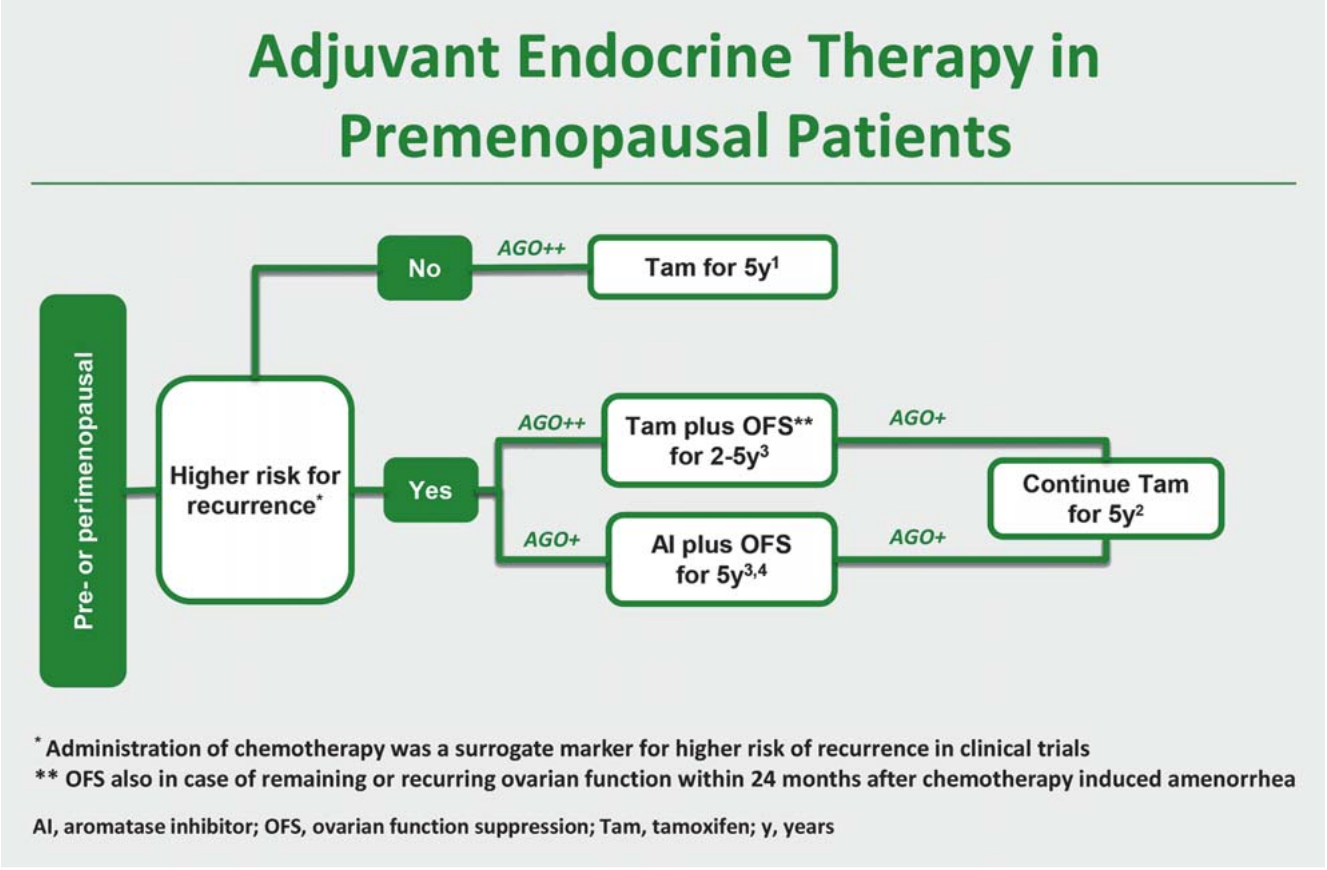
▶ **Fig. 2** Algorithm (Neo)adjuvant Therapy of HER2-positive Breast Cancer.

[1] Gianni L et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 25–32. [2] Tolaney SM et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol 2019; 37: 1868–1875. [3] Perez EA et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014; 32: 3744–3752. [4] Cameron D et al., Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017; 389: 1195–1205. [5] Martin M et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 1688–1700. [6] von Minckwitz G et al., APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017; 377: 122–131. [7] Piccart M et al. Interim overall survival analysis of APHINITY (BIG 4–11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019; Abstr. GS01-04. [8] Gianni L et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014; 15: 640. [9] von Minckwitz G et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380: 617–628. [10] Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Waldron-Lynch M, Eng-Wong J, Kirk S, Cortés J. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer 2018; 89: 27–35.

vant setting. Based on therapy response (pCR/non pCR) different postneoadjuvant therapy options should be offered after surgery. In initially node positive patients (cN+) with pCR trastuzumab and pertuzumab should be completed for one year. In patients with a pCR and low risk of recurrence (cN0) a deescalation to trastuzumab monotherapy is recommended. Patients with non pCR should be treated with 14 cycles T-DM1 q3w as postneoadjuvant therapy.

Algorithm Adjuvant Endocrine Therapy in Premenopausal Patients (▶ **Fig. 3**)

Although recruitment was more than 10 years ago SOFT and TEXT trials are the main evidence for the treatment recommendations for premenopausal patients. However, it must be noticed that therapy practice and indication for chemotherapy have changed since the recruitment and generalization of data for the current patient population might be limited. Therefore, the recommendations and the algorithms were simplified. Patients with a low risk



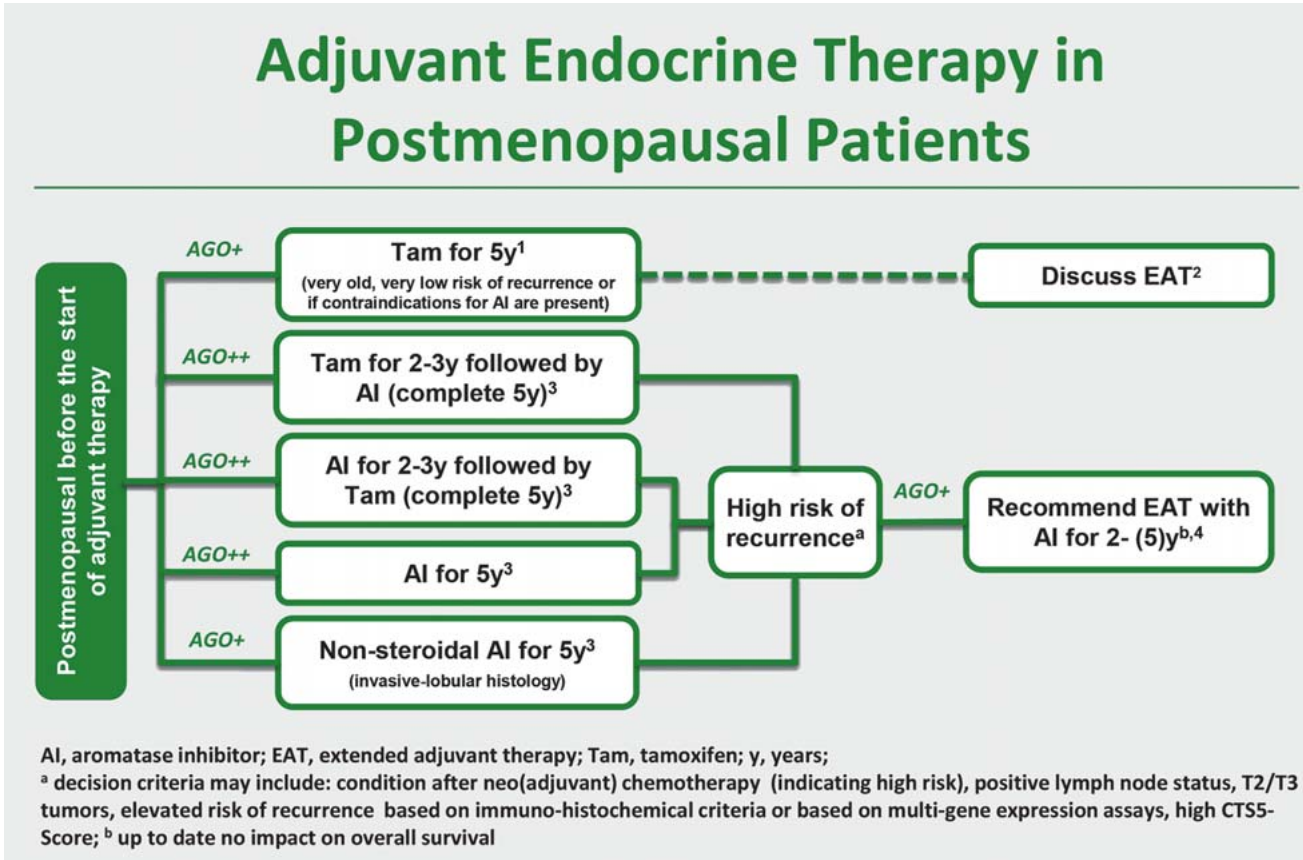
▶ **Fig. 3** Algorithm Adjuvant Endocrine Therapy in Premenopausal Patients.
[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771–784. [2] Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381: 805–806. [3] Goss PE, Ingle JN, Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005; 97: 1262–1271. [4] Francis PA, Regan MM, Fleming GF et al. The SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015; 372: 436–446. [5] Pagani O, Regan MM, Walley BA et al. TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014; 371: 107–118.

of recurrence may receive just tamoxifen, patients with a higher risk of recurrence should be treated with ovarian function suppression (OFS) in addition to tamoxifen, and patients with a higher risk of recurrence can be considered for an aromatase inhibitor and OFS (for 5 years). Patients do not need to be treated with chemotherapy prior to receiving an OFS. In the above-mentioned trials, chemotherapy can be considered as a surrogate marker for high-risk. In case a patient has a high risk of recurrence and does not for whatever reason receive (neo)adjuvant chemotherapy, the use of an AI an OFS is still indicated. In general, in HR+/HER2− breast cancer, age is an independent risk factor. Patients being amenorrheic after chemotherapy can start with Tamoxifen. OFS can be added later when the menstruation/premenopausal status has been regained. An AI should only be added when the ovarian function is sufficiently and reliably suppressed. Tamoxifen can be extended for up to 10 years. An extended adjuvant therapy with 5 years of tamoxifen should also be offered to those patients with ovarian suppression and tamoxifen or AI for their initial treatment.

If the patient is confirmed as being postmenopausal within the first 5 years, endocrine therapy can be continued after 5 years of tamoxifen with 2.5–5 years or letrozole.

Algorithm Adjuvant Endocrine Therapy in Postmenopausal Patients (▶ **Fig. 4**)

In postmenopausal women there has been an extensive discussion about the use of tamoxifen in comparison with an AI or sequential use of tamoxifen and an AI. Two metaanalyses have been published during the last years and both suggest that AIs should be preferred to tamoxifen. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, either upfront AI or sequential treatment with tamoxifen followed by an AI or vice versa was superior regarding mortality in postmenopausal patients. In summary, depending on the individual risk profile an AI should be part of the endocrine treatment in the first 5 years for at least 2–

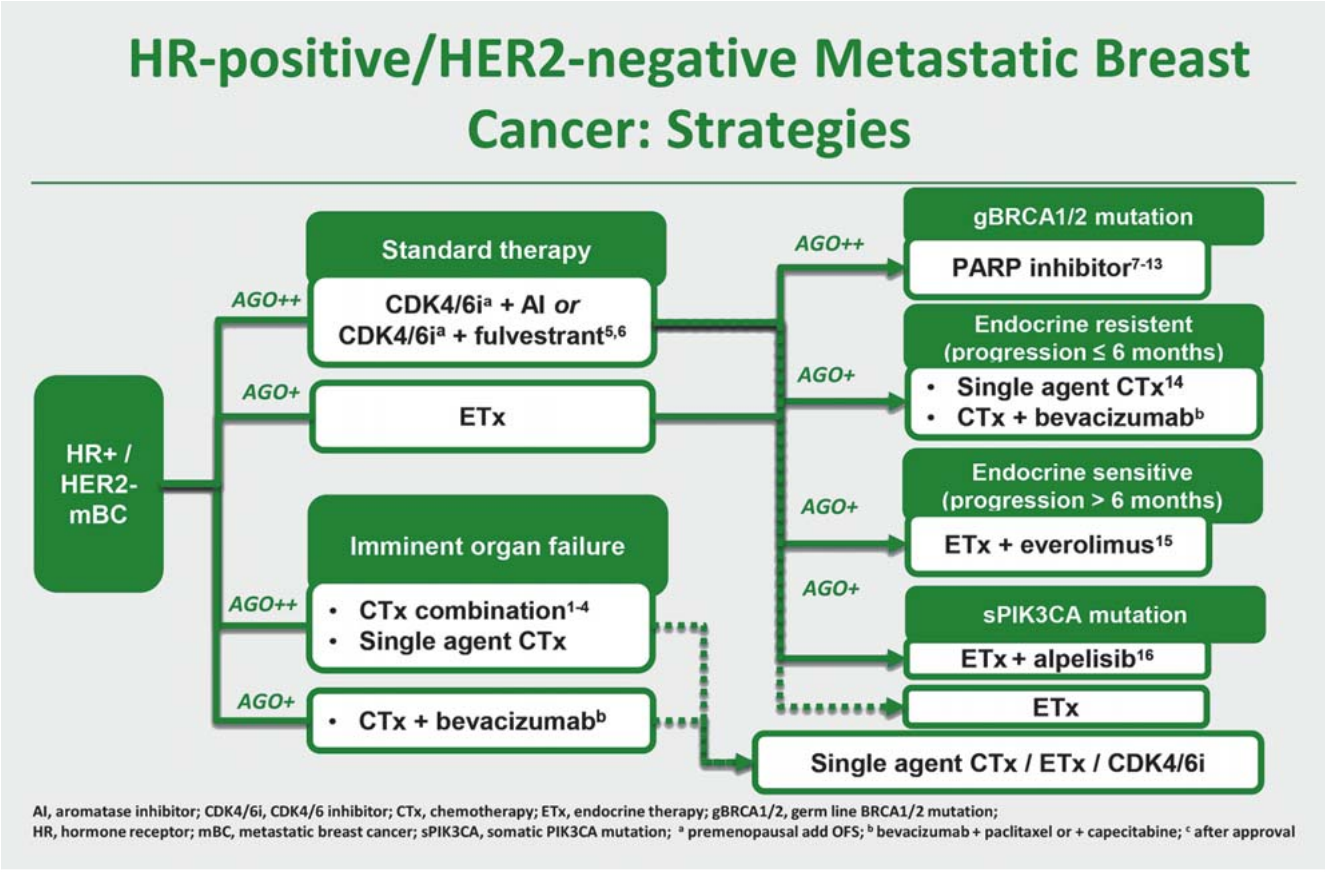


▶ **Fig. 4** Algorithm Adjuvant Endocrine Therapy in Postmenopausal Patients.
[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771–784. [2] Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381: 805–806. [3] Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015; 386: 1341–1352. [4] Gray R (EBCTCG) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22 192 women in 11 randomised trials. SABCS 2018; GS3-03.

3 years. In patients with low risk of recurrence, tamoxifen therapy upfront is still an option. After 5 years of tamoxifen, extended therapy with 5 years of tamoxifen is an option in patients with higher risk of recurrence – but switching to an AI for 2–5 years should be preferred. If patients received an AI (upfront or switch), patients at higher risk should be offered 2–5 additional years of AI. It is important to take into consideration the risk benefit and the tolerability of the endocrine therapy. Treatment can be adapted to individual needs. This is preferred to stopping prematurely.

Algorithm HR-positive/HER2-negative Metastatic Breast Cancer: Strategies (▶ Fig. 5)

Recent evidence from previous years has resulted in additional therapeutic options for treating the advanced or metastasic hormone receptor (HR-)positive and HER2-negative breast cancer. In order to reach the therapeutic goal of maintaining as high a quality of life as possible, today the endocrine-based therapy is considered to be the standard of care first-line treatment. Thus, CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) are administered in first line together with an aromatase inhibitor or fulvestrant. Only if a very rapid remission is required due to severe symptoms or impending organ failure, cytostatic drugs, if necessary combined with bevacicumab, should be used as first-line therapy. Second-line therapy options depend on the aggressiveness of progressive disease and the patient's wish for therapy. In case of a germline mutation (gBRCA1/2mt), therapy with PARP inhibitors should be offered. In addition, depending on endocrine sensitivity and resistance further endocrine mono or combination therapies are available. Besides the combination with everolimus, in case of a somatic PIK3CA mutation the use of alpelisib is a valuable therapeutic option. In case of endocrine resistance cytostatic drugs should be offered as further-line therapy.



▶ **Fig. 5** Algorithm HR-positive/HER2-negative Metastatic Breast Cancer: Strategies.

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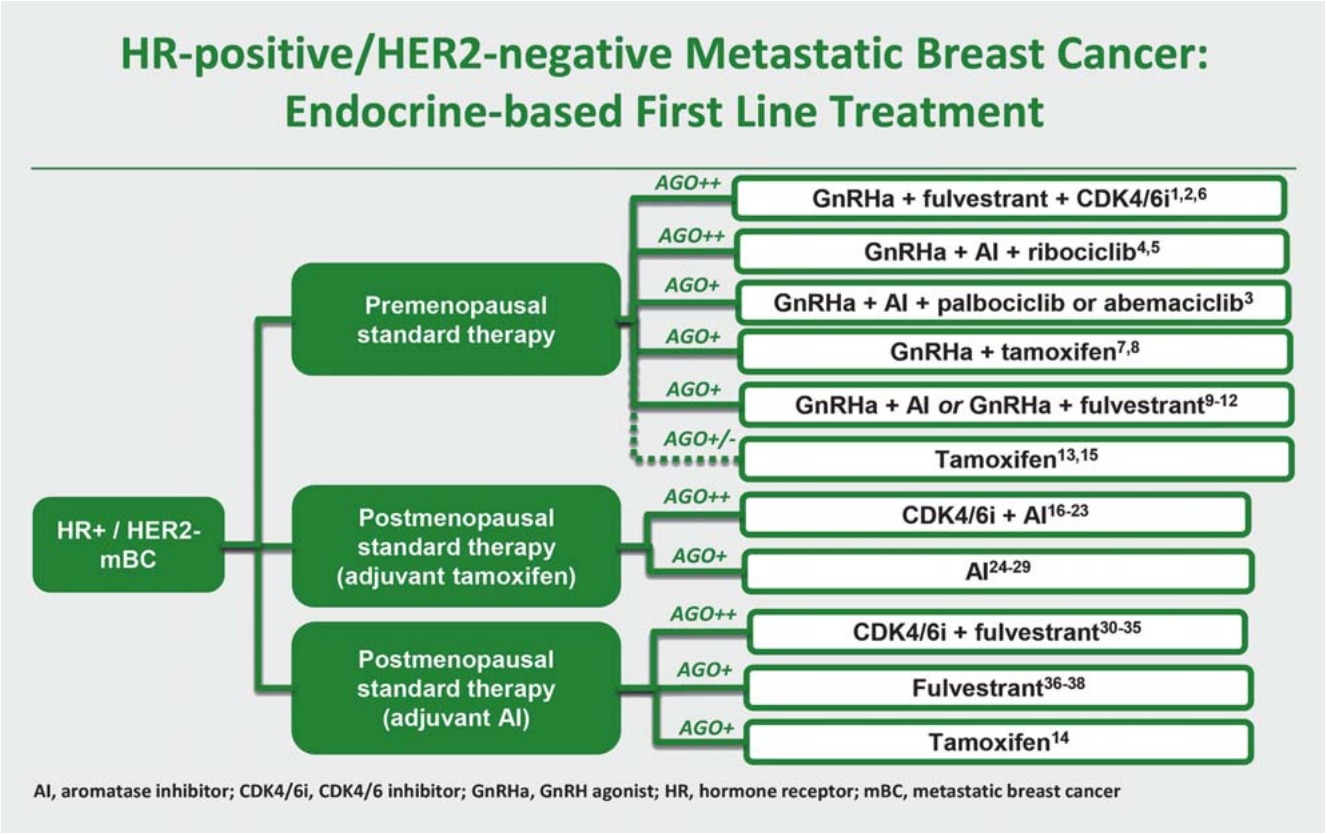
Algorithm HR-positive/HER2-negative Metastatic Breast Cancer: Endocrine-based First Line Treatment (▶ **Fig. 6**)

Data from PALOMA-, MONALEESA- and MONARCH-studies showed significant and clinically relevant improvements of progression-free survival in pre-, peri- and postmenopause if CDK4/6 inhibitors had been used. Currently, data referring to overall survival are only available for individual drug combinations in defined situations. If CDK4/6 inhibitors are not administered, the initial treatment strategy in premenopausal patients is to shutdown the ovarian function (e.g. with GnRH analogues) combined with tamoxifen. In case of tumor progression or if tamoxifen is contraindicated, a third-generation aromatase inhibitor plus a GnRH analogue can be administered. Fulvestrant plus GnRH analogue is a further option. In postmenopausal patients depending on the previous adjuvant therapy, aromatase inhibitors or tamoxifen can be administered. After a previous therapy with an aromatase inhibitor fulvestrant should be considered.



▶ **Fig. 6** Algorithm HR-positive/HER2-negative Metastatic Breast Cancer: Endocrine-based First Line Treatment.

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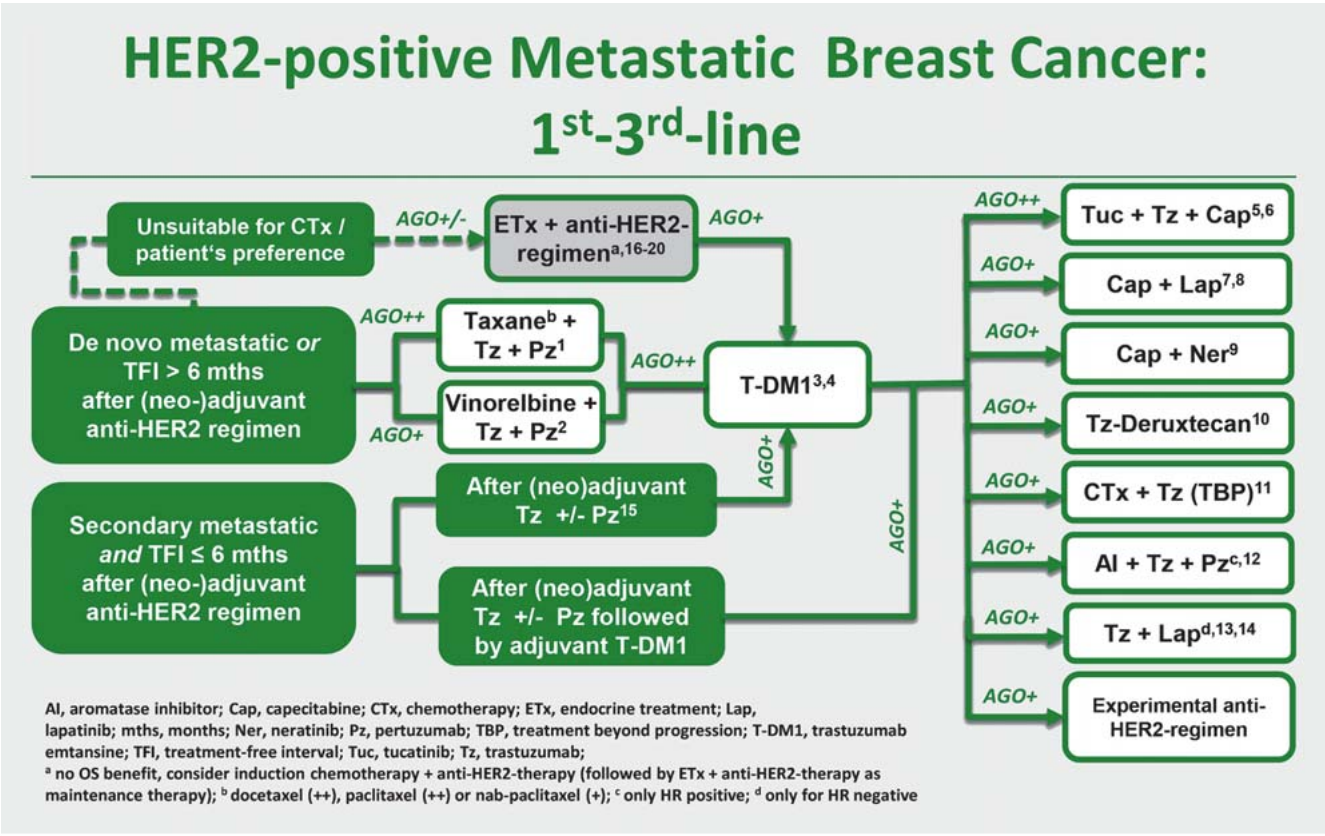
Algorithm HER2-positive Metastatic Breast Cancer: 1st–3rd line (▶ **Fig. 7**)

In HER2-positive breast cancer with de novo metastases or a treatment-free interval (TFI) > 6 months, taxane-based chemotherapy plus dual antibody blockade with trastuzumab and pertuzumab is recommended as first-line combination. In patients not suitable for chemotherapy or according to patient's preference, combination of endocrine therapy and anti-HER2 therapy might be an option. In these patients as well as in secondary metastatic breast cancer with a TFI ≤ 6 months after (neo-)adjuvant anti-HER2 treatment with dual blockade, T-DM1 is the preferred second-line option. In case of progression after two prior lines of anti-HER2 therapy, including patients after (neo)adjuvant therapy with trastuzumab +/− pertuzumab followed by adjuvant T-DM1, tucatinib in combination with trastuzumab and capecitabine is a new anti-HER2 combination therapy that results in improved overall survival. There is a plethora of further anti-HER2 treatment options including trastuzumab deruxtecan and neratinib in combination with capecitabine representing new therapeutic options in heavily pretreated patients with HER2-positive advanced breast cancer.

Algorithm Triple-negative Metastatic Breast Cancer (▶ **Fig. 8**)

In advanced or metastatic triple-negative breast cancer (TNBC) evaluation of PD-L1 status and germline BRCA mutation (gBRCAmt) is needed as a basis for standard-of-care therapy decision making because the optimal choice of therapies depends on these two biomarkers. In patients with PDL-1-negative/gBRCAwt, paclitaxel or capecitabine plus bevacizumab, cisplatin plus gemcitabine or carboplatin +/− nab-paclitaxel are recommended treatment options. In later lines, the antibody-drug-conjugate sacituzumab govitecan offers promising activity.



▶ **Fig. 7** Algorithm HER2-positive Metastatic Breast Cancer: 1st–3rd-line.

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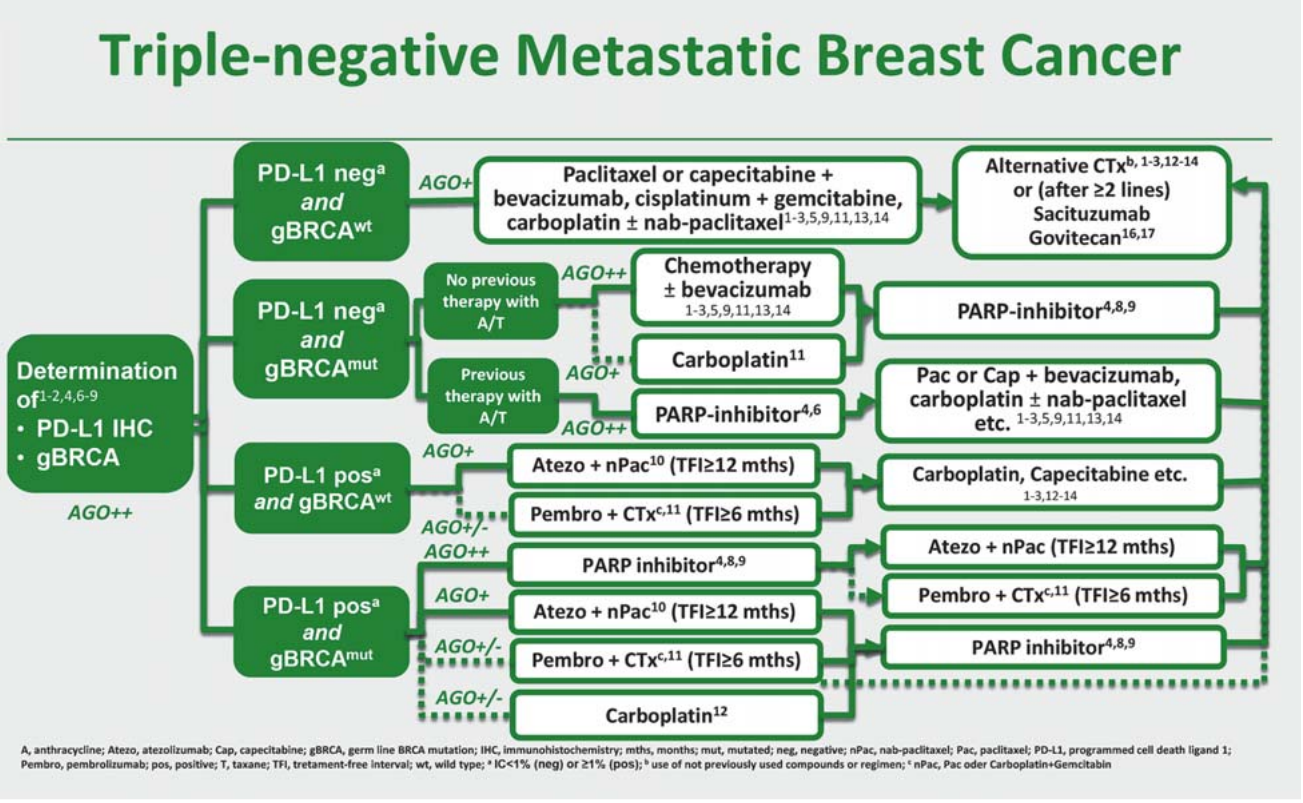

▶ **Fig. 8** Algorithm Triple-negative Metastatic Breast Cancer.

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In patients with PDL-1-negative/gBRCAmt, PARP inhibitors should be considered after anthracycline and taxane pretreatment and chemotherapy +/− bevacizumab in chemotherapy-naïve patients. For those patients with PD-L1-positive/gBRCAwt metastatic breast cancer, the combination of nab-paclitaxel and the immune checkpoint-inhibitor (ICI) atezolizumab is recommended. In addition, a combination of the ICI pembrolizumab and first-line chemotherapy (i.e. paclitaxel or nab-paclitaxel or carboplatin plus gemcitabine) could be considered. Finally, in PDL-1-positive/gBRCA mutant patients, either nab-paclitaxel plus atezolizumab or PARP inhibitors are recommended. The choice of further therapies after tumor progression depends on PD-L1 and gBRCA status, clinical presentation, pretreatments and approval status.

Conclusion

The treatment options shown in these algorithms are based on the 2021 AGO recommendations, but cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, etc. must be considered for the actual treatment choice. In individual cases, other evidence-based treatment options (not listed here) may also be appropriate and justified. However, theses treatment algorithms are intended to intensify structured treatment decision by providing reproducible and evidence-based treatment paths and may be helpful for a broad treatment landscape.

Conflict of Interest

Consultancy: Sanofi-Aventis, Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Johnson & Johnson, Seagen, MSD, PierreFabre, Amgen, Gilead, DaiichiSankyo.
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Honoraria: Sanofi-Aventis, Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Johnson & Johnson, Seagen, MSD, PierreFabre, Amgen, Gilead, DaiichiSankyo.

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