

# AGO Algorithms for the Treatment of Breast Cancer: Update 2021

## AGO-Algorithmen zur Behandlung von Brustkrebs: Update 2021



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**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 Brustkrebskrankungen 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**.

**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 escalated 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

► **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.

**Format legend:**

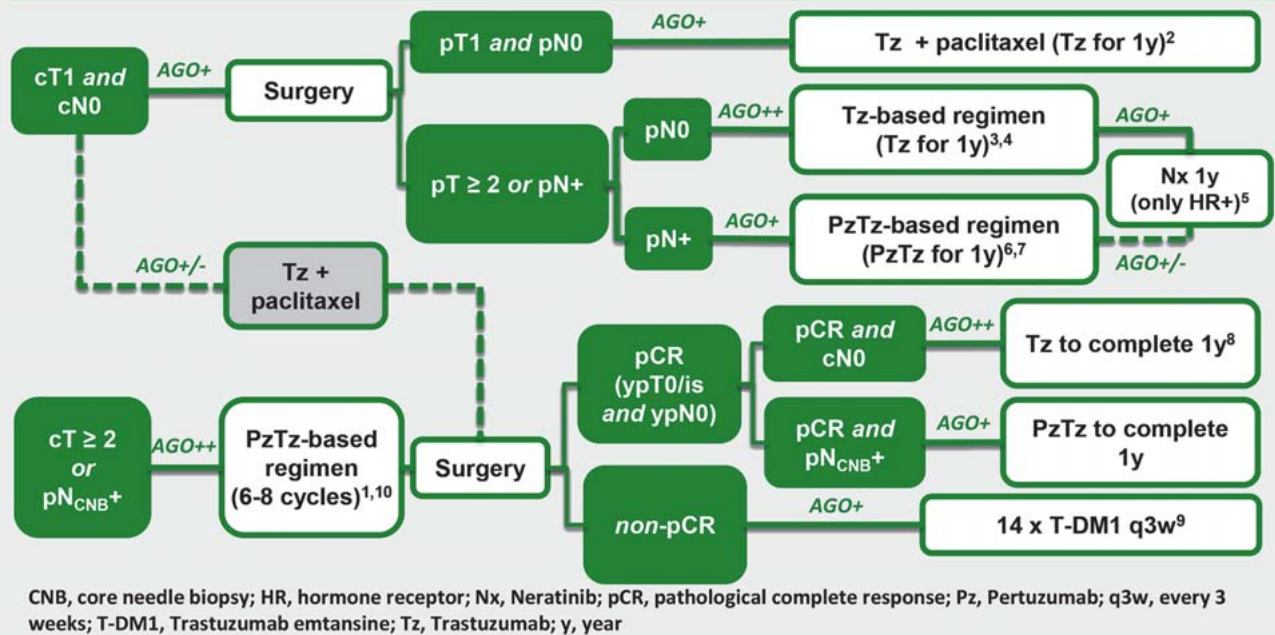
- Text Definitions, features, parameters
- Text Therapy with grade of recommendation AGO+ or AGO++
- Text Therapy with grade of recommendation AGO+/- (case by case decision)
- Recommended path with grade of recommendation AGO+ oder AGO++
- Path of case by case decision (grade of recommendation AGO+/-)
- Arrow points to the next therapy option at progression
- AGO++ AGO grade of recommendation of this path

► **Fig. 1** Format legend for the AGO algorithms.

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-

# (Neo)adjuvant Therapy of HER2-positive Breast Cancer



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

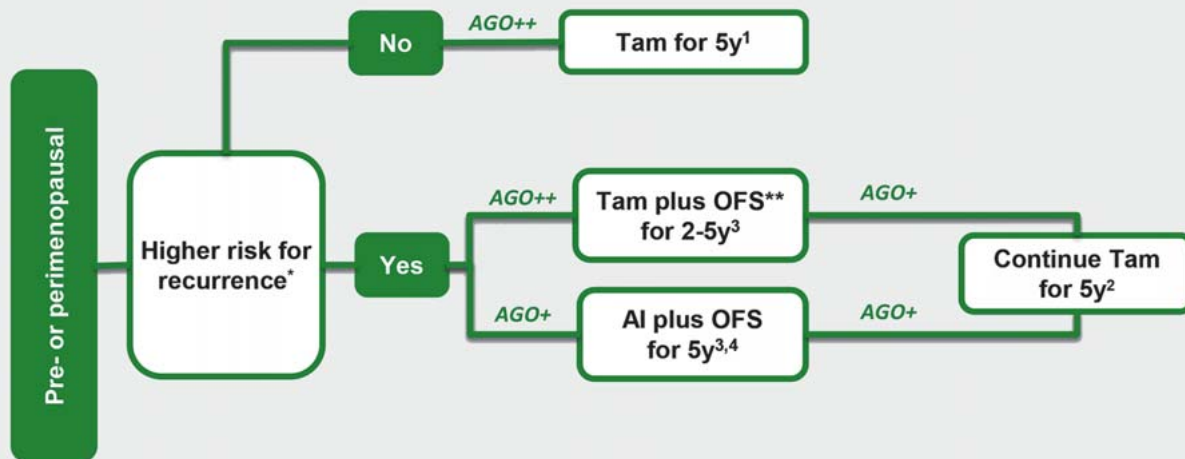
<sup>1</sup> Gianni L et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32. <sup>2</sup> Tolaney SM et al. 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. <sup>3</sup> 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. <sup>4</sup> 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. <sup>5</sup> 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. <sup>6</sup> 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. <sup>7</sup> 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*. <sup>8</sup> 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. <sup>9</sup> von Minckwitz G et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2019; 380: 617–628. <sup>10</sup> 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

## Adjuvant Endocrine Therapy in Premenopausal Patients



\* Administration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials

\*\* OFS also in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea

AI, aromatase inhibitor; OFS, ovarian function suppression; Tam, tamoxifen; y, years

► **Fig. 3** Algorithm Adjuvant Endocrine Therapy in Premenopausal Patients.

<sup>1</sup> 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. <sup>2</sup> 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. <sup>3</sup> 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. <sup>4</sup> 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. <sup>5</sup> 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 and 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.

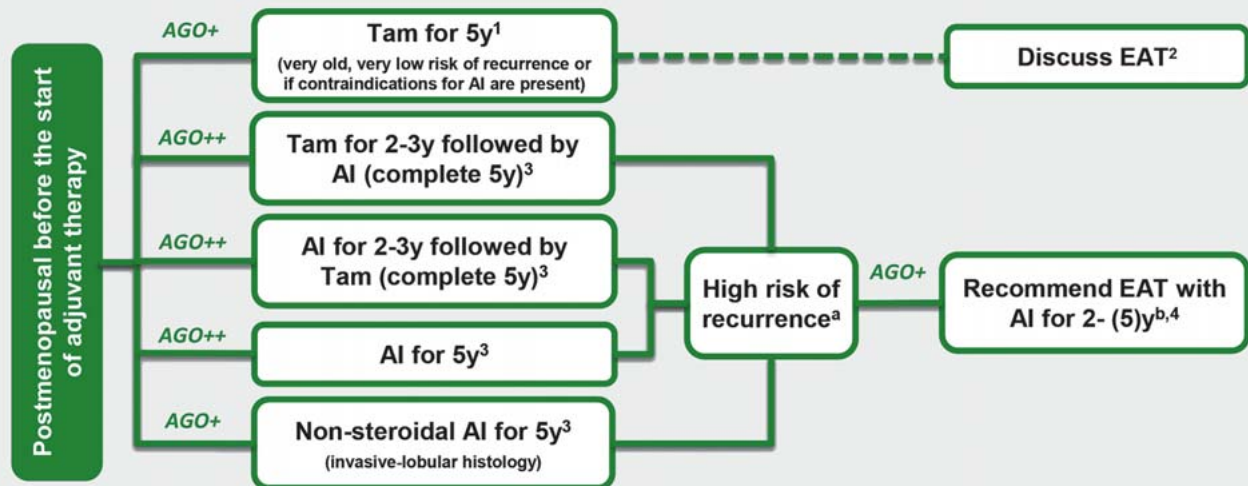
If the patient is confirmed as being postmenopausal within the first 5 years, endocrine therapy can be continued after 5 years of tamoxifen with 2.5–5 years or letrozole.

### 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 meta-analyses 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–



# Adjuvant Endocrine Therapy in Postmenopausal Patients



AI, aromatase inhibitor; EAT, extended adjuvant therapy; Tam, tamoxifen; y, years;

<sup>a</sup> decision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, high CTSS-Score; <sup>b</sup> up to date no impact on overall survival

► Fig. 4 Algorithm Adjuvant Endocrine Therapy in Postmenopausal Patients.

<sup>1</sup> 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. <sup>2</sup> 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. <sup>3</sup> 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. <sup>4</sup> 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.

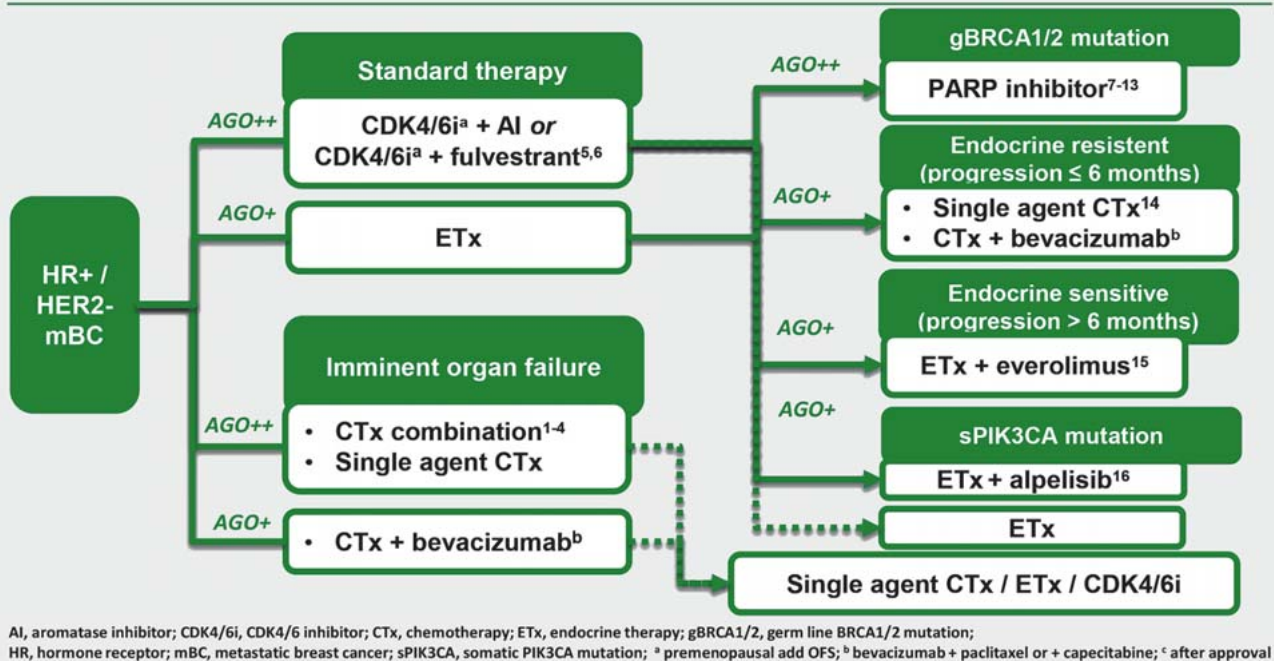
3 years. In patients with low risk of recurrence, tamoxifen therapy upfront is still an option. After 5 years of tamoxifen, extended therapy with 5 years of tamoxifen is an option in patients with higher risk of recurrence – but switching to an AI for 2–5 years should be preferred. If patients received 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 metastatic hormone receptor (HR-)positive and HER2-negative breast cancer. In order to reach the therapeutic goal of maintaining as high a qual-

ity 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 bevacicumb, 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.

# HR-positive/HER2-negative Metastatic Breast Cancer: Strategies



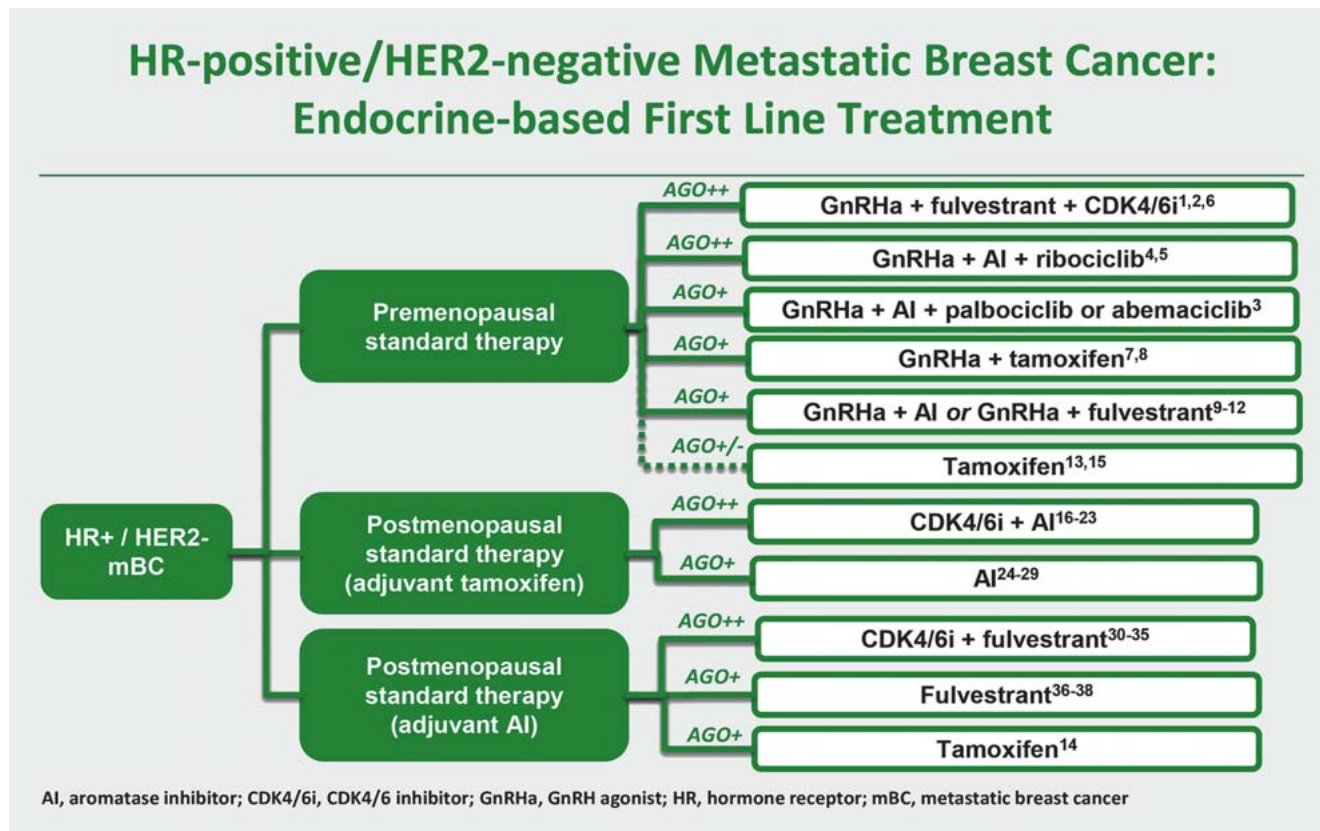
► **Fig. 5** Algorithm HR-positive/HER2-negative Metastatic Breast Cancer: Strategies.

<sup>1</sup> Qi WX, Tang LN, He AN et al. Comparison between doublet agents versus single agent in metastatic breast cancer patients previously treated with an anthracycline and a taxane: A meta-analysis of four phase III trials. *Breast* 2013; 22: 314–319. <sup>2</sup> Belfiglio M, Fanizza C, Tinari N et al., Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. *J Cancer Res Clin Oncol* 2012; 138: 221–229. <sup>3</sup> Pallis AG, Boukovinas I, Ardavanis A et al. A multicenter randomized phase III trial of vinorelbine/gemcitabine doublet versus capecitabine monotherapy in anthracycline- and taxane-pretreated women with metastatic breast cancer. *Ann Oncol* 2012; 23: 1164–1169. <sup>4</sup> Dear RF, McGeechan K, Jenkins MC et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2013; (12): CD008792. doi:10.1002/14651858.CD008792.pub2. <sup>5</sup> Petrelli F, Ghidini A, Pedersini R et al. Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019; 174: 597–604. doi:10.1007/s10549-019-05133-y. PMID: 30659432. <sup>6</sup> Rossi V, Berchiolla P, Giannarelli D et al. Should All Patients With HR-Positive HER2-Negative Metastatic Breast Cancer Receive CDK 4/6 Inhibitor As First-Line Based Therapy? A Network Meta-Analysis of Data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG and FACT Trials. *Cancers (Basel)* 2019; 11: pii: E1661. doi:10.3390/cancers11111661. <sup>7</sup> Robson M et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med* 2017; 377: 523–533. <sup>8</sup> Robson ME, Tung N, Conte P et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019; 30: 558–566. doi:10.1093/annonc/mdz012. PMID: 30689707. <sup>9</sup> Robson M, Ruddy KJ, Im SA et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. *Eur J Cancer* 2019; 120: 20–30. doi:10.1016/j.ejca.2019.06.023. PMID: 31446213. <sup>10</sup> Litton J et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018; 379: 753–763. doi:10.1056/NEJMoa180290510. <sup>11</sup> Turner NC, Telli ML, Rugo HS et al., ABRAZO Study Group. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO). *Clin Cancer Res* 2019; 25: 2717–2724. doi:10.1158/1078-0432.CCR-18-1891. PMID: 30563931. <sup>12</sup> Ettl J, Quek RGW, Lee KH et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. *Ann Oncol* 2018; 29: 1939–1947. doi:10.1093/annonc/mdy257. PMID: 30124753. <sup>13</sup> Hurvitz SA, Gonçalves A, Rugo HS et al. Talazoparib in Patients with a Germline BRCA-Mutated Advanced Breast Cancer: Detailed Safety Analyses from the Phase III EMBRACA Trial. *Oncologist* 2020; 25: e439–e450. doi:10.1634/theoncologist.2019-0493. PMID: 31767793. <sup>14</sup> Cardoso F, Senkus E, Costa A et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC4). *Ann Oncol* 2018; 29: 1634–1657. <sup>15</sup> Kornblum NS et al. PRECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy. *SABCs* 2016; #S1-02. <sup>16</sup> André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D, SOLAR-1 Study Group. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2019; 380: 1929–1940.

## 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.

<sup>1</sup> Turner N et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2015; 373: 209–219. <sup>2</sup> Loibl S et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. *Oncologist* 2017; 22: 1028–1038. <sup>3</sup> Layman RM et al. Comparative effectiveness of palbociclib plus letrozole vs. letrozole for metastatic breast cancer in US-real world clinical practises. *ESMO* 2019; #329P. <sup>4</sup> Tripathy D et al. First-line ribociclib vs. placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA-7 trial. *SABCS2017; GS-26*. <sup>5</sup> Im SA, Lu YS, Bardia A et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med* 2019; 381: 307–316. doi:10.1056/NEJMoa1903765. PMID:31166679. <sup>6</sup> Sledge GW jr., Toi M, Neven P et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. *JAMA Oncol* 2019. doi:10.1001/jamaoncol.2019.4782 [Epub ahead of print]. PMID:31563959. <sup>7</sup> Klijn JG, Blamey RW, Boccardo F et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19: 343–353. <sup>8</sup> Rugo HS et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. *J Clin Oncol* 2016; 34: 3069–3103. <sup>9</sup> Forward DP, Cheung KL, Jackson L et al. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer* 2004; 90: 590–594. <sup>10</sup> Park IH, Ro J, Lee KS et al. Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. *J Clin Oncol* 2010; 28: 2705–2711. <sup>11</sup> Carlson RW et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. *J Clin Oncol* 2010; 28: 3917–3921. <sup>12</sup> Bartsch R, Bago-Horvath Z et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. *Eur J Cancer* 2012; 48: 1932–1938. <sup>13</sup> Taylor CW, Green S, Dalton WS et al. Multicenter randomized clinical trial of



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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.

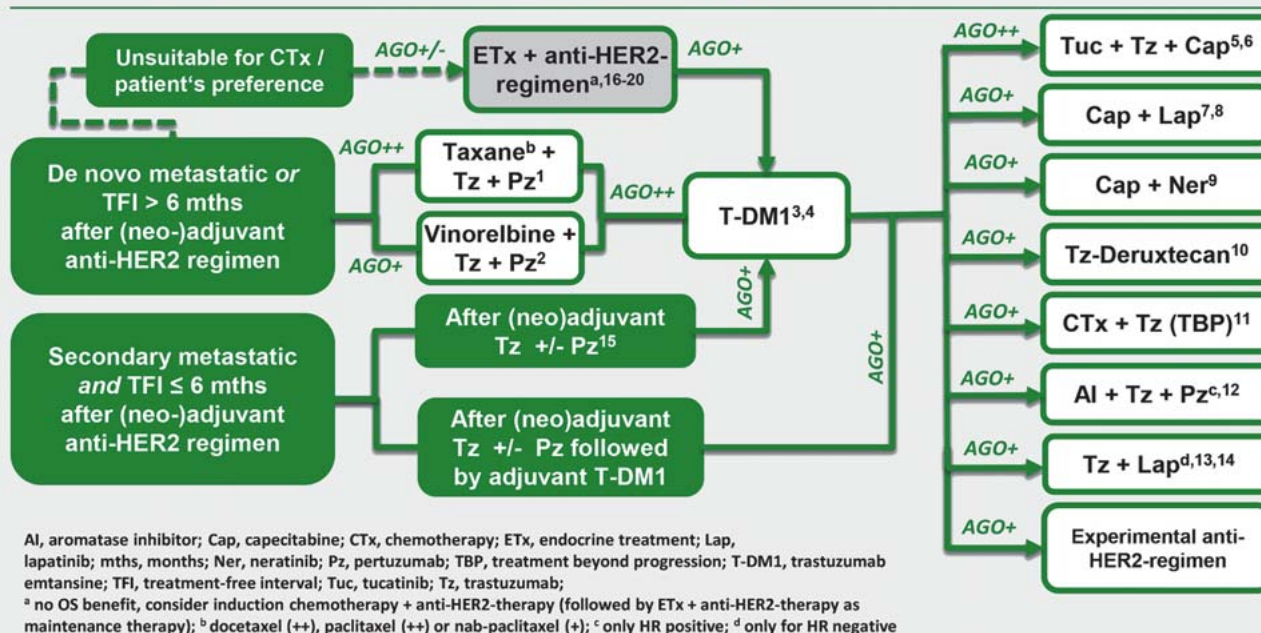
There is a plethora of further anti-HER2 treatment options including trastuzumab deruxtecan and neratinib in combination with capecitabine representing new therapeutic options in heavily pretreated patients with HER2-positive advanced breast cancer.

## 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.



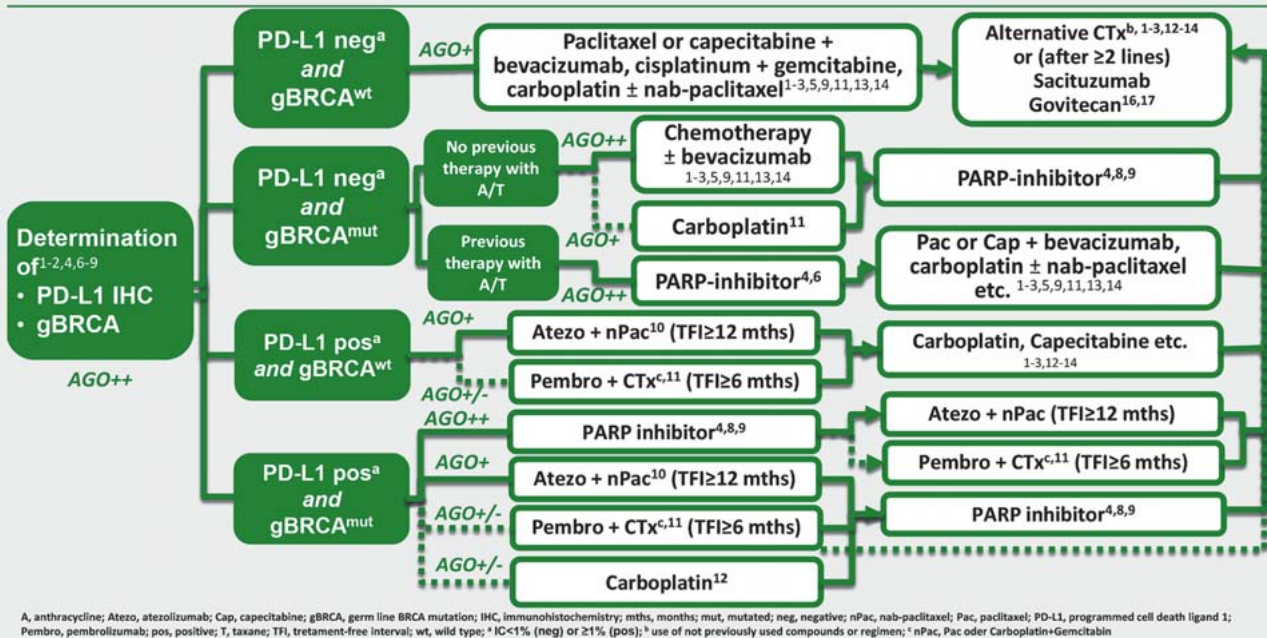
# HER2-positive Metastatic Breast Cancer: 1<sup>st</sup>-3<sup>rd</sup>-line



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

<sup>1</sup> Swain SM, Baselga J, Kim SB et al.; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372: 724–734. <sup>2</sup> Perez EA, López-Vega JM, Petit T et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res* 2016; 18: 126. <sup>3</sup> Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791. <sup>4</sup> Krop IE, Lin NU, Blackwell K et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol* 2015; 26: 113–119. <sup>5</sup> Murthy RK, Loi S, Okines A et al. 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# Triple-negative Metastatic Breast Cancer



► **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, these 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

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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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