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Guidelines Breast  
Version 2021.1E

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# Diagnosis and Treatment of Patients with Early and Advanced Breast Cancer

## Therapy algorithms

### Preamble:

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 (not listed here) 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.



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





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# Therapy Algorithms

## ■ Version 2021:

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### ■ Format legend:

-  Definitions, features, parameters
-  Therapy with grade of recommendation AGO+ or AGO++
-  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

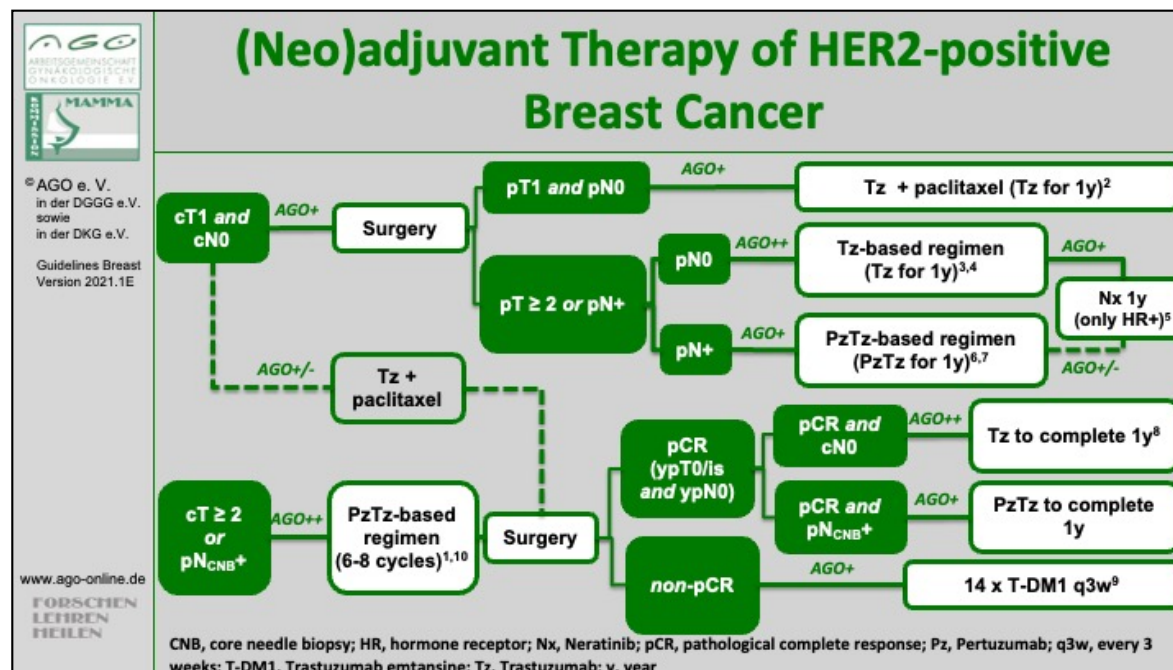
# Content

## ■ eBC

- (Neo)adjuvant therapy of HER2-positive breast cancer
- Axillary surgery and neoadjuvant chemotherapy (NACT)
- Adjuvant endocrine therapy in premenopausal patients
- Adjuvant endocrine therapy in postmenopausal patients

## ■ mBC

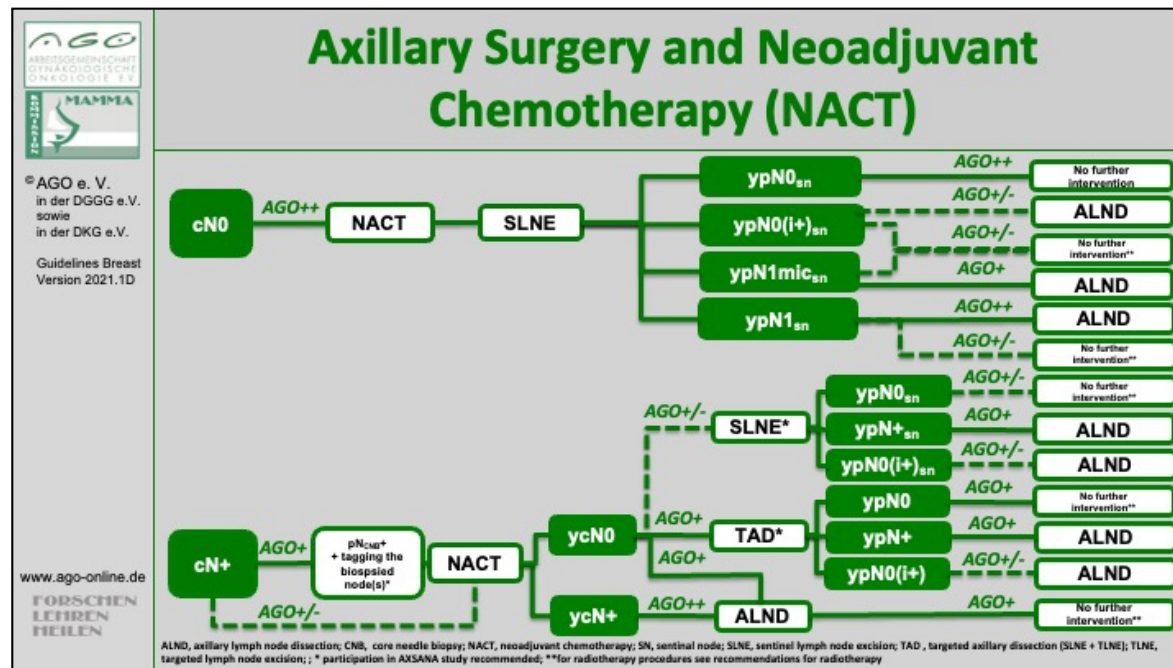
- HR-positive/HER2-negative metastatic breast cancer: strategies
- HR-positive/HER2-negative metastatic breast cancer: endocrine-based first line treatment
- HER2-positive metastatic breast cancer: 1st-3rd-line
- Triple-negative metastatic breast cancer



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(22):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;32:3744-52
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(12):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. GS 01-04

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.



Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies

1. Reimer T, Gerber B. Quality-of-life considerations in the treatment of early-stage breast cancer in the elderly. *Drugs Aging*. 2010 Oct 1;27(10):791-800.
2. Tuttle TM, Shamliyan T, Virnig BA, et al. The impact of sentinel lymph node biopsy and magnetic resonance imaging on important outcomes among patients with ductal carcinoma in situ. *J Natl Cancer Inst Monogr*. 2010;2010(41):117-20. Review.
3. Gerber B, Heintze K, Stubert J, et al. Axillary lymph node dissection in early-stage invasive breast cancer: is it still standard today? *Breast Cancer Res Treat*. 2011 Aug;128(3):613-24.
4. D'Angelo-Donovan DD, Dickson-Witmer D, Petrelli NJ. Sentinel lymph node biopsy in breast cancer: A history and current clinical recommendations. *Surg Oncol*. 2012 Jan 9.
5. Galimberti V, Cole BF, Zurrada S, et al. International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013 Apr;14(4):297-305.
6. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among

Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017 Sep 12;318(10):918-926.

Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy

1. Kuehn T, Bauerfeind I, Fehm T, et al.: Sentinel-lymph-node biopsy with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective multi-center cohort study. Lancet Oncol 2013;14(7):609-18.
2. Boughey JC, Suman VJ, Mittendorf EA, et al.: Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310(14):1455-61.
3. Fu JF, Chen HL, Yang J, et al. Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: a meta-analysis. PLoS One. 2014 Sep 11;9(9):e105316
4. Lee HD, Ahn SG, Lee SA, et al. Prospective Evaluation of the Feasibility of Sentinel Lymph Node Biopsy in Breast Cancer Patients with Negative Axillary Conversion after Neoadjuvant Chemotherapy. Cancer Res Treat. 2014 Aug 29. doi: 10.4143/crt.2013.208. [Epub ahead of print]
5. Boileau JF, Poirier B, Basik M, et al. Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: The SN FNAC Study. J Clin Oncol. 2015;33(3):258-264.
6. Boughey JC, Ballman KV, Le-Petross HAT et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). Ann Surg. 2015 Nov 26. [Epub ahead of print]
7. Ryu JM, Lee SK, Kim JY, et al. Predictive Factors for Nonsentinel Lymph Node Metastasis in Patients With Positive Sentinel Lymph Nodes After Neoadjuvant Chemotherapy: Nomogram for Predicting Nonsentinel Lymph Node Metastasis. Clin Breast Cancer. 2017 Nov;17(7):550-55
8. Galimberti V, Ribeiro Fontana SK, Maisonneuve P. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol 2016;42(3) 361-8
9. Martelli G, Miceli R, Folli S, et al. Sentinel node biopsy after primary chemotherapy in cT2 N0/1 breast cancer patients: Long-term results of a retrospective study. Eur J Surg Oncol. 2017 Nov;43(11):2012-2020.

10. Palmer JAV, Flippo-Morton T, Walsh KK, et al. Application of ACOSOG Z1071: Effect of Results on Patient Care and Surgical Decision-Making. Clin Breast Cancer. 2017 Oct 12. pii: S1526-8209(17)30492-5.
11. Fernandez-Gonzalez S, Falo C, Pla MJ, et al: The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures. Clin Breast Cancer. 2017 Sep 4. pii: S1526-8209(17)30565-7. doi: 10.1016/j.clbc.2017.08.014. [Epub ahead of print]
12. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Classe JM, Loaec C, Gimbergues P et al. Breast Cancer Res Treat 2018; doi.org/10.1007/s10549-5004-7

#### Axillary intervention after PST

1. Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg. 2018 Nov;105(12):1541-1552.
2. Balic M, Thomssen C, Würstlein R, Gnant M, Harbeck N. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.
3. Classe JM, Loaec C, Gimbergues P et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019 Jan;173(2):343-352.

#### TAD (+SLNE) after PST, if pN1 (CNB prior to PST and ycN0

1. Allweis TM, Menes T, Rotbart N et al. Ultrasound guided tattooing of axillary lymph nodes in breast cancer patients prior to neoadjuvant therapy, and identification of tattooed nodes at the time of surgery. Eur J Surg Oncol. 2019 Nov 16. pii: S0748-7983(19)31445-3.
2. Balasubramian R, Morgan C, Shaari E et al. Wire guided localisation for targeted axillary node dissection is accurate in axillary staging in node positive breast cancer following neoadjuvant chemotherapy. Eur J Surg Oncol. 2019 Dec 11. pii: S0748-7983(19)31500-8.
3. Coufal O, Zapletal O, Gabrielová L et al. Targeted axillary dissection and sentinel lymph node biopsy in breast cancer patients after

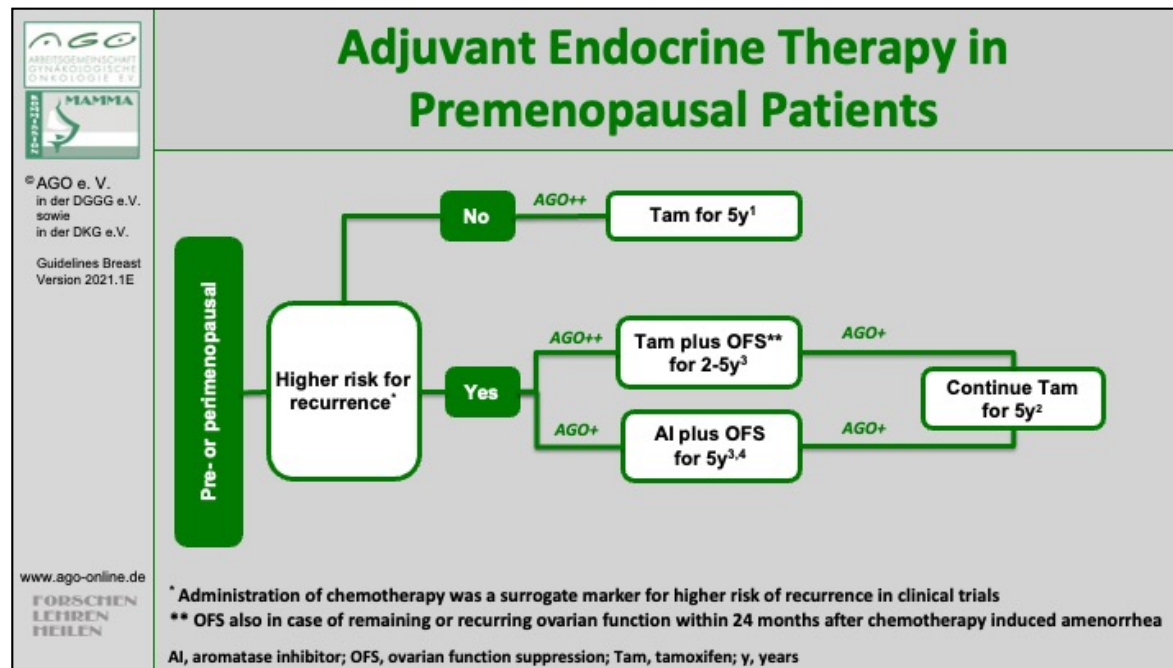


neoadjuvant chemotherapy - a retrospective study. *Rozhl Chir.* Winter 2018;97(12):551-557.

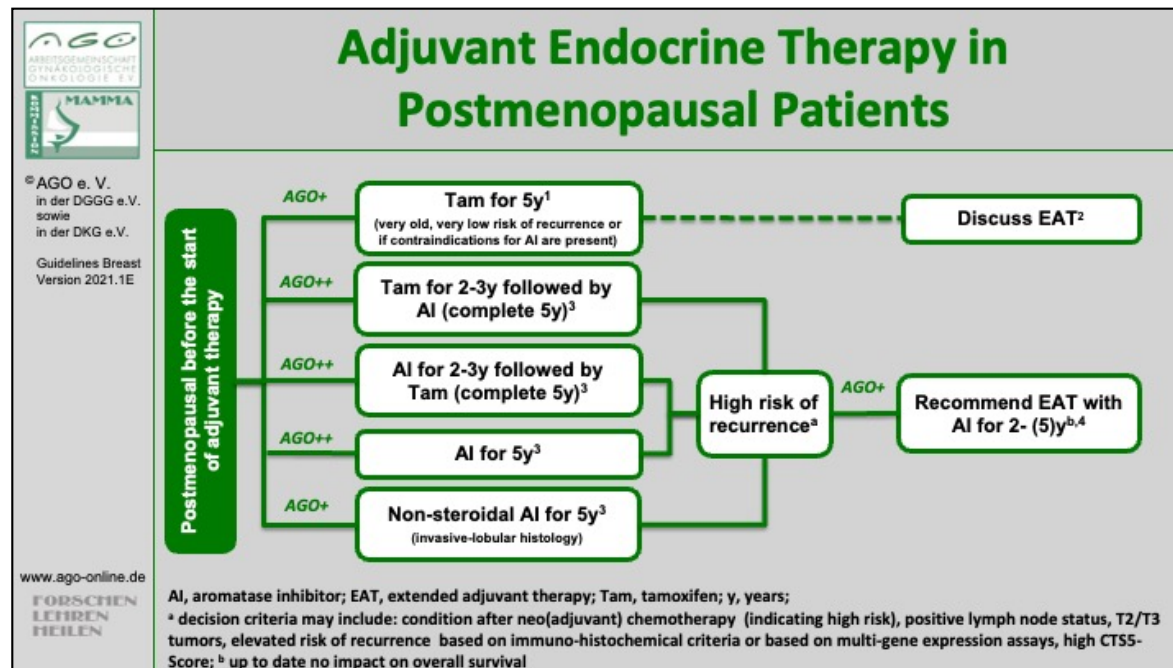
4. Ditsch N, Rubio IT, Gasparri ML et al.. Breast and axillary surgery in malignant breast disease: a review focused on literature of 2018 and 2019. *Curr Opin Obstet Gynecol.* 2020 Feb;32(1):91-99.
5. Flores-Funes D, Aguilar-Jiménez J, Martínez-Gálvez M et al. Validation of the targeted axillary dissection technique in the axillary staging of breast cancer after neoadjuvant therapy: Preliminary results. *Surg Oncol.* 2019 Sep;30:52-57. doi: 10.1016/j.suronc.2019.05.019
6. Gandhi A, Coles C, Makris A et al. Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology. *Clin Oncol (R Coll Radiol).* 2019 Sep;31(9):664-668.
7. García-Moreno JL, Benjumeda-Gonzalez AM, Amerigo-Góngora M et al. Targeted axillary dissection in breast cancer by marking lymph node metastasis with a magnetic seed before starting neoadjuvant treatment. *J Surg Case Rep.* 2019 Dec 4;2019(11):rjz344.
8. Greenwood HI, Wong JM, Mukhtar RA et al. Feasibility of Magnetic Seeds for Preoperative Localization of Axillary Lymph Nodes in Breast Cancer Treatment. *AJR Am J Roentgenol.* 2019 Oct;213(4):953-957.
9. Hellingman D, Donswijk ML, Winter-Warnars GAO et al. Feasibility of radioguided occult lesion localization of clip-marked lymph nodes for tailored axillary treatment in breast cancer patients treated with neoadjuvant systemic therapy. *EJNMMI Res.* 2019 Oct 24;9(1):94.
10. Kanesalingam K, Sriram N, Heilat G et al. Targeted axillary dissection after neoadjuvant systemic therapy in patients with node-positive breast cancer. *ANZ J Surg.* 2019 Dec 17. doi: 10.1111/ans.15604.
11. Natsiopoulou I, Intzes S, Liappis T et al. Axillary Lymph Node Tattooing and Targeted Axillary Dissection in Breast Cancer Patients Who Presented as cN+ Before Neoadjuvant Chemotherapy and Became cN0 After Treatment. *Clin Breast Cancer.* 2019 Jun;19(3):208-215.
12. Simons JM, van Nijnatten TJA, van der Pol CC et al. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Meta-analysis. *Ann Surg.* 2019 Mar;269(3):432-442.
13. Simons JM, van Pelt MLMA, Marinelli AWKS et al. Excision of both pretreatment marked positive nodes and sentinel nodes

improves axillary staging after neoadjuvant systemic therapy in breast cancer. Br J Surg. 2019 Nov;106(12):1632-1639.

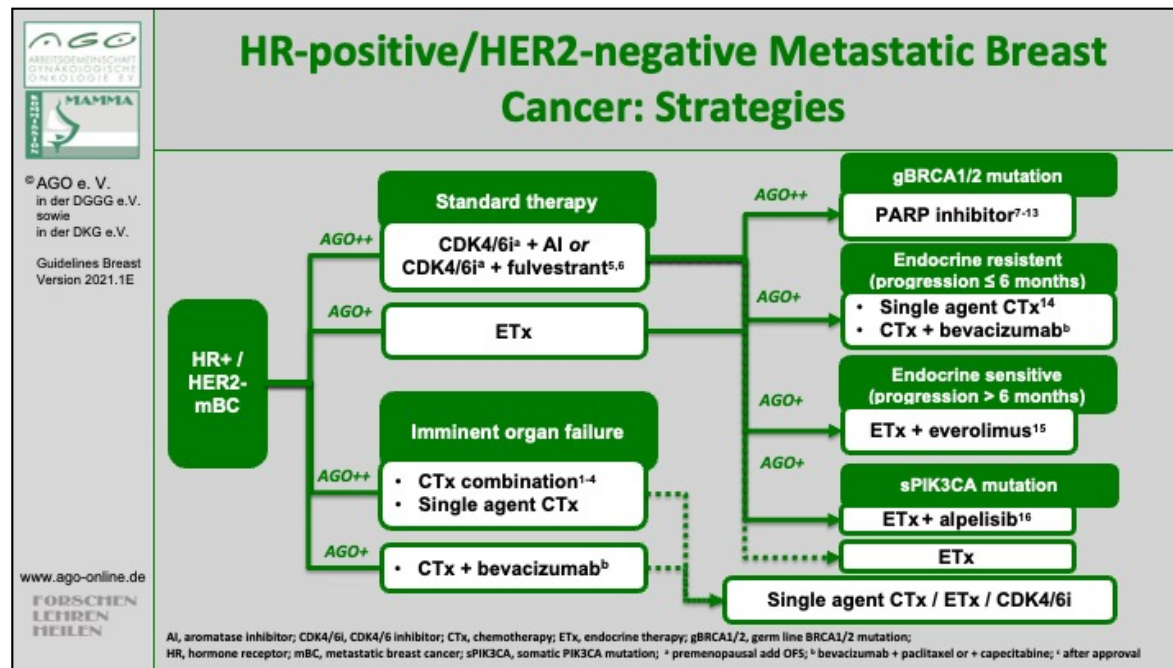
14. Tee SR, Devane LA, Evoy D et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg. 2018 Nov;105(12):1541-1552



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;378:771-84.
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(17):1262-71.
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(5):436-46.
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(2):107-18.



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;378:771-84.
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(10001):1341-52.
4. Gray R (EBCTCG ) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03



### Chemotherapy mBC

1. 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(3):314-9;
2. 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(2):221-9.
3. 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(5):1164-9.
4. Cochrane analysis Dear RF, McGeechan K, Jenkins MC, et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2013 Dec 18;(12):CD008792. doi: 10.1002/14651858.CD008792.pub

### CDK4/6i metaanalysis

1. 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 Apr;174(3):597-604. doi:810.1007/s10549-019-05133-y. PMID:30659432

2. Rossi V, Berchialla 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 Oct 26;11(11). pii: E1661. doi: 10.3390/cancers11111661.

### Olaparib

1. Robson M, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med.* 2017;377(6):523-533.
2. 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 Apr 1;30(4):558-566. doi: 10.1093/annonc/mdz012. PMID:30689707
3. 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 Oct;120:20-30. doi: 10.1016/j.ejca.2019.06.023. PMID:31446213

### Talazoparib

1. 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
2. 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 May 1;25(9):2717-2724. doi: 10.1158/1078-0432.CCR-18-1891. PMID:30563931
3. 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 Sep 1;29(9):1939-1947. doi: 10.1093/annonc/mdy257. PMID:30124753

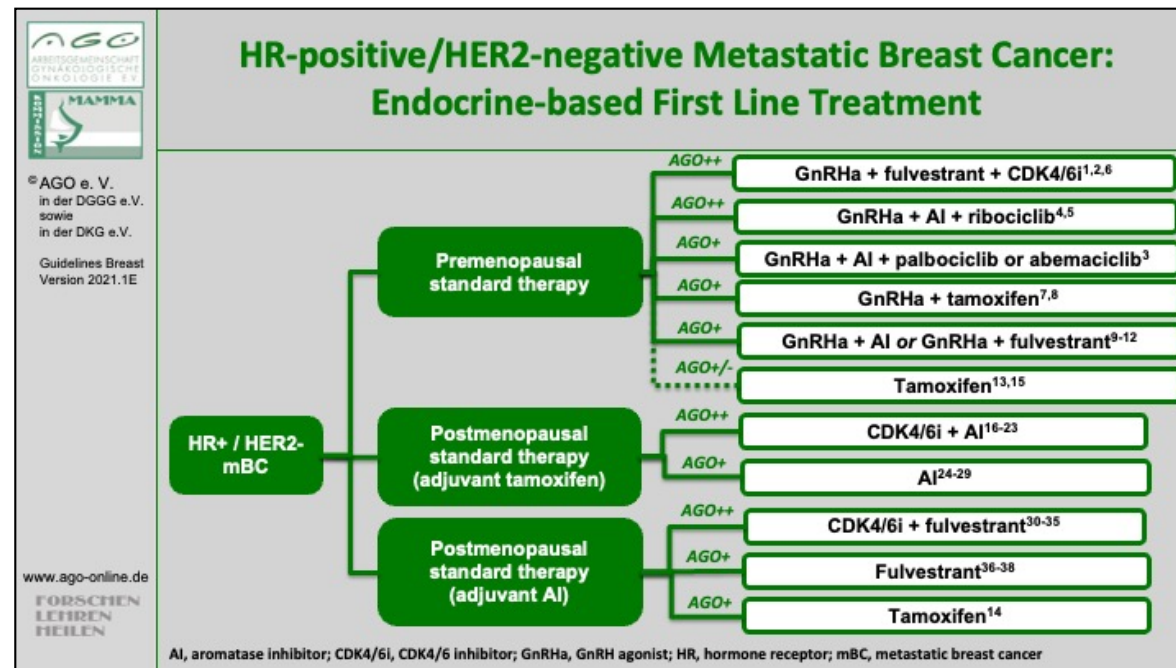
4. Hurvitz SA, Gonçalves A, Rugo HS, et al., Talazoparib in Patients with a Germline BRCA-Mutated Advanced Breast Cancer: Detailed Safety Analyses from the Phase III EMBRACA Trial. *Oncologist*. 2019 Nov 25. pii: theoncologist.2019-0493. doi: 10.1634/theoncologist.2019-0493. [Epub ahead of print] PMID:31767793

#### Chemotherrapy 2th line

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol*. 2018;29(8):1634-1657

#### ET+ Ev/Alp

1. 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
2. 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 May 16;380(20):1929-1940.



### GnRHa plus fulvestrant plus palbociclib

1. Turner N et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015; 373:209-219
2. 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(9):1028-1038.

### GnRHa plus AI plus palbociclib

1. 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

### GnRHa plus AI/Tamoxifen plus ribociclib

1. 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. SABCS 2017, GS-26



2. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med. 2019 Jul 25;381(4):307-316. doi: 10.1056/NEJMoa1903765. PMID:31166679

#### GnRH plus Fulvestrant + Abemaciclib

1. 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 Sep 29. doi: 10.1001/jamaoncol.2019.4782. [Epub ahead of print] PMID:31563959

#### GnRHa plus tamoxifen (vs. OFS or tam)

1. 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(2):343-53.
2. Rugo HS, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016 ;34(25):3069-103.

#### GnRHa plus AI (first or second line)

1. 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(3):590-4.
2. 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(16):2705-11.
3. 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(25):3917-21.

#### GnRHa plus fulvestrant

1. Bartsch R, Bago-Horvath Z, et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. *European Journal of Cancer* 48: 1932–1938, 2012.

#### Ovarian function suppression (OFS), tamoxifen

1. Taylor CW, Green S, Dalton WS, et al: Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998;16:994-999.
2. Osborne CK: Tamoxifen in the treatment of breast cancer. *N Engl J Med* 1998;339
3. Crump M, Sawka CA, DeBoer G, et al: An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first line endocrine therapy for premenopausal women with metastatic breast cancer. *Breast Cancer Res Treat* 1997;44:201-210.

#### Letrozole and palbociclib (vs. letrozole alone)

1. Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016;375(20):1925-1936.
2. Finn RS, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16(1):25-35.
3. Im SA, Mukai H, Park IH, et al. Palbociclib Plus Letrozole as First-Line Therapy in Postmenopausal Asian Women With Metastatic Breast Cancer: Results From the Phase III, Randomized PALOMA-2 Study. *J Glob Oncol*. 2019 May;5:1-19. doi: 10.1200/JGO.18.00173. PMID:31125276
4. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019 Apr;174(3):719729. doi: 10.1007/s10549-018-05125-4. PMID:30632023

#### Letrozol plus Ribociclib

1. Hortobagyi GN, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 2016;375(18):17381748.

2. Yardley DA, Hart L, Favret A, et al. Efficacy and Safety of Ribociclib With Letrozole in US Patients Enrolled in the MONALEESA-2 Study. Clin Breast Cancer. 2019 Aug;19(4):268-277.e1. doi: 10.1016/j.clbc.2019.02.007.

#### Non-steroidal AI plus Abemaciclib

1. Goetz MP, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017 ;35(32):3638-3646.
2. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 Jan 17;5:5. doi: 10.1038/s41523-018-0097-z. eCollection 2019. PMID:30675515

#### Aromatase inhibitors

1. Bonnetterre J, et al: Anastrozole versus Tamoxifen as First-Line Therapy for Advanced Breast Cancer in 668 Postmenopausal Women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and tolerability Study. J Clin Oncol 2000;18:3748-3757
2. Thürlimann B, et al: Anastrozole (Arimidex) versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95 – a substudy of the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) trial. Breast Cancer Res Treat 2004;85:247-254
3. Bonnetterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92
4. Mouridsen, H, et al, Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group Journal of Clinical Oncology. J Clin Oncol. 2003;21(11):2101-9.
5. Paridaens R, et al; European Organization for the Research and Treatment of Cancer (EORTC)- Investigational Drug Branch for Breast Cancer (IDBBC). Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol. 2003 Sep;14(9):1391-8.
6. Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2009;(4):CD003370. 5. Xu HB, Liu YJ, Li L. Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: a literature-based meta-analysis. Clin Breast Cancer. 2011;11(4):246-51.

#### Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone)

1. Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul 16;373(3):209-19.
2. Turner NC et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer N Engl J Med 2018; 379:1926-1936 DOI: 10.1056/NEJMoa1810527

#### Fulvestrant plus Ribociclib

1. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472. doi: 10.1200/JCO.2018.78.9909. PMID:29860922
2. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2019 Dec 11. doi: 10.1056/NEJMoa1911149. [Epub ahead of print]

#### Fulvestrant plus Abemaciclib

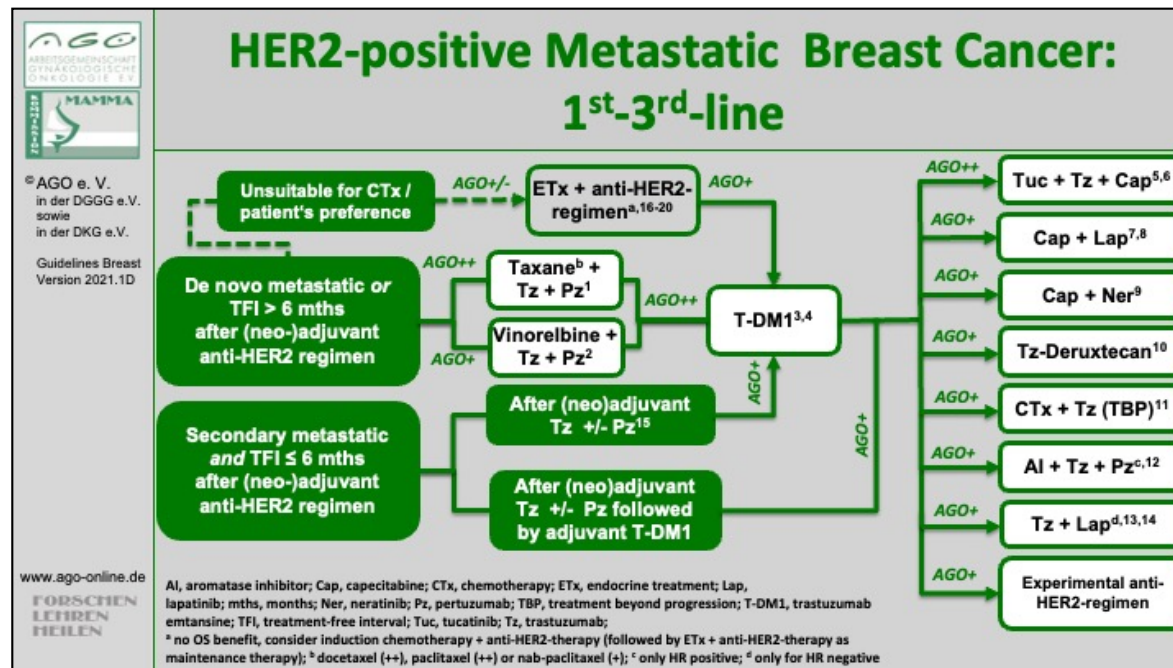
1. Sledge GW Jr, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875-2884.
2. Sledge GW Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2019 Sep 29. doi: 10.1001/jamaoncol.2019.4782. [Epub ahead of print] PMID:31563959

#### Fulvestrant 500 mg (vs. anastrozole)

1. Ellis MJ, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol. 2015;33(32):3781-7
2. Robertson JF, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON):

an international, randomised, double-blind, phase 3 trial. Lancet. 2016 ;388(10063):2997-3005.

3. Di Leo A, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337.



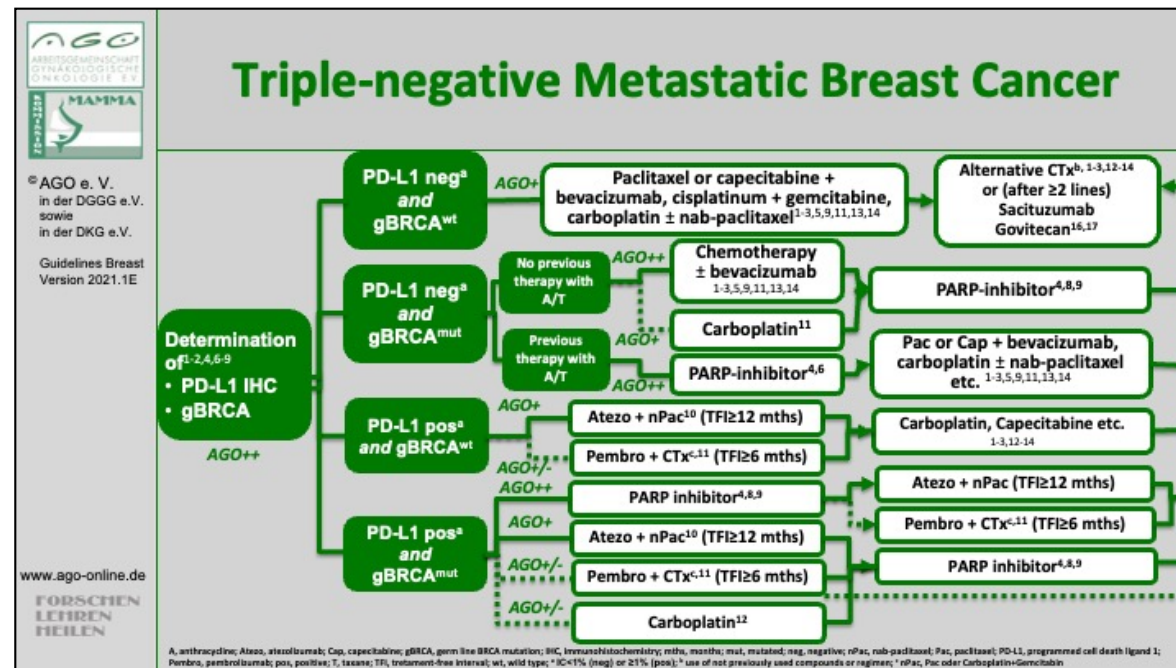
1. Swain SM, Baselga J, Kim SB, et al. CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372(8):724-34.
2. Perez EA, López-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab 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(1):126.
3. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91
4. 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(1):113-9.
5. Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020; 382 (7): 597–609.

6. Lin NU, Borges V, Anders C et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *J Clin Oncol* 2020; 38 (23): 2610–2619.
7. Cameron D, Casey M, Press M et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat* 2008;112(3):533-43.
8. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355(26):2733–2743.
9. Saura C, Oliveira M, Feng Y-H et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With  $\geq 2$  HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol* 2020; 38 (27): 3138–3149.
10. Modi S, Saura C, Yamashita T, et al. Trastuzumab-Deruxtecan in previously treated HER2-positive breast cancer. *New Eng J Med* 2020; DOI: 10.1056/NEJMoa1914510
11. von Minckwitz G, Schwedler K, Schmidt M, GBG 26/BIG 03-05 study group and participating investigators et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011;47(15):2273-81.
12. Rimawi M, Ferrero J-M, La Haba-Rodriguez J de et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. *J Clin Oncol* 2018; 36 (28): 2826–28.
13. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol* 2012;30(21):2585-92.
14. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women

with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28(7):1124-30

15. Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:2078-99
16. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27(33):5529-37.
17. Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. Breast. 2012;21(1):27-33.
18. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27(33):5538-46.
19. Burstein HJ, Cirincione CT, Barry WT et al. Endocrine Therapy With or Without Inhibition of Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Fulvestrant With or Without Lapatinib for Postmenopausal Women With Hormone Receptor-Positive Advanced Breast Cancer-CALGB 40302 (Alliance). J Clin Oncol 2014;32:3959-3966.
20. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. PERTAIN Study Group. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol 2018;36(28):2826-2835. DOI: 10.1200/JCO.2017.76.7863. PMID:30106636





- Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634-1657
- Condorelli R, Mosele F, Verret B, et al. Genomic alterations breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2019; 30; 365-373
- Hu XC, Zhang J, Xu BH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2015;16(4):436-46.
- Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-763.
- Miles DW, Diéras V, Cortés J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013;24(11):2773-80.
- Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med

(2007) 357(26):2666–2676.

7. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* (2005) 23(4):792–799.
8. Robson M, Im S-A, Senkus E et al: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med* 2017;377:523-533
9. Robson M, Tung N, Conte P. et al. Qlympia AD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metasttic breast cancer. *Ann Oncol* 2019;30:558-566
10. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018 Nov 29;379(22):2108-2121.
11. Cortes J, Cescon DW, Rugo HS et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* 2020; 396 (10265): 1817–1828.
12. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med*. 2018;24(5):628-637
13. Twelves C, Cortes J, Vahdat L, et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies [published correction appears in *Breast Cancer Res Treat*. 2015 Jan;149(1):313]. *Breast Cancer Res Treat*. 2014;148(3):553-561.
14. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. *Ann Oncol*. 2018;29(8):1763-1770.
15. Zielinski C, Láng I, Inbar M, et al TURANDOT investigators. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as

first line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, noninferiority, phase 3 trial. *Lancet Oncol* 2016;17(9):1230-9.

16. Bardia A, Tolaney SM, Loirat D et al. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). *Ann Oncol* 2020 (31 (suppl\_4)): S1142-S1215. 10.1016/annonc/annonc325.
17. Bardia A, Mayer IA, Vahdat LT et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. *N Engl J Med* 2019; 380 (8): 741–751.