



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2022.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

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, special tumor biology 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.

Therapy Algorithms

- **Version 2021:**
Schneeweiss / Bauerfeind / Fehm / Müller / Thomssen / Witzel / Wöckel / Janni
- **Version 2022:**
Schneeweiss/ Müller with the Breast Committee of the AGO
- **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++
 - Crossing without transition
 - Path of case by case decision (grade of recommendation AGO+/-)
 - Arrow points to the next therapy option
 - AGO grade of recommendation of this path

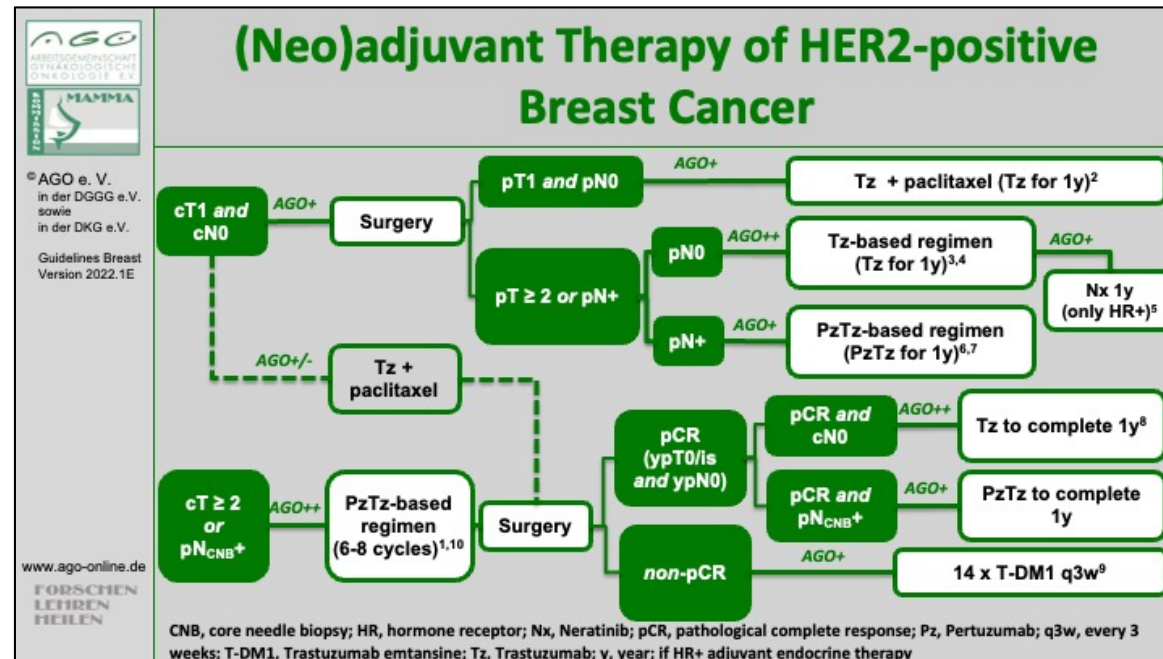
Content

■ eBC

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

■ mBC

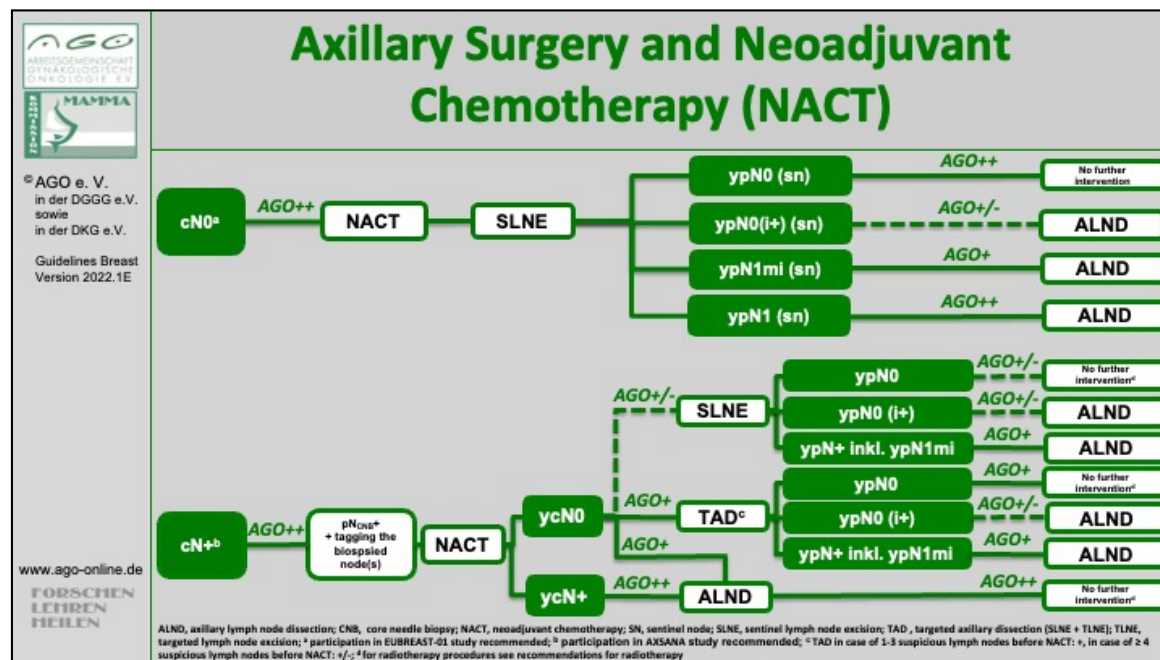
- HR-positive / HER2-negative metastatic breast cancer: strategies
- HR-positive / HER2-negative metastatic breast cancer: endocrine-based first line treatment
- HER2-positive metastatic breast cancer: 1st-3rd-line
- Triple-negative metastatic breast cancer



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. Chan A, Moy B, Mansi J, et al.; ExteNET Study Group. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. *Clin Breast Cancer.* 2021;21(1):80-91
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.

9. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.
10. Schmid P, Cortes J, Puztai L et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.
11. P. Schmid, J. Cortes, R. Dent et al. KEYNOTE-522: Phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC). ESMO 2021 Abstract #VP7_2021

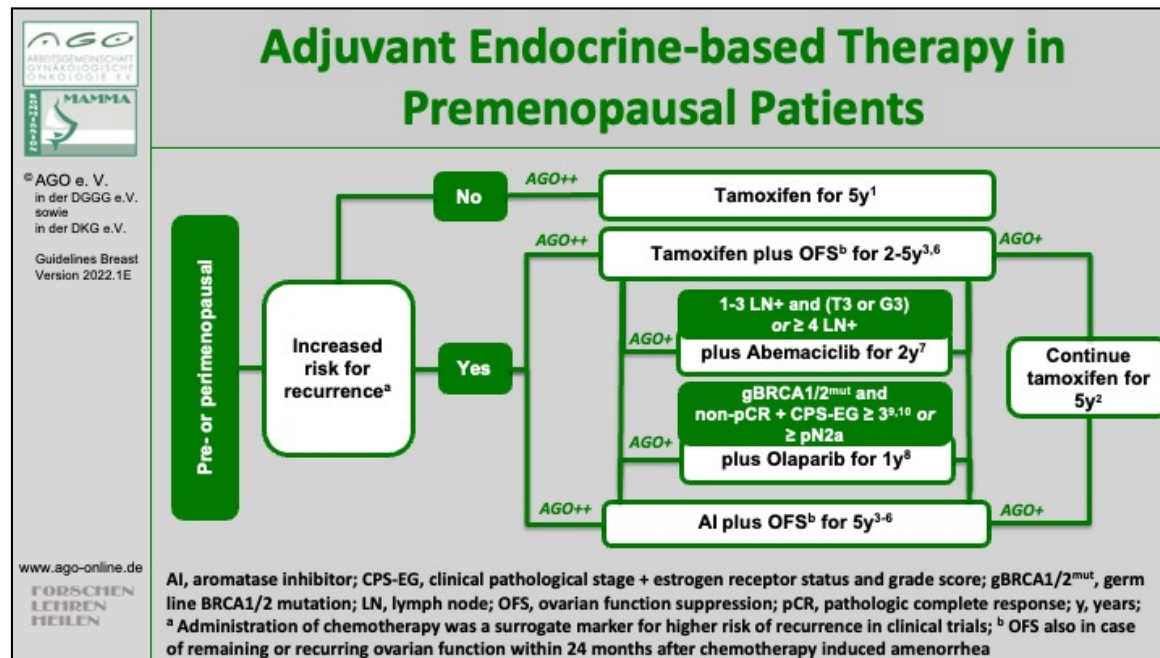


1. Giuliano AE, Ballman, KV, McCall L et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The acosog z0011 (alliance) randomized clinical trial. JAMA 2017, 318, 918-926
2. Reimer TS, Nekljudova V, Loibl, S et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/i t1-2) in the context of breast conserving therapy: First results following commencement of the intergroup-sentinel-mamma (insema) trial. Geburtsh Frauenheilk 2017, 77, 149-157
3. Gion M, Pérez-García JM, Llombart-Cussac A et al. Surrogate endpoints for early-stage breast cancer: a review of the state of the art, controversies, and future prospects. Ther Adv Med Oncol 2021, 13:17588359211059587.
4. Chiec, L.; Shah A.N. Risk-based Approaches for Optimizing Treatment in HER2-Positive Early Stage Breast Cancer. Semin Oncol 2020, 47:249-258.
5. Cortazar, P.; Geyer, C.E., Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol 2015, 22, 1441-1446.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018, 19, 27-39.
7. Cirier, J.; Body, G.; Jourdan, M.L.; Bedouet, L.; Fleurier, C.; Pilloy, J.; Arbion, F.; Ouldamer, L. [impact of pathological complete response to neoadjuvant chemotherapy in invasive breast cancer according to molecular subtype]. Gynecologie, obstetrique, fertilité & senologie 2017, 45, 535-544.

8. Gustavo Werutsky, G.; Untch, M.; Hanusch, C.; Fasching, P.A.; Blohmer, J.U.; Seiler, S.; Denkert, C.; Tesch, H.; Jackisch, C.; Gerber, B., et al. Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. *Eur J Cancer* 2020, 130, 92-101.
9. Kuehn, T.; Bauerfeind, I.; Fehm, T.; Fleige, B.; Hausschild, M.; Helms, G.; Lebeau, A.; Liedtke, C.; von Minckwitz, G.; Nekljudova, V., et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (sentina): A prospective, multicentre cohort study. *Lancet Oncol* 2013, 14, 609-618.
10. Boughey, J.C.; Suman, V.J.; Mittendorf, E.A.; Ahrendt, G.M.; Wilke, L.G.; Taback, B.; Leitch, A.M.; Kuerer, H.M.; Bowling, M.; Flippo-Morton, T.S., 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, 1455-1461.
11. Carter, S.; Neuman, H.; Mamounas, E.P.; Bedrosian, I.; Moulder, S.; Montero, A.J.; Jagsi, R. Debating the optimal approach to nodal management after pathologic complete response to neoadjuvant chemotherapy in patients with breast cancer. *American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting 2019*, 39, 42-48.
12. Simons, J.M.; van Nijnatten, T.J.A.; van der Pol, C.C.; Luiten, E.J.T.; Koppert, L.B.; Smidt, M.L. 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, 269, 432-442.
13. Tee, S.R.; Devane, L.A.; Evoy, D.; Rothwell, J.; Geraghty, J.; Prichard, R.S.; McDermott, E.W. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg* 2018, 105, 1541-1552.
14. Schneeweiss, A.; Mobus, V.; Tesch, H.; Hanusch, C.; Denkert, C.; Lubbe, K.; Huober, J.; Klare, P.; Kummel, S.; Untch, M., et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (geparocto-gbg 84): A randomised phase iii trial. *Eur J Cancer* 2019, 106, 181-192.
15. Barron, A.U.; Hoskin, T.L.; Day, C.N.; Hwang, E.S.; Kuerer, H.M.; Boughey, J.C. Association of low nodal positivity rate among patients with erbb2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. *JAMA surgery* 2018.
16. Samiei, S.; Simons, J.M.; Engelen, S.M.E.; Beets-Tan, R.G.H.; Classe, J.M.; Smidt, M.L. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: A systematic review and meta-analysis. *JAMA surgery* 2021, e210891.
17. Tadros, A.B.; Yang, W.T.; Krishnamurthy, S.; Rauch, G.M.; Smith, B.D.; Valero, V.; Black, D.M.; Lucci, A., Jr.; Caudle, A.S.; DeSnyder, S.M., et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. *JAMA surgery* 2017, 152, 665-670.

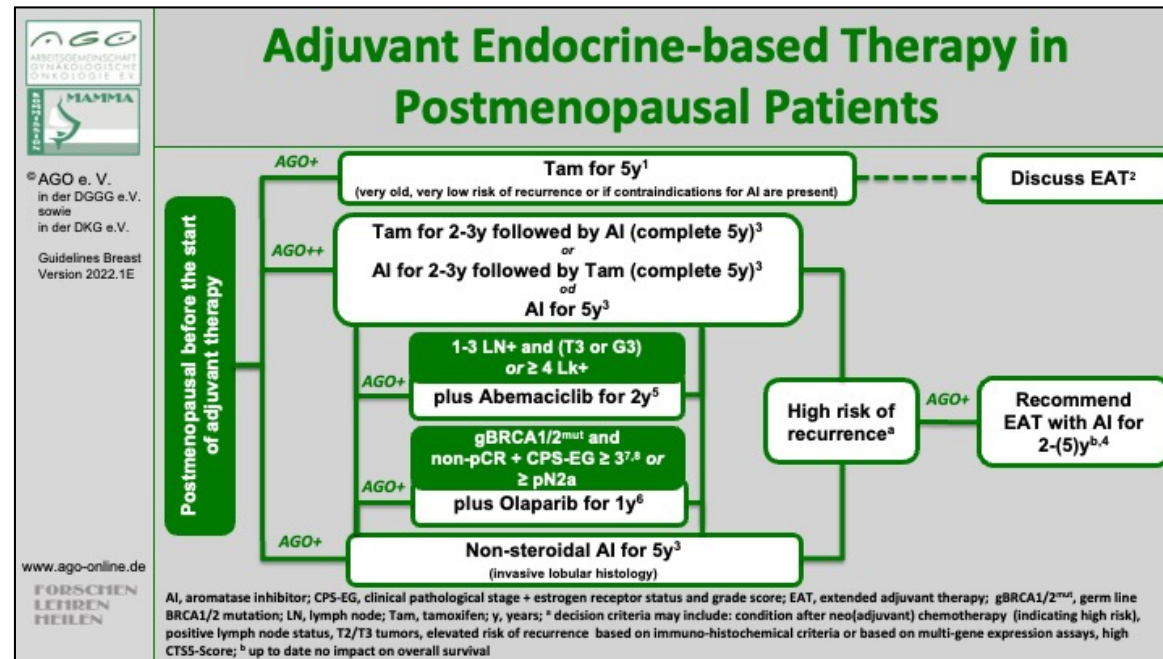
18. Samiei, S.; van Nijnatten, T.J.A.; de Munck, L.; Keymeulen, K.; Simons, J.M.; Kooreman, L.F.S.; Siesling, S.; Lobbes, M.B.I.; Smidt, M.L. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. *Ann Surg* 2018.
19. Kuemmel, S.; Heil, J.; Rueland, A.; Seiberling, C.; Harrach, H.; Schindowski, D.; Lubitz, J.; Hellerhoff, K.; Ankel, C.; Graßhoff, S.T., et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (tad) in node-positive breast cancer patients. *Ann Surg* 2020.
20. Banys-Paluchowski, M.; Gasparri, M.L.; de Boniface, J.; Gentilini, O.; Stickeler, E.; Hartmann, S.; Thill, M.; Rubio, I.T.; Di Micco, R.; Bonci, E.A., et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: Current status, knowledge gaps, and rationale for the eubrest-03 axsana study. *Cancers* 2021, 13.
21. Hartmann, S.; Kühn, T.; de Boniface, J.; Stachs, A.; Winckelmann, A.; Frisell, J.; Wiklander-Bråkenhielm, I.; Stubert, J.; Gerber, B.; Reimer, T. Carbon tattooing for targeted lymph node biopsy after primary systemic therapy in breast cancer: Prospective multicentre tattoo trial. *Br J Surg* 2021.
22. Barrio, A.V.; Montagna, G.; Mamtani, A.; Sevilimedu, V.; Edelweiss, M.; Capko, D.; Cody, H.S., 3rd; El-Tamer, M.; Gemignani, M.L.; Heerdt, A., et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-a rare event. *JAMA oncology* 2021.
23. Wong S.M.; Almana N.; Choi J.; Hu J.; Gagnon H.; Natsuhara K.; Shen A.H.; DeSantis S.; Dominici L.; Golshan M.; Weiss A.; Bellon J.; Mittendorf E.A.; King T.A. Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer. *Ann Surg Oncol* 2019, 26:3502-3509.
24. Canavese G.; Tinterri C.; Carli F.; Garrone E.; Spinaci S.; Della Valle A.; Barbieri E.; Marrazzo E.; Bruzzi P.; Dozin B.; Correlation between outcome and extent of residual disease in the sentinel node after neoadjuvant chemotherapy in clinically fine-needle proven node-positive breast cancer patients. *Eur J Surg Oncol* 2021, 47:1920-1927.
25. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; Stempel, M.; Raiss, M.; Mamtani, A.; Tadros, A.B.; El-Tamer, M.; Morrow, M. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. *Ann Surg Oncol* 2019, 26:4238-4243.
26. Boughey, J.C.; Ballman, K.V.; Hunt, K.K.; McCall, L.M.; Mittendorf, E.A.; Ahrendt, G.M.; Wilke, L.G.; Le-Petross, H.T. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: Results from the american college of surgeons oncology group z1071 trial (alliance). *J Clin Oncol* 2015, 33, 3386-3393.
27. Schwentner, L.; Helms, G.; Nekljudova, V.; Ataseven, B.; Bauerfeind, I.; Ditsch, N.; Fehm, T.; Fleige, B.; Hauschild, M.; Heil, J., et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - results from the multi-center sentina trial. *Breast* 2017, 31, 202-207.

28. Le-Petross, H.T.; McCall, L.M.; Hunt, K.K.; Mittendorf, E.A.; Ahrendt, G.M.; Wilke, L.G.; Ballman, K.V.; Boughey, J.C. Axillary ultrasound identifies residual nodal disease after chemotherapy: Results from the american college of surgeons oncology group z1071 trial (alliance). *AJR Am J Roentgenol* 2018, 210, 669-676.
29. Kim, W.H.; Kim, H.J.; Park, H.Y.; Park, J.Y.; Chae, Y.S.; Lee, S.M.; Cho, S.H.; Shin, K.M.; Lee, S.Y. Axillary pathologic complete response to neoadjuvant chemotherapy in clinically node-positive breast cancer patients: A predictive model integrating the imaging characteristics of ultrasound restaging with known clinicopathologic characteristics. *Ultrasound in medicine & biology* 2019, 45, 702-709.
30. Liedtke, C.; Gorlich, D.; Bauerfeind, I.; Fehm, T.; Fleige, B.; Helms, G.; Lebeau, A.; Staebler, A.; Ataseven, B.; Denkert, C., et al. Validation of a nomogram predicting non-sentinel lymph node metastases among patients with breast cancer after primary systemic therapy - a transsentina substudy. *Breast Care (Basel)* 2018, 13, 440-446.
31. Moo, T.A.; Jochelson, M.S.; Zabor, E.C.; Stempel, M.; Raiss, M.; Mamtani, A.; Tadros, A.B.; El-Tamer, M.; Morrow, M. Is clinical exam of the axilla sufficient to select node-positive patients who downstage after nac for slnb? A comparison of the accuracy of clinical exam versus mri. *Ann Surg Oncol* 2019, 26, 4238-4243.
32. Kantor, O.; Sipsy, L.M.; Yao, K.; James, T.A. A predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer. *Ann Surg Oncol* 2018, 25, 1304-1311.
- 33.

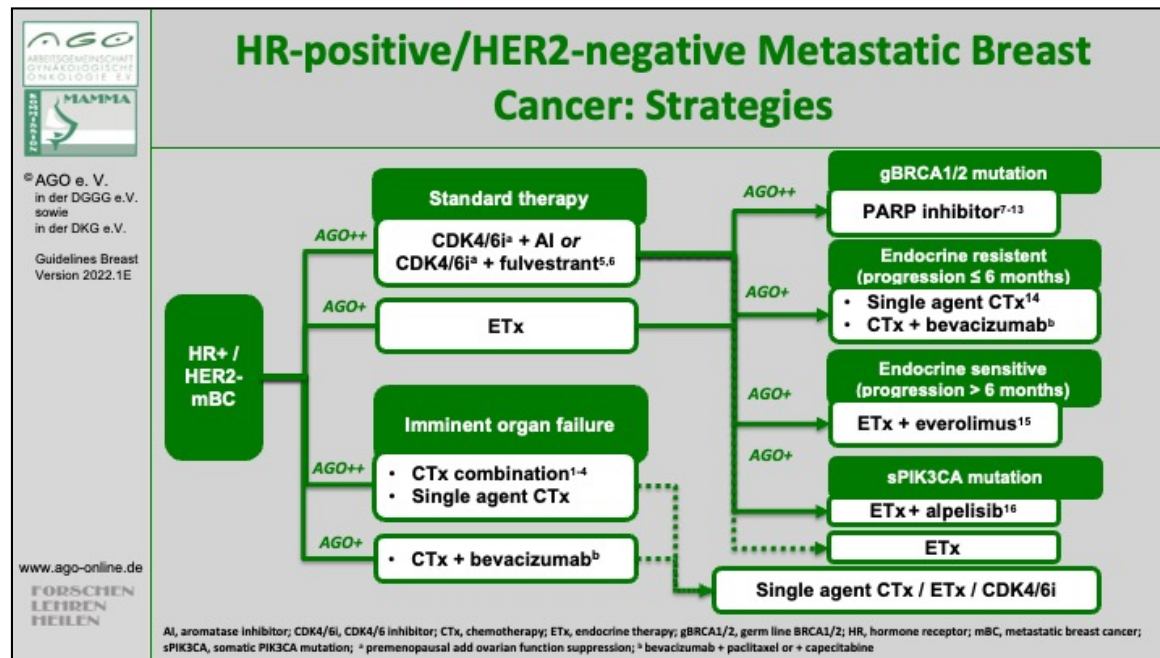


1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771-84.
2. Davies C, Pan H, Godwin J et al. Long-term effects of continuing 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. 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.
4. 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.
5. Bradley R, Braybrooke J, Gray R et al. Aromatase Inhibitors versus Tamoxifen in premenopausal women with ER + early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7.030 women in four randomised trials. *SABCS 2021, GS2-04*.
6. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. *SABCS 2021, GS2-05*.
7. Harbeck N, Rastogi P, Martin M, et al. MonarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol.* 2021;32:1571-1581.

8. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. 2021;384(25):2394-2405.
9. Mittendorf EA, Jeruss JS, Tucker SL, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol*. 2011;29:1956-62.
10. Loibl S, Weber K, Huober J, et al. Risk Assessment after Neoadjuvant Chemotherapy in Luminal Breast Cancer Using a Clinicomolecular Predictor. *Cancer Res*. 2018;24:3358-3365.



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
5. Harbeck N, Rastogi P, Martin M, et al. MonarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol.* 2021;32:1571-1581.
6. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med.* 2021;384(25):2394-2405.
7. Mittendorf EA, Jeruss JS, Tucker SL, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol.* 2011;29:1956-62.
8. Loibl S, Weber K, Huober J, et al. Risk Assessment after Neoadjuvant Chemotherapy in Luminal Breast Cancer Using a Clinicomolecular Predictor. *Cancer Res.* 2018;24:3358-3365.



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 meta-analysis

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:10.1007/s10549-019-05133-y. PMID:30659432

2. 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 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; 379:753763 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

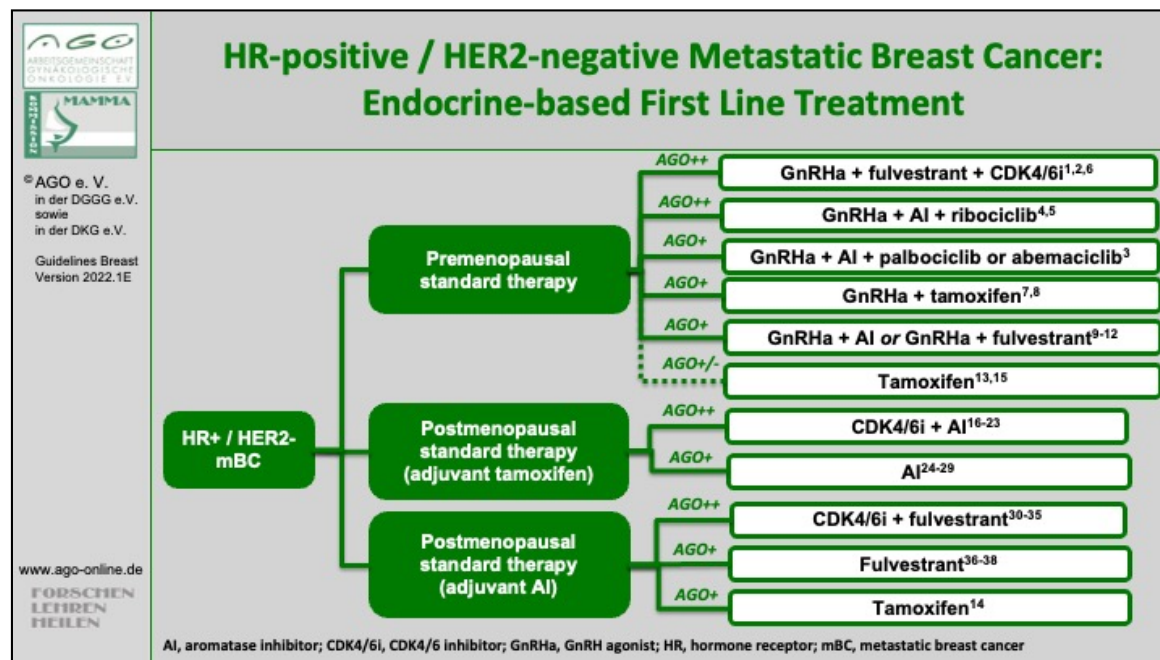
Chemotherrapy 2th line

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

3. DeMichele A, Cristofanilli M, Brufsky A et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. Breast Cancer Res. 2021 Mar 24;23(1):37.

GnRHa plus AI/Tamoxifen plus ribociclib

4. 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
5. 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

6. 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)

7. 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.
8. 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)

9. 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.
10. 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.
11. 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

12. 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

13. 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.
14. Osborne CK: Tamoxifen in the treatment of breast cancer. N Engl J Med 1998;339

15. 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)

16. Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016;375(20):1925-1936.
17. Finn RS, Rugo HS, Gelmon KA, Cristofanilli M, et al. (2021) Long-Term Pooled Safety Analysis of Palbociclib in Combination with Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Updated Analysis with up to 5 Years of Follow-Up. *Oncologist* 26:e749-e755.
18. 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
19. 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

20. Hortobagyi GN, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 2016;375(18):17381748.
21. 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

22. Goetz MP, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017 ;35(32):3638-3646.
23. 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

24. Bonneterre 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

25. 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
26. Bonnetterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma *Cancer* 2001 92
27. 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.
28. 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.
29. 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)

30. Turner NC et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer *N Engl J Med* 2018.
31. 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

32. 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
33. 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

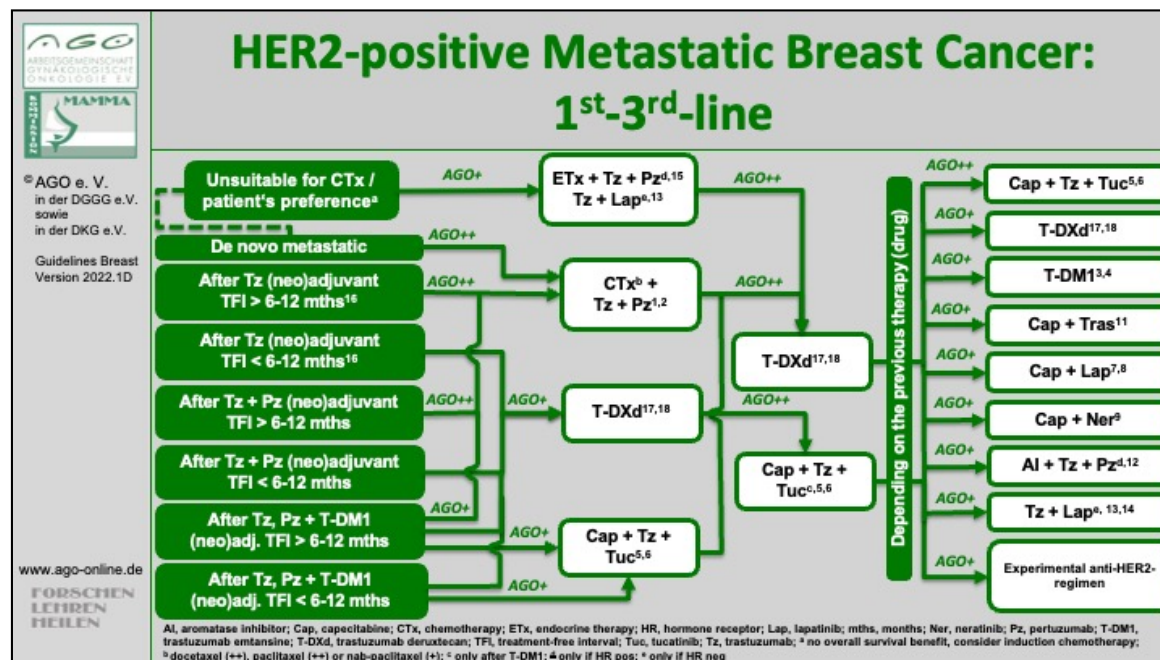
34. Sledge GW Jr, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast

Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875-2884.

35. 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)

36. 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
37. 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.
38. 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.

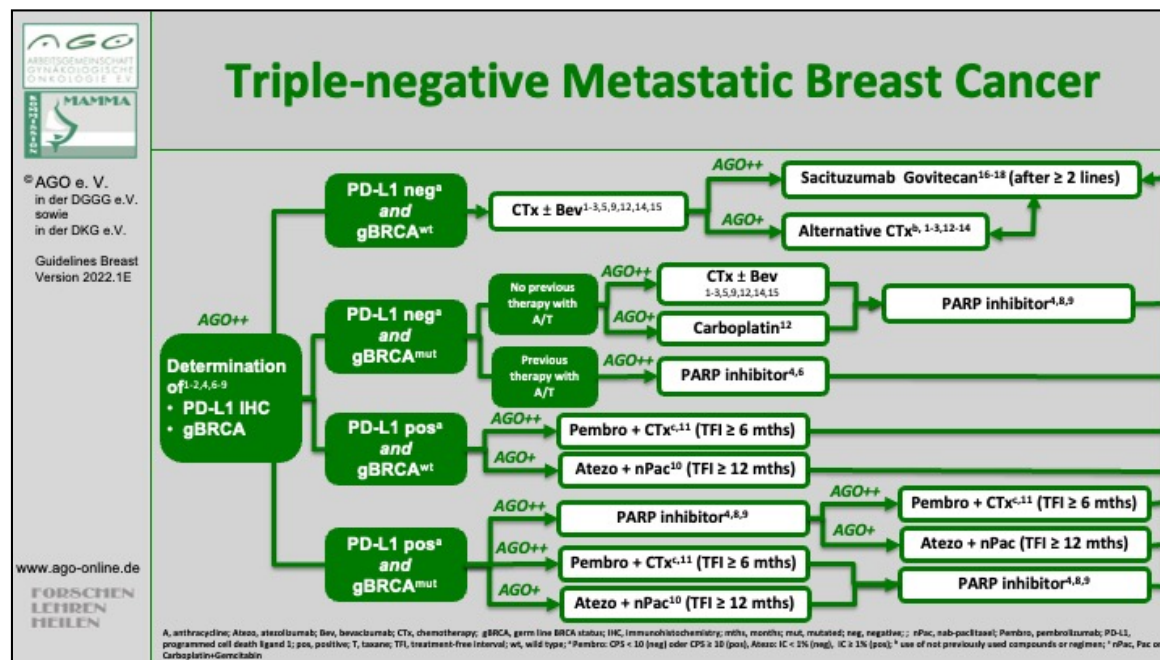


1. Swain SM, Baselga J, Kim SB, et al. CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372(8):724-34.
2. Perez EA, López-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab 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 ≥ 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):1124-3.
15. 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.
16. Paracha N, Reyes A, Diéras V et al. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. *Breast Cancer Res Treat* 2020; 180 (3): 597–609.
17. Modi S, Saura C, Yamashita T et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2020; 382 (7): 610–621.
18. Cortés J, Kim SB, Chung, WP, et al., Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients with HER2+ Metastatic Breast Cancer: Results of the Randomized Phase 3 Study DESTINY-Breast03. ESMO, 2021; Presidential symposium 1,

Abstract No. LBA1



- 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.
- 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.
- 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 metastatic 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.
18. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. 2021;384(16):1529-1541.