Guidelines Breast
Version 2025.1E

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LEHREN
HEILEN

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

* Substances without published evidence based on at least one phase III/II b trial were omitted

Guidelines Breast
Version 2025.1E

Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2024 :**
  Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Kolberg-Liedtke/ Loibl / Lüftner / Lux / von Minckwitz / Möbus / Müller / Park-Simon / Rody / Schaller / Scharl / Schmidt / Schmutzler / Schmidt / Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2025 :**
  Hartkopf / Lüftner

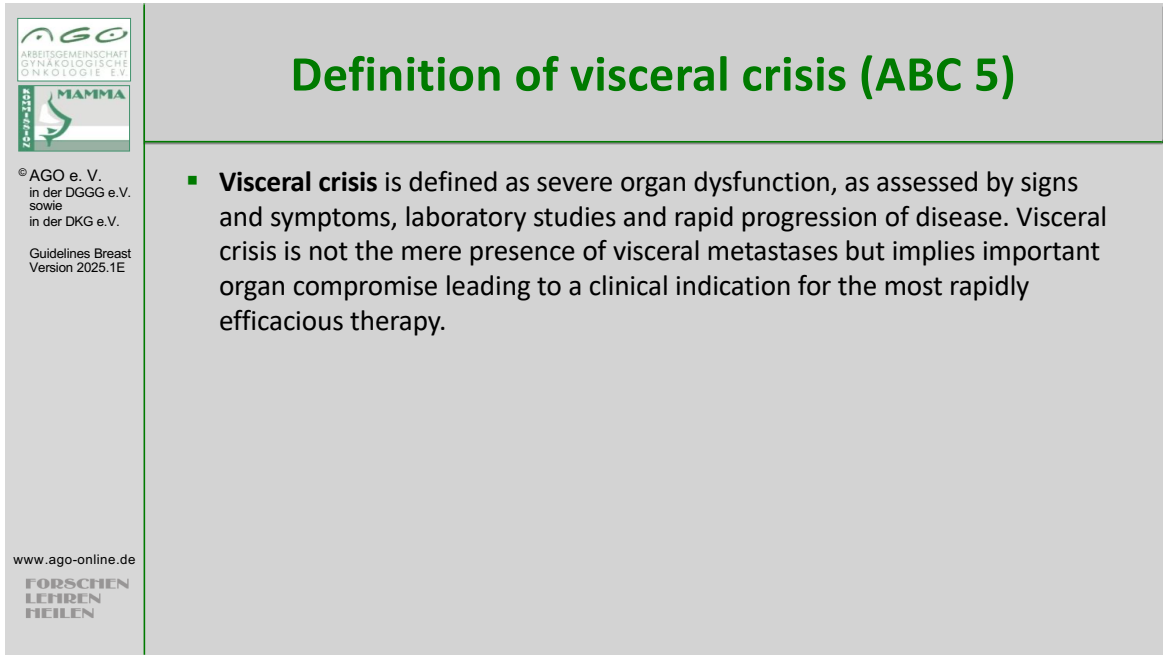
Metastatic Breast Cancer
Systemic therapy

GR: A **AGO: ++**

- **Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities and secondary primaries)**
- **Assess subjective and objective toxicities, symptoms, and performance as well as quality of life (QoL) status repeatedly**
- **Use dosages according to published protocols**
- **Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. In slowly growing disease, longer intervals are acceptable.**

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.



International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Metastatic Breast Cancer
Endocrine resistance

Primary endocrine resistance:

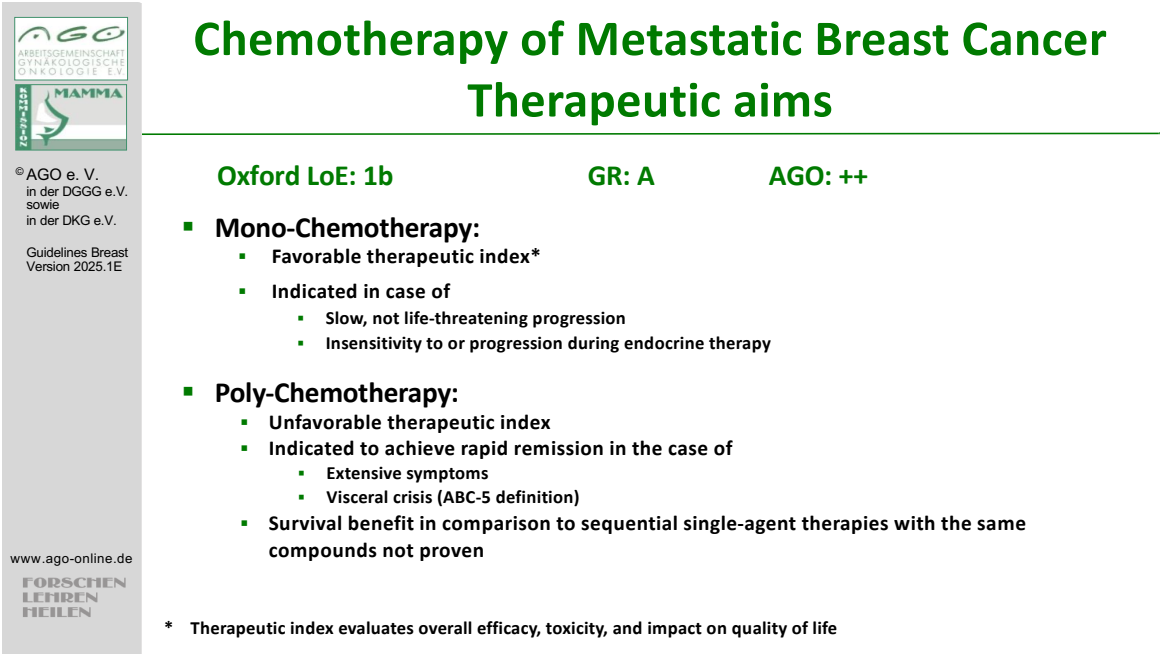
- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ET for MBC**

Secondary (required) endocrine resistance:

- **Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET**
- **PD ≥ 6 months after initiation of ET for MBC**

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.



International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Combination vs single agent

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.

Cochrane analysis

1. 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

Metastatic Breast Cancer
Duration of cytotoxic therapy

	Oxford		
	LoE	GR	AGO
▪ **As long as therapeutic index* remains positive**	1a	A	++
▪ Treatment until progression	2b	B	+
▪ Treatment until best response	2b	B	+/-
▪ Change to alternative regimen before progression	2b	B	+/-
▪ **Stop therapy in case of**	1c	A	++
▪ Progression			
▪ Non tolerable toxicity			

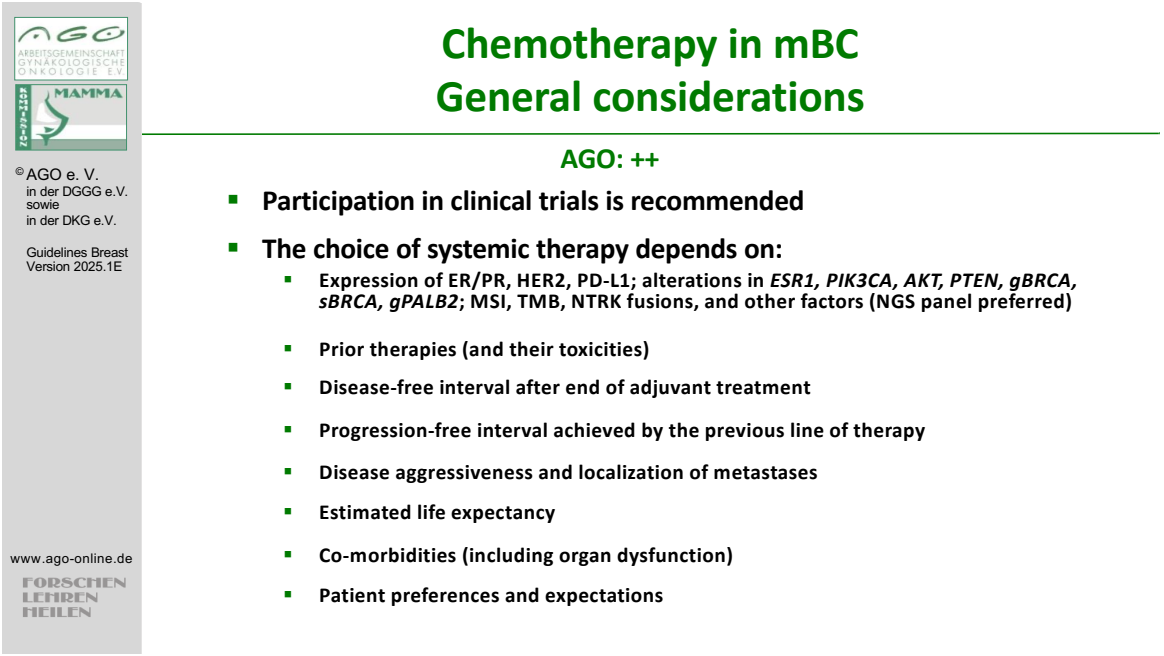
* Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.Change to alternative regimen before progression

Treatment until progression

1. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol. 2011;29:2144-9.
2. Alba E, Ruiz-Borrego M, Margelí M, et al. Maintenance treatment with pegylated liposomal doxorubicin versus observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study. Breast Cancer Res Treat. 2010;122(1):169-76
3. Park YH, Jung KH, Im SA, et al. Phase III, multicenter, randomized trial of maintenance chemotherapy versus observation in patients with metastatic breast cancer after achieving disease control with six cycles of gemcitabine plus paclitaxel as first-line chemotherapy: KCSG-BR07-02. J Clin Oncol. 2013;31(14):1732-9.



International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
2. Sharon H. Giordano, Sarah Temin, Sarat Chandarlapaty et al.: ASCO Clinical Practice Guideline Update Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: J Clin Oncol 2019; 36:2736-2740.
3. Condorelli R, Mosele F, Verret B, et al. Genomic alternations breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2019; 30; 365-373

ER/PR

1. Campbell FC, Blamey RW, Elston CW, et al. Quantitative oestradiol receptor values in primary breast cancer and response of metastases to endocrine therapy. *Lancet*. 1981;2(8259):1317–1319.

HER2

1. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19(10):2587–2595.

2. Modi S, Park H, Murthy RK, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low–expressing advanced breast cancer: Results from a phase Ib study. J Clin Oncol. 2020;38(17):1887-1896. doi: 10.1200/JCO.19.02318.

PD-L1

1. 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.
2. 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 Dec 5;396(10265):1817-1828.

ESR1:

1. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 34:2961-8. doi: 10.1200/JCO.2016.67.3061
2. Bidard F-C, Hardy-Bessard A-C, Dalenc F, et al. Switch to Fulvestrant and Palbociclib versus No Switch in Advanced Breast Cancer with Rising ESR1 Mutation during Aromatase Inhibitor and Palbociclib Therapy (PADA-1): A Randomised, Open-Label, Multicentre, Phase 3 Trial. Lancet Oncol. 2022 Nov;23(11):1367-1377.
3. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338. Epub 2022 May 18.

PIK3CA/AKT/PTEN

1. Andre F, Ciruelos E, Rubovszky G. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380:1929–1940
2. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2023 May 31;388(22):2058-2070. DOI: 10.1056/NEJMoa2214131.

BRCA/PALB2

1. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. 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.
3. Tung NM, Robson ME, Ventz S, TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

MSI/NTRAK

1. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018 Dec;15(12):731-747. doi: 10.1038/s41571-018-0113-0.
2. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 Jul 28;357(6349):409-413. doi: 10.1126/science.aan6733. Epub 2017 Jun 8.

Limitations of palliative chemotherapy

1. Ribeiro JT, Macedo LT, Curigliano G, et al. Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: back to the future? Ann Oncol. 2012;23(3):547-55.
2. Adamowicz K, Jassem J, Katz A, Saad ED. Assessment of quality of life in advanced breast cancer. An overview of randomized phase III trials. Cancer Treat Rev. 2012;38(5):554-8.

Treatment of Metastatic Breast Cancer
Markers to determine treatment indications

Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (*ESR1*) (metastases, plasma)	1b	B	++
▪ Alpelisib / Inavolisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	*PIK3CA, AKT1, PTEN* alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low/-pos. (prim. tumor, better: metastasis) HER2-ultralow (prim. tumor, better: metastasis)	1b 2b	A B	++ +/-
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	*gBRCA1/2*-mutation	1a	A	++
	sBRCA1/2/gPALB2	2b	B	+

Endocrine therapy:

1. Campbell FC, Blamey RW, Elston CW, et al. Quantitative oestradiol receptor values in primary breast cancer and response of metastases to endocrine therapy. *Lancet*. 1981;2(8259):1317–1319.

Elacestrant:

1. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338. Epub 2022 May 18.

Alpelisib/Inavolisib:

1. André F, Ciruelos E, Rubovszky G et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 380:1929-1940. doi: 10.1056/NEJMoa1813904
2. Turner NC, Im S-A, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. N Engl J Med. 2024 Oct 31;391(17):1584-1596. doi: 10.1056/NEJMoa2404625.

Capivasertib

1. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2023 May 31;388(22):2058-2070. DOI: 10.1056/NEJMoa2214131.

Trastuzumab Deruxtecan

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
2. Modi S, W. Jacot, T Yamashita et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20
3. Bardia A et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. (2024) N Engl J Med. 391;22

Chemotherapy

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Anti-HER2-Therapy

1. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19(10):2587–2595.
2. Modi S, Park H, Murthy RK, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low–expressing advanced breast cancer: Results from a phase Ib study. J Clin Oncol. 2020;38(17):1887-1896. doi: 10.1200/JCO.19.02318.

Checkpoint-Inhibitors

1. 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.

2. 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 Dec 5;396(10265):1817-1828.

PARP-Inhibitors

1. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. 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.
3. Tung NM, Robson ME, Ventz S, TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

mBC - HER2-negative / HR-positive
1st-Line Chemotherapy (if indicated)

	Oxford LoE	Oxford GR	AGO
Monotherapy:			
Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A_{lip})	1b	A	++
Vinorelbine	3b	B	+
Capecitabine	2b	B	+
Nab-paclitaxel	2b	B	+
Polychemotherapy:			
A + T	1b	A	++
Paclitaxel + capecitabine	2b	B	+
Docetaxel + capecitabine after adj. A	1b	A	+
T + gemcitabine after adj. A	2b	B	++
A + C or A_{lip} + C	1b	B	++

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Single Agents

1. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. Cancer Treat Rev. 2010;36(1):69-74.
2. Belfiglio M, Fanizza C, Tinari N, et al. Consorzio Interuniversitario Nazionale per la BioOncologia (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. O'Brien ME, Wigler N, Inbar M, et al. CAELYX Breast Cancer Study Group : Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004;15(3):440-449.
4. O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. Oncologist. 2012;17:476-84.
5. Gradishar WJ, Krasnojon D, Cheporov S, et al. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in

patients with metastatic breast cancer: final analysis of overall survival. Clin Breast Cancer. 2012;12(5):313-21.
6. Vogel C, O'Rourke M, Winer E, et al: Vinorelbine as first-line chemotherapy for advanced breast cancer in women 60 years of age or older. Ann Oncol. 1999;10(4):397-402

Polychemotherapy

Metaanalysis

1. Belfiglio M, Fanizza C, Tinari N, et al. Consorzio Interuniversitario Nazionale per la BioOncologia (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.

Cochrane analysis containing taxane based regimens

1. Ghersi D, Willson ML, Chan MM, et al. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 10;6:CD003366.

After anthracycline treatment two studies could show a survival benefit

1. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20(12):2812-2823.
2. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008;26(24):3950-3957.

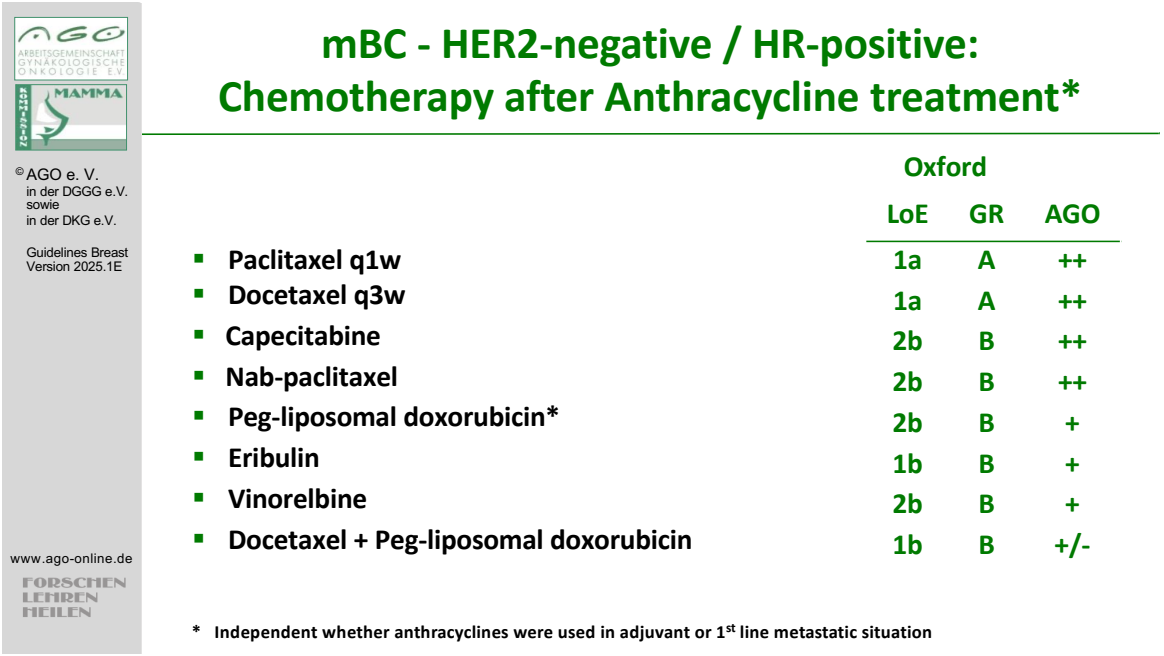
Doxorubicin/docetaxel vs. Doxorubincin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL

1. Cassier PA, Chabaud S, Trillet-Lenoir V, et al. A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. Breast Cancer Res Treat. 2008;109(2):343-50.

Other combinations

1. Lück HJ, Du Bois A, Loibl S, et al: Capecitabine plus paclitaxel versus epirubicin plus paclitaxel as first-line treatment for metastatic breast cancer: efficacy and safety results of a randomized, phase III trial by the AGO Breast Cancer Study Group. Breast Cancer Res Treat. 2013;139(3):779-87. doi: 10.1007/s10549-013-2589-8.

2. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol. 2002;20(14):3114-3121.
3. Batist G, Ramakrishnan G, Sekhar Rao C et al (2001) Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulted doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized multicenter trial of metastatic breast cancer J. Clin Oncol 19: 1444-1454



International consensus

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

Cochrane analysis taxane-containing regimens for metastatic breast cancer

1. Ghersi D, Willson ML, Chan MM, et al.Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 Jun 10;6:CD003366.

Nab-paclitaxel

1. Puglisi F, Rea D, Kroes MA, et al. Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review. Cancer Treat Rev. 2016 Feb;43:36-49.

Erubilin

1. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23.
2. 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. Breast Cancer Res Treat. 2014;148:553-61.

mBC - HER2-negative / HR-positive:
Chemotherapy after pretreatment *

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab-Deruxtecan			
- after prior chemotherapy with HER2-low	1b	A	++
- without prior chemotherapy and not suitable for further endocrine therapy, with HER2-low	1b	B	+
- not suitable for further endocrine therapy, with HER2-ultralow	2b	B	+/-
▪ Sacituzumab Govitecan	1b	A	++
▪ Capecitabin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ (Peg)-liposomal Doxorubicin	2b	B	+
▪ Taxane re-challenge**	2b	B	+
▪ Anthracycline re-challenge**	3b	C	+
▪ Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+

* See approval details for previous therapy
** at least 1 year recurrence free after adjuvant therapy

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Trastuzumab Deruxtecan

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
2. Modi S, W. Jacot, T Yamashita et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20
3. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. N Engl J Med. 2024;391(22).

Sacituzumab Govitecan

1. Rugo HS, Bardia A, Marmé F et al. (2023) Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet 402(10411):1423–1433.

Capecitabine

1. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004;40(4):536-542.

Eribulin

1. Lück H-J, Schmidt M, Hesse Tet al. (2023) Incidence and Resolution of Eribulin-Induced Peripheral Neuropathy (IRENE) in Locally Advanced or Metastatic Breast Cancer: Prospective Cohort Study. Oncologist 28(12):e1152-e1159. doi:10.1093/oncolo/oyad191
2. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23.
3. 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. Breast Cancer Res Treat. 2014;148:553-61.
4. Scarpace SL. Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. Clin Ther. 2012;34(7):1467-73.
5. Pivot X, Im SA, Guo M, Marmé F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. Breast Cancer. 2018;25(3):370-374.
6. Ohtani S, Nakayama T, Yoshinami T, et al. Bi-weekly eribulin therapy for metastatic breast cancer: a multicenter phase II prospective study (JUST-STUDY). Breast Cancer. 2018;25(4):438-446.

Taxane re-challenge

1. Guo X, Loibl S, Untch M, et al. Re-Challenging Taxanes in Recurrent Breast Cancer in Patients Treated with (Neo-) Adjuvant Taxane-Based Therapy. Breast Care (Basel). 2011;6(4):279-283.

Anthracycline re challenge

1. Twelves C, Jove M, Gombos A, et al. Cytotoxic chemotherapy: Still the mainstay of clinical practice for all subtypes metastatic breast cancer. Crit Rev Oncol Hematol. 2016. pii: S1040-8428(16)30021-X. doi: 10.1016/j.critrevonc.2016.01.021. [Epub ahead of print] Review.

Metronomic chemotherapy

1. Munzone E, Regan MM, Cinieri Set al. (2023) Efficacy of Metronomic Oral Vinorelbine, Cyclophosphamide, and Capecitabine vs Weekly Intravenous Paclitaxel in Patients With Estrogen Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: Final Results From the Phase 2 METEORA-II Randomized Clinical Trial. JAMA Oncol 9(9):1267–1272. doi:10.1001/jamaoncol.2023.2150
2. Yin W, Pei G, Liu G, et al. Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials. Oncotarget 2015;36:39365-72.
3. Yoshimoto M, Takao S, Hirata M, et al. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother Pharmacol. 2012;70(2):331-8.
4. Fedele P, Marino A, Orlando L, et al. Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. Eur J Cancer. 2012;48(1):24-9.
5. Addeo R, Sgambato A, Cennamo G, et al. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. Clin Breast Cancer. 2010;10(4):301-6.
6. Colleoni M, Orlando L, Sanna G, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann Oncol. 2006;17(2):232-8.
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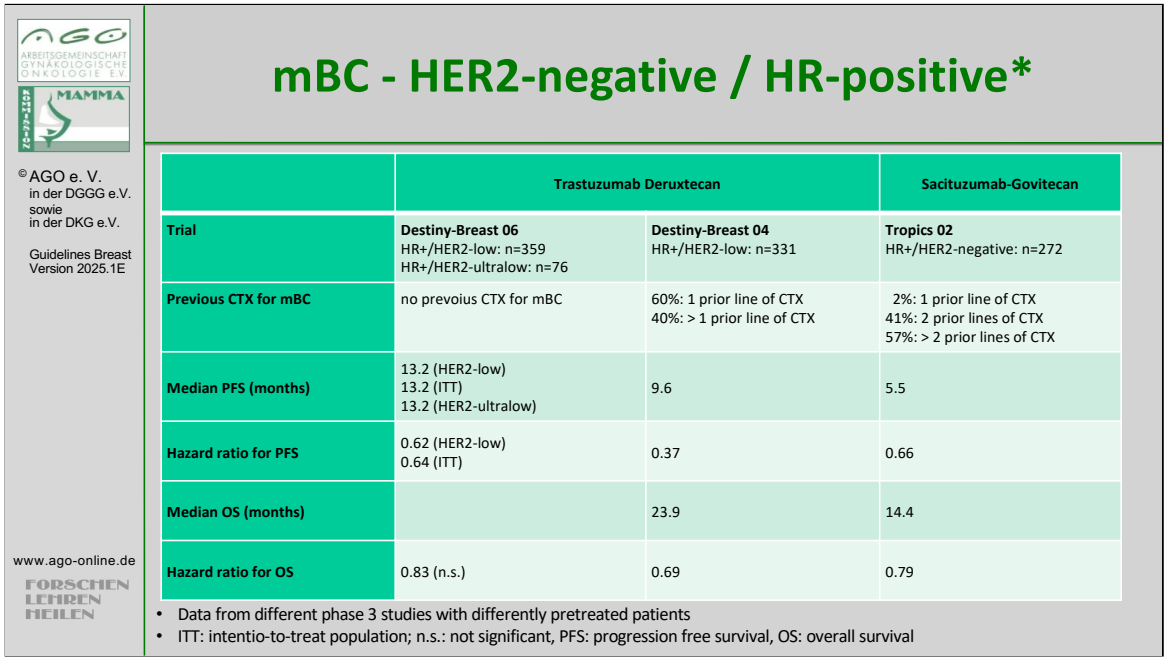


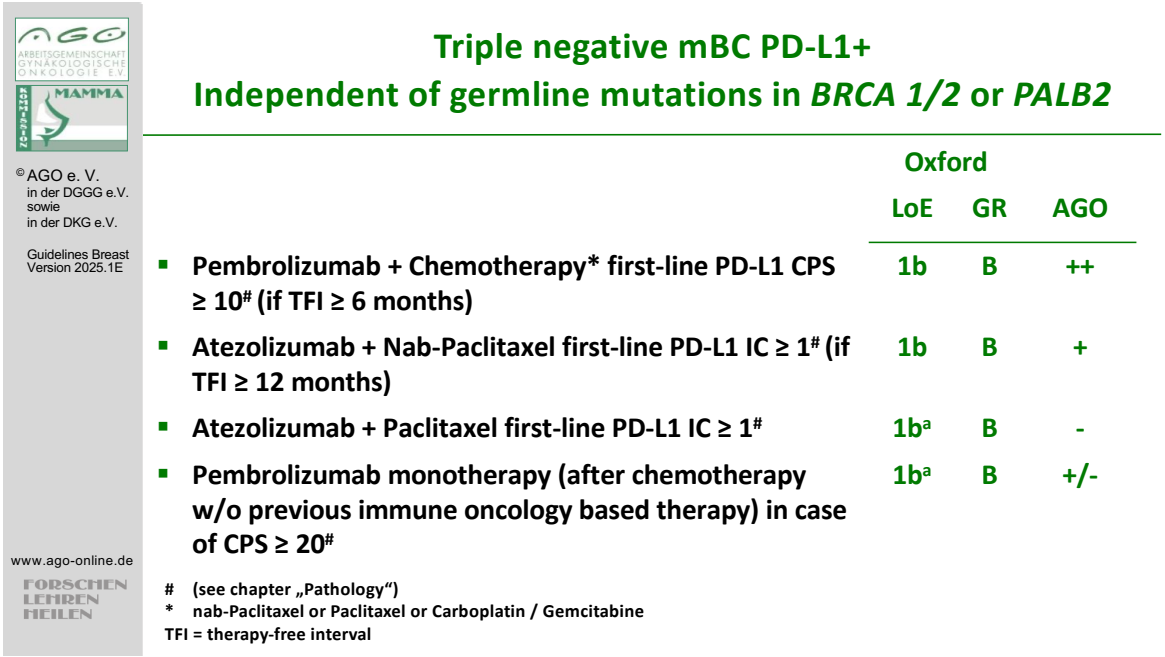
Trastuzumab Deruxtecan

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
2. Modi S, W. Jacot, T Yamashita et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20
3. Modi S, Jacot W, Iwata H et al. (2023) Trastuzumab Deruxtecan(T-DXd) Versus Treatment of Physician's Choice (TPC) in Patients With HER2-Low Unresectable and/or Metastatic Breast Cancer: Updated Survival Results of the Randomized, Phase 3 DESTINY-Breast04 Study, ESMO 2023
4. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. N Engl J Med. 2024;391(22).

Sacituzumab Govitecan

1. Rugo HS, Bardia A, Marmé F et al. (2022) Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. J Clin Oncol 40(29):3365–3376. doi:10.1200/JCO.22.01002
2. Rugo HS, Bardia A, Marmé F et al. (2023) Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3

trial. Lancet 402(10411):1423–1433.



International consensus

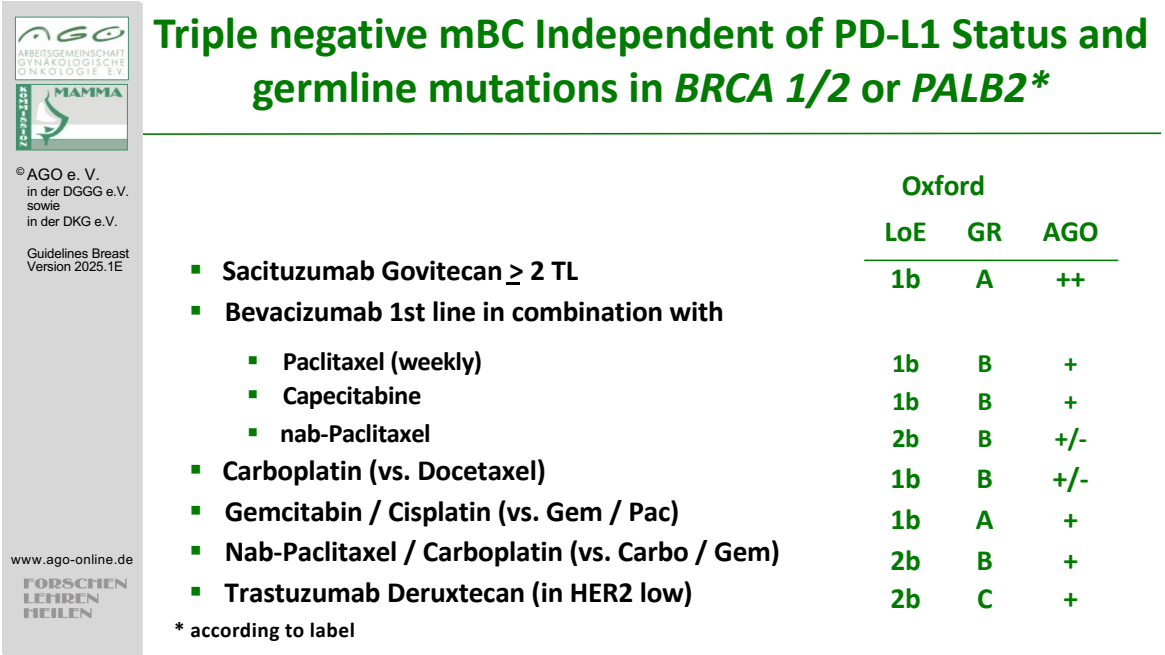
1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Checkpoint-inhibitoren:

1. 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.
2. 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.
3. Schmid P, Rugo HS, Adams S et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020; 21 (1): 44–59.
4. IMpassion131 investigators. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-

controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer.Ann Oncol

5. Winer EP, Lipatov O, Im SA, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial.Lancet Oncol. 2021 Apr;22(4):499-511. doi: 10.1016/S1470-2045(20)30754-3. Epub 2021 Mar 4.



International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Sacituzumab Govitecan:

1. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541. doi: 10.1056/NEJMoa2028485.

Bevacizumab as first-line therapy

1. 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. doi: 10.1093/annonc/mdt276.
2. Roberts et al., RIBBON-1: Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Chemotherapy With or Without Bevacizumab for First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative, Locally Recurrent or Metastatic Breast Cancer, J Clin Oncol 29:1252-1260, 2011

3. 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.
4. Miles D, Chan A, Luc Y, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 28:3239-3247, 2010
5. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol. 2015;33(21):2361-9.
6. 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, non-inferiority, phase 3 trial. Lancet Oncol 2016;17(9):1230-9. doi: 10.1016/S1470-2045(16)30154-1.
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.

Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:

1. 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

Gemcitabin/Cisplatin (vs. GemPac)

1. 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.

Nab-Paclitaxel / Carboplatin

1. Yardley DA, Coleman R, Conte P, tnAcity investigators. 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.

Trastuzumab Deruxtecan *(*T-DXD)

1. Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20

Treatment Options in mBC with BRCA 1/2 or gPALB2 mutations

	Oxford LoE	GR	AGO
▪ **Carboplatin (vs. docetaxel) (if Platinum-naive)**	1b	B	+
▪ **PARP-Inhibitors (HER2-negative mBC)**			
▪ **HER2-negative, g*BRCA 1/2* mutation**			
▪ **Olaparib**	1b	A	++
▪ **Talazoparib**	1b	A	++
▪ **s*BRCA* 1/2 mutation**			
▪ **Olaparib**	2b	B	+
▪ ***gPALB2* mutation**			
▪ **Olaparib**	2b	B	+

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

Carboplatin (vs. Docetaxel) in gBRCA mutation

1. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) Tutt A, Ellis P, Kilburn L, et al. San Antonio Breast Cancer Symposium 2014; S3-01.

PARP Inhibitoren:

1. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. 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.
3. Tung NM, Robson ME, Ventz S, TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous

Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

HER2-pos. mBC

1st line without pretreatment or after Trastuzumab

	Oxford LoE	Oxford GR	AGO
Primary metastatic			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
After Trastuzumab in the adjuvant setting (TFI > 6 months)			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
After pretreatment with only Trastuzumab in the adjuvant setting (TFI ≤ 6 months)			
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1	2b	B	+/-
▪ Chemotherapy + Trastuzumab + Pertuzumab	4	D	+/-
As maintenance therapy following chemotherapy + antibody therapy (HR+)			
▪ Palbociclib+ endokrine therapy + Trastuzumab + Pertuzumab	1b	A	+

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
2. Giordano SH, Franzoi MAB, Temin S (2022) Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. J Clin Oncol 40(23):2612–2635. doi:10.1200/JCO.22.00519

Metaanalyse post trastuzumab

1. 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.

Docetaxel + trastuzumab + pertuzumab

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.

Paclitaxel weekly + trastuzumab + pertuzumab

1. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015; 10;33(5):442-7.
2. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. Breast Cancer Res Treat 2016;158:91e7. http://dx.doi.org/ 10.1007/s10549-016-3851-7
3. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Eur J Cancer. 2022;170:90-98. doi: 10.1016/j.ejca.2022.03.001.

Nab-Paclitaxel + trastuzumab + pertuzumab

1. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Eur J Cancer. 2022;170:90-98. doi: 10.1016/j.ejca.2022.03.001.
2. Polito L, Shim J, Hurvitz SA, Dang CT et al. (2023) Real-World First-Line Use of Pertuzumab With Different Taxanes for Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: A Comparative Effectiveness Study Using US Electronic Health Records. JCO Oncol Pract 19(7):435–445. doi:10.1200/OP.22.00565

Vinorelbine + trastuzumab + pertuzumab

1. 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.

Trastuzumab Deruxtecan

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
2. Hurvitz SA, Hegg R, Chung et al. (2023) Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 401(10371):105–117. doi:10.1016/S0140-6736(22)02420-5

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. 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.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

Palbociclib+ET+Trastuzumab+Pertuzumab

1. Metzger O, Mandrekar S, DeMichele A, et al. A randomized, open-label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy vs. anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor-positive (HR+)/HER2-positive metastatic breast cancer. SABCS 2024.

HER2-pos. mBC

1st line after Trastuzumab / Pertuzumab +/- TDM-1

	Oxford LoE	GR	AGO
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	++
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1 (TFI < 6-12 months)	5	D	+/-
▪ Capecitabine + Lapatinib	1b	B	+/-
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting and T-DM1 in the post-neoadjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabine + Trastuzumab	5	D	+
▪ Capecitabine + Lapatinib	5	D	+/-
As maintenance therapy following chemotherapy + antibody therapy (HR+)			
▪ Palbociclib+ endokrine therapy + Trastuzumab + Pertuzumab	1b	A	+

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
2. Giordano SH, Franzoi MAB, Temin S (2022) Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. J Clin Oncol 40(23):2612–2635. doi:10.1200/JCO.22.00519

Reinduction of chemotherapy + trastuzumab + pertuzumab

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. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015; 10;33(5):442-7.
3. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. Breast Cancer Res Treat 2016;158:91e7. http://dx.doi.org/ 10.1007/s10549-016-3851-7
4. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Eur J Cancer.

2022;170:90-98. doi: 10.1016/j.ejca.2022.03.001.
5. 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.

Trastuzumab Deruxtecan
1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
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T-DM1
1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. 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.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

Capecitabine + lapatinib
1. Cameron D, Casey M, Press M et al. E. 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.
2. 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.

Tucatinib + trastuzumab/ capecitabine
1. 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.
2. 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

Palbociclib+ET+Trastuzumab+Pertuzumab

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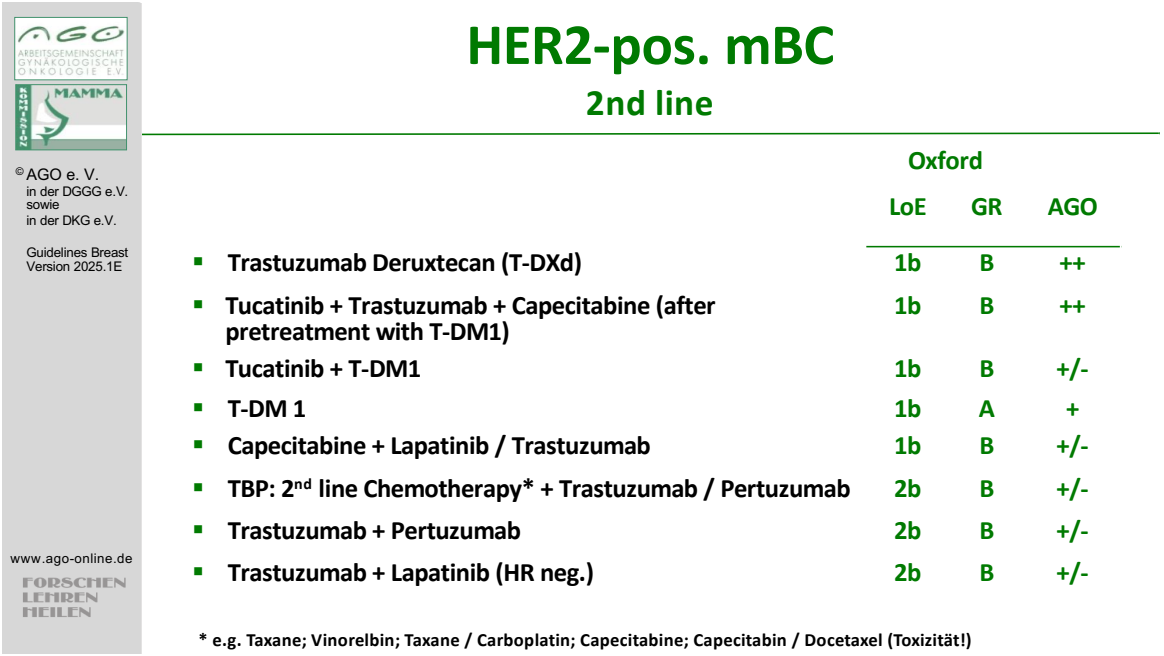

HER2-pos. mBC

2nd line

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab Deruxtecan (T-DXd)	1b	B	++
▪ Tucatinib + Trastuzumab + Capecitabine (after pretreatment with T-DM1)	1b	B	++
▪ Tucatinib + T-DM1	1b	B	+/-
▪ T-DM 1	1b	A	+
▪ Capecitabine + Lapatinib / Trastuzumab	1b	B	+/-
▪ TBP: 2nd line Chemotherapy* + Trastuzumab / Pertuzumab	2b	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+/-

* e.g. Taxane; Vinorelbin; Taxane / Carboplatin; Capecitabine; Capecitabin / Docetaxel (Toxizität!)

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
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Trastuzumab Deruxtecan

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Tucatinib + trastuzumab + capecitabine

1. 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.

2. 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

Tucatinib + T-DM1

1. Hurvitz et al. HER"CLIMB-02: Primary Anaylsis of a randomized, double-blind phase 3 trila of tucatinib and trastuzumab emtansine for previously treated Her2-positive metastatic breast cancer. SABCS 2023

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. 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.
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Capecitabine + lapatinib

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2. 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.

TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)

1. von Minckwitz G, Schwedler K, Schmidt M, et al; GBG 26/BIG 03-05 study group and participating investigators. 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.

Chemotherapy + trastuzumab + pertuzumab

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.
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3. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. Breast Cancer Res Treat 2016;158:91e7. http://dx.doi.org/ 10.1007/s10549-016-3851-7
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<u>Trastuzumab + pertuzumab</u>

1. Baselga, J. et al. Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that progessed during prior Trastuzumab therapy. JCO 2010;28:1138-1144

<u>Trastuzumab + lapatinib vs, lapatinib</u>

1. 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.
2. 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

HER2-pos. mBC

≥ third-line

Depending on the previous therapy (substance)	Oxford LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine	1b	B	++
▪ Trastuzumab Deruxtecan	1b	B	++
▪ T-DM 1	1b	A	+
▪ Capecitabine + Trastuzumab / Lapatinib	1b	B	+
▪ Capecitabine + Neratinib	1b	B	+/-

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.ASCO recommendation.
2. Giordano SH, Franzoi MAB, Temin S (2022) Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. J Clin Oncol 40(23):2612–2635. doi:10.1200/JCO.22.00519

Metaanalyse post T-DM1

1. Yokoe T, Kurozumi S, Nozawa K et al. Clinical benefit of treatment after trastuzumab emtansine for HER2-positive metastatic breast cancer: a real-world multi-centre cohort study in Japan (WJOG12519B). Breast Cancer 2021

Metaanalysis after taxane/ trastuzumab

1. 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.

Tucatinib + trastuzumab + capecitabine

1. 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.
2. 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

Trastuzumab Deruxtecan

1. 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.
2. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
3. Hurvitz SA, Hegg R, Chung et al. (2023) Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 401(10371):105–117. doi:10.1016/S0140-6736(22)02420-5
4. André F, Hee Park Y, Kim et al. (2023) Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. Lancet 401(10390):1773–1785. doi:10.1016/S0140-6736(23)00725-0

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. 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.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

Capecitabine + lapatinib

1. Cameron D, Casey M, Press M et al. E. 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.

2. 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.

Neratinib + capecitabine

1. 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.

HER2-pos. mBC

No Chemotherapy possible or desired

Guidelines Breast
Version 2025.1E

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Lapatinib + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Aromatase inhibitor + Trastuzumab + Pertuzumab (HR+)	2b	B	+
▪ Ribociclib + ET + Trastuzumab + Pertuzumab (HR+)	3b	C	+/-
▪ Abemaciclib + Fulvestrant + Trastuzumab (HR+)	2b	B	+
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.ASCO recommendation
2. Giordano SH, Franzoi MAB, Temin S (2022) Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. J Clin Oncol 40(23):2612–2635. doi:10.1200/JCO.22.00519

Trastuzumab and AI (in HR+)

1. Kaufman B, 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 Nov 20;27(33):5529-37.
2. Giordano SH, et al. American Society of Clinical Oncology. 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 Jul 1;32(19):2078-99.
3. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.
4. Huober J, 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.
5. Giordano SH, et al. American Society of Clinical Oncology. 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 Jul 1;32(19):2078-99.
6. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.

Lapatinib and AI (in HR+)

1. 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 Nov 20;27(33):5538-46.
2. Riemsma R, Forbes CA, Amonkar MM, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.
3. Grassadonia A, Caporale M, Tinari N, et al. Effect of targeted agents on the endocrine response of breast cancer in the neoadjuvant setting: a systematic review. J Cancer. 2015 May 12;6(6):575-82.
4. Giordano SH, Temin S, Kirshner JJ, et al; American Society of Clinical Oncology. 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 Jul 1;32(19):2078-99.

AI and trastuzumab + pertuzumab (in HR+)

1. 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 Oct 1;36(28):2826-2835. doi: 10.1200/JCO.2017.76.7863. PMID:30106636
2. Arpino G, de la Haba Rodríguez, Juan, Ferrero J-M , et al. (2023) Pertuzumab, Trastuzumab, and an Aromatase Inhibitor for HER2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer: PERTAIN Final Analysis. Clin Cancer Res 29(8):1468–1476. doi:10.1158/1078-0432.CCR-22-1092

Ribociclib + ET + trastuzumab + pertuzumab

1. Janni W, Fehm TN, Mueller V, et al. Omission of chemotherapy and addition of the CDK4/6 inhibitor ribociclib in HER2-positive and hormone-receptor positive metastatic breast cancer – Second interim efficacy analysis of the randomized phase III DETECT V trial. Ann Oncol. 2024 Sep;35(Suppl 2):S362.

Abemaciclib + fulvestrant + trastuzumab

1. Tolaney S, Wardley AM, Zambelli S et al., monarcHER: A randomized Phase 2 study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer (ABC). Ann Oncol 2019, 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394

Trastuzumab + pertuzumab

1. Baselga, J. et al. Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that progessed during prior Trastuzumab therapy. JCO 2010;28:1138-1144

Trastuzumab + lapatinib vs. lapatinib (in HR-)

1. 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.

Trastuzumab mono

1. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-48.
2. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.