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Guidelines Breast  
Version 2024.1E

FORSCHEN  
LEHREN  
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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## 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



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# Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

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## ■ Versions 2002–2023:

**Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /  
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## ■ Version 2024:

**Park-Simon / Schmidt**

## Metastatic Breast Cancer (mBC) Disease-Free and Overall Survival

	Oxford LoE
▪ In MBC, an increase in survival over time has been shown in clinical trials	1b
▪ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)	1b
▪ Targeted drugs in combination with chemotherapy can induce substantial survival benefits	1b

### International consensus

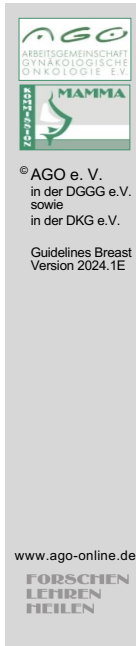
1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

### Increase

1. Petrelli F, Barni S. Surrogate endpoints in metastatic breast cancer treated with targeted therapies: an analysis of the first-line phase III trials. Med Oncol. 2014;31:776.

### Multiple lines

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;22:314-9.



## 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  $\geq$  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..

## Treatment of Metastatic Breast Cancer Markers for Indication

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

### Endocrine therapy - ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. *Cancer* 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. *Ann Oncol*.29:145-153. doi: 10.1093/annonc/mdx483
3. 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
4. FC, Hardy-Bessard AC, Dalenc F, et al.; PADA-1 investigators. 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.
5. Berger F, Marce M, Delalogue S, et al.; PADA-1 investigators Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. *BMJ Open*. 2022 Mar 3;12(3):e055821.

### Alpelisib

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

### Capivasertib

1. Turner NC, Oliveira M, Howell S et al. (2022) Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPitello-291 trial. *N Engl J Med* 388(22):2058–2070. doi:10.1056/NEJMoa221413123
2. Hopcroft L, Wigmore EM, Williamson SC (2023) Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. *NPJ Breast Cancer* 9(1):64. doi:10.1038/s41523-023-00571-w

### Chemotherapy

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.

### 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.

### 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.: KEYNOTE-355 Investigators. 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.
3. Hattori M, Masuda N, Takano T, et al. Pembrolizumab plus chemotherapy in Japanese patients with triple-negative breast cancer: Results from KEYNOTE-355. *Cancer Med*. 2023 May;12(9):10280-10293.

#### 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.

#### Bone modifying drugs

1. Aktas B, Kasimir-Bauer S, Lehmann N, et al.: Validity of bone marker measurements for monitoring response to bisphosphonate therapy with zoledronic acid in metastatic breast cancer. *Oncol Rep*. 2013;30(1):441–447.
2. Loftus LS, Edwards-Bennett S, Sokol GH. Systemic therapy for bone metastases. *Cancer Control*. 2012;19(2):145–153.
3. Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. *J Natl Cancer Inst*. 2012;104(14):1059–1067.

#### CTC monitoring (any therapy)

1. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2014;15:406-14.

2. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol.* 2014;32(31):3483-9.



# Metastatic Breast Cancer Treatment Rationale

Oxford LoE: 1b

GR: A

AGO: ++

## ■ Mono-Chemotherapy:

- Favorable therapeutic index\*
- Indicated in case of
  - Slow, not life-threatening progression
  - Insensitivity to or progression during endocrine therapy

## ■ Poly-Chemotherapy:

- Unfavorable therapeutic index
- Indicated to achieve rapid remission in the case of
  - Extensive symptoms
  - Visceral crisis (ABC-5 definition)
- Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

\* 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.

### 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



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## Definition of Visceral Crisis (ABC 5)

- **Visceral crisis** is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious 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.

## 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.

# Metastatic Breast Cancer

## Duration of Cytotoxic Therapy

	Oxford		
	LoE	GR	AGO
■ <b>As long as therapeutic index* remains positive</b>	<b>1a</b>	<b>A</b>	<b>++</b>
■ Treatment until progression	<b>2b</b>	<b>B</b>	<b>+</b>
■ Treatment until best response	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ Change to alternative regimen before progression	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ <b>Stop therapy in case of</b>	<b>1c</b>	<b>A</b>	<b>++</b>
■ 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
2. Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1351-60.
3. Mustacchi G, Bines J, Alba E, et al. Impact of post-progression therapy on overall survival (OS) in the IMELDA randomized phase III trial evaluating the addition of capecitabine (CAP) to maintenance bevacizumab (BEV) for HER2-negative metastatic breast cancer (mBC) San Antonio Breast Cancer Conference 2016 Abstract P5-15-06

### 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.

## Chemotherapy in mBC

### General Considerations - Drug Selection

AGO: ++

- Participation in clinical trials is recommended
- The choice of systemic therapy depends on:
  - ER/PR, HER2, PD-L1-Status, gBRCA-Status (evtl. sBRCA-Status, evtl. PALB2), PIK3CA, AKT, PTEN, evtl. MSI, NTRK, ggf. mESR1, other (NGS Panel preferred)
  - Prior therapies (and their toxicities)
  - Disease-free interval after end of adjuvant treatment
  - Progression-free interval achieved by the previous line of therapy
  - Disease aggressiveness and localization of metastases
  - Estimated life expectancy
  - Co-morbidities (including organ dysfunction)
  - Patient preferences and expectations

#### 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

#### Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better

1. Moinpour CM, Donaldson GW, Liepa AM, et al. Evaluating health-related quality-of-life therapeutic effectiveness in a clinical trial with extensive nonignorable missing data and heterogeneous response: results from a phase III randomized trial of gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer. Qual Life Res. 2012;21(5):765-75.

#### 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.

#### PD-L1-Status

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.

#### PIK3CA

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

#### Endocrine therapy - ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. *Cancer* 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. *Ann Oncol.*29:145-153. doi: 10.1093/annonc/mdx483
3. 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
4. Bidard F-C, Hardy-Bessard A-C, Bachelot T, et al. Fulvestrant-palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of circulating ESR1 mutation in HR+ HER2- metastatic breast cancer patients: Results of PADA-1, a UCBG-GINECO randomized phase 3 trial. *SABCS 2021; GS3-05.*

#### MSI/NTRAK

1. 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



## mBC - HER2-negative / HR-positive 1<sup>st</sup>-Line Chemotherapy (if indicated)

	Oxford		
	LoE	GR	AGO
▪ <b>Monotherapy:</b>			
▪ Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
▪ Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A <sub>lip</sub> )	1b	A	++
▪ Vinorelbine	3b	B	+
▪ Capecitabine	2b	B	+
▪ Nab-paclitaxel	2b	B	+
▪ <b>Polychemotherapy:</b>			
▪ 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 <sub>lip</sub> + 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. Doxorubicin/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-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized multicenter trial of metastatic breast cancer *J. Clin Oncol* 19: 1444-1454

## mBC - HER2-negative / HR-positive: Chemotherapy after Anthracycline Treatment\*

	Oxford		
	LoE	GR	AGO
▪ Paclitaxel q1w	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabine	2b	B	++
▪ Nab-paclitaxel	2b	B	++
▪ Peg-liposomal doxorubicin*	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ Docetaxel + Peg-liposomal doxorubicin	1b	B	+/-

\* Independent whether anthracyclines were used in adjuvant or 1<sup>st</sup> line metastatic situation

### 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. Gherzi 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.

### Eribulin

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 \*

- Trastuzumab-Deruxtecan (if HER2-low)
- Sacituzumab Govitecan
- Capecitabin
- Eribulin
- Vinorelbine
- (Peg)-liposomal Doxorubicin
- Taxane re-challenge\*\*
- Anthracycline re-challenge\*\*
- Metronomic therapy (e.g. cyclophos. + MTX)

Oxford		
LoE	GR	AGO
1b	A	++
1b	A	++
2b	B	+
1b	B	+
2b	B	+
2b	B	+
2b	B	+
3b	C	+
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. 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

### 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.
2. Rugo HS et al. Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2– Metastatic Breast Cancer (mBC). SABCS 2022, Abstr GS1-11

### 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

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<b>mBC - HER2-negative / HR-positive*</b>				
	<b>Trastuzumab Deruxtecan</b>	<b>Hazard Ratio</b>	<b>Sacituzumab-Gov.</b>	<b>Hazard Ratio</b>
	<b>HR-pos / HER2-low</b>	<b>relative to</b>	<b>HR-pos / HER2-neg</b>	<b>relative to</b>
	<b>(331 patients)</b>	<b>control</b>	<b>(272 patients)</b>	<b>control</b>
<b>previous lines of chemotherapy in mBC</b>	<b>all patients</b>		<b>all patients</b>	
<b>1 line</b>	61%	0.66 for OS	0%	
<b>2 lines</b>			44%	0.85 for OS n.s.
<b>≥ 2 lines</b>	40%	0.76 for OS n.s.		
<b>≥ 3 lines</b>			60%	0.75 for OS
<b>PFS (months)</b>	9.6	0.37	5.5	0.66
<b>OS (months)</b>	23.9	0.69	14.4	0.79

\* Data from two different phase 3 studies with differently pretreated patients  
kA: keine Angabe, n.s.: not significant, PFS: Progression free survival, OS: Overall survival



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FORSCHEN  
LEBEN  
HEILEN

1. 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
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5. Fachinformationen Enhertu und Trodelvy

## Triple Negative mBC PD-L1+ Independent of Germline Mutation in *BRCA 1/2* or *PALB2*

	Oxford		
	LoE	GR	AGO
■ <b>Pembrolizumab + Chemotherapy* first-line PD-L1 CPS ≥ 10<sup>#</sup> (if TFI ≥ 6 months)</b>	<b>1b</b>	<b>B</b>	<b>++</b>
■ <b>Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC ≥ 1<sup>#</sup> (if TFI ≥ 12 months)</b>	<b>1b</b>	<b>B</b>	<b>+</b>
■ <b>Atezolizumab + Paclitaxel first-line PD-L1 IC ≥ 1<sup>#</sup></b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>-</b>
■ <b>Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) in case of CPS ≥ 20<sup>#</sup></b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>

<sup>#</sup> (see chapter „Pathology“)

\* nab-Paclitaxel or Paclitaxel or Carboplatin / Gemcitabine

TFI = therapy-free interval

### 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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## Triple Negative mBC Independent of PD-L1 Status and Germline Mutations in *BRCA 1/2* or *PALB2*\*

- **Sacituzumab Govitecan  $\geq 2$  TL**
- **Bevacizumab 1st line in combination with**
  - Paclitaxel (weekly)
  - Capecitabine
  - nab-Paclitaxel
- **Carboplatin (vs. Docetaxel)**
- **Gemcitabin / Cisplatin (vs. Gem / Pac)**
- **Nab-Paclitaxel / Carboplatin (vs. Carbo / Gem)**
- **Trastuzumab Deruxtecan (in HER2 low)**

LoE	Oxford	
	GR	AGO
1b	A	++
1b	B	+
1b	B	+
2b	B	+/-
1b	B	+/-
1b	A	+
2b	B	+
2b	C	+

\* according to label

### 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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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 Mutation

	Oxford		
	LoE	GR	AGO
▪ Carboplatin (vs. docetaxel) (if Platinum-naive)	1b	B	+
▪ PARP-Inhibitors (HER2-negative mBC)			
▪ HER2-negative, gBRCA 1/2 mutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ sBRCA 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) / Carboplatin 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 bei triple negativ und BRCA 1/2 Mutation

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8. Lynce F, Robson M (2023) Clinical Use of PARP Inhibitors in BRCA Mutant and Non-BRCA Mutant Breast Cancer. *Cancer Treat Res* 186:91–102. doi:10.1007/978-3-031-30065-3\_6



## HER2-pos. mBC

### 1st line without Pretreatment or after Trastuzumab

	Oxford		
	LoE	GR	AGO
<b>Primary metastatic</b>			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
<b>After Trastuzumab in the adjuvant setting (TFI &gt; 6 months)</b>			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
<b>After pretreatment with only Trastuzumab in the adjuvant setting (TFI ≤ 6 months)</b>			
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1	2b	B	+/-
▪ Chemotherapy + Trastuzumab + Pertuzumab	4	D	+/-

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:  
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

1. 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>

#### Nab-Paclitaxel + trastuzumab + pertuzumab

1. Bachelot T, Puglisi F, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Conference Abstract # P4-21-04

#### 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 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

#### 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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## HER2-pos. mBC

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

	Oxford		
	LoE	GR	AGO
<b>After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting</b>			
▪ 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	+/-
<b>After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting and T-DM1 in the post-neoadjuvant setting</b>			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabine + Trastuzumab	5	D	+
▪ Capecitabine + Lapatinib	5	D	+/-

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:  
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

1. 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](http://dx.doi.org/10.1007/s10549-016-3851-7)

4. Bachelot T, Puglisi F, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Conference Abstract # P4-21-04
5. 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
6. 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.

#### ADC Trastuzumab Deruxtecan

1. Hurvitz SA, Hegg R, Chung WP, et al. 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. Im SA, Jacot W, Ganju V, Chiu JWY, Xu B, Hamilton E, Madhusudan S, Iwata H, Altintas S, Henning JW, Curigliano G, Perez-Garcia JM, Kim SB, Petry V, Huang CS, Li W, Frenel JS, Antolin S, Yeo W, Bianchini G, Loi S, Tsurutani J, Egorov A, Liu Y, Cathcart J, Ashfaq S, Cortés J. *Lancet.* 2022 Dec 6:S0140-6736(22)02420-5. doi: 10.1016/S0140-6736(22)02420-5
2. KropalTrastuzumab deruxtecan vs physician’s choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY-Breast02. SABCS 2022. Abstr GS2-01

#### 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. 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.
3. Delea TE, Tappenden P, Sofrygin O, et al. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. *Eur J Health Econ.* 2012;13(5):589-603.
4. Ang FLI, Rowland A, Modi ND et al. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. *J Cancer* 2020; 11 (11): 3327–3333.
5. Gavilá J, La Haba J de, Bermejo B et al. A retrospective, multicenter study of the efficacy of lapatinib plus trastuzumab in HER2-positive metastatic breast cancer patients previously treated with trastuzumab, lapatinib, or both: the Trastyvere study. *Clin Transl Oncol* 2020; 22 (3): 420–428.
6. Prat A, Pascual T, Angelis C de et al. HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual HER2 Blockade. *J Natl Cancer Inst* 2020; 112 (1): 46–54.

#### 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

## 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: 2 <sup>nd</sup> 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!)

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:  
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

1. 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 Deruxtecan

1. 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
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

### 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

### 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. 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.
3. Delea TE, Tappenden P, Sofrygin O, et al. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. *Eur J Health Econ*. 2012;13(5):589-603.
4. Ang FLI, Rowland A, Modi ND et al. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. *J Cancer* 2020; 11 (11): 3327–3333.
5. Gavilá J, La Haba J de, Bermejo B et al. A retrospective, multicenter study of the efficacy of lapatinib plus trastuzumab in HER2-positive metastatic breast cancer patients previously treated with trastuzumab, lapatinib, or both: the Trastyvere study. *Clin Transl Oncol* 2020; 22 (3): 420–428.
6. Prat A, Pascual T, Angelis C de et al. HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual



HER2 Blockade. J Natl Cancer Inst 2020; 112 (1): 46–54.

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.

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

1. ardozo 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.

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; 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](http://dx.doi.org/10.1007/s10549-016-3851-7)
4. Bachelot T, Puglisi F, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Conference Abstract # P4-21-04
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.
6. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 2017;31:244-259
7. 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

8. Urruticoechea A, Rizwanullah M, Im SA, et al. PHEREXA: a phase III study of trastuzumab (H) p capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. J Clin Oncol 2016;34(15\_suppl). abstr. 504

#### 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 progressed during prior Trastuzumab therapy. JCO 2010;28:1138-1144

#### Trastuzumab + lapatinib vs, lapatinib

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	+/-

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:  
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

ASCO recommendation

1. 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 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
3. 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.
3. Ang FLI, Rowland A, Modi ND et al. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. *J Cancer* 2020; 11 (11): 3327–3333.
4. Gavilá J, La Haba J de, Bermejo B et al. A retrospective, multicenter study of the efficacy of lapatinib plus trastuzumab in HER2-positive metastatic breast cancer patients previously treated with trastuzumab, lapatinib, or both: the Trastyvere study. *Clin Transl Oncol* 2020; 22 (3): 420–428.
5. Prat A, Pascual T, Angelis C de et al. HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual HER2 Blockade. *J Natl Cancer Inst* 2020; 112 (1): 46–54.

#### 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  $\geq 2$  HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol* 2020; 38 (27): 3138–3149.

## HER2-pos. mBC

### No Chemotherapy Possible or Desired

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

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:  
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

ASCO recommendation

1. 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, Pippin 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

#### Abemaciclib + fulvestrant + trastuzumab

1. Tolaney S, Wardley AM, Zambelli S et al., monarchHER: 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
2. Tolaney SM, Goel S, Nadal J et al.(2023) Overall survival and exploratory biomarker analyses of abemaciclib plus trastuzumab with or without fulvestrant vs trastuzumab plus chemotherapy in HR+, HER2+ metastatic breast cancer patients. Clin Cancer Res. doi:10.1158/1078-0432.CCR-23-1209

#### 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 progressed 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.
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

#### 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.