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FORSCHEN
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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Chemotherapie mit oder ohne zielgerichtete Substanzen* beim metastasierten Mammakarzinom

* Es werden nur Substanzen mit publizierten Studienergebnissen basierend auf zumindest einer publizierten Studie Phase III oder IIb berücksichtigt.




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Chemotherapie mit oder ohne zielgerichtete Substanzen bei metastasiertem Mammakarzinom

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- **Version 2022:**
Lux / Schütz

<div>  Chemotherapie Krankheitsfreies- und Gesamtüberleben </div>									
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	Oxford LoE								
▪ Eine Verbesserung der Überlebenszeit beim metastasierten Mammakarzinom wurde in Studien gezeigt	1b								
▪ Mehrere Linien der sequenziellen Therapie sind von Vorteil (gleiche Wirksamkeit, geringere Toxizität)	1b								
▪ Besonders für Kombinationen einer Chemotherapie mit zielgerichteten Substanzen wurde ein entsprechender Überlebensvorteil festgestellt	1b								

International consensus

- 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

- 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

- 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.



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Endokrine Resistenz bei metastasiertem Mammakarziom

Primäre endokrine Resistenz:

- Rezidiv innerhalb der ersten zwei Jahre unter einer adjuvanten endokrinen Therapie (ET)
- Progress innerhalb der ersten 6 Monate unter einer laufenden endokrinen first-line-Therapie beim metastasierten Mammakarzinom

Sekundäre (erworbene) endokrine Resistenz:

- Rezidiv unter einer adjuvanten ET, aber erst nach den ersten 2 Jahren oder innerhalb 12 Monate nach abgeschlossener adjuvanter ET
- Progression \geq 6 Monate nach Initiierung einer ET in der metastasierten Situation

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.

Metastasiertes Mammakarzinoms (mBC) Prädiktive Faktoren für Ansprechen					
Therapie	Faktor	Oxford			AGO
		LoE	GR		
▪ Endokrine Therapie	ER / PR (Primärtumor, besser Metastase) Ansprechen auf vorherige Therapie autokrine Rezeptormutation (ESR1)	1a	A		++
		2b	B		++
		1b ^d	A		+
▪ Alpelisib	PIK3CA Mutation (Primärtumor, Metastase, Plasma)	1b	A		+
▪ Chemotherapie	Ansprechen auf vorherige Therapie	1b	A		++
▪ Anti-HER2- Therapie	HER2 (Primärtumor, besser Metastase)	1a	A		++
▪ Checkpoint-Inhibitoren	PD-L1 positivity ^a (PD-L1ic, CPS) in TNBC (Primärtumor oder Metastase)	1b	B		++
▪ PARP-Inhibitoren	gBRCA1/2-Mutation	1a	A		++
▪ Beliebige Therapie	CTC monitoring	1b	A		+*

* In klinischen Studien
Siehe auch Kapitel „Pathologie“

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. 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.

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

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.

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.

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.



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Chemotherapie des metastasierten Mammakarzinoms

Ziele

Oxford LoE: 1b
GR: A
AGO: ++

- **Monochemotherapie**
 - **Günstiger therapeutischer Index***
 - **Indiziert bei**
 - langsame, nicht lebensbedrohliche Progression
 - Resistenz oder Progression unter endokrin-basierter Therapie
- **Polychemotherapie:**
 - Ungünstiger therapeutischer Index
 - Indiziert zum Erzielen einer schnellen Remission bei
 - ausgeprägten Symptomen
 - viszeraler Krise (ABC 5-Definition)
 - Überlebensvorteil im Vergleich zur sequenziellen Gabe der gleichen Substanzen ist nicht bewiesen

* Der therapeutische Index berücksichtigt Effektivität, Toxizität, und Lebensqualität

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..

Metastasiertes Mammakarzinom Systemtherapie

GR: A

AGO: ++

- **Bewertung der Compliance vor und während der Therapie (insbesondere bei älteren Patientinnen, bei reduziertem AZ oder relevanten Komorbiditäten bzw. Zweitmalignomen)**
- **Regelmäßige Beurteilung der Lebensqualität, subjektiver und objektiver Toxizitäten, des AZ und von Symptomen**
- **Dosierung entsprechend publizierten Protokollen**
- **Beurteilung der Tumorlast ca. alle 2 Monate, d. h. alle 2–4 Zyklen; bei langsam progredienter Krankheit sind längere Intervalle akzeptabel**

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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Metastasiertes Mammakarzinom

Dauer der Chemotherapie

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Solange wie der therapeutische Index* positiv bleibt ■ Therapie bis zur Progression ■ Therapie bis zum besten Ansprechen ■ Wechsel auf alternatives Schema vor einer Progression ■ Therapiestopp bei ■ Progression ■ Nicht tolerabler Toxizität 	<div style="border-top: 1px solid green; padding-top: 5px;">1a</div> 2b <div style="border-top: 1px solid green; padding-top: 5px;">2b</div> 2b <div style="border-top: 1px solid green; padding-top: 5px;">2b</div> 1c	<div style="border-top: 1px solid green; padding-top: 5px;">A</div> B <div style="border-top: 1px solid green; padding-top: 5px;">B</div> B <div style="border-top: 1px solid green; padding-top: 5px;">A</div>	<div style="border-top: 1px solid green; padding-top: 5px;">++</div> + <div style="border-top: 1px solid green; padding-top: 5px;">+/-</div> +/- <div style="border-top: 1px solid green; padding-top: 5px;">++</div>

* Der therapeutische Index berücksichtigt Effektivität, Toxizität, und Lebensqualität

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.



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Systemtherapie beim mBC

Allgemeine Überlegungen

AGO: ++

- Teilnahme an Studien wird empfohlen
- Die Wahl der medikamentösen Therapie ist abhängig von:
 - ER / PR, HER2, PD-L1-Status, gBRCA-Status (ggf. sBRCA-Status, ggf. PALB2), PIK3CA, ggf. MSI, NTRK, ggf. mESR1, andere (siehe Mutationsdiagnostik)
 - Frühere Behandlungen (und ihre Toxizitäten)
 - Rezidivfreies Intervall nach Ende der adjuvanten Therapie
 - Progressionsfreies Intervall und Remission der vorherigen Therapie
 - Aggressivität der Erkrankung, Lokalisation der Metastasen
 - Geschätzte Lebenserwartung
 - Begleiterkrankungen (einschließlich Organfunktionen)
 - Erwartungen und Präferenzen der Patientinnen / Patienten

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-negativ / HR-positiv Erstlinienbehandlung Chemotherapie			
	Oxford		
	LoE	GR	AGO
■ Monochemotherapie			
■ Paclitaxel (q1w) (T), Docetaxel (q3w),	1a	A	++
■ Doxorubicin, Epirubicin, Peg-liposomales Doxorubicin(A _{lip})	1b	A	++
■ Vinorelbin	3b	B	+
■ Capecitabin	2b	B	+
■ Nab-Paclitaxel	2b	B	+
■ Polychemotherapie:			
■ A + T	1b	A	++
■ Paclitaxel + Capecitabin	2b	B	+
■ Docetaxel + Capecitabin nach adj. A	1b	A	+
■ T + Gemcitabin nach adj. A	2b	B	++
■ A + C oder A _{lip} + C	1b	B	++
Berücksichtigung der Vorbehandlung: * bei ER pos. Erkrankung nur indiziert, wenn eine endokrine Therapie nicht oder nicht mehr in Frage kommt			

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. Gherzi 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-negativ / HR-positiv Chemotherapie nach Anthrazyklin-Vorbehandlung*			
	Oxford		
	LoE	GR	AGO
▪ Paclitaxel (q1w)	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabin	2b	B	++
▪ Nab-Paclitaxel	2b	B	++
▪ Peg-liposomales Doxorubicin*	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbin	2b	B	+
▪ Docetaxel + Peg-liposomales Doxorubicin	1b	B	+/-

* Unabhängig davon, ob Anthrazykline in der adjuvanten oder first line metastasierten Situation verwendet wurden

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-negativ / HR-positiv Chemotherapie nach Taxan- und Anthrazyklin-Vorbehandlung			
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D www.ago-online.de FORSCHEN LEHREN HEILEN	▪ Capecitabin	Oxford LoE GR AGO	
	▪ Eribulin	2b	B ++
	▪ Vinorelbin	1b	B ++
	▪ (Peg)-liposomales Doxorubicin	2b	B ++
	▪ Taxan Re-Challenge*	2b	B +
	▪ Anthrazyklin Re-Challenge*	2b	B +
	▪ Metronomische Therapie (z. B. Cyclophos. und MTX)	3b	C +
	▪ Gemcitabin + Cisplatin / Carboplatin	2b	B +
		2b	B +/-
* Mindestens 1 Jahr rezidivfrei nach adjuvanter Gabe			

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.

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. 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.
3. 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.
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Taxane re-challenge

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Anthracycline re challenge

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Metronomic chemotherapy

1. 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.
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3. 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.
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Gemcitabine + cisplatin / carboplatinum

1. Li HC, Russell CA Gemcitabine and platinum-based chemotherapy in metastatic breast cancer. Oncology (Williston Park). 2004

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2. Perez EA Gemcitabine and platinum combinations in patients with breast cancer previously treated with anthracyclines and/or taxanes. Clin Breast Cancer. 2004 Jan;4 Suppl 3:S113-6

Gemcitabine + capecitabine

1. Park JS, Jeung HC, Rha SY, et al. Phase II gemcitabine and capecitabine combination therapy in recurrent or metastatic breast cancer patients pretreated with anthracycline and taxane. Cancer Chemother Pharmacol. 2014;74(4):799-808

Gemcitabine + Vinorelbine

1. Martín M, Ruiz A, Muñoz M, Balil A, et al. Spanish Breast Cancer Research Group (GEICAM) trial Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8(3):219-225.
2. Kim JH, Oh SY, Kwon HC, et al. Phase II study of gemcitabine plus cisplatin in patients with anthracycline- and taxane- pretreated metastatic breast cancer. Cancer Res Treat. 2008;40(3):101-5.

Triple negative mBC PD-L1+ unabhängig von Keimbahnmutation in <i>BRCA 1/2</i> oder <i>PALB2</i>			
	Oxford		
	LoE	GR	AGO
▪ Pembrolizumab + Chemo* first-line PD-L1 CPS $\geq 10^{\#}$ (wenn TFI ≥ 6 Monate)	1b	B	++
▪ Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC $\geq 1^{\#}$ (wenn TFI ≥ 12 Monate)	1b	B	+
▪ Atezolizumab + Paclitaxel first line PD-L1 IC $\geq 1^{\#}$	1b ^a	B	-
▪ Pembrolizumab-Monotherapie (nach Chemo- therapie ohne Immun-Vorthherapie) bei CPS $\geq 20^{\#}$	1b ^a	B	+/-

(siehe Kapitel „Pathologie“)
 * nab-Paclitaxel oder Paclitaxel oder Carboplatin / Gemcitabin
 TFI = Therapie-freies Intervall

International consensus


- 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:

- 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.
- 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.
- Adams S, Diéras V, Barrios CH et al. Patient-reported outcomes from the phase III IMpassion130 trial of atezolizumab plus nab-paclitaxel in metastatic triple-negative breast cancer. Ann Oncol 2020; 31 (5): 582–589.
- 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.

5. Cortés J, Lipatov O, Im S-A et al. KEYNOTE-119: Phase III study of pembrolizumab (pembro) versus single-agent chemotherapy (chemo) for metastatic triple negative breast cancer (mTNBC). *Annals of Oncology* 2019; 30: v859-v860.
6. Adams S, Schmid P, Rugo HS et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. *Ann Oncol* 2019; 30 (3): 397–404.
7. 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*. 2021 Aug;32(8):994-1004. doi: 10.1016/j.annonc.2021.05.801. Epub 2021 Jul
8. KEYNOTE-119 investigators. 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.
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FORSCHEN
LEHREN
HEILEN

Triple negative mBC unabhängig von PD-L1 Status und Keimbahnmutation in *BRCA 1/2* oder *PALB2*

	Oxford		
	LoE	GR	AGO
▪ Sacituzumab Govitecan (≥ 2nd line)	1b	B	++
▪ Bevacizumab 1st line in Kombination mit			
▪ Paclitaxel (wöchentlich)	1b	B	+
▪ Capecitabin	1b	B	+
▪ Nab-Paclitaxel	2b	B	+/-
▪ Carboplatin (vs. Docetaxel)	1b	B	+/-
▪ Gemcitabin / Cisplatin (vs. Gem / Pac)	1b	A	+
▪ Nab-Paclitaxel / Carboplatin (vs. Carbo / Gem)	2b	B	+

International consensus

- 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.

Bevacizumab as first-line therapy

- 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.
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- 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.
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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.

Sacituzumab Govitecan:

1. Bardia A, Tolaney SM, Loirat D et al. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Ann Oncol 2020 (31 (suppl_4)): S1142-S1215. 10.1016/annonc/annonc325.
2. Bardia A, Mayer IA, Vahdat LT et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med 2019; 380 (8): 741–751.
3. 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.

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 D, Coleman R, Conte P, et al. nab-paclitaxel + carboplatin or gemcitabine vs gemcitabine/carboplatin as first-line treatment for patients with triple-negative metastatic breast cancer: Results from the randomized phase 2 portion of the tnAcity trial. SABCS 2016 Abstract #P5-15-03

mBC mit Mutation für <i>BRCA 1/2</i> oder <i>PALB2</i>			
	Oxford		
	LoE	GR	AGO
▪ Standardtherapie entsprechend gBRCA1/2 negativ			++
▪ Carboplatin (vs. Docetaxel) (wenn Platin-naiv)	1b	B	+
▪ PARP-Inhibitoren (HER2-negative Karzinome)			
▪ HER2-negativ, <i>BRCA 1/2</i> Keimbahnmutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ Somatische <i>BRCA 1/2</i> Mutation (Keimbahnentestung Standard)			
▪ Olaparib	2b	B	+/-
▪ <i>PALB2</i> Keimbahnmutation			
▪ Olaparib	2b	B	+/-

International consensus

- 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

- 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

- Robson M, Tung N, Conte P. et al. Qlympia AD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30:558-566
- 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.
- Robson M, Im S-A, Senkus E et al: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med

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4. Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol* 2020; 38 (36): 4274–4282.
5. Taylor AM, Chan DLH, Tio M, et al. PARP (Poly ADP-Ribose Polymerase) inhibitors for locally advanced or metastatic breast cancer. *Cochrane Database Syst Rev*. 2021 Apr 22;4(4):CD011395. doi: 10.1002/14651858.CD011395.pub2.

HER2-pos. mBC			
1st line ohne Vorthherapie oder nach Trastuzumab			
	Oxford		
	LoE	GR	AGO
Primär metastasiert			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
Nach Trastuzumab adjuvant (TFI > 6 Monate)			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
Nach ausschließlich Trastuzumab adjuvant (TFI < 6 Monate)			
▪ Trastuzumab Deruxtecan (T-DXd)	5	D	+
▪ T-DM1	2b	B	+/-
▪ Chemotherapie + Trastuzumab + Pertuzumab	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, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-99

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](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.

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.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	HER2-pos. mBC		
	1st line nach Trastuzumab / Pertuzumab +/- TDM-1		
	Oxford		
	LoE	GR	AGO
Nach Trastuzumab / Pertuzumab (neo-)adjuvant			
▪ Reinduktion CTx + Trastuzumab + Pertuzumab (TFI > 6-12 Monate)	5	D	++
▪ Trastuzumab Deruxtecan (T-DXd) (TFI < 6-12 Monate)	5	D	+
▪ T-DM1 (TFI < 6-12 Monate)	5	D	+/-
▪ Capecitabin + Lapatinib	1b	B	+/-
Nach Trastuzumab / Pertuzumab (neo-)adjuvant <u>und</u> T-DM1 post-neoadjuvant			
▪ Reinduktion CTx + Trastuzumab + Pertuzumab (TFI > 6-12 Monate)	5	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabin + Trastuzumab	5	D	+
▪ Capecitabin + Lapatinib	5	D	+/-

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

International consensus

- 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

- Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-99

Reinduction of chemotherapy + trastuzumab + pertuzumab

- 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.
- 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.
- 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.

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.
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.
1. 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.
2. 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 + Capecitabin (nach T-DM1-Vorthherapie)	1b	B	++
▪ T-DM 1	1b	A	+
▪ Capecitabin + Lapatinib / Trastuzumab	1b	B	+/-
▪ TBP: 2 nd line Chemotherapie* + Trastuzumab / Pertuzumab	2b	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg. Tumor)	2b	B	+/-

* z. B. Taxane; Vinorelbin; Taxane / Carboplatin; Capecitabin; 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, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-99

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

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.
1. 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.
2. 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. 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.

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>
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) ± 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 ≥ 3rd-line			
In Abhängigkeit der Vorthherapie (Substanz)	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabin	1b	B	++
▪ Trastuzumab-Deruxtecan	1b	B	+
▪ T-DM 1	1b	A	+
▪ Capecitabin + Trastuzumab / Lapatinib	1b	B	+
▪ Capecitabin + Neratinib	1b	B	+
▪ Margetuximab + Chemotherapie	1b	B	+/-
▪ Experimentelle Anti-HER2-Regime	5	D	+

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

1. Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-99

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

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

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.
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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 ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020; 38 (27): 3138–3149.

Margetuximab

1. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Apr; 7(4): 1–12. Published online 2021 Jan 22. doi: 10.1001/jamaoncol.2020.7932





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Guidelines Breast
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FORSCHEN
LEBEN
HEILEN

HER2-pos. mBC

Keine Chemotherapie möglich / erwünscht

- Trastuzumab + Aromatase-Inhibitor (HR+)
- Lapatinib + Aromatase-Inhibitor (HR+)
- Aromatase-Inhibitor + Trastuzumab + Pertuzumab (HR+)
- Abemaciclib + Trastuzumab + Fulvestrant
- Trastuzumab + Pertuzumab
- Trastuzumab + Lapatinib (HR neg.)
- Trastuzumab mono

Oxford		
LoE	GR	AGO
2b	B	+/-
2b	B	+/-
2b	B	+
2b ^a	B	+/-
2b	B	+/-
2b	B	+
2b	B	+/-

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:
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Trastuzumab and AI (in HR+)

- 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.
- 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.
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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

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

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.