

# 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

### ■ Versionen 2002–2020:

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/ Müller / Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz /  
Stickeler / Thill / Thomssen / Untch

### ■ Version 2021:

Jackisch / Schmidt

## Chemotherapie

### Krankheitsfreies- und Gesamtüberleben

	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

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.

## 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			
		LoE	GR	AGO	
▪ Endokrine Therapie	ER/PR (Primärtumor, besser Metastase)	1a	A	++	
	Ansprechen auf vorherige Therapie	2b	B	++	
	autokrine Rezeptormutation (ESR1)	2b	B	+	
▪ 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 <sup>#</sup> (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++	
▪ PARP-Inhibitoren	gBRCA1/2-Mutation	1a	A	++	
▪ Bone modifying drugs	Knochenmetastasen	1a	A	++	
▪ Beliebige Therapie	CTC monitoring	1b	A	+*	

\* In klinischen Studien; # Siehe auch Kapitel „Pathologie“

### Endocrine therapy

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

### 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

*Oncol.* 2018;29(8):1634–1657.

### Anti-HER2-Therapy

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

to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014;32(31):3483-9.

## 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..

## Metastasiertes Mammakarzinom

### Dauer der Chemotherapie

	Oxford		
	LoE	GR	AGO
▪ Solange wie der therapeutische Index* positiv bleibt	<b>1a</b>	<b>A</b>	<b>++</b>
▪ Therapie bis zur Progression	<b>2b</b>	<b>B</b>	<b>+</b>
▪ Therapie bis zum besten Ansprechen	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ Wechsel auf alternatives Schema vor einer Progression	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ Therapiestopp bei	<b>1c</b>	<b>A</b>	<b>++</b>
▪ Progression			
▪ Nicht tolerabler Toxizität			

\*Der therapeutische Index berücksichtigt Effektivität, Toxizität, und Lebensqualität

#### 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. Change to alternative regimen before progression
- 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.
- 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

- 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.
- 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.

# 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, PIK3CA, ggf. MSI, NTRK, 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

#### 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

	LoE	Oxford GR	AGO
<b>■ Monochemotherapie</b>			
▪ Paclitaxel (q1w) (T), Docetaxel (q3w),	1a	A	++
▪ Doxorubicin, Epirubicin, Peg-liposomales Doxorubicin(A <sub>lip</sub> )	1b	A	++
▪ Vinorelbin	3b	B	+
▪ Capecitabin	2b	B	+
▪ Nab-Paclitaxel	2b	B	+
<b>■ Polychemotherapie:</b>			
▪ 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 <sub>lip</sub> + 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. 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-negativ / HR-positiv** **Chemotherapie nach Anthrazyklin-Vorbehandlung\***

- **Paclitaxel (q1w)**
- **Docetaxel q3w**
- **Capecitabin**
- **Nab-Paclitaxel**
- **Peg-liposomales Doxorubicin\***
- **Eribulin**
- **Vinorelbin**
- **Docetaxel + Peg-liposomales Doxorubicin**

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
2b	B	++
2b	B	++
2b	B	+
1b	B	+
2b	B	+
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

- Capecitabin
- Eribulin
- Vinorelbin
- (Peg)-liposomales Doxorubicin
- Taxan Re-Challenge\*
- Anthrazyklin Re-Challenge\*
- Metronomische Therapie (z.B. Cyclophos. und MTX)
- Gemcitabin + Cisplatin / Carboplatin

Oxford		
LoE	GR	AGO
2b	B	++
1b	B	++
2b	B	++
2b	B	+
2b	B	+
3b	C	+
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.
4. Pivot X, Im SA, Guo M, Marmé F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting

from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. Breast Cancer. 2018;25(3):370-374.

5. Ohtani S, Nakayama T, Yoshinami T, et al. Bi-weekly eribulin therapy for metastatic breast cancer: a multicenter phase II prospective study (JUST-STUDY). Breast Cancer. 2018;25(4):438-446.

#### Taxane re-challenge

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

#### Anthracycline re challenge

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

#### Metronomic chemotherapy

1. 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.
2. Yoshimoto M, Takao S, Hirata M, et al. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother Pharmacol. 2012;70(2):331-8.
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.
4. Addeo R, Sgambato A, Cennamo G, et al. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. Clin Breast Cancer. 2010;10(4):301-6.
5. Colleoni M, Orlando L, Sanna G, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann Oncol. 2006;17(2):232-8.
6. Krajnak S, Schnatz C, Almstedt K et al. Low-dose metronomic chemotherapy as an efficient treatment option in metastatic breast cancer-results of an exploratory case-control study. Breast Cancer Res Treat 2020; 182 (2): 389–399.

#### Gemcitabine + cisplatin / carboplatinum

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

Dec;18(14 Suppl 12):17-22

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 *BRCA 1/2* oder *PALB2*

	Oxford		
	LoE	GR	AGO
▪ Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC $\geq 1^{\#}$ (wenn TFI $\geq 12$ Monate)	1b	B	+
▪ Atezolizumab + Paclitaxel first line PD-L1 IC $\geq 1^{\#}$	1b <sup>a</sup>	B	-
▪ Pembrolizumab + Chemo* first-line PD-L1 CPS $\geq 10^{\#}$ (wenn TFI $\geq 6$ Monate)	1b	B	+/-
▪ Pembrolizumab-Monotherapie (nach Chemotherapie ohne Immun-Vortherapie) bei CPS $\geq 20^{\#}$	1b <sup>a</sup>	B	+/-

<sup>#</sup> (siehe Kapitel „Pathologie“)

\* nab-Paclitaxel oder Paclitaxel oder Carboplatin / Gemcitabine

TFI = Therapie-freies Intervall

### International consensus

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

### Checkpoint-inhibitoren:

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121.
2. Cortes J, Cescon DW, Rugo HS et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396 (10265): 1817–1828.
3. 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.
4. 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.

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

- Bevacizumab zusätzlich zur first-line Zytostatikatherapie
- Sacituzumab Govitecan (nach Vorbehandlung mit mind. 2 Standardtherapielinien)
- Carboplatin (vs. Docetaxel)
- Gemcitabin/Cisplatin (vs. Gem/Pac)
- Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)

Oxford		
LoE	GR	AGO
1b	B	+
1b <sup>a</sup>	B	+
1b	B	+/-
1b	A	+
2b <sup>a</sup>	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.

### Bevacizumab as first-line therapy

1. Miles DW, Diéras V, Cortés J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013;24(11):2773-80. doi: 10.1093/annonc/mdt276.

### 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.

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 *BRCA* 1/2 oder *PALB2*

	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</i> 1/2 Keimbahnmutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	B	++
▪ Somatische <i>BRCA</i> 1/2 Mutation (Keimbahntestung Standard)			
▪ Olaparib	2b	B	+/-
▪ <i>PALB2</i> Keimbahnmutation			
▪ 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

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

2017;377:523-533

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.

## Metastasiertes Mammakarzinom Bevacizumab beim HER2-neg. mBC

	Oxford		
	LoE	GR	AGO
■ <b>1<sup>st</sup> line in Kombination mit:</b>			
■ Paclitaxel (wöchentlich)	1b	B	+
■ Capecitabin	1b	B	+
■ Anthracyklinen	2b	B	+/-
■ Nab-Paclitaxel	2b	B	+/-
■ Docetaxel (dreiwöchentlich)	1b	B	+/-
■ <b>Cap+Bev als Erhaltung nach Doc + Bev</b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>
■ <b>2<sup>nd</sup> line in Kombination mit:</b>			
■ Taxanen	1b	B	+/-
■ Capecitabin	1b	B	+/-
■ Gemcitabin oder Vinorelbin	1b	B	-
■ <b>Ab 2<sup>nd</sup> line als Behandlung durch multiple Linien</b>	<b>1b</b>	<b>B</b>	<b>-</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.

### First-line chemotherapy and bevacizumab

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

### Taxane and bevacizumab first-line

- 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.
- Miles D, Chan A, Luc Y, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 28:3239-3247, 2010

### Nab-Paclitaxel and bevacizumab first-line

1. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol. 2015;33(21):2361-9.

#### Capecitabine and bevacizumab first-line

1. 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.
2. 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.

#### Cap+Bev as maintenance after Doc+Bev

1. 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.
2. 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

#### Second-line chemotherapy and bevacizumab

1. Brufsky et al., RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy for Second-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 29:4286-4293. 201

#### 2nd line as treatment through multiple lines

1. Vrdoljak E, Marschner N, Zielinski C, et al. Final results of the TANIA randomised phase III trial of bevacizumab after progression on first-line bevacizumab therapy for HER2-negative locally recurrent/metastatic breast cancer. Ann Oncol. 2016;27(11):2046-2052.

## HER2-pos. mBC

### Therapie nach Trastuzumab oder ohne Vorbehandlung (+ Chemotherapie)

	Oxford		
	LoE	GR	AGO
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
▪ 1 <sup>st</sup> line Chemotherapie* + Trastuzumab	1b	B	+
▪ TBP: 2 <sup>nd</sup> line Capecitabin + Trastuzumab	2b	B	+
▪ Capecitabin + Lapatinib	1b	B	+
▪ Taxan + Lapatinib	1b	B	+/-
▪ Taxan + Trastuzumab + Everolimus	1b	B	-

\* Taxane; Vinorelbine; Paclitaxel/Carboplatin; Capecitabine/Docetaxel,

#### 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

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.

#### 1<sup>st</sup> line chemotherapy + trastuzumab

1. Andersson M, Lidbrink E, Bjerre K. et al.: Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab With Vinorelbine Plus Trastuzumab As First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The HERNATA Study. *J Clin Oncol* 2011;29(3):264-71.
2. Valero V, Forbes J, Pegramet M D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-Gene-Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. *J Clin Oncol* 2011;29(2):149-56.
3. Dawood S, Broglio K, Buzdaret AU et al.: Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review. *J Clin Oncol* 2010;28(1):92-8.
4. Robert N, Leyland-Jones B, Asmaret L et al.: Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel in Women With HER-2–Overexpressing Metastatic Breast Cancer. *J Clin Oncol* 2006;24(18):2786-92.

5. Wardley AM, Pivot X, Morales-Vasquez F et al.: Randomized Phase II Trial of First-Line Trastuzumab Plus Docetaxel and Capecitabine Compared With Trastuzumab Plus Docetaxel in HER2-Positive Metastatic Breast Cancer. J Clin Oncol. 2010;28(6):976-83.
6. 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.

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

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.

#### Capecitabine + lapatinib

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.

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.

When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.

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.

#### Taxanes+ lapatinib

- Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: a phase III randomized, double-blind study of 580 patients. J Clin Oncol. (2007 ASCO Annual Meeting Proceedings Part I) (2007) 25(18S):1011.
- Gelmon KA et al., Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31, J Clin Oncol. 2015;33(14):1574-83

#### Taxane + trastuzumab + everolimus

1. Hurvitz SA et al., Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial, Lancet Oncol. 2015;16(7):816-29
2. Yardley D, Hurvitz S, Jiang Z-f, et al. Everolimus plus trastuzumab and paclitaxel as first-line therapy in women with HER2+ advanced breast cancer: Overall survival results from BOLERO-1. SABCS 2016, Poster Session 4 - Treatment: Advanced Therapy - Targeted, Abstract No. P4-22-13

#### Trastuzumab + aromatase inhibitors (if ER+)

1. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM Study. J Clin Oncol 2009;27:5529–37

#### Lapatinib + aromatase inhibitors (if ER+)

1. Johnston S, Pippen Jr J, Pivot X, et al. Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. J Clin Oncol 2009;27(33):5538-46.

## HER2-pos. mBC

### weitere Therapiemöglichkeiten nach Trastuzumab

	Oxford		
	LoE	GR	AGO
■ <b>T-DM 1</b> (Rückfall innerhalb von 6 Monaten und nach Taxan und Trastuzumab)	<b>2b</b>	<b>B</b>	<b>+</b>
■ <b>Trastuzumab + Lapatinib (HR neg. tumor)</b>	<b>2b</b>	<b>B</b>	<b>+</b>
■ <b>Trastuzumab mono</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ <b>Trastuzumab + Aromatase-Inhibitoren (ER+)</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>Lapatinib + Aromatase-Inhibitoren (ER+)</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>AI + Trastuzumab + Pertuzumab</b>			<b>+</b>
■ <b>Abemaciclib + Trastuzumab + Fulvestrant</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>Trastuzumab + Pertuzumab</b>			<b>+/-</b>

\* siehe Kapitel „Endokrine +/- targeted Therapie“

#### 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

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.

#### T-DM1 after rapid progress

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 + 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

#### 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.

#### Trastuzumab + aromatase inhibitors (if ER+)

1. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM Study. J Clin Oncol 2009;27:5529–37

#### Lapatinib + aromatase inhibitors (if ER+)

1. Johnston S, Pippen Jr J, Pivot X, et al. Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. J Clin Oncol 2009;27(33):5538-46.

#### AI + Trastuzumab + Pertuzumab

1. Rimawi M, Ferrero J-M, La Haba-Rodriguez J de et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol 2018; 36 (28): 2826–28

#### Abemaciclib + Trastuzumab + Fulvestrant

1. Tolaney SM, Wardley AM, Zambelli S et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarchHER): a randomised, open-label, phase 2 trial. Lancet Oncol 2020; 21 (6): 763–775.

#### Trastuzumab + Pertuzumab

1. Baselga J, Gelmon KA, Verma S 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. J Clin Oncol 2010; 28 (7): 1138–1144

## HER2-pos. mBC

### Therapie nach Trastuzumab/Pertuzumab

	Oxford		
	LoE	GR	AGO
▪ <b>T-DM 1</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>TBP: 2<sup>nd</sup> line Chemotherapie + Trastuzumab</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>2<sup>nd</sup> line Chemotherapie* + Trastuzumab</b>	<b>5</b>	<b>D</b>	<b>+/-</b>
+ Pertuzumab (falls noch nicht gegeben)			
▪ Taxane + Trastuzumab + Pertuzumab	<b>5</b>	<b>D</b>	<b>+</b>
▪ Capecitabin + Trastuzumab + Pertuzumab	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>
▪ <b>Capecitabin + Lapatinib</b>	<b>1b</b>	<b>B</b>	<b>+</b>

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

#### International consensus

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

#### 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

#### 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.

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.
- 2.

Taxane + trastuzumab + pertuzumab

1. 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
2. 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

Capecitabine + Trastuzumab + Pertuzumab

1. Urruticoechea A, Rizwanullah M, Im SA, et al. PHEREXA: a phase III study of trastuzumab (H) þ 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

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. When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.



4. 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.

## HER2-pos. mBC

### Therapie nach T-DM 1

	Oxford		
	LoE	GR	AGO
▪ <b>Tucatinib + Trastuzumab + Capecitabin</b>	<b>1b</b>	<b>B</b>	<b>++</b>
▪ <b>Neratinib + Capecitabin</b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>Capecitabin + Lapatinib</b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>Capecitabin + Trastuzumab + Pertuzumab</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Trastuzumab Deruxtecan</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Experimentelle Anti-HER2-Regime</b>	<b>5</b>	<b>D</b>	<b>+</b>

#### International consensus

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

#### 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

#### Metaanalyse nach Taxan / 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

#### 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.

#### 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.

#### Capecitabine + Trastuzumab + Pertuzumab

1. Urruticoechea A, Rizwanullah M, Im S-A et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced

Disease Progression During or After Trastuzumab-Based Therapy. J Clin Oncol 2017; 35 (26): 3030–303

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.

## Metastasiertes Mammakarzinom

### Lapatinib beim HER2-positiven mBC

#### ■ In Kombination mit

- Trastuzumab für schwer vorbehandelte Patientinnen (HR neg.)
- Paclitaxel als 1<sup>st</sup> line
- Capecitabin als > 2<sup>nd</sup> line
- Vinorelbin
- AI bei ER positiver Erkrankung

#### ■ bei Patientinnen mit Hirnmetastasen (Radioresistenz) in Kombination mit Capecitabin

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

#### 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

#### Taxanes+ lapatinib

1. Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: a phase III randomized, double-blind study of 580 patients. J Clin Oncol. (2007 ASCO Annual Meeting Proceedings Part I) (2007) 25(18S):1011.
2. Gelmon KA et al., Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31, J Clin Oncol. 2015;33(14):1574-83

#### 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.

#### Vinorelbine + Lapatinib

1. Janni W, Sarosiek T, Karaszewska B, et al. Final overall survival analysis of a phase II trial evaluating vinorelbine and lapatinib in women with ErbB2 overexpressing metastatic breast cancer. Breast. 2015;24(6):769-73.

#### Lapatinib + aromatase inhibitors (if ER+)

1. Johnston S, Pippen Jr J, Pivot X, et al. Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. J Clin Oncol 2009;27(33):5538-46.

#### Brain metastases (radioresistance)

1. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2008;26:1993-9.

# Immundiagnostik und Immuntherapien

## Immundiagnostik

- Tumorgewebe: Bestimmung PD-L1 IC-Status beim TNBC
- Blut: Bestimmung von immunologischen Parametern

## Systemische Immuntherapien

- Atezolizumab + Nab-Paclitaxel first-line TNBC, PD-L1 IC  $\geq 1^{\#}$
- Atezolizumab + Paclitaxel first line TNBC, PD-L1 IC  $\geq 1^{\#}$
- Pembrolizumab + Chemo\* bei TNBC & PD-L1 CPS  $\geq 10^{\#}$
- Pembrolizumab-Monotherapie (nach Chemotherapie ohne Immun-Vortherapie) bei CPS  $\geq 20^{\#1}$

Oxford		
LoE	GR	AGO

1b	B	+
5	D	--
1b	B	+
1b <sup>a</sup>	B	-
1b	B	+/-
1b <sup>a</sup>	B	+/-

# (siehe Kapitel „Pathologie“)

\* nab-Paclitaxel oder Paclitaxel oder Carboplatin / Gemcitabin

<sup>1</sup> CAVE: keine Zulassung

## 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.
- Miles D, Andre F, Gligorov J et al. IMpassion131: Phase III study comparing 1L atezolizumab with paclitaxel vs placebo with paclitaxel in treatment-naïve patients with inoperable locally advanced or metastatic triple negative breast cancer (mTNBC). Ann Oncol 2017; 28: v105.
- 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.
- 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.

7. 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.