

Diagnostik und Therapie primärer und metastasierter 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.

Chemotherapie mit oder ohne zielgerichtete Substanzen bei metastasiertem Mammakarzinom

- **Versionen 2002–2017:**

Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
Jackisch / Janni / von Minckwitz / Möbus / Müller /
Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz /
Stickeler / Thill / Thomssen / Untch

- **Version 2018:**

Liedtke / Möbus

International consensus

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

Chemotherapie

Krankheitsfreies und Gesamtüberleben

	<u>Oxford LoE</u>
▪ Eine Verbesserung der Überlebenszeit beim metastasierten Mammakarzinom wurde in einigen retrospektiven Analysen gezeigt	2a
▪ Allerdings haben Patientinnen mit einer metastasierten Erkrankung heute mehr adjuvante Therapie erhalten und müssen deshalb als therapieresistenter angesehen werden	2a
▪ 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, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 2017;31:244-259

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

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

International consensus

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

Therapie des metastasierten Mamma- karzinoms – Prädiktive Faktoren

Therapie	Faktor	Oxford		
		LoE	GR	AGO
Endokrine Therapie	ER/PR Rezeptorstatus (Primärtumor, Metastase)	1a	A	++
	vorheriges Ansprechen	2b	B	++
Chemotherapie	vorheriges Ansprechen	1b	A	++
Anti-HER2-zielgerichtete Therapie	HER2 (Primärtumor, besser Metastase)	1a	A	++
Bone modifying drugs	Knochenmetastasen	1a	A	++
Beliebige Therapie	CTC monitoring	1b	A	+*
* In klinischen Studien				
(andere potenzielle biologische Faktoren: siehe Kapitel „Prädiktive Faktoren“)				

CTC monitoring

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.

Palliative Chemotherapie Ziele

Oxford LoE: 1b

GR: A

AGO: ++

■ Monochemotherapie

- Günstiger therapeutischer Index
- Indiziert bei
 - Langsamer, nicht lebensbedrohlicher Progression
 - Resistenz oder Progression unter endokriner Therapie

■ Polychemotherapie:

- Ungünstiger therapeutischer Index
- Indiziert zum Erzielen einer schnellen Remission bei
 - ausgeprägten Symptomen
 - Lebensbedrohlichen Metastasen
- 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, Costa A, Senkus E, et al. 3rd_ESO-ESMO_international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 2017;31:244-259;

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

Palliative Systemtherapie

GR: A

AGO: ++

- **Bewertung der Compliance vor und während der Therapie (insbesondere bei älteren Patientinnen, bei reduziertem AZ oder relevanten Komorbiditäten)**
- **Regelmäßige Beurteilung 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. Die Beurteilung einer Zielläsion muss adäquat sein, bei langsam progredienter Krankheit sind längere Intervalle akzeptabel.**

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Palliative Chemotherapie

Dauer

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

International consensus

- 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;

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.

Chemotherapie beim mBC – Allgemeine Überlegungen: Substanzwahl

AGO: ++

■ Die Wahl des Zytostatikums ist abhängig von:

- ER/PR, HER2; Kombination mit Biologicals
- Frühere Behandlungen (und ihre Toxizitäten)
- Rezidivfreies Intervall nach Ende der adjuvanten Therapie
- Aggressivität der Erkrankung, Lokalisation der Metastasen
- Geschätzte Lebenserwartung
- Begleiterkrankungen (einschließlich Organfunktionen)
- Erwartungen und Präferenzen der Patienten

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

International consensus

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;

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.

mBC – HER2-negativ/HR-positiv

Palliative Chemotherapie Erstlinienbehandlung*

■ Monochemotherapie

- Paclitaxel (q1w) (T), Docetaxel (q3w),
- Doxorubicin, Epirubicin, Mitoxantron (A), Peg-liposomales Doxorubicin(A_{lip})
- Vinorelbin
- Capecitabin
- Nab-Paclitaxel

■ Polychemotherapie:

- A + T
- Paclitaxel + Capecitabin
- Docetaxel + Capecitabin nach adj. A
- T + Gemcitabin nach adj. A
- A + C oder A_{lip} + C

	Oxford		
	LoE	GR	AGO
1a	A	++	
1b	A	++	
3b	B	+	
2b	B	+	
2b	B	+	
1b	A	++	
2b	B	+	
1b	A	+	
2b	B	++	
1b	B	++	

Berücksichtigung der Vorbehandlung:

* bei ER pos. Erkrankung nur indiziert, wenn eine endokrine Therapie nicht oder nicht mehr in Frage kommt

International consensus

- 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;

Single Agents

- 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.
- 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.
- 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.
- 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.
- 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_vs_eprubicin_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 Palliative 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

- 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;

Cochrane analysis taxane-containing regimens for metastatic breast cancer

- Gheri 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

- 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

- 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.
- 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 Palliative Chemotherapie nach Taxan- und Anthrazyklin-Vorbehandlung

	Oxford		
	LoE	GR	AGO
▪ Experimentelle Therapien in Studien			++
▪ Capecitabin	2b	B	++
▪ Eribulin	1b	B	++
▪ Vinorelbin	2b	B	++
▪ (Peg)-liposomales Doxorubicin	2b	B	+
▪ Taxan Re-Challenge*	2b	B	+
▪ Anthrazyklin Re-Challenge*	3b	C	+
▪ Metronomische Therapie (z.B. Cyclophos. und MTX)	2b	B	+
▪ Gemcitabin + Cisplatin / Carboplatin	2b	B	+/-
▪ Gemcitabin + Capecitabin	2b	B	+/-
▪ Gemcitabin + Vinorelbin	1b	B	-

* Mindestens 1 Jahr rezidivfrei nach adjuvanter Gabe

International consensus

- 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;

Capecitabine

- 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

- 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.
- 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.
- 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.

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.

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.

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FORSCHEN
 LEHREN
 HEILEN

Tripel negatives mBC unabhängig von Keimbahnmutation für BRCA 1/2

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Experimentelle Therapien innerhalb von Studien 			++
<ul style="list-style-type: none"> Chemotherapie wie bei Patientinnen mit HR-pos / HER2-neg mBC 			+/-
<ul style="list-style-type: none"> Carboplatin (vs. Docetaxel) 	1b ^a	B	+/-
<ul style="list-style-type: none"> Gemcitabin/Cisplatin (vs. Gem/Pac) 	1b	A	+
<ul style="list-style-type: none"> Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem) 	2b ^a	B	+
<ul style="list-style-type: none"> Bevacizumab zusätzlich zur first-line Zytostatikatherapie 	1b	B	+

International consensus

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;

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, Gilett C, et al. San Antonio Breast Cancer Symposium 2014; S3-01.

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

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.

mBC mit Keimbahnmutation für BRCA 1/2

	Oxford		
	LoE	GR	AGO
▪ Experimentelle Therapien innerhalb von Studien			++
▪ Carboplatin (vs. Docetaxel) (wenn Platin-naiv)	1b	B	+
▪ PARP-Inhibitoren			
▪ Olaparib (HER2-negativ)	1b	B	+
▪ Olaparib (HER2-positiv)	5	D	+/-

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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, 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
- Litton J, Rugo HS, Ettl J et al: EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced germline BRCA-mutation breast cancer. SABCS 2017, S6-07

Bevacizumab beim HER2-neg. metastasierten Mammakarzinom

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

International consensus

- 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;

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

- 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. 2011

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.

Erstlinientherapie beim HER2-pos. metastasierten Mammakarzinom

- Docetaxel + Trastuzumab + Pertuzumab
- Paclitaxel (wk) + Trastuzumab + Pertuzumab
- nab-Paclitaxel + Trastuzumab + Pertuzumab
- Vinorelbin + Trastuzumab + Pertuzumab
- T-DM 1 (Rückfall innerhalb von 6 Monaten und nach Taxan und Trastuzumab)
- 1st line Chemotherapie* + Trastuzumab
- Trastuzumab mono
- Taxan + Lapatinib
- Taxan + Trastuzumab + Everolimus
- Trastuzumab + Aromatase-Inhibitoren (ER+)
- Lapatinib + Aromatase-Inhibitoren (ER+)

Oxford		
LoE	GR	AGO
1b	A	++
2b	B	++
3b ^a	C	+
3b	B	+
2b	B	+
1b	B	+
2b	B	+/-
1b	B	+/-
1b	B	-
2b	B	+/-**
2b	B	+/-**

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

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

International consensus

- 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;

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

Docetaxel + 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.

Paclitaxel weekly + trastuzumab + pertuzumab

- 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.
- 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.

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

1st 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.

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.

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

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.

2nd line Therapie bei HER2-pos. mBC (nach Vorbehandlung mit Trastuzumab)

	Oxford		
	LoE	GR	AGO
▪ T-DM 1	1b	A	++
▪ TBP: 2nd line Chemotherapie + Trastuzumab	2b	B	+
▪ BP: 2nd line Chemotherapie + Trastuzumab + Pertuzumab	5	D	+/-
▪ 2nd line Chemotherapie* + Trastuzumab + Pertuzumab (falls noch nicht gegeben)	5	D	+/-
▪ Taxane + Trastuzumab + Pertuzumab	5	D	+
▪ Capecitabine + Trastuzumab + Pertuzumab	1b^a	B	+/-
▪ Capecitabine + Lapatinib	1b	B	+
▪ Trastuzumab + Lapatinib (HR neg. tumor)	2b	B	+

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

International consensus

- 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;

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

T-DM1

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

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.

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

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;

Any other 2nd-Line chemotherapy + 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;

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;

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.

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

Weitere Therapielinien bei HER2-pos. metastasiertem Mammakarzinom

	Oxford		
	LoE	GR	AGO
■ Vorbehandlung mit Trastuzumab			
■ T-DM 1	1b	A	++
■ Capecitabine + Lapatinib	1b	B	+
■ Vinorelbine + Lapatinib	2b	B	+/-
■ Trastuzumab + Lapatinib (HR neg. Pat.)	2b	B	+
■ Chemotherapie + Trastuzumab („treatment beyond progression“)	2b	B	+
■ Pertuzumab + Trastuzumab	2b	B	+
■ Vinorelbine + Trastuzumab + Everolimus (Trastuzumab resistent, Taxan vorbehandelt)	1b	B	+/-
■ Daten nach Vorbehandlung mit Trastuzumab und Pertuzumab und für TBP mit Pertuzumab sind bislang nicht verfügbar.			
■ Experimentelle Anti-HER2-Regime	5	D	+
■ Für Patienten nach Trastuzumab und Pertuzumab Vor- behandlung, Therapie gemäß obenstehender Empfehlungen	5	D	+

International consensus

- 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;

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

T-DM1

- Krop IE, Kim SB, González-Martín A, et al. TH3RESA Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(7):689-99. study collaborators.

Capecitabine + Lapatinib

- 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.

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.

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

TBP: 2nd-line chemotherapy + trastuzumab

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.

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

Vinorelbine + Trastuzumab + Everolimus

1. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2014;15(6):580-91

Lapatinib beim HER2-positiven metastasierten Mammakarzinom

	Oxford		
	LoE	GR	AGO
■ In Kombination mit			
■ Trastuzumab für schwer vorbehandelte Patientinnen (HR neg.)	2b	B	+
■ Paclitaxel als 1 st line	1b	B	+/-
■ Capecitabin als > 2 nd line	1b	B	+
■ Vinorelbin	2b	B	+/-
■ AI bei ER positiver Erkrankung	2b	B	+/-
■ Bei Patientinnen mit Hirnmetastasen (Radioresistenz) in Kombination mit Capecitabine			
	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.
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Taxanes+ lapatinib

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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

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2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355(26):2733–2743.

Vinorelbine + Lapatinib



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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.

<div>  <small>ARBEITSGEMEINSCHAFT GYNAKOLOGISCHE ONKOLOGIE e.V.</small>  <small>MAMMA</small> <small>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</small> <small>Guidelines Breast Version 2018.1D</small> </div>	<div>Immundiagnostik und Immuntherapien*</div>		
	<div> <div>Oxford</div> <div>LoE GR AGO</div> </div>		
<div> <div>■ Immundiagnostik</div> <div> <div>■ Bestimmung von immunologischen Parametern im peripheren Blut</div> </div> </div>	5	D	--
<div> <div>■ Lokale Immuntherapien:</div> <div> <div>■ Imiquimod topisch bei Hautmetastasen</div> </div> </div>	4	C	+/-
<div> <div>■ Systemische Immuntherapien (einschließlich u.g. Therapien)</div> <div> <div>nur in kontrollierten klinischen Studien</div> <div> <div>■ HER2-Vakzinierung in Hochrisikokollektiven Immunomodulation (z.B. Zugabe von Nov-2 zur Chemo AC –T)</div> <div>■ Intradermale Vakzinierung von Dendritischen Zellen</div> <div>■ Aktive Vakzinierungen</div> <div>■ Passive Vakzinierungen</div> <div>■ Therapie mit Onkoviren</div> <div>■ Zytokine</div> <div>■ Checkpoint inhibitors (PD1; PDL-1;...)</div> </div> </div> </div>			++
<div>* Studienteilnahme empfohlen</div>			