


Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN


Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2018:**
 Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
 Jackisch / Janni / Kolberg-Liedtke / von Minckwitz /
 Möbus / Müller / Rody / Schaller / Scharl /
 Schmutzler / Schneeweiss / Schütz / Stickeler / Thill /
 Thomssen / Untch

- **Version 2019:**
 Jackisch /Lux

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

	<h2>Metastatic Breast Cancer Disease-Free and Overall Survival</h2>	
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p>	<ul style="list-style-type: none"> ■ An increase in survival over time in MBC has been shown in some retrospective analyses ■ Patients with MBC today have been pretreated more extensive with chemotherapy (+/- targeted therapy). Thus, these tumors must be considered more drug resistant ■ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity) ■ Targeted drugs in combination with chemotherapy can induce substantial survival benefits 	<p>Oxford LoE</p> <p>2a</p> <p>2a</p> <p>1b</p> <p>1b</p>
<p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>		

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

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.



© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Metastatic Breast Cancer Endocrine Resistance

Primary endocrine resistance:

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

Secondary endocrine resistance:

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

International consensus

1. Cardoso F, 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

Metastatic Breast Cancer Predictive Factors				
Therapy	Factor	Oxford		
		LoE	GR	AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better metastasis)	1a	A	++
Checkpoint-Inhibitors (Atezolizumab)	PD-L1 IC# positive in TNBC	1b	B	+
PARP inhibitors	gBRCA 1/2 mutation	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*
* Within clinical trials (for additional potential biological factors see chapter „Predictive factors“) (# ≥ 1% on I,mmune cells (IC) (for more information see chapter “pathology”))				

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

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.

PARP-Inhibitoren

1. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-763.

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.



© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Metastatic Breast Cancer Treatment Rationale

GR: A

AGO: ++

Oxford LoE: 1b

- **Mono-Chemotherapy:**
 - Favorable therapeutic index
 - Indicated in case of
 - Slow, not life-threatening progression
 - Insensitivity to or progression during endocrine therapy
- **Poly-Chemotherapy:**
 - Unfavorable therapeutic index
 - Indicated to achieve rapid remission in the case of
 - Extensive symptoms
 - Visceral crisis (ABC-4 definition)
 - Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

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

International consensus


1. Cardoso F, 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

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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1


www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Definition of visceral crisis (ABC 4)

- **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 visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.**

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



© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Metastatic Breast Cancer

Cytotoxic and Targeted Therapy


GR: A

AGO: ++

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

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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Metastatic Breast Cancer

Duration of Cytotoxic Therapy

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

- **As long as therapeutic index remains positive**
 - Treatment until progression
 - Treatment until best response
 - Change to alternative regimen before progression
- **Stop therapy in case of**
 - Progression
 - Non tolerable toxicity

International consensus


- 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

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

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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

- Participation in clinical trials is highly recommended
- The choice of systemic therapy to be used is depending on on:
 - ER / PR, HER2, PD-L1 status, gBRCA status
 - Previous treatments (and their toxicities)
 - Disease-free interval after end of adjuvant treatment
 - Progression-free intervall of the previous line of therapy
 - Aggressiveness of disease and localization of metastases
 - Estimated life expectancy
 - Co-morbidities (including organ dysfunction)
 - Patient preferences and expectations

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

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.

MBC HER2-negative/HR-positive 1 st -Line Therapy Chemotherapy*			
	Oxford		
	LoE	GR	AGO
Monotherapy: <ul style="list-style-type: none"> Paclitaxel (q1w), Docetaxel (q3w) Doxorubicin, epirubicin, mitoxantrone (A) Peg. liposomal doxorubicin (A_{lip}) Vinorelbine Capecitabine Nab-paclitaxel 	1a	A	++
	1b	A	++
	3b	B	+
	2b	B	+
	2b	B	+
Polychemotherapy: <ul style="list-style-type: none"> A + T Paclitaxel + capecitabine Docetaxel + capecitabine after adj. A T + gemcitabine after adj. A A + C or A_{lip} + C 	1b	A	++
	2b	B	+
	1b	A	+
	2b	B	++
	1b	B	++

* In ER pos. patients only if endocrine therapy is not indicated or should be discontinued

© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2019.1

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

International consensus

- 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

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.

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_metastaticbreast 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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

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

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

International consensus

- 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


- 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


- 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.



ARBEITSGEMEINSCHAFT
GYNAKOLOGISCHE
ONKOLOGIE e.V.



123456789101112

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

	Oxford		
	LoE	GR	AGO
■ Capecitabine	2b	B	++
■ Eribulin	1b	B	++
■ Vinorelbine	2b	B	++
■ (Peg)-liposomal Doxorubicin	2b	B	+
■ Taxane re-challenge*	2b	B	+
■ Anthracycline re-challenge*	3b	C	+
■ Metronomic therapy (eg. cyclophos. + MTX)	2b	B	+
■ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-
■ Gemcitabine + Capecitabine	2b	B	+/-
■ Gemcitabine + Vinorelbine	1b	B	-

* At least one year disease-free after adjuvant treatment

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

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.

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.



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Triple Negative mBC Independent of GenomicBRCA 1/2 Mutation

Oxford

LoE	GR	AGO
		+/-
1b ^a	B	+/-
1b	A	+
2b ^a	B	+
1b	B	+
1b	B	+

- Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC
- Carboplatin (vs. Docetaxel)
- Gemcitabine/Cisplatin (vs. Gem/Pac)
- Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)
- Bevacizumab added to first line cytotoxic therapy
- Atezolizumab plus nab-paclitaxel first-line, in PD-L1 IC positivity[#]

(# ≥ 1% on I,mmune cells (IC) (for more information see chapter “pathology”)

International consensus

- 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

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

- 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)

- 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

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.

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.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	mBC with Genomic BRCA 1/2 Mutation		
<ul style="list-style-type: none"> Standard of care i.e.; gBRCA1/2 negative disease Carboplatin (vs. Docetaxel) (if Platinum-naïve) 	Oxford		
	LoE	GR	AGO
	1b	B	++
			+
<ul style="list-style-type: none"> PARP inhibitors <ul style="list-style-type: none"> HER2-negative <ul style="list-style-type: none"> Olaparib Talazoparib HER2-positive <ul style="list-style-type: none"> Olaparib Talazoparib 	1b	B	+
	1b	B	+/-
	5	D	+/-
	5	D	+/-

International consensus

- 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

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

3. 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.
4. 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.

Metastatic Breast Cancer Bevacizumab Treatment in HER2-neg. Disease			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> 1st line in combination with: <ul style="list-style-type: none"> Paclitaxel (q1w) Capecitabine Anthracyclines Nab-Pac Docetaxel (q3w) Cap+Bev as maintenance after Doc+Bev 2nd line in combination with: <ul style="list-style-type: none"> Taxanes Capecitabine Gemcitabine or vinorelbine 2nd line as treatment through multiple lines 	1b 1b 2b 2b 1b 1b ^a	B B B B B B	+ + +/- +/- +/- +/- +/- - -



© AGO e. V.
in der DGGG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

International consensus

- 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

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.



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

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	+/-**

- Docetaxel + trastuzumab + pertuzumab
- Paclitaxel (wk) + trastuzumab + pertuzumab
- Nab-Paclitaxel + trastuzumab + pertuzumab
- Vinorelbine + Trastuzumab + Pertuzumab
- T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)
- 1st line chemotherapy* + trastuzumab
- Trastuzumab mono
- Taxanes + lapatinib
- Taxanes + trastuzumab + everolimus
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

* Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel
** see chapter Endocrine +/- targeted

International consensus

- 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

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

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.

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.

2 nd line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)			
	Oxford		
	LoE	GR	AGO
■ T-DM 1	1b	A	++
■ TBP: 2nd line chemotherapy + trastuzumab	2b	B	+
■ BP: 2nd line chemotherapy + trastuzumab + pertuzumab	5	D	+/-
■ Any other 2nd line chemotherapy* + trastuzumab + pertuzumab)	5	D	+/-
■ Taxane + trastuzumab + pertuzumab	5	D	+
■ Capecitabine + trastuzumab + pertuzumab	1b ^a	B	+/-
■ Capecitabine + lapatinib	1b	B	+
■ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+

* e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

International consensus

- 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

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)

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, 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) p capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. J Clin Oncol 2016;34(15_suppl). abstr. 504

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

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer		
	Oxford		
	LoE	GR	AGO
■ Pretreatment with Trastuzumab			
■ T-DM 1	1b	A	++
■ Capecitabine + lapatinib	1b	B	+
■ Vinorelbine + lapatinib	2b	B	+/-
■ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+
■ Chemotherapy + trastuzumab („treatment beyond progression“)	2b	B	+
■ Trastuzumab + pertuzumab	2b	B	+
■ Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)	1b	B	+/-
■ Neither data for patients pretreated with trastuzumab and pertuzumab nor data for treatment beyond progression available.			
■ Experimental anti-HER2-regimen	5	D	+
■ For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.	5	D	+

International consensus

- 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

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

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.

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



© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2019.1

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Lapatinib in HER2-positive Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ In combination with			
▪ Trastuzumab for heavily pre-treated pts (HR negative)	2b	B	+
▪ Paclitaxel in 1 st line	1b	B	+/-
▪ Capecitabine in > 2 nd line	1b	B	+
▪ Vinorelbine	2b	B	+/-
▪ AI in ER positive disease	2b	B	+/-
▪ In patients with brain metastasis (radioresistance) in combination with 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.
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, Pippin 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.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de FORSCHEN LEHREN HEILEN</p>	Immunodiagnostic Tests and Immunotherapy*		
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Immunodiagnostic tests: <ul style="list-style-type: none"> Blood: Immunological parameters Tumor tissue: PD-L1 IC status in TNBC Local immunotherapy <ul style="list-style-type: none"> Imiquimod topically for skin metastasis Systemic immunotherapy: <ul style="list-style-type: none"> Atezolizumab plus nab-paclitaxel in TNBC & PD-L1 IC positivity Other immunotherapies in clinical trials, only HER2-vaccination in high risk population Immunomodulation (e.g. addition of Nov-2 to AC-T) Dendritic cell intradermal vaccination Active vaccination Passive vaccination Therapy with oncolytic viruses Cytokines 	5 1b 4 1b	D B C B	-- + +/- +
* Study participation recommended			

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.