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Guidelines Breast
Version 2023.1E

FORSCHEN
LEHREN
HEILEN

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

Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2022:**

Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
Jackisch / Janni / Kolberg-Liedtke / Lüftner / Lux / von Minckwitz /
Möbus / Müller / Rody / Schaller / Scharl / Schmidt / Schmutzler /
Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2023:**

Loibl / Untch

Metastatic Breast Cancer (mBC)

Disease-Free and Overall Survival

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

International consensus

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

Increase

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

Multiple lines

- Qi WX, Tang LN, He AN, et al. Comparison between doublet agents versus single agent in metastatic breast cancer patients previously treated with an anthracycline and a taxane: a meta-analysis of four phase III trials. Breast. 2013;22:314-9.

Metastatic Breast Cancer Endocrine Resistance

Primary endocrine resistance:

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

Secondary (required) endocrine resistance:

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

International consensus

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

Treatment of Metastatic Breast Cancer

Predictive Factors for response

Therapy	Factor	Oxford		
		LoE	GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (<i>ESR1</i>)	2b	B	+
▪ Alpelisib	<i>PIK3CA</i> mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Trastuzumab Deruxtecan	HER2-low or HER2-positive	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity [#] (PD-L1c, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	<i>gBRCA1/2</i> -mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++

see chapter „pathology“

Endocrine therapy

1. Campbell FC, Blamey RW, Elston CW, et al. Quantitative oestradiol receptor values in primary breast cancer and response of metastases to endocrine therapy. *Lancet*. 1981;2(8259):1317–1319.

Endocrine therapy - ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. *Cancer* 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. *Ann Oncol*.29:145-153. doi: 10.1093/annonc/mdx483
3. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. *J Clin Oncol*. 34:2961-8. doi: 10.1200/JCO.2016.67.3061

Alpelisib

1. André F, Ciruelos E, Rubovszky G et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 380:1929-1940. doi: 10.1056/NEJMoa1813904

Chemotherapy

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)[†]. *Ann Oncol*. 2018;29(8):1634–1657.

Anti-HER2-Therapy

1. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19(10):2587–2595.

Checkpoint-Inhibitors

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018 Nov 29;379(22):2108-2121.
2. Cortes J, Cescon DW, Rugo HS et al.: KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020 Dec 5;396(10265):1817-1828.

PARP-Inhibitors

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

Bone modifying drugs

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

CTC monitoring (any therapy)

1. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol.* 2014;15:406-14.
2. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol.* 2014;32(31):3483-9.

Metastatic Breast Cancer Treatment Rationale

Oxford LoE: 1b

GR: A

AGO: ++

■ Mono-Chemotherapy:

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

■ Poly-Chemotherapy:

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

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

International consensus


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

Combination vs single agent

1. Qi WX, Tang LN, He AN, et al. Comparison between doublet agents versus single agent in metastatic breast cancer patients previously treated with an anthracycline and a taxane: A meta-analysis of four phase III trials. Breast. 2013;22(3):314-9;
2. Belfiglio M, Fanizza C, Tinari N, et al. Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. J Cancer Res Clin Oncol. 2012;138(2):221-9.
3. Pallis AG, Boukovinas I, Ardavanis A, et al. A multicenter randomized phase III trial of vinorelbine/gemcitabine doublet versus capecitabine monotherapy in anthracycline- and taxane-pretreated women with metastatic breast cancer. Ann Oncol. 2012;23(5):1164-9.

Cochrane analysis

1. Dear RF, McGeechan K, Jenkins MC, et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2013 Dec 18;(12):CD008792. doi: 10.1002/14651858.CD008792.pub



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Definition of Visceral Crisis (ABC 5)

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

International consensus

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

Metastatic Breast Cancer Systemic Therapy

GR: A

AGO: ++

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

International consensus

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

Metastatic Breast Cancer

Duration of Cytotoxic Therapy

	Oxford		
	LoE	GR	AGO
■ As long as therapeutic index* remains positive	1a	A	++
■ Treatment until progression	2b	B	+
■ Treatment until best response	2b	B	+/-
■ Change to alternative regimen before progression	2b	B	+/-
■ Stop therapy in case of	1c	A	++
■ Progression			
■ Non tolerable toxicity			

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

International consensus

- Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649. Change to alternative regimen before progression
- Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1351-60.
- Mustacchi G, Bines J, Alba E, et al. Impact of post-progression therapy on overall survival (OS) in the IMELDA randomized phase III trial evaluating the addition of capecitabine (CAP) to maintenance bevacizumab (BEV) for HER2-negative metastatic breast cancer (mBC) San Antonio Breast Cancer Conference 2016 Abstract P5-15-06

Treatment until progression

- Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol. 2011;29:2144-9.
- Alba E, Ruiz-Borrego M, Margelí M, et al. Maintenance treatment with pegylated liposomal doxorubicin versus observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study. Breast Cancer Res Treat. 2010;122(1):169-76
- Park YH, Jung KH, Im SA, et al. Phase III, multicenter, randomized trial of maintenance chemotherapy versus observation in patients

with metastatic breast cancer after achieving disease control with six cycles of gemcitabine plus paclitaxel as first-line chemotherapy: KCSG-BR07-02. J Clin Oncol. 2013;31(14):1732-9.

Chemotherapy in mBC

General Considerations - Drug Selection

AGO: ++

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

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
2. Sharon H. Giordano, Sarah Temin, Sarat Chandarlapaty et al.: ASCO Clinical Practice Guideline Update Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: J Clin Oncol 2019; 36:2736-2740.
3. Condorelli R, Mosele F, Verret B, et al. Genomic alternations breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2019; 30; 365-373

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

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

Limitations of palliative chemotherapy

1. Ribeiro JT, Macedo LT, Curigliano G, et al. Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: back to the future? Ann Oncol. 2012;23(3):547-55.

2. Adamowicz K, Jassem J, Katz A, Saad ED. Assessment of quality of life in advanced breast cancer. An overview of randomized phase III trials. Cancer Treat Rev. 2012;38(5):554-8.

PD-L1-Status

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121.

PIK3CA

1. Andre F, Ciruelos E, Rubovszky G. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380:1929–1940

Endocrine therapy - ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. Cancer 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
3. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 34:2961-8. doi: 10.1200/JCO.2016.67.3061
4. Bidard F-C, Hardy-Bessard A-C, Bachelot T, et al. Fulvestrant-palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of circulating ESR1 mutation in HR+ HER2- metastatic breast cancer patients: Results of PADA-1, a UCBG-GINECO randomized phase 3 trial. SABCS 2021; GS3-05.

MSI/NTRAK

1. Condorelli R, Mosele F, Verret B, et al. Genomic alternations breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2019; 30; 365-373

mBC HER2-negative / HR-positive 1st-Line Chemotherapy (if indicated)

	Oxford		
	LoE	GR	AGO
Monotherapy:			
▪ Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
▪ Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A _{lip})	1b	A	++
▪ Vinorelbine	3b	B	+
▪ Capecitabine	2b	B	+
▪ Nab-paclitaxel	2b	B	+
Polychemotherapy:			
▪ A + T	1b	A	++
▪ Paclitaxel + capecitabine	2b	B	+
▪ Docetaxel + capecitabine after adj. A	1b	A	+
▪ T + gemcitabine after adj. A	2b	B	++
▪ A + C or A _{lip} + C	1b	B	++

International consensus

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

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 versus epirubicin plus paclitaxel as first-line treatment for metastatic breast cancer: efficacy and safety results of a randomized, phase III trial by the AGO Breast Cancer Study Group. Breast Cancer Res Treat. 2013;139(3):779-87. doi: 10.1007/s10549-013-2589-8.

2. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *J Clin Oncol*. 2002;20(14):3114-3121.
3. Batist G, Ramakrishnan G, Sekhar Rao C et al (2001) Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized multicenter trial of metastatic breast cancer *J. Clin Oncol* 19: 1444-1454

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

- Paclitaxel q1w
- Docetaxel q3w
- Capecitabine
- Nab-paclitaxel
- Peg-liposomal doxorubicin
- Eribulin
- Vinorelbine
- Docetaxel + Peg-liposomal doxorubicin

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

- 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-negative / HR-positive: Chemotherapy after Pretreatment *

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

* See approval details for previous therapy

** at least 1 year recurrence free after adjuvant therapy

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

International consensus

- Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.
- Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20
- Rugo HS et al. Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2– Metastatic Breast Cancer (mBC). SABCS 2022, Abstr GS1-11

Capecitabine

- 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.

3. Scarpace SL. Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. *Clin Ther.* 2012;34(7):1467-73.
4. Pivot X, Im SA, Guo M, Marmé F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. *Breast Cancer.* 2018;25(3):370-374.
5. Ohtani S, Nakayama T, Yoshinami T, et al. Bi-weekly eribulin therapy for metastatic breast cancer: a multicenter phase II prospective study (JUST-STUDY). *Breast Cancer.* 2018;25(4):438-446.

Taxane re-challenge

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

Anthracycline re challenge

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

Metronomic chemotherapy

1. Yin W, Pei G, Liu G, et al. Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials. *Oncotarget* 2015;36:39365-72.
2. Yoshimoto M, Takao S, Hirata M, et al. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. *Cancer Chemother Pharmacol.* 2012;70(2):331-8.
3. Fedele P, Marino A, Orlando L, et al. Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. *Eur J Cancer.* 2012;48(1):24-9.
4. Addeo R, Sgambato A, Cennamo G, et al. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. *Clin Breast Cancer.* 2010;10(4):301-6.
5. Colleoni M, Orlando L, Sanna G, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. *Ann Oncol.* 2006;17(2):232-8.
6. Krajnak S, Schnatz C, Almstedt K et al. Low-dose metronomic chemotherapy as an efficient treatment option in metastatic breast cancer-results of an exploratory case-control study. *Breast Cancer Res Treat* 2020; 182 (2): 389–399.

Gemcitabine + 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.

ADC

1. Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20
2. Rugo HS et al. Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2– Metastatic Breast Cancer (mBC). SABCS 2022, Abstr GS1-11

mBC HER2-negative / HR-positive*				
	Trastuzumab Deruxtecan HR pos, Her 2 low (331 Patients)	Hazard Ratio compared to the control arm Chemotherapy	Sacituzumab Govitecan HR pos/ Her 2 neg (272 Patients)	Hazard Ratio compared to the control arm Chemotherapy
Previous therapy				
Chemotherapy for Metastatic disease	All Patients		All Patients	
1 Line	61%	0,54 for PFS	0 %	
2 Lines	37%	0,47 for PFS	44%	0,85 for OS
3-4 Lines	3 %	0,47 for PFS	60 %	0,75 for OS
Endocrine Therapy for Metastatic disease	All Patients		(> 6 Months, 86 % of patients) None or < 6 Months	0,79 for OS 0,88 for OS
1 Line	32%	NE	NE	
2 Lines	33%	NE	40 %	
3 Lines and more	27 %	NE	NE	
without CDK 4/6 plus endocrine therapy	30 %	0,42 for PFS	≤ 12 Months 59%	0,68 for OS
with CDK 4/6 plus endocrine therapy	70%	0,55 für PFS	> 12 Monate 39%	0,98 for OS
PFS (Months)	10.1	0,51	5.5	0,66
OS (Months)	23.9	0,64	14.4	0,79

*Data from two different prospective phase 3 studies with different patient cohorts
NE Not evaluated, PFS Progression free survival, OS Overall survival, HR Hazard ratio



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Guidelines Breast
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FORSCHEN
LEBEN
HEILEN

1. HS Rugo, A Bardia, F. Marme et al. Overall survival results from the phase 3 TROPICS- 02 study of sacituzumab govitecan vs treatment of physicians choice in patients with HR+/Her2- metastatic breast cancer. LBA76. ESMO 2022
2. S Modi, W. Jacot, T Yamashita et al. Trastuzumab Deruxtecan in previously treated Her 2 low advanced breast cancer. N Engl J Med 2022;387:9-20

Triple negative mBC PD-L1+ Independent of germline mutation in *BRCA 1/2*

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

(see chapter „Pathology“)
 * nab-Paclitaxel or Paclitaxel or Carboplatin / Gemcitabine
 TFI = therapy-free interval

International consensus

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

Checkpoint-inhibitoren:

1. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121.
2. Cortes J, Cescon DW, Rugo HS et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396 (10265): 1817–1828.
3. Adams S, Diéras V, Barrios CH et al. Patient-reported outcomes from the phase III IMpassion130 trial of atezolizumab plus nab-paclitaxel in metastatic triple-negative breast cancer. Ann Oncol 2020; 31 (5): 582–589.
4. Schmid P, Rugo HS, Adams S et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020; 21 (1): 44–59.
5. Cortés J, Lipatov O, Im S-A et al. KEYNOTE-119: Phase III study of pembrolizumab (pembro) versus single-agent chemotherapy (chemo) for metastatic triple-negative breast cancer (mTNBC). Annals of Oncology. 2019; 30: 350–359.

negative breast cancer. *Ann Oncol*. 2021 Aug;32(8):994-1004. doi: 10.1016/j.annonc.2021.05.801. Epub 2021 Jul

8. KEYNOTE-119 investigators. Winer EP, Lipatov O, Im SA, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021 Apr;22(4):499-511. doi: 10.1016/S1470-2045(20)30754-3. Epub 2021 Mar 4.
9. KEYNOTE-355 Investigators. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020 Dec 5;396(10265):1817-1828. doi: 10.1016/S0140-6736(20)32531-9.

Triple negative mBC independent of PD-L1 Status and Germline Mutations in *BRCA* ½ or *PALB2**

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

* According to label

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

International consensus

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

Bevacizumab as first-line therapy

- Miles DW, Diéras V, Cortés J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013;24(11):2773-80. doi: 10.1093/annonc/mdt276.
- 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
- 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
- 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.
- Zielinski C, Láng I, Inbar M, et al TURANDOT investigators. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line

Sacituzumab Govitecan:

1. Bardia A, Mayer IA, Vahdat LT et al. Sacituzumab Govitecan in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2019; 380 (8): 741–751.
2. Bardia A, Hurvitz SA, Tolane SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541. doi: 10.1056/NEJMoa2028485.

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

1. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med. 2018;24(5):628-637

Gemcitabin/Cisplatin (vs. GemPac)

1. Hu XC, Zhang J, Xu BH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2015;16(4):436-46.

Nab-Paclitaxel / Carboplatin

Yardley DA, Coleman R, Conte P, tnAcity investigators. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol. 2018;29(8):1763-1770.

Trastuzumab Deruxtecan (T-DXD)

1. Modi S et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20

Treatment Options in mBC with BRCA 1/2 or gPALB2 Mutation

	Oxford		
	LoE	GR	AGO
▪ Carboplatin (vs. docetaxel) (if Platinum-naïve)	1b	B	+
▪ PARP-Inhibitors (HER2-negative mBC)			
▪ HER2-negative, gBRCA 1/2 mutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ sBRCA 1/2 mutation			
▪ Olaparib	2b	B	+/-
▪ gPALB2 mutation			
▪ Olaparib	2b	B	+/-

International consensus

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

Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation

- The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) Tutt A, Ellis P, Kilburn L, et al. San Antonio Breast Cancer Symposium 2014; S3-01.

PARP Inhibitoren bei triple negativ und BRCA 1/2 Mutation

- Robson M, Tung N, Conte P. et al. Qlympia AD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30:558-566
- Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-763.
- Robson M, Im S-A, Senkus E et al: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med

2017;377:523-533

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

HER2-pos. mBC

1st line without Pretreatment or after Trastuzumab

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

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

International consensus

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

ASCO recommendation

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

Metaanalyse post trastuzumab

- Paracha N, Reyes A, Diéras V et al. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat 2020; 180 (3): 597–609.

Docetaxel + trastuzumab + pertuzumab

1. Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-34.

Paclitaxel weekly + trastuzumab + pertuzumab

1. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2015; 10;33(5):442-7.
2. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. *Breast Cancer Res Treat* 2016;158:91e7. [http://dx.doi.org/ 10.1007/s10549-016-3851-7](http://dx.doi.org/10.1007/s10549-016-3851-7)

Nab-Paclitaxel + trastuzumab + pertuzumab

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

Vinorelbine + trastuzumab + pertuzumab

1. Perez EA, López-Vega JM, Petit T, et al: Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res*. 2016;18(1):126.

Trastuzumab Deruxtecan

1. Cortés J, Kim SB, Chung, WP, et al., Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients with HER2+ Metastatic Breast Cancer: Results of the Randomized Phase 3 Study DESTINY-Breast03. ESMO, 2021; Presidential symposium 1, Abstract No. LBA1

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783-91.
2. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol*

2015;26(1):113-9.

3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

HER2-pos. mBC

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

	Oxford		
	LoE	GR	AGO
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	++
▪ Trastuzumab Deruxtecan (T-DXd)	4	D	+
▪ T-DM1 (TFI < 6-12 months)	5	D	+/-
▪ Capecitabine + Lapatinib	1b	B	+/-
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting and T-DM1 in the post-neoadjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	4	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabine + Trastuzumab	5	D	+
▪ Capecitabine + Lapatinib	5	D	+/-

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

International consensus

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

ASCO recommendation

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

Reinduction of chemotherapy + trastuzumab + pertuzumab

- Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.
- Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015; 33(5):442-7.
- Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing

metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. *Breast Cancer Res Treat* 2016;158:91e7. [http://dx.doi.org/ 10.1007/s10549-016-3851-7](http://dx.doi.org/10.1007/s10549-016-3851-7)

4. Bachelot T, Puglisi F, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Conference Abstract # P4-21-04
5. Perez EA, López-Vega JM, Petit T, et al: Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res.* 2016;18(1):126.

ADC Trastuzumab Deruxtecan

1. Hurvitz SA, Hegg R, Chung WP, et al: Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet.* 2023 Jan 14;401(10371):105-117. doi: 10.1016/S0140-6736(22)02420-5.
2. Krop I; Park YH; Kim S-B; et al:
Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY-Breast02. *SABCS 2022.* Abstr GS2-01

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367:1783-91.
2. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol* 2015;26(1):113-9.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. *J Comp Eff Res* 2020.

Capecitabine + lapatinib

1. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat.* 2008;112(3):533-43.

2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; 355(26):2733–2743.
3. Delea TE, Tappenden P, Sofrygin O, et al. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. *Eur J Health Econ*. 2012;13(5):589-603.
4. Ang FLI, Rowland A, Modi ND et al. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. *J Cancer* 2020; 11 (11): 3327–3333.
1. Gavilá J, La Haba J de, Bermejo B et al. A retrospective, multicenter study of the efficacy of lapatinib plus trastuzumab in HER2-positive metastatic breast cancer patients previously treated with trastuzumab, lapatinib, or both: the Trastyvere study. *Clin Transl Oncol* 2020; 22 (3): 420–428.
2. Prat A, Pascual T, Angelis C de et al. HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual HER2 Blockade. *J Natl Cancer Inst* 2020; 112 (1): 46–54.

Tucatinib + trastuzumab/ capecitabine

1. Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med* 2020; 382 (7): 597–609.
2. Lin NU, Borges V, Anders C et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *J Clin Oncol* 2020; 38 (23): 2610–2619

HER2-pos. mBC

2nd line

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab Deruxtecan (T-DXd)	1b	B	++
▪ Tucatinib + Trastuzumab + Capecitabine (after pretreatment with T-DM1)	1b	B	++
▪ T-DM 1	1b	A	+
▪ Capecitabine + Lapatinib / Trastuzumab	1b	B	+/-
▪ TBP: 2 nd line Chemotherapy* + Trastuzumab / Pertuzumab	2b	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+/-

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

Level of Evidence and Grade of Recommendation are based on the following publication and extrapolation from these publications:
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- Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31 (12): 1623–1649.

ASCO recommendation

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

Trastuzumab Deruxtecan

- Cortés J, Kim SB, Chung WP, et al., Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients with HER2+ Metastatic Breast Cancer: Results of the Randomized Phase 3 Study DESTINY-Breast03. ESMO, 2021; Presidential symposium 1, Abstract No. LBA1

Tucatinib + trastuzumab + capecitabine

- Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med

2020; 382 (7): 597–609.

2. Lin NU, Borges V, Anders C et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol 2020; 38 (23): 2610–2619

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol 2015;26(1):113-9.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

Capecitabine + lapatinib

1. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112(3):533-43.
2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355(26):2733–2743.
3. Delea TE, Tappenden P, Sofrygin O, et al. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. Eur J Health Econ. 2012;13(5):589-603.
4. Ang FLI, Rowland A, Modi ND et al. Early Adverse Events predict Survival Outcomes in HER2-positive Advanced Breast Cancer Patients treated with Lapatinib plus Capecitabine. J Cancer 2020; 11 (11): 3327–3333.
1. Gavilá J, La Haba J de, Bermejo B et al. A retrospective, multicenter study of the efficacy of lapatinib plus trastuzumab in HER2-positive metastatic breast cancer patients previously treated with trastuzumab, lapatinib, or both: the Trastyvere study. Clin Transl Oncol 2020; 22 (3): 420–428.
2. Prat A, Pascual T, Angelis C de et al. HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual HER2 Blockade. J Natl Cancer Inst 2020; 112 (1): 46–54.

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

1. von Minckwitz G, Schwedler K, Schmidt M, et al; GBG 26/BIG 03-05 study group and participating investigators. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer*. 2011;47(15):2273-81.

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

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

Chemotherapy + trastuzumab + pertuzumab

1. Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-34.
2. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2015; 33(5):442-7.
3. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. *Breast Cancer Res Treat* 2016;158:91e7. <http://dx.doi.org/10.1007/s10549-016-3851-7>
4. Bachelot T, Puglisi F, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Conference Abstract # P4-21-04
5. Perez EA, López-Vega JM, Petit T, et al: Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res*. 2016;18(1):126.
6. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). *Breast* 2017;31:244-259
7. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol*. 2018;29(8):1634-1657
8. Urruticoechea A, Rizwanullah M, Im SA, et al. PHEREXA: a phase III study of trastuzumab (H) 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

Trastuzumab + pertuzumab

1. Baselga, J. et al. Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that progressed during prior Trastuzumab therapy. JCO 2010;28:1138-1144

Trastuzumab + lapatinib vs, lapatinib

1. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30(21):2585-92.
2. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010;28(7):1124-30

HER2-pos. mBC

≥ third-line

Depending on the previous therapy (substance)	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine	1b	B	++
▪ Trastuzumab Deruxtecan	1b	B	+
▪ T-DM 1	1b	A	+
▪ Capecitabine + Trastuzumab / Lapatinib	1b	B	+
▪ Capecitabine + Neratinib	1b	B	+
▪ Margetuximab + Chemotherapy	1b	B	+/-

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

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

ASCO recommendation

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

Metaanalyse post T-DM1

1. Yokoe T, Kurozumi S, Nozawa K et al. Clinical benefit of treatment after trastuzumab emtansine for HER2-positive metastatic breast cancer: a real-world multi-centre cohort study in Japan (WJOG12519B). Breast Cancer 2021

Metaanalysis after taxane/ trastuzumab

1. Paracha N, Reyes A, Diéras V et al. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review

and network meta-analysis. Breast Cancer Res Treat 2020; 180 (3): 597–609.

Tucatinib + trastuzumab + capecitabine

1. Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020; 382 (7): 597–609.
2. Lin NU, Borges V, Anders C et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol 2020; 38 (23): 2610–2619

Trastuzumab Deruxtecan

1. Modi S, Saura C, Yamashita T et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382 (7): 610–621.
2. Cortés J, Kim SB, Chung, WP, et al., Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients with HER2+ Metastatic Breast Cancer: Results of the Randomized Phase 3 Study DESTINY-Breast03. ESMO, 2021; Presidential symposium 1, Abstract No. LBA1

T-DM1

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol 2015;26(1):113-9.
3. Ramagopalan SV, Pisoni R, Zenin A et al. Comparative effectiveness of trastuzumab emtansine versus lapatinib plus capecitabine for HER2+ metastatic breast cancer. J Comp Eff Res 2020.

Capecitabine + lapatinib

1. Cameron D, Casey M, Press M et al. E. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112(3):533-43.
2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355(26):2733–2743.

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

Neratinib + capecitabine

1. Saura C, Oliveira M, Feng Y-H et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020; 38 (27): 3138–3149.

Margetuximab

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

HER2-pos. mBC

No Chemotherapy Possible or Desired

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

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

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

ASCO recommendation

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

Trastuzumab and AI (in HR+)

- Kaufman B, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TANDEM study. J Clin Oncol. 2009 Nov 20;27(33):5529-37.
- Giordano SH, et al. American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99.

3. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). *Curr Med Res Opin.* 2012 Aug;28(8):1263-79.
4. Huober J, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. *Breast.* 2012 ;21(1):27-33.
5. Giordano SH, et al. American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2014 Jul 1;32(19):2078-99.
6. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). *Curr Med Res Opin.* 2012 Aug;28(8):1263-79.

Lapatinib and AI (in HR+)

1. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009 Nov 20;27(33):5538-46.
2. Riemsma R, Forbes CA, Amonkar MM, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). *Curr Med Res Opin.* 2012 Aug;28(8):1263-79.
3. Grassadonia A, Caporale M, Tinari N, et al. Effect of targeted agents on the endocrine response of breast cancer in the neoadjuvant setting: a systematic review. *J Cancer.* 2015 May 12;6(6):575-82.
4. Giordano SH, Temin S, Kirshner JJ, et al; American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2014 Jul 1;32(19):2078-99.

AI and trastuzumab + pertuzumab (in HR+)

1. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al.; PERTAIN Study Group. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. *J Clin Oncol.* 2018 Oct 1;36(28):2826-2835. doi: 10.1200/JCO.2017.76.7863. PMID:30106636

Abemaciclib + fulvestrant + trastuzumab

1. Tolaney S, Wardley AM, Zambelli S et al., monarchHER: A randomized Phase 2 study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer (ABC). Ann Oncol 2019, 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394

Trastuzumab + pertuzumab

1. Baselga, J. et al. Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that progressed during prior Trastuzumab therapy. JCO 2010;28:1138-1144

Trastuzumab + lapatinib vs. lapatinib (in HR-)

1. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30(21):2585-92.
2. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010;28(7):1124-30

Trastuzumab mono

1. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-48.
2. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.