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# 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



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## Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2020:**

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Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2021:**

Jackisch / Schmidt

## 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 similar 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		AGO
		LoE	GR	
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (ESR1)	2b	B	+
▪ Alpelisib	PIK3CA mutation (prim. tumor, metastases, plasma)	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	gBRCA1/2-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++
▪ Any therapy	CTC monitoring	1b	A	++

\* In clinical trials; # 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)<sup>†</sup>. *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
■ <b>As long as therapeutic index* remains positive</b>	<b>1a</b>	<b>A</b>	<b>++</b>
■ Treatment until progression	<b>2b</b>	<b>B</b>	<b>+</b>
■ Treatment until best response	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ Change to alternative regimen before progression	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ <b>Stop therapy in case of</b>	<b>1c</b>	<b>A</b>	<b>++</b>
■ 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, PIK3CA, e.g. MSI, NTRK (clinical actionability of molecular targets)
  - 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

#### 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 1<sup>st</sup>-Line Chemotherapy\*

	Oxford		
	LoE	GR	AGO
<b>Monotherapy:</b>			
▪ Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
▪ Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A <sub>lip</sub> )	1b	A	++
▪ Vinorelbine	3b	B	+
▪ Capecitabine	2b	B	+
▪ Nab-paclitaxel	2b	B	+
<b>Polychemotherapy:</b>			
▪ 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 <sub>lip</sub> + C	1b	B	++

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

### 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. Gherzi D, Willson ML, Chan MM, et al. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 10;6:CD003366.

#### After anthracycline treatment two studies could show a survival benefit

1. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20(12):2812-2823.
2. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008;26(24):3950-3957.

#### Doxorubicin/docetaxel vs. Doxorubicin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL

1. Cassier PA, Chabaud S, Trillet-Lenoir V, et al. A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. Breast Cancer Res Treat. 2008;109(2):343-50.

#### Other combinations

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

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

## mBC HER2-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 1<sup>st</sup> 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

- Ghersi 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 Taxane and Anthracycline Treatment

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

\* At least one year disease-free after adjuvant treatment

### International consensus

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

### Capecitabine

1. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004;40(4):536-542.

### Eribulin

1. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23.
2. Twelves C, Cortes J, Vahdat L, et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat. 2014;148:553-61.
3. Scarpace SL. Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. Clin Ther. 2012;34(7):1467-73.
4. Pivot X, Im SA, Guo M, Marmé F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting

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

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

#### Taxane re-challenge

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

#### Anthracycline re challenge

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

#### Metronomic chemotherapy

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

#### Gemcitabine + cisplatin / carboplatinum

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

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

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

#### Gemcitabine + capecitabine

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

#### Gemcitabine + Vinorelbine

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

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

	Oxford		
	LoE	GR	AGO
■ <b>Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC <math>\geq 1</math><sup>#</sup></b> (if TFI $\geq 12$ months)	<b>1b</b>	<b>B</b>	<b>+</b>
■ <b>Atezolizumab + Paclitaxel first line PD-L1 IC <math>\geq 1</math><sup>#</sup></b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>-</b>
■ <b>Pembrolizumab + Chemo* first-line PD-L1 CPS <math>\geq 10</math><sup>#</sup></b> (after TFI $\geq 6$ months)	<b>1b</b>	<b>B</b>	<b>+/-</b>
■ <b>Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) if CPS <math>\geq 20</math><sup>#</sup></b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>

<sup>#</sup> (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



metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. *Ann Oncol* 2019; 30 (3): 397–404.

# Triple negative mBC independent of PD-L1 Status and Germline Mutations in *BRCA* 1/2

- Bevacizumab in addition to first-line chemotherapy
- Sacituzumab Govitecan (after pretreatment with 2 standard therapies)
- Carboplatin (vs. Docetaxel)
- Gemcitabin/Cisplatin (vs. Gem/Pac)
- Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)

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

## International consensus

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

## Bevacizumab as first-line therapy

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

#### Gemcitabin/Cisplatin (vs. GemPac)

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

#### Nab-Paclitaxel / Carboplatin

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

## Treatment options in mBC with BRCA 1/2 or gPALB2 Mutation

	Oxford		
	LoE	GR	AGO
■ <b>Standard of care, i.e. as in gBRCA 1/2 wildtype disease</b>			++
■ <b>Carboplatin (vs. Docetaxel) (if Platinum-naive)</b>	<b>1b</b>	<b>B</b>	<b>+</b>
■ <b>PARP-Inhibitors (HER2-negative mBC)</b>			
■ <b>HER2-negative, gBRCA 1/2 mutation</b>			
■ Olaparib	1b	A	++
■ Talazoparib	1b	B	++
■ <b>sBRCA 1/2 mutation</b>	2b	B	+/-
■ Olaparib			
■ <b>gPALB2 mutation</b>	2b	B	+/-
■ Olaparib			

### International consensus

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

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

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

### PARP Inhibitoren bei triple negativ und BRCA 1/2 Mutation

1. Robson M, Tung N, Conte P. et al. Qlympia AD final overall survival and tolerability results: Olaparib 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
2. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753-763.
3. Robson M, Im S-A, Senkus E et al: Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med

2017;377:523-533

4. Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol* 2020; 38 (36): 4274–4282.

## Metastatic Breast Cancer

### Bevacizumab Treatment in HER2-neg. Disease

	Oxford LoE	GR	AGO
▪ <b>1<sup>st</sup> line in combination with:</b>			
▪ Paclitaxel (q1w)	1b	B	+
▪ Capecitabine	1b	B	+
▪ Anthracyclines	2b	B	+/-
▪ Nab-Pac	2b	B	+/-
▪ Docetaxel (q3w)	1b	B	+/-
▪ <b>Cap+Bev as maintenance after Doc+Bev</b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>
▪ <b>2<sup>nd</sup> line in combination with:</b>			
▪ Taxanes	1b	B	+/-
▪ Capecitabine	1b	B	+/-
▪ Gemcitabine or vinorelbine	1b	B	-
▪ <b>2<sup>nd</sup> line as treatment through multiple lines</b>	<b>1b</b>	<b>B</b>	<b>-</b>

#### International consensus

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

#### First-line chemotherapy and bevacizumab

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

#### Taxane and bevacizumab first-line

- Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med (2007) 357(26):2666–2676.
- Miles D, Chan A, Luc Y, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 28:3239-3247, 2010

#### Nab-Paclitaxel and bevacizumab first-line

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

#### Capecitabine and bevacizumab first-line

1. Zielinski C, Láng I, Inbar M, et al TURANDOT investigators. Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, non-inferiority, phase 3 trial. Lancet Oncol 2016;17(9):1230-9. doi: 10.1016/S1470-2045(16)30154-1.
2. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol (2005) 23(4):792–799.

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

1. Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1351-60.
2. Mustacchi G, Bines J, Alba E, et al. [ Impact of post-progression therapy on overall survival (OS) in the IMELDA randomized phase III trial evaluating the addition of capecitabine (CAP) to maintenance bevacizumab (BEV) for HER2-negative metastatic breast cancer (mBC) San Antonio Breast Cancer Conference 2016 Abstract P5-15-06

#### Second-line chemotherapy and bevacizumab

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

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

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

# HER2-positive mBC

## After Trastuzumab or w/o Pretreatment (+ Chemotherapy)

	Oxford		
	LoE	GR	AGO
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ Nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbine + Trastuzumab + Pertuzumab	3b	B	+
▪ 1 <sup>st</sup> line Chemotherapy* + Trastuzumab	1b	B	+
▪ TBP: 2 <sup>nd</sup> line Capecitabine + Trastuzumab	2b	B	+
▪ Capecitabine + Lapatinib	1b	B	+
▪ Taxane + Lapatinib	1b	B	+/-
▪ Taxane + Trastuzumab + Everolimus	1b	B	-

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

### International consensus

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

### ASCO recommendation

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



2. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. *Breast Cancer Res Treat* 2016;158:91e7. [http://dx.doi.org/ 10.1007/s10549-016-3851-7](http://dx.doi.org/10.1007/s10549-016-3851-7)

#### Nab-Paclitaxel + trastuzumab + pertuzumab

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

#### Vinorelbine + trastuzumab + pertuzumab

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

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

1. Andersson M, Lidbrink E, Bjerre K. et al.: Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab With Vinorelbine Plus Trastuzumab As First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The HERNATA Study. *J Clin Oncol* 2011;29(3):264-71.
2. Valero V, Forbes J, Pegramet M D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-Gene-Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. *J Clin Oncol* 2011;29(2):149-56.
3. Dawood S, Broglio K, Buzdaret AU et al.: Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review. *J Clin Oncol* 2010;28(1):92-8.
4. Robert N, Leyland-Jones B, Asmaret L et al.: Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel in Women With HER-2–Overexpressing Metastatic Breast Cancer. *J Clin Oncol* 2006;24(18):2786-92.
5. Wardley AM, Pivot X, Morales-Vasquez F et al.: Randomized Phase II Trial of First-Line Trastuzumab Plus Docetaxel and Capecitabine Compared With Trastuzumab Plus Docetaxel in HER2-Positive Metastatic Breast Cancer. *J Clin Oncol.* 2010;28(6):976-83.
6. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol.* 2015;33(5):442-7.

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

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.

#### 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.

#### 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.

# HER2-positive mBC

## Further Therapy Options after Trastuzumab

	Oxford		
	LoE	GR	AGO
■ <b>T-DM 1</b> (Recurrence after 6 months and after taxanes and trastuzumab)	<b>2b</b>	<b>B</b>	<b>+</b>
■ <b>Trastuzumab + Lapatinib (HR-negative tumor)</b>	<b>2b</b>	<b>B</b>	<b>+</b>
■ <b>Trastuzumab mono</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
■ <b>Trastuzumab + Aromatase-Inhibitors (ER+)</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>Lapatinib + Aromatase-Inhibitors (ER+)</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>AI + Trastuzumab + Pertuzumab</b>			<b>+</b>
■ <b>Abemaciclib + Trastuzumab + Fulvestrant</b>	<b>2b</b>	<b>B</b>	<b>+/-*</b>
■ <b>Trastuzumab + Pertuzumab</b>			<b>+/-</b>

\* See Chapter „endocrine +/- targeted 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.

### 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

2012;30(21):2585-92.

2. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010;28(7):1124-30

#### Trastuzumab mono

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

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

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

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

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

#### AI + Trastuzumab + Pertuzumab

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

#### Abemaciclib + Trastuzumab + Fulvestrant

1. Tolaney SM, Wardley AM, Zambelli S et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarchER): a

randomised, open-label, phase 2 trial. Lancet Oncol 2020; 21 (6): 763–775.

#### Trastuzumab + Pertuzumab

1. Baselga J, Gelmon KA, Verma S et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010; 28 (7): 1138–1144

# HER2-positive mBC

## Therapy after Trastuzumab/Pertuzumab

	Oxford		
	LoE	GR	AGO
▪ <b>T-DM 1</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>TBP: 2<sup>nd</sup> line Chemotherapy + Trastuzumab</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>2<sup>nd</sup> line Chemotherapy* + Trastuzumab</b> <b>+ Pertuzumab (if not used before)</b>	<b>5</b>	<b>D</b>	<b>+/-</b>
▪ <b>Taxane + Trastuzumab + Pertuzumab</b>	<b>5</b>	<b>D</b>	<b>+</b>
▪ <b>Capecitabine + Trastuzumab + Pertuzumab</b>	<b>1b<sup>a</sup></b>	<b>B</b>	<b>+/-</b>
▪ <b>Capecitabine + Lapatinib</b>	<b>1b</b>	<b>B</b>	<b>+</b>

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

### International consensus

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

### ASCO recommendation

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

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.

Taxane + trastuzumab + pertuzumab

1. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 2017;31:244-259
2. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634-1657

Capecitabine + Trastuzumab + Pertuzumab

1. Urruticoechea A, Rizwanullah M, Im SA, et al. PHEREXA: a phase III study of trastuzumab (H) þ capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. J Clin Oncol 2016;34(15\_suppl). abstr. 504

Capecitabine + lapatinib

1. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112(3):533-43.
2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355(26):2733–2743.
3. When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.
4. Delea TE, Tappenden P, Sofrygin O, et al. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. Eur J Health Econ. 2012;13(5):589-603.



# HER2-positive mBC

## Therapy after T-DM 1

- **Tucatinib + Trastuzumab + Capecitabine**
- **Neratinib + Capecitabine**
- **Capecitabine + Lapatinib**
- **Capecitabine + Trastuzumab + Pertuzumab**
- **Trastuzumab Deruxtecan**
- **Experimental anti-HER2 regimes**

Oxford		
LoE	GR	AGO
<b>1b</b>	<b>B</b>	<b>++</b>
<b>1b</b>	<b>B</b>	<b>+</b>
<b>1b</b>	<b>B</b>	<b>+</b>
<b>1b</b>	<b>B</b>	<b>+/-</b>
<b>2b</b>	<b>B</b>	<b>+</b>
<b>5</b>	<b>D</b>	<b>+</b>

### International consensus

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

### ASCO recommendation

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

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

#### Neratinib + Capecitabine

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

#### Capecitabine + Lapatinib

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#### Capecitabine + Trastuzumab + Pertuzumab

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#### Trastuzumab-Deruxtecan

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382 (7): 610–621.

## Metastatic Breast Cancer

### Lapatinib in HER2-positive Disease

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

#### Trastuzumab + lapatinib vs lapatinib

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#### Taxanes+ lapatinib

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#### 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+)

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#### Brain metastases (radioresistance)

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# Immunodiagnostic Tests and Immunotherapy

	Oxford		
	LoE	GR	AGO
<b>■ Immundiagnostik</b>			
■ Tumor tissue: PD-L1 IC status in TNBC	1b	B	+
■ Blood: Immunological parameters	5	D	--
<b>■ Systemic Immunotherapies</b>			
■ Atezolizumab + Nab-Paclitaxel first-line TNBC, PD-L1 IC $\geq 1^{\#}$	1b	B	+
■ Atezolizumab + Paclitaxel first line TNBC, PD-L1 IC $\geq 1^{\#}$	1b	B	-
■ Pembrolizumab + Chemo* in TNBC & PD-L1 CPS $\geq 10^{\#}$	1b	B	+/-
■ Pembrolizumab-Monotherapy (after chemotherapy without Immun oncology pretreatment ) if CPS $\geq 20^{\#1}$	1b <sup>a</sup>	B	+/-
<p><b># (see-chapter „Pathology“)</b>  <b>* nab-Paclitaxel or Paclitaxel or Carboplatin/Gemcitabine</b>  <b><sup>1</sup> CAVE: no label</b></p>			

## Checkpoint-inhibitoren:

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