



# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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## 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

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Schmutzler / Schmidt / Schneeweiss / Schütz / Stickeler / Thill /  
Thomssen / Untch**

- **Version 2025 :**

**Hartkopf / Lüftner**

# 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.

# 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.

# Metastatic Breast Cancer

## Endocrine resistance

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### 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

# Chemotherapy of Metastatic Breast Cancer

## Therapeutic aims

**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

# Metastatic Breast Cancer

## Duration of cytotoxic therapy

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

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

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

# Chemotherapy in mBC

## General considerations

**AGO: ++**

- **Participation in clinical trials is recommended**
- **The choice of systemic therapy depends on:**
  - **Expression of ER/PR, HER2, PD-L1; alterations in *ESR1*, *PIK3CA*, *AKT*, *PTEN*, *gBRCA*, *sBRCA*, *gPALB2*; MSI, TMB, NTRK fusions, and other factors (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**

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# Treatment of Metastatic Breast Cancer

## Markers to determine treatment indications



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Therapy	Factor	LoE	GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation ( <i>ESR1</i> ) (metastases, plasma)	1b	B	++
▪ Alpelisib / Inavolisib	<i>PIK3CA</i> mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capiwasertib	<i>PIK3CA</i> , <i>AKT1</i> , <i>PTEN</i> alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low/-pos. (prim. tumor, better: metastasis)	1b	A	++
	HER2-ultralow (prim. tumor, better: metastasis)	2b	B	+/-
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity <sup>#</sup> (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	<i>gBRCA1/2</i> -mutation	1a	A	++
	<i>sBRCA1/2/gPALB2</i>	2b	B	+

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# mBC - HER2-negative / HR-positive 1<sup>st</sup>-Line Chemotherapy (if indicated)

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	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	++

# mBC - HER2-negative / HR-positive: Chemotherapy after Anthracycline treatment\*

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- 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

# mBC - HER2-negative / HR-positive: Chemotherapy after pretreatment \*

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Trastuzumab-Deruxtecan                             <ul style="list-style-type: none"> <li>- after prior chemotherapy with HER2-low</li> <li>- without prior chemotherapy and not suitable for further endocrine therapy, with HER2-low</li> <li>- not suitable for further endocrine therapy, with HER2-ultralow</li> </ul> </li> </ul>	1b	A	++
	1b	B	+
	2b	B	+/-
Sacituzumab Govitecan	1b	A	++
Capecitabin	2b	B	+
Eribulin	1b	B	+
Vinorelbine	2b	B	+
(Peg)-liposomal Doxorubicin	2b	B	+
Taxane re-challenge**	2b	B	+
Anthracycline re-challenge**	3b	C	+
Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+

- Trastuzumab-Deruxtecan
    - after prior chemotherapy with HER2-low
    - without prior chemotherapy and not suitable for further endocrine therapy, with HER2-low
    - not suitable for further endocrine therapy, with HER2-ultralow
- 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

# mBC - HER2-negative / HR-positive\*

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	Trastuzumab Deruxtecan		Sacituzumab-Govitecan
<b>Trial</b>	<b>Destiny-Breast 06</b> HR+/HER2-low: n=359 HR+/HER2-ultralow: n=76	<b>Destiny-Breast 04</b> HR+/HER2-low: n=331	<b>Tropics 02</b> HR+/HER2-negative: n=272
<b>Previous CTX for mBC</b>	no previous CTX for mBC	60%: 1 prior line of CTX 40%: > 1 prior line of CTX	2%: 1 prior line of CTX 41%: 2 prior lines of CTX 57%: > 2 prior lines of CTX
<b>Median PFS (months)</b>	13.2 (HER2-low) 13.2 (ITT) 13.2 (HER2-ultralow)	9.6	5.5
<b>Hazard ratio for PFS</b>	0.62 (HER2-low) 0.64 (ITT)	0.37	0.66
<b>Median OS (months)</b>		23.9	14.4
<b>Hazard ratio for OS</b>	0.83 (n.s.)	0.69	0.79

- Data from different phase 3 studies with differently pretreated patients
- ITT: intentio-to-treat population; n.s.: not significant, PFS: progression free survival, OS: overall survival

# Triple negative mBC PD-L1+

## Independent of germline mutations in *BRCA 1/2* or *PALB2*

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- **Pembrolizumab + Chemotherapy\* first-line PD-L1 CPS  $\geq 10^{\#}$  (if TFI  $\geq 6$  months)**
- **Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC  $\geq 1^{\#}$  (if TFI  $\geq 12$  months)**
- **Atezolizumab + Paclitaxel first-line PD-L1 IC  $\geq 1^{\#}$**
- **Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) in case of CPS  $\geq 20^{\#}$**

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

# (see chapter „Pathology“)

\* nab-Paclitaxel or Paclitaxel or Carboplatin / Gemcitabine

TFI = therapy-free interval

# Triple negative mBC Independent of PD-L1 Status and germline mutations in *BRCA 1/2* or *PALB2*\*

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- Sacituzumab Govitecan  $\geq$  2 TL
- 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)

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

\* according to label

# Treatment Options in mBC with BRCA 1/2 or gPALB2 mutations

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	Oxford		
	LoE	GR	AGO
■ Carboplatin (vs. docetaxel) (if Platinum-naive)	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	+

# 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** **+**
- Vinorelbine + 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** **+/-**

### As maintenance therapy following chemotherapy + antibody therapy (HR+)

- Palbociclib+ endokrine therapy + Trastuzumab + Pertuzumab **1b** **A** **+**

# 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 | +/- |

### As maintenance therapy following chemotherapy + antibody therapy (HR+)

- |   |    |   |   |
|---|----|---|---|
| ▪ Palbociclib+ endokrine therapy + Trastuzumab + Pertuzumab | 1b | A | + |
|---|----|---|---|

# HER2-pos. mBC

## 2nd line

### Oxford

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

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

# HER2-pos. mBC

## ≥ third-line

Oxford

### Depending on the previous therapy (substance)

- Tucatinib + Trastuzumab + Capecitabine
- Trastuzumab Deruxtecan
- T-DM 1
- Capecitabine + Trastuzumab / Lapatinib
- Capecitabine + Neratinib

LoE	GR	AGO
1b	B	++
1b	B	++
1b	A	+
1b	B	+
1b	B	+/-

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# HER2-pos. mBC

## No Chemotherapy possible or desired

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### Oxford

	LoE	GR	AGO
▪ Trastuzumab + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Lapatinib + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Aromatase inhibitor + Trastuzumab + Pertuzumab (HR+)	2b	B	+
▪ Ribociclib + ET + Trastuzumab + Pertuzumab (HR+)	3b	C	+/-
▪ Abemaciclib + Fulvestrant + Trastuzumab (HR+)	2b	B	+
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-