

# 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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# Metastatic Breast Cancer (mBC)

## Disease-Free and Overall Survival

Oxford  
LoE

1b

- 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

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# 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

# Treatment of Metastatic Breast Cancer

## Predictive Factors for Response

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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)	1b <sup>#</sup>	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 <sup>#</sup> (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
■ PARP-Inhibitors	gBRCA1/2-mutation	1a	A	++
■ Any therapy	CTC monitoring	1b	A	+*

\* In clinical trials

# see chapter „pathology“

# 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

# 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.

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# 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.

# 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
1a	A	++
2b	B	+
2b	B	+/-
2b	B	+/-
1c	A	++

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

# 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 (p.r.n. sBRCA status, p.r.n. PALB2), PIK3CA, p.r.n. MSI, NTRK, p.r.n. mESR1 (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

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# mBC HER2-negative / HR-positive

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

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Oxford		
LoE	GR	AGO
<hr/>		
1a	A	++
1b	A	++
3b	B	+
2b	B	+
2b	B	+
1b	A	++
2b	B	+
1b	A	+
2b	B	++
1b	B	++

### ■ Monotherapy:

- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A<sub>lip</sub>)
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

### ■ Polychemotherapy:

- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- T + gemcitabine after adj. A
- A + C or A<sub>lip</sub> + C

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

# 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	+/-

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\* Independent whether anthracyclines were used in adjuvant or 1<sup>st</sup> line metastatic situation

# mBC HER2-negative / HR-positive: Chemotherapy after Taxane and Anthracycline Treatment

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- **Capecitabine**
- **Eribulin**
- **Vinorelbine**
- **(Peg)-liposomal Doxorubicin**
- **Taxane re-challenge\***
- **Anthracycline re-challenge\***
- **Metronomic therapy (e.g. cyclophos. + MTX)**
- **Gemcitabine + Cisplatin / Carboplatin**

Oxford		
LoE	GR	AGO
<b>2b</b>	<b>B</b>	<b>++</b>
<b>1b</b>	<b>B</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>3b</b>	<b>C</b>	<b>+</b>
<b>2b</b>	<b>B</b>	<b>+</b>
<b>2b</b>	<b>B</b>	<b>+/-</b>

# Triple negative mBC PD-L1+

## Independent of germline mutation in *BRCA 1/2*

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	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

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- **Sacituzumab Govitecan ( $\geq$  2nd line)**
- **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)**

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>2b</b>	<b>B</b>	<b>+/-</b>
<b>1b</b>	<b>B</b>	<b>+/-</b>
<b>1b</b>	<b>A</b>	<b>+</b>
<b>2b</b>	<b>B</b>	<b>+</b>

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

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	Oxford		
	LoE	GR	AGO
■ Standard of care i.e. gBRCA 1/2-negative disease			++
■ 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

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Oxford		
LoE	GR	AGO
<b>Primary metastatic</b>		
1b	A	++
2b	B	++
2b	C	+
<b>After Trastuzumab in the adjuvant setting (TFI &gt; 6 months)</b>		
1b	A	++
2b	B	++
2b	C	+
3b	B	+
<b>After pretreatment with only Trastuzumab in the adjuvant setting (TFI &lt; 6 months)</b>		
5	D	+
2b	B	+/-
5	D	+/-

### Primary metastatic

- Docetaxel + Trastuzumab + Pertuzumab
- Paclitaxel (weekly) + Trastuzumab + Pertuzumab
- nab-Paclitaxel + Trastuzumab + Pertuzumab

### After Trastuzumab in the adjuvant setting (TFI > 6 months)

- Docetaxel + Trastuzumab + Pertuzumab
- Paclitaxel (weekly) + Trastuzumab + Pertuzumab
- nab-Paclitaxel + Trastuzumab + Pertuzumab
- Vinorelbin + Trastuzumab + Pertuzumab

### After pretreatment with only Trastuzumab in the adjuvant setting (TFI < 6 months)

- Trastuzumab Deruxtecan (T-DXd)
- T-DM1
- Chemotherapy + Trastuzumab + Pertuzumab

# 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)	5	D	++
■ Trastuzumab Deruxtecan (T-DXd) (TFI < 6-12 months)	5	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)	5	D	+
■ T-DXd	5	D	+
■ Tucatinib + Capecitabine + Trastuzumab	5	D	+
■ Capecitabine + Lapatinib	5	D	+/-

# HER2-pos. mBC

## 2nd line

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### 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 <sup>nd</sup> line Chemotherapy* + Trastuzumab / Pertuzumab	2b	B	+/-
■ Trastuzumab + Pertuzumab	2b	B	+/-
■ Trastuzumab + Lapatinib (HR neg.)	2b	B	+/-

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\* 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
- Margetuximab + Chemotherapy
- Experimental anti-HER2 regimens

LoE GR AGO

1b	B	++
1b	B	+
1b	A	+
1b	B	+
1b	B	+
1b	B	+/-
5	D	+

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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	+
■ Abemaciclib + Trastuzumab + Fulvestrant	2b <sup>a</sup>	B	+/-
■ Trastuzumab + Pertuzumab	2b	B	+/-
■ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
■ Trastuzumab mono	2b	B	+/-