



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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- **Versions 2002–2023:**

**Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
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/ Möbus / Müller / Rody / Schaller / Scharl / Schmidt / Schmutzler /
Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch**

- **Version 2024:**

Park-Simon / 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
- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)
- Targeted drugs in combination with chemotherapy can induce substantial survival benefits

1b

1b

1b

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

Markers for Indication

Oxford

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	<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 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 [#] (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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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	++

* 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 (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

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

	Oxford LoE	GR	AGO
--	---------------	----	-----

■ Monotherapy:

- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A_{lip})
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

1a	A	++
1b	A	++
3b	B	+
2b	B	+
2b	B	+

■ Polychemotherapy:

- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- T + gemcitabine after adj. A
- A + C or A_{lip} + C

1b	A	++
2b	B	+
1b	A	+
2b	B	++
1b	B	++

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 1st line metastatic situation

mBC - HER2-negative / HR-positive: Chemotherapy after Pretreatment *

Oxford

LoE GR AGO

	LoE	GR	AGO
▪ Trastuzumab-Deruxtecan (if HER2-low)	1b	A	++
▪ 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	+

* See approval details for previous therapy

** at least 1 year recurrence free after adjuvant therapy



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mBC - HER2-negative / HR-positive*

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	Trastuzumab Deruxtecan HR-pos / HER2-low (331 patients)	Hazard Ratio relative to control	Sacituzumab-Gov. HR-pos / HER2-neg (272 patients)	Hazard Ratio relative to control
previous lines of chemotherapy in mBC	all patients		all patients	
1 line	61%	0.66 for OS	0%	
2 lines			44%	0.85 for OS n.s.
≥ 2 lines	40%	0.76 for OS n.s.		
≥ 3 lines			60%	0.75 for OS
PFS (months)	9.6	0.37	5.5	0.66
OS (months)	23.9	0.69	14.4	0.79

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* Data from two different phase 3 studies with differently pretreated patients
kA: keine Angabe, n.s.: not significant, PFS: Progression free survival, OS: Overall survival

Triple Negative mBC PD-L1+ Independent of Germline Mutation in *BRCA 1/2* or *PALB2*

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Pembrolizumab + Chemotherapy* first-line PD-L1 CPS $\geq 10^{\#}$ (if TFI ≥ 6 months) 	1b	B	++
<ul style="list-style-type: none"> ■ Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC $\geq 1^{\#}$ (if TFI ≥ 12 months) 	1b	B	+
<ul style="list-style-type: none"> ■ Atezolizumab + Paclitaxel first-line PD-L1 IC $\geq 1^{\#}$ 	1b^a	B	-
<ul style="list-style-type: none"> ■ Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) in case of CPS $\geq 20^{\#}$ 	1b^a	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 ≥ 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 Mutation

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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	+
▪ 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	+/-

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 | +/- |

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	++
▪ Tucatinib + 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!)

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	+
▪ Abemaciclib + Trastuzumab + Fulvestrant	2b	B	+
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-