Guidelines Breast
Version 2023.1E

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

Guidelines Breast
Version 2023.1E

- **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

Guidelines Breast
Version 2023.1E

	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

Guidelines Breast
Version 2023.1E

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 ≥ 6 months after initiation of ET for MBC**

Guidelines Breast
Version 2023.1E

Treatment of Metastatic Breast Cancer
Predictive Factors for response

Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ 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	++
▪ 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-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	g*BRCA1/2*-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++

see chapter „pathology“

Guidelines Breast
Version 2023.1E

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.

Guidelines Breast
Version 2023.1E

Guidelines Breast
Version 2023.1E

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.**

Guidelines Breast
Version 2023.1E

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

Guidelines Breast
Version 2023.1E

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, g*BRCA*-Status (evtl. s*BRCA*-Status, evtl. PALB2), *PIK3CA*, *AKT*, *PTEN* , evtl. MSI, NTRK, ggf. m*ESR1*, 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)

Guidelines Breast
Version 2023.1E

	Oxford LoE	Oxford 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	++

Guidelines Breast
Version 2023.1E

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

	Oxford		
	LoE	GR	AGO
▪ Paclitaxel q1w	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabine	2b	B	++
▪ Nab-paclitaxel	2b	B	++
▪ Peg-liposomal doxorubicin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ Docetaxel + Peg-liposomal doxorubicin	1b	B	+/-

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

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

Guidelines Breast
Version 2023.1E

	Oxford		
	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

mBC HER2-negative / HR-positive*

Guidelines Breast
Version 2023.1E

	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 Metastastatic 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 **with CDK 4/6 plus endocrine therapy**	**30 %** **70%**	**0,42 for PFS** **0,55 für PFS**	**≤ 12 Months 59%** **> 12 Monate 39%**	**0,68 for OS** **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

Guidelines Breast
Version 2023.1E

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

	Oxford LoE	Oxford 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

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

Guidelines Breast
Version 2023.1E

	Oxford		
	LoE	GR	AGO
▪ Sacituzumab Govitecan	1b	A	++
▪ Bevacizumab 1st line in combination with			
▪ Paclitaxel (weekly)	1b	B	+
▪ Capecitabine	1b	B	+
▪ nab-Paclitaxel	2b	B	+/-
▪ Carboplatin (vs. Docetaxel)	1b	B	+/-
▪ Gemcitabin / Cisplatin (vs. Gem / Pac)	1b	A	+
▪ Nab-Paclitaxel / Carboplatin (vs. Carbo / Gem)	2b	B	+
▪ Trastuzumab Deruxtecan (in HER2 low)	2b	C	+/-

* According to label

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

Guidelines Breast
Version 2023.1E

	Oxford		
	LoE	GR	AGO
▪ Carboplatin (vs. docetaxel) (if Platinum-naive)	1b	B	+
▪ PARP-Inhibitors (HER2-negative mBC)			
▪ HER2-negative, g*BRCA 1/2* mutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ s*BRCA* 1/2 mutation			
▪ Olaparib	2b	B	+/-
▪ *gPALB2* mutation			
▪ Olaparib	2b	B	+/-

Guidelines Breast
Version 2023.1E

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	+/-

Guidelines Breast
Version 2023.1E

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	+/-

Guidelines Breast
Version 2023.1E

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: 2nd 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!)

Guidelines Breast
Version 2023.1E

HER2-pos. mBC

≥ third-line

Depending on the previous therapy (substance)	Oxford LoE	Oxford 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	+/-

HER2-pos. mBC

No Chemotherapy Possible or Desired

Guidelines Breast
Version 2023.1E

	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	+/-