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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 2002–2018:**
  Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Kolberg-Liedtke / von Minckwitz / Möbus / Müller / Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2019:**
  Jackisch /Lux

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Metastatic Breast Cancer
Disease-Free and Overall Survival

	Oxford LoE
▪ An increase in survival over time in MBC has been shown in some retrospective analyses	2a
▪ Patients with MBC today have been pretreated more extensive with chemotherapy (+/- targeted therapy). Thus, these tumors must be considered more drug resistant	2a
▪ 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

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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 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**

Metastatic Breast Cancer
Predictive Factors

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Therapy	Factor	Oxford LoE	Oxford GR	AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better metastasis)	1a	A	++
Checkpoint-Inhibitors (Atezolizumab)	PD-L1 IC# positive in TNBC	1b	B	+
PARP inhibitors	gBRCA 1/2 mutation	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

* Within clinical trials

(for additional potential biological factors see chapter„Predictive factors“)

(# ≥ 1% on I,mmune cells (IC) (for more information see chapter “ pathology”)

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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-4 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

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Definition of visceral crisis (ABC 4)

- **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 visceral compromise leading to a clinical indica-tion for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.**

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Metastatic Breast Cancer
Cytotoxic and Targeted 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. Assessment of a target lesion may be sufficient. In slowly growing disease, longer intervals are acceptable.**

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Metastatic Breast Cancer
Duration of Cytotoxic Therapy

	Oxford LoE	Oxford 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			

Chemotherapy for MBC – General Considerations: Drug Selection

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AGO: ++

- **Participation in clinical trials is highly recommended**
- **The choice of systemic therapy to be used is depending on on:**
  - **ER / PR, HER2, PD-L1 status, gBRCA status**
  - **Previous treatments (and their toxicities)**
  - **Disease-free interval after end of adjuvant treatment**
  - **Progression-free intervall of the previous line of therapy**
  - **Aggressiveness of disease 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
1st-Line Therapy Chemotherapy*

	Oxford LoE	Oxford GR	AGO
Monotherapy:			
Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
Doxorubicin, epirubicin, mitoxantrone (A) 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	++

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

MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

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	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: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

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	Oxford		
	LoE	GR	AGO
▪ Capecitabine	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 (eg. cyclophos. + MTX)	2b	B	+
▪ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-
▪ Gemcitabine + Capecitabine	2b	B	+/-
▪ Gemcitabine + Vinorelbine	1b	B	-

* At least one year disese-free after adjuvant treatment

Triple Negative mBC Independent of GenomicBRCA 1/2 Mutation

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	Oxford LoE	Oxford GR	AGO
▪ Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC			+/-
▪ Carboplatin (vs. Docetaxel)	1b[a]	B	+/-
▪ Gemcitabine/Cisplatin (vs. Gem/Pac)	1b	A	+
▪ Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)	2b[a]	B	+
▪ Bevacizumab added to first line cytotoxic therapy	1b	B	+
▪ Atezolizumab plus nab-paclitaxel firt-line, in PD-L1 IC positivity[#]	1b	B	+

(# ≥ 1% on I,mmune cells (IC) (for more information see chapter " pathology")

mBC with Genomic BRCA 1/2 Mutation

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	Oxford LoE	Oxford GR	AGO
▪ Standard of care i.e.; gBRCA1/2 negative disease			++
▪ Carboplatin (vs. Docetaxel) (if Platinum-naive)	1b	B	+
▪ PARP inhibitors			
▪ HER2-negative			
▪ Olaparib	1b	B	+
▪ Talazoparib	1b	B	+/-
▪ HER2-positive			
▪ Olaparib	5	D	+/-
▪ Talazoparib	5	D	+/-

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Metastatic Breast Cancer
Bevacizumab Treatment in HER2-neg. Disease

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

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ Docetaxel + trastuzumab + pertuzumab	1b	A	++
▪ Paclitaxel (wk) + trastuzumab + pertuzumab	2b	B	++
▪ Nab-Paclitaxel + trastuzumab + pertuzumab	3b[a]	C	+
▪ Vinorelbine + Trastuzumab + Pertuzumab	3b	B	+
▪ T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)	2b	B	+
▪ 1st line chemotherapy* + trastuzumab	1b	B	+
▪ Trastuzumab mono	2b	B	+/-
▪ Taxanes + lapatinib	1b	B	+/-
▪ Taxanes + trastuzumab + everolimus	1b	B	-
▪ Trastuzumab + aromatase inhibitors (if ER+)	2b	B	+/-**
▪ Lapatinib + aromatase inhibitors (if ER+)	2b	B	+/-**

* Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel

** see chapter Endocrine +/- targeted

2nd line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)

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	Oxford LoE	GR	AGO
▪ T-DM 1	1b	A	++
▪ TBP: 2nd line chemotherapy + trastuzumab	2b	B	+
▪ BP: 2nd line chemotherapy + trastuzumab + pertuzumab	5	D	+/-
▪ Any other 2nd line chemotherapy* + trastuzumab + pertuzumab)	5	D	+/-
▪ Taxane + trastuzumab + pertuzumab	5	D	+
▪ Capecitabine + trastuzumab + pertuzumab	1b[a]	B	+/-
▪ Capecitabine + lapatinib	1b	B	+
▪ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+

* e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

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	Oxford LoE	Oxford GR	Oxford AGO
Pretreatment with Trastuzumab			
T-DM 1	1b	A	++
Capecitabine + lapatinib	1b	B	+
Vinorelbine + lapatinib	2b	B	+/-
Trastuzumab + lapatinib (HR neg. disease)	2b	B	+
Chemotherapy + trastuzumab *(„treatment beyond progression“)*	2b	B	+
Trastuzumab + pertuzumab	2b	B	+
Vinorelbine + trastuzumab + everolimus *(trastuzumab resistant, taxane pretreated)*	1b	B	+/-
Neither data for patients pretreated with trastuzumab and pertuzumab nor data for treatment beyond progression available.			
Experimental anti-HER2-regimen	5	D	+
For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.	5	D	+

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Lapatinib in HER2-positive Metastatic Breast Cancer

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

Immunodiagnostic Tests and Immunotherapy*

	Oxford LoE	GR	AGO
Immunodiagnostic tests:			
Blood: Immunological parameters	5	D	--
Tumor tissue: PD-L1 IC status in TNBC	1b	B	+
Local immunotherapy			
Imiquimod topically for skin metastasis	4	C	+/-
Systemic immunotherapy:			
Atezolizumab plus nab-paclitaxel in TNBC & PD-L1 IC positivity	1b	B	+
Other immuntherapies in clinical trials, only			
HER2-vaccination in high risk population			
Immunomodulation (e.g. addition of Nov-2 to AC –T			
Dendritic cell intradermal vaccination			
Active vaccination			
Passive vaccination			
Therapy with oncolytic viruses			
Cytokines			

* Study participation recommended