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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 2002–2020:**
  Albert /Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Kolberg-Liedtke / Lüftner / Lux / von Minckwitz / Möbus / Müller / Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2021:**
  Jackisch / Schmidt

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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	1b
▪ Multiple lines of sequential therapy are beneficial (at least similar efficacy, less toxicity)	1b
▪ Targeted drugs in combination with chemotherapy can induce substantial survival benefits	1b

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**

Treatment of Metastatic Breast Cancer
Predictive Factors for response

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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	+
▪ 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	gBRCA1/2-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	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**

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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.**

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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

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, PIK3CA, e.g. MSI, NTRK (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
1st-Line Chemotherapy*

	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	++

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

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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

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

	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 (e.g. cyclophos. + MTX)	2b	B	+
▪ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-

* At least one year disese-free after adjuvant treatment

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

	Oxford		
	LoE	GR	AGO
▪ 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 + Chemo* first-line PD-L1 CPS ≥10# (after TFI ≥ 6 months)	1b	B	+/-
▪ Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) if 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 1/2*

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	Oxford		
	LoE	GR	AGO
▪ Bevacizumab in addition to first-line chemotherapy	1b	B	+
▪ Sacituzumab Govitecan (after pretreatment with 2 standard therapies)	1b[a]	B	+
▪ Carboplatin (vs. Docetaxel)	1b	B	+/-
▪ Gemcitabin/Cisplatin (vs. Gem/Pac)	1b	A	+
▪ Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)	2b[a]	B	+

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

	Oxford LoE	Oxford GR	AGO
▪ **Standard of care, i.e. as in gBRCA 1/2 wildtype disease**			++
▪ **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	B	++
▪ **s*BRCA* 1/2 mutation**	2b	B	+/-
▪ **Olaparib**			
▪ ***gPALB2* mutation**	2b	B	+/-
▪ **Olaparib**			

Metastatic Breast Cancer
Bevacizumab Treatment in HER2-neg. Disease

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	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	-

HER2-positive mBC

After Trastuzumab or w/o Pretreatment (+ Chemotherapy)

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	Oxford		
	LoE	GR	AGO
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ Nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbine + Trastuzumab + Pertuzumab	3b	B	+
▪ 1st line Chemotherapy* + Trastuzumab	1b	B	+
▪ TBP: 2nd line Capecitabine + Trastuzumab	2b	B	+
▪ Capecitabine + Lapatinib	1b	B	+
▪ Taxane + Lapatinib	1b	B	+/-
▪ Taxane + Trastuzumab + Everolimus	1b	B	-

* Taxane; Vinorelbine; Paclitaxel/Carboplatin; Capecitabine/Docetaxel,

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HER2-positive mBC

Further Therapy Options after Trastuzumab

	Oxford		
	LoE	GR	AGO
▪ T-DM 1 (Recurrence after 6 months and after taxanes and trastuzumab)	2b	B	+
▪ Trastuzumab + Lapatinib (HR-negative tumor)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-
▪ Trastuzumab + Aromatase-Inhibitors (ER+)	2b	B	+/-*
▪ Lapatinib + Aromatase-Inhibitors (ER+)	2b	B	+/-*
▪ AI + Trastuzumab + Pertuzumab			+
▪ Abemaciclib + Trastuzumab + Fulvestrant	2b	B	+/-*
▪ Trastuzumab + Pertuzumab			+/-

* See Chapter „endocrine +/- targeted Therapy“

HER2-positive mBC
Therapy after Trastuzumab/Pertuzumab

	Oxford LoE	GR	AGO
▪ T-DM 1	1b	A	++
▪ TBP: 2nd line Chemotherapy + Trastuzumab	2b	B	+
▪ 2nd line Chemotherapy* + Trastuzumab	5	D	+/-
+ Pertuzumab (if not used before)			
▪ Taxane + Trastuzumab + Pertuzumab	5	D	+
▪ Capecitabine + Trastuzumab + Pertuzumab	1b[a]	B	+/-
▪ Capecitabine + Lapatinib	1b	B	+

* e.g. Vinorelbine; Taxane/Carboplatin; Capecitabine/Docetaxel (Toxicity!)

HER2-positive mBC
Therapy after T-DM 1

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	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine	1b	B	++
▪ Neratinib + Capecitabine	1b	B	+
▪ Capecitabine + Lapatinib	1b	B	+
▪ Capecitabine + Trastuzumab + Pertuzumab	1b	B	+/-
▪ Trastuzumab Deruxtecan	2b	B	+
▪ Experimental anti-HER2 regimes	5	D	+

Metastatic Breast Cancer
Lapatinib in HER2-positive Disease

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	Oxford LoE	Oxford GR	Oxford 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	+/-

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Immunodiagnostic Tests and Immunotherapy

	Oxford LoE	Oxford GR	Oxford AGO
Immundiagnostik			
Tumor tissue: PD-L1 IC status in TNBC	1b	B	+
Blood: Immunological parameters	5	D	--
Systemic Immunotherapies			
Atezolizumab + Nab-Paclitaxel first-line TNBC, PD-L1 IC ≥1#	1b	B	+
Atezolizumab + Paclitaxel first line TNBC, PD-L1 IC ≥1#	1b	B	-
Pembrolizumab + Chemo* in TNBC & PD-L1 CPS ≥10#	1b	B	+/-
Pembrolizumab-Monotherapy (after chemotherapy without Immun oncology pretreatment) if CPS ≥20# [1]	1b[a]	B	+/-

(see-chapter„Pathology“)
* nab-Paclitaxel or Paclitaxel or Carboplatin/Gemcitabine
[1] CAVE: no label