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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

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Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2017:**
  Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck / Jackisch / Janni / von Minckwitz / Möbus / Müller / Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2018:**
  Liedtke / Möbus

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Disease-Free and Overall Survival in Metastatic Breast Cancer

	Oxford LoE
▪ An increase in survival over time in MBC has been shown in some retrospective analyses	2a
▪ Patients with MBC today have received more adjuvant treatment and in this regard can 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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Endocrine Resistance in Metastatic Breast Cancer

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**

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

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Treatment of Metastatic Breast Cancer
Predictive Factors

Therapy	Factor	Oxford LoE	Oxford GR	Oxford 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	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

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

* Within clinical trials

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Cytotoxic Therapy Goals

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**
    - **Imminent life-threatening metastasis**
  - **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

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)**
- **Assess subjective and objective toxicities, symptoms, and performance 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.**

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

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Cytotoxic Therapy Duration

	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			

Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

- **The choice of cytotoxic drugs to be used is dependent on:**
  - **ER / PR, HER2; combination with biologicals**
  - **Previous treatments (and their toxicities)**
  - **Disease-free interval after end of adjuvant treatment**
  - **Aggressiveness of disease and localization of metastases**
  - **Estimated life expectancy**
  - **Co-morbidities (including organ dysfunction)**
  - **Patient preferences and expectations**

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

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MBC HER2-negative/HR-positive
Cytotoxic 1st-Line Therapy*

	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

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MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

	Oxford		
	LoE	GR	AGO
▪ Experimental therapies within studies			++
▪ 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 Genomic BRCA 1/2 Mutation

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	Oxford		
	LoE	GR	AGO
▪ Experimental therapies within studies			++
▪ 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	+

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mBC with Genomic BRCA 1/2 Mutation

	Oxford LoE	Oxford GR	AGO
▪ Experimental therapies within studies			++
▪ Carboplatin (vs. Docetaxel) (if Platinum-naive)	1b	B	+
▪ PARP inhibitors			
▪ Olaparib (HER2-negative)	1b	B	+
▪ Olaparib (HER2-positive)	5	D	+/-

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Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

	Oxford		
	LoE	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	-

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First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

	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

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

	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!)

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Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

	Oxford LoE	Oxford GR	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	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	AGO
Immunodiagnostic tests:			
Immunological parameters in peripheral blood	5	D	--
Local immunotherapy			
Imiquimod topically for skin metastasis	4	C	+/-
Systemic immunotherapy - including items below – only within clinical trials:			++
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			
Checkpoint inhibitors (PD1; PDL-1; …)			

* Study participation recommended