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Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*Substances are only discussed if there is at least published evidence based on one phase III / IIb study available

Chemotherapy ±Targeted Drugs in Metastatic Breast Cancer

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- **Version 2002:**
  von Minckwitz / Schaller / Untch

- **Versions 2003–2016:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / von Minckwitz / Möbus / Müller / Rody / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen

- **Version 2017:**
  Fehm / Jackisch

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Disease-Free and Overall Survival in Metastatic Breast Cancer

	Oxford / AGO LoE / GR
➢ An increase in survival over time in MBC has been shown in some retrospective analyses	2a
➢ However, patients with MBC today have received more adjuvant treatment and have therefore to be considered more drug resistant	2a
➢ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)	1b
➢ Especially 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 initiating ET for MBC**

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References

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

Treatment of Metastatic Breast Cancer
Predictive Factors

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Therapy	Factor	Oxford / AGO LoE	GR	
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	+*

(other potentially biological factors see chapter „Predictive factors“)

*Within clinical trials

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References

Cytotoxic Therapy
Goals

Oxford LoE: 1b **GR: A** **AGO: ++**

Mono-Chemotherapy:

- Favourable therapeutic index
- Indicated in case of
  - Slow, not life-threatening progression
  - Insensitive to or progression during endocrine therapy

Poly-Chemotherapy:

- Unfavourable therapeutic index
- Indicated to achieve rapid remission in the case of
  - Extensive symptoms
  - Imminent life-threatening metastases
- 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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References

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 might be sufficient. In slowly growing disease, longer intervals are acceptable.**

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References

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

Cytotoxic Therapy Duration

	Oxford / AGO LoE	GR	
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**			

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Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends 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 dysfunctions)**
- **Patients preference and expectations**

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References

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 / AGO LoE	GR	
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. disease only if endocrine therapy is not or not anymore indicated

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

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	Oxford / AGO LoE	/ GR	
➢ 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 Doxo	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

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	Oxford / AGO LoE	GR	
➢ 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

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Triple Negative Metastatic Breast Cancer

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	Oxford / AGO LoE	GR	
➢ Experimental therapies within studies			++
➢ Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC			+
➢ Carboplatin (vs. Docetaxel)	1b[a]	B	+/-
➢ in gBRCA mutation	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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Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

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	Oxford / AGO LoE / GR		
➢ **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 / AGO LoE	/ GR	
➢ 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 / AGO LoE	/ GR	
➢ T-DM 1	1b	A	++
➢ TBP: 2nd line chemotherapy + trastuzumab	2b	B	+
➢ TBP: 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

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	Oxford / AGO LoE	GR	
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 / AGO LoE / GR		
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 metastases (radioresistance) in combination with capecitabine**	**2b**	**B**	**+/-**

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Immunodiagnostic Tests and Immunotherapy*

	Oxford / AGO LoE	/ GR	
Immunodiagnostic tests:			
Immunological parameters in peripheral blood	**5**	**D**	**--**
Local immunotherapy			
➢ **Imiquimod topically for skin metastases**	**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;…)**

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Further Information

References

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***Study participation recommended**