



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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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 2002–2019:**

**Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
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Stickeler / Thill / Thomssen / Untch**

- **Version 2020:**

Lüftner / Albert

Metastatic Breast Cancer Disease-Free and Overall Survival

Oxford
LoE

- In MBC, an increase in survival over time has been shown in some retrospective analyses
- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)
- Targeted drugs in combination with chemotherapy can induce substantial survival benefits

2a

1b

1b

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Endocrine Resistance

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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 \geq 6 months after initiation of ET for MBC

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Predictive Factors

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Therapy	Factor	Oxford		
		LoE	GR	AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	prior response	2b	B	++
Chemotherapy	prior response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better in 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 immune cells (IC) (for more information see chapter “ pathology”)

Metastatic Breast Cancer Treatment Rationale

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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

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 indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.**

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. In slowly growing disease, longer intervals are acceptable.**

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Duration of Cytotoxic Therapy

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- **As long as therapeutic index remains positive**
 - Treatment until progression
 - Treatment until best response
 - Change to alternative regimen before progression

- **Stop therapy in case of**
 - Progression
 - Non tolerable toxicity

Oxford		
LoE	GR	AGO
1a	A	++
2b	B	+
2b	B	+/-
2b	B	+/-
1c	A	++

Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

- Participation in clinical trials is highly recommended
- The choice of systemic therapy depends on:
 - ER / PgR, 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 Therapy Chemotherapy*

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	Oxford		
	LoE	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 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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- Paclitaxel q1w
- Docetaxel q3w
- Capecitabine
- Nab-paclitaxel
- Peg-liposomal doxorubicin
- Eribulin
- Vinorelbine
- Docetaxel + Peg-liposomal doxorubicin

	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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- **Capecitabine**
- **Eribulin**
- **Vinorelbine**
- **(Peg)-liposomal Doxorubicin**
- **Taxane re-challenge***
- **Anthracycline re-challenge***
- **Metronomic therapy (e.g. cyclophos. + MTX)**
- **Gemcitabine + Cisplatin / Carboplatin**
- **Gemcitabine + Capecitabine**
- **Gemcitabine + Vinorelbine**

	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	+/-
Gemcitabine + Capecitabine	2b	B	+/-
Gemcitabine + Vinorelbine	1b	B	-

* At least one year disease-free after adjuvant treatment

Triple Negative MBC

Independent of gBRCA 1/2 Mutation

Oxford		
LoE	GR	AGO

■ Atezolizumab plus nab-paclitaxel first-line, if PD-L1 IC positive[#]	1b	B	+
■ 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	+

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

MBC with gBRCA 1/2 Mutation

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- Standard of care i.e.; gBRCA 1/2-negative disease
- Carboplatin (vs. Docetaxel) (if Platinum-naive)

- PARP inhibitors
 - HER2-negative
 - Olaparib
 - Talazoparib

Oxford		
LoE	GR	AGO
		++
1b	B	+
1b	A	++
1b	B	+

Metastatic Breast Cancer

Bevacizumab Treatment in HER2-neg. Disease

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■ 1st line in combination with:

- Paclitaxel (q1w)
- Capecitabine
- Anthracyclines
- Nab-Pac
- Docetaxel (q3w)

■ Cap+Bev as maintenance after Doc+Bev

■ 2nd line in combination with:

- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

■ 2nd line as treatment through multiple lines

Oxford		
LoE	GR	AGO
1b	B	+
1b	B	+
2b	B	+/-
2b	B	+/-
1b	B	+/-
1b ^a	B	+/-
1b	B	+/-
1b	B	+/-
1b	B	-
1b	B	-

First Line Therapy in HER2-Positive MBC

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	Oxford		
	LoE	GR	AGO
■ Docetaxel + trastuzumab + pertuzumab	1b	A	++
■ Paclitaxel (weekly) + 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	+
■ 1 st 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 in HER2-positive MBC (Trastuzumab-Pretreated)

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- **T-DM 1**
- **TBP: 2nd line chemotherapy + trastuzumab**
- **BP: 2nd line chemotherapy + trastuzumab
+ pertuzumab**
- **Any other 2nd line chemotherapy* + trastuzumab
+ pertuzumab)**
 - Taxane + trastuzumab + pertuzumab
 - Capecitabine + trastuzumab + pertuzumab
- **Capecitabine + lapatinib**
- **Trastuzumab + lapatinib (HR-neg. disease)**

	Oxford		
	LoE	GR	AGO
	1b	A	++
	2b	B	+
	5	D	+/-
	5	D	+/-
	5	D	+
	1b^a	B	+/-
	1b	B	+
	2b	B	+

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

Further Lines of Therapy in HER2-Positive Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
1b	A	++	
1b	B	+	
2b	B	+/-	
2b	B	+	
2b	B	+	
2b	B	+	
1b	B	+/-	
2b ^a	B	+/-	

■ Pretreatment with Trastuzumab

- T-DM 1
- Capecitabine + lapatinib
- Vinorelbine + lapatinib
- Trastuzumab + lapatinib (HR-neg. disease)
- Chemotherapy + trastuzumab („*treatment beyond progression*“)
- Trastuzumab + pertuzumab
- Vinorelbine + trastuzumab + everolimus
(*trastuzumab resistant, taxane pretreated*)
- Abemaciclib + Trastuzumab + Fulvestrant

■ Data for patients pretreated with trastuzumab and pertuzumab or for treatment beyond progression with pertuzumab are not available.

- Trastuzumab-Deruxtecan 2b B +/-
- Experimental anti-HER2-regimen 5 D +
- For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above. 5 D +

Lapatinib in HER2-positive Metastatic Breast Cancer

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- **In combination with**
 - Trastuzumab for heavily pre-treated pts (HR-negative)
 - Paclitaxel in 1st line
 - Capecitabine in > 2nd line
 - Vinorelbine
 - AI in ER-positive disease
- **In patients with brain metastasis (radioresistance) in combination with capecitabine**

Oxford		
LoE	GR	AGO

2b	B	+
1b	B	+/-
1b	B	+
2b	B	+/-
2b	B	+/-
2b	B	+/-

Immunodiagnostic Tests and Immunotherapy

	Oxford		
	LoE	GR	AGO
■ Immunodiagnostic tests:			
■ Tumor tissue: PD-L1 IC status in TNBC	1b	B	+
■ Blood: Immunological parameters	5	D	--
■ Systemic immunotherapy:			
■ Atezolizumab and nab-paclitaxel in PD-L1 IC positive TNBC first line	1b	B	+
■ Other immunotherapies 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			
■ Local immunotherapy			
■ Imiquimod topically for skin metastasis	4	C	+/-