

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer



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Neoadjuvant (Primary) Systemic Therapy

Neoadjuvant Systemic Therapy

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- **Versions 2002–2017:**
**Bauerfeind / Blohmer / Costa / Dall /
Fersis / Friedrich / Göhring / Harbeck /
Heinrich / Huober / Jackisch / Kaufmann /
Liedtke / Loibl / Lux / von Minckwitz /
Müller / Nitz / Schneeweiss / Schütz /
Solomayer / Untch**
- **Version 2018:**
Mundhenke / Schneeweiss

Subtype-specific Strategies for Systemic Treatment

AGO

If chemotherapy is indicated due to tumor biology consider systemic treatment before surgery (neoadjuvant)

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HR+/HER2- and „low risk“

- Endocrine therapy without chemotherapy

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HR+/HER2- and „high risk“

- Conventionally dosed AT-based chemotherapy
- Dose dense chemotherapy
- Followed by endocrine therapy

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HER2+

- Trastuzumab (plus Pertuzumab neoadjuvant at high risk)
 - Sequential A/T-based regimen with concurrent T + H
 - Anthracycline-free, platinum-containing regimen
 - Anthracycline-free, taxane-containing regimen

++

++

+

+

Triple-negativ (TNBC)

- Conventionally dosed AT-based chemotherapy
- Dose dense chemotherapy
- Neoadjuvant platinum-containing chemotherapy

++

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+

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

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	Oxford		
	LoE	GR	AGO
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)	1a	A	
▪ Pathological complete response is associated with improved survival	1b	A	
▪ Can achieve operability in primary inoperable tumors	1b	A	
▪ Improved options for breast conserving surgery	1b	A	
▪ Decreases rate of axillary lymph node dissection	3b	C	
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B	
▪ Allows individualization of post-neoadjuvant treatment*	2b	B	

* Study participation recommended

Neoadjuvant Systemic Chemotherapy - Indications

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- **Inflammatory breast cancer**
- **Inoperable breast cancer**
- **Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**
- **If similar postoperative adjuvant chemotherapy is indicated**

Oxford		
LoE	GR	AGO
2b	B	++
1c	A	++
1b	B	++
1b	A	+

Neoadjuvant Systemic Chemotherapy Response Prediction I

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Factor	LoE ₀ x2001	CTS	GR	AGO
▪ Young age	1a	B	A	+
▪ cT1 / cT2 tumors o. N0 o. G3	1a	B	A	++
▪ Negative hormone receptor status	1a	B	A	++
▪ ER+ und negativer PgR-Status	2a	B	B	++
▪ Triple negative breast cancer	1a	B	A	++
▪ Positive HER2 status	1a	B	A	++
▪ Non-lobular tumor type	1a	B	A	+
▪ Early clinical response	1b	B	A	+

Neoadjuvant Systemic Therapy Response Prediction II

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Factor	LoE ₂₀₀₉	CTS	GR	AGO
▪ Multigene signatures	III	C	B	+/-
▪ Ki-67	I	B	A	+
▪ Tumor infiltrating lymphocytes*	I	B	B	+
▪ PIK3CA mutation in HER2 positive BC	I	B	B	+/-
▪ gBRCA in TNBC	II	B	B	+
▪ Homologous recombination deficiency	IV	C	C	+/-

* defined as dense lymphocytic infiltration of inner peritumoral stroma
outside of the invasion front (> 50% lymphocytes of stromal area)

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules



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- **Standard protocols used in the adjuvant setting with a duration of at least 18 weeks***
- **Taxane followed by anthracycline**
- **Platinum in TNBC (irrespective of BRCA status)**
- **Nab-Paclitaxel weekly instead of Paclitaxel weekly**

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

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**FORSCHEN
LEHREN
HEILEN**

* See chapter Adjuvant Chemotherapy

Neoadjuvant Systemic Therapy

Recommended Methods of Monitoring of Response

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- **Breast ultrasound**
- **Palpation**
- **Mammography**
- **MRI**
- **PET(-CT)**
- **Clip tumor region**
- **Clip positive lymph node**

Oxford		
LoE	GR	AGO
2b	B	++
2b	B	++
2b	B	++
2b	B	+
2b	B	+/-
5	D	++
3	C	+/-

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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- **Trastuzumab in combination with chemotherapy**
- **Pertuzumab + trastuzumab in combination with chemotherapy**
- **Lapatinib in combination with chemotherapy**
- **Lapatinib + trastuzumab in combination with chemotherapy**
- **Two anti-HER2 agents without chemotherapy**

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

Neoadjuvant Targeted Therapy in HER2 Negative Tumors

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Bevacizumab in combination with chemotherapy

- In hormone receptor positive BC
- In TNBC

Oxford		
LoE	GR	AGO
1b	B	-
1b	B	+/-

Neoadjuvant Systemic Therapy Procedures in Case of Early Response

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**In case of early response following 6 to 12 weeks of
neoadjuvant chemotherapy:**

- **Complete all chemotherapy before surgery i.e. ≥ 18
weeks of treatment**
- **In case of response after 2 cycles of DAC in HR
positive breast cancer consider 8 instead of 6 cycles
of DAC**

	Oxford		
	LoE	GR	AGO
1b	A	++	
2b	C	+	

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response

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In case of no change:

- Completion of NST followed by surgery
- Continuation of NST with non cross-resistant regimen
 - AC or EC x 4 → D x 4 or Pw x 12
 - DAC x 2 → NX x 4

In case of progressive disease:

- Stop of NST and surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

Oxford		
LoE	GR	AGO
2b	C	++
2b	B	+
2b	B	+
1b	B	+
4	D	++
4	D	+/-

* Study participation recommended

Neoadjuvant Systemic Therapy

Loco-regional Surgery

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- **Clip previous tumor region during surgery**
- **Appropriate surgery following NST**
- **Microscopically clear margins**
- **Tumor resection according to most recent imaging result**

Oxford		
LoE	GR	AGO
5	D	++
2b	C	++
2	B	++
2	B	+

Axillary Intervention Before or After NACT

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SLNB vor oder nach NACT bei cN0						
SLNB vor NACT				2b	B	+/-
SLNB nach NACT				2b	B	+
Weitere operative Therapie in Abhängigkeit von SLNB						
cN-Status (vor Therapie)	pN-Status (vor Therapie)	ycN-Status (nach Therapie)	operatives Vorgehen nach Therapie			
cN0	pN0(sn)	-	Nihil	1a	A	+
cN0	pN+(sn) analog ACOSOG Z0011	ycN0	Nihil Re-SN alleine ALND	5 2b 3	D B B	+ - +/-
cN0	pN+(sn) nicht analog ACOSOG Z0011	ycN0	Re-SN alleine ALND Axilla XRT	2b 2b 2b	B B B	- + +
cN0	Nicht durchgeführt	ypN0(SN) ycN0 ypN+(SN)	SN alleine ALND ALND	2b 2b 2b	B B B	+ +/- +
cN+	cN+ (CNB/FNA)	ycN0 ycN+ (CNB/FNA)	SN alleine ALND ALND	2b 2b 2b	B B B	+/- + ++

Neoadjuvant Systemic Therapy

Indications for Mastectomy

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- **Positive margins after repeated excisions**
- **Radiotherapy not feasible**
- **In case of clinical complete response**
 - **Inflammatory breast cancer (in case of pCR)**
 - **Multicentric lesions**
 - **cT4a-c breast cancer**

Oxford		
LoE	GR	AGO
3b	C	++
5	D	++
2b	C	+/-
2b	C	+/-
2b	B	+/-

Neoadjuvant Systemic Therapy

Timing of Diagnosis, Surgery and Radiotherapy

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	Oxford		
	LoE	GR	AGO
Initiation of therapy			
Necessary delay of therapy does not impact prognosis (even if > 4 weeks)	2b	B	
Surgery			
After nadir of leucocyte count (2 to 4 weeks after last course of chemotherapy)	2b	B	++
Radiotherapy within 2–3 months after BCS	2b	B	++

Adjuvant Systemic Therapy after Neoadjuvant Systemic Therapy

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	Oxford		
	LoE	GR	AGO
■ Endocrine treatment in endocrine responsive disease	1a	A	++
■ Complete trastuzumab treatment for 1 year in HER2-positive disease	2b	B	++
■ Complete pertuzumab treatment for 1 year in HER2-positive disease	1b	B	+/-
■ if N+ or HR-	2b	B	+
■ If insufficient response in case of non-pCR (invasive residual tumor in the breast and / or axillary nodes) after adequate NACT (antracyclines, taxanes, 18 weeks)			
■ Capecitabine adjuvant in TNBC	2b	B	+
■ Capecitabine adjuvant in HR+/Her-2- BC	2b	B	+/-
■ Experimental therapies in controlled trials	5	D	+

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer



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	LoE	GR	AGO
<ul style="list-style-type: none"> Postmenopausal patients: <ul style="list-style-type: none"> Who are inoperable and cannot / will not receive chemotherapy Optimizes the option for breast conserving therapy Aromatase inhibitors (for > 3 months) Aromatase inhibitor + lapatinib (HER2+ BC) 	2a	B	+
	1b	A	+
	1a ^a	B	+
	2b	B	+/-
<ul style="list-style-type: none"> Premenopausal patients <ul style="list-style-type: none"> Who are inoperable and cannot / will not receive chemotherapy Tamoxifen Aromatase inhibitors + LHRHa 	5	C	+
	2b	C	+
	1b	C	+/-
<ul style="list-style-type: none"> Concurrent chemo-endocrine therapy 	1b	A	-
<ul style="list-style-type: none"> Prognostic score: <ul style="list-style-type: none"> PEPI: pTN-Stadium, ER expression and Ki-67 expression after neoadjuvant endocrine therapy 	1b	B	+

^a Optimal duration of neoadjuvant endocrine therapy is unknown.

No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)