# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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## Neoadjuvant
## (Primary) Systemic Therapy

# Neoadjuvant Systemic Therapy



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- **Versions 2002–2019:**
  **Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweiss / Schütz / Solomayer / Untch**

- **Version 2020:**
  **Jackisch / Schneeweiss**

# Subtype-specific Strategies for Systemic Treatment



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| | AGO |
|---|---|
| **If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred** | |
| **HR+/HER2- and „low-risk"** | |
| ▪ Endocrine therapy without chemotherapy | ++ |
| **HR+/HER2- and „high-risk"** | |
| ▪ Conventionally dosed AT- based chemotherapy (q3w) | + |
| ▪ Dose dense chemotherapy (including weekly schedule) | ++ |
| ▪ Followed by endocrine therapy | ++ |
| **HER2+** | |
| ▪ Trastuzumab (plus Pertuzumab in N+ or NST) | ++ |
| ▪ Sequential A/T-based regimen with concurrent T + anti-HER2 therapy | ++ |
| ▪ Anthracycline-free, platinum-containing regimen | + |
| ▪ Anthracycline-free, taxane-containing regimen | + |
| **Triple-negative (TNBC)** | |
| ▪ Conventionally dosed AT-based chemotherapy | + |
| ▪ Dose dense chemotherapy (AT - based including weekly schedule) | ++ |
| ▪ Neoadjuvant platinum-containing chemotherapy | + |

# HER2+ Early Breast Cancer
## Neo-/adjuvant and postneoadjuvant Therapy



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**Adjuvant Therapy:**
**low risk of recurrence**
**Rezidivrisiko**
**Paclitaxel$_{weekly\ x\ 12}$ + Trastuzumab[1]**

- elderly or fragile patients

  or

- pT1, pN0

**Adjuvant Therapy:**
**high risk of recurrence**
**CHT + Trastuzumab + Pertuzumab[2]**

- Node-positive (pN+)
- Irrespective of ER-status[5]

**Neoadjuvant Therapy[3]**
**Trastuzumab + Pertuzumab**

- Node-positive (cN+/pN+)

  or

- cT $\geq$ 2

**Postneoadjuvant Therapy[4]**
**Trastuzumab +/- Pertuzumab**
**or T-DM1**

In case of pCR:

- Trastuzumab
- Trastuzumab + Pertuzumab
  - Node-positive prior NST
  - Irrespective of ER-status

In case of non-pCR:

- T-DM1

**Total duration of anti-HER2-therapy: 1 year**

1.Tolaney SM, *et al*. J Clin Oncol April 2019; 2. von Minckwitz G, *et al.* N Engl J Med 2017; 377:122–131 (inkl. Suppl.); 3. Gianni L, *et al.* Lancet Oncol 2012;13:25-32;
4. von Minckwitz G, *et al*. N Engl J Med 2019; 380:617-628, 5. Piccart M, et al. SABCS 2019 (abs GS1-04)

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# Neoadjuvant Systemic Chemotherapy Clinical Benefit

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Leads to improvement of prognosis by individualization of post-neoadjuvant therapy | 1b | A | |
| ▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response | 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 | |

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# Neoadjuvant Systemic Chemotherapy - Indications

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Inflammatory breast cancer | 2b | B | ++ |
| ▪ Inoperable breast cancer | 1c | A | ++ |
| ▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation | 1b | B | ++ |
| ▪ If similar postoperative adjuvant chemotherapy is indicated | 1b | A | ++ |
| ▪ To allow a risk adapted postoperative therapy | 1b | A | ++ |

# Neoadjuvant Systemic Chemotherapy
# Response Prediction I



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| Factor | LoE$_{Ox2001}$ | 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+ and negative 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 | + |

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# Neoadjuvant Systemic Therapy
# Response Prediction II

| 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 | +/- |
| ▪ g*BRCA* | II | B | B | + |
| ▪ Homologous recombination deficiency | IV | C | C | +/- |

* LPBC is defined as dense lymphocytic infiltration of inner peritumoral stroma outside of invasion front (> 50% of stromal area are covered by lymphocytes)

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# Neoadjuvant Systemic Chemotherapy
# Recommended Regimens and Schedules

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Standard protocols used in the adjuvant setting with a duration of at least 18 weeks* | 1a | A | ++ |
| ▪ Taxane followed by anthracycline | 1a | A | + |
| ▪ Platinum in TNBC (irrespective of BRCA status) | 1a | B | + |
| ▪ Nab-Paclitaxel weekly instead of Paclitaxel weekly | 1b | B | + |

* See chapter Adjuvant Chemotherapy

# Neoadjuvant Systemic Therapy
# Recommended Methods of Monitoring of Response



| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Breast ultrasound | 2b | B | ++ |
| ▪ Palpation | 2b | B | ++ |
| ▪ Mammography | 2b | B | ++ |
| ▪ MRI | 2b | B | + |
| ▪ PET(-CT) | 2b | B | +/- |
| ▪ Clip tumor region | 5 | D | ++ |
| ▪ Clip placement in pN+ | 3 | C | +/- |

# Neoadjuvant Targeted Therapy in HER2 Positive Tumors



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Trastuzumab in combination with chemotherapy | 1b | A | ++ |
| ▪ Pertuzumab + trastuzumab in combination with chemotherapy | 2b | B | ++ |
| ▪ Two anti-HER2 agents without chemotherapy | 2b | B | +/- |

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# Neoadjuvant Systemic Therapy Procedures in Case of Early Response

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| **In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:** | | | |
| ▪ **Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment** | **1b** | **A** | **++** |
| ▪ **In case of response after 2 cycles of TAC in HR positive breast cancer consider 8 instead of 6 cycles of TAC** | **2b** | **C** | **+** |

# Neoadjuvant Systemic Therapy
# Procedures in Case of No Early Response



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| | Oxford LoE | GR | AGO |
|---|---|---|---|
| **In case of no change:** | | | |
| ▪ Completion of neoadjuvant chemotherapy (NST) followed by surgery | 2b | C | ++ |
| ▪ Continuation of NST with non cross-resistant regimen | 2b | B | + |
| ▪ AC or EC x 4 → D x 4 or Pw x 12 | 2b | B | + |
| ▪ DAC x 2 → NX x 4 | 1b | B | + |
| **In case of progressive disease:** | | | |
| ▪ Stop NST and proceed to surgery or radiotherapy | 4 | D | ++ |
| ▪ Additional adjuvant chemotherapy with non cross-resistant regimen | 4 | D | +/- |

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# Axillary Interventions in NST

| | | | | Oxford | | AGO |
|---|---|---|---|---|---|---|
| | | | | LoE | GR | |
| SLNE following NST | | | | 2b | B | ++ |
| SLNE prior NST | | | | 2b | B | +/- |
| Further surgical procedures depending on SLNE status | | | | | | |
| cN-status (before NST) | pN-status (before NST) | N-status (after NST) | Surgical Procedure (after NST) | | | |
| cN0 | pN0(sn) | ycN0 | None | 1a | A | + |
| cN0 | pN+(sn) according to ACOSOG Z0011 | ycN0 | None | 1b | B | + |
| cN0 | pN+(sn) not according to ACOSOG Z0011 | ycN0 | ALND or Axillary RT | 2b | B | + |
| cN0 | Not done | ypN0 (sn) | SLNE only | 2b | B | ++ |
| | | $ypN1_{mic}$ (sn) | ALND<br>Axillary RT | 2b<br>5 | C<br>D | +<br>+/- |
| | | ypN1 (sn) | ALND<br>Axillary RT | 2b<br>5 | C<br>D | ++<br>+/- |
| cN+ | $pN+_{CNB}$ | ycN0 | SLNE only*<br>TAD (TLNE + SLNE)*<br>ALND* | 2b<br>2b<br>2b | B<br>B<br>B | +/-<br>+<br>+ |
| cN+ | $pN+_{CNB}$ | ycN+ | ALND<br>Axillary RT | 2<br>5 | B<br>D | ++<br>- |

NST=Neoadjuvant Systemic Therapy; ALND=Axillary Lymph Node Dissection; SLNE=Sentinel Lymph Node Excision; TAD=Targeted Axillary Dissection; TLNE=Targeted Lymph Node Excision; RT=Radiotherapy – *Trial participation recommended

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# Neoadjuvant Systemic Therapy
# Loco-regional Surgery

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Clip tumor region before NST | 5 | D | ++ |
| ▪ Appropriate surgery following NST | 2b | C | ++ |
| ▪ Microscopically clear margins | 2 | B | ++ |
| ▪ Tumor resection according to most recent imaging result | 2 | B | + |

# Neoadjuvant Systemic Therapy
# Indications for Mastectomy



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Positive margins after repeated excisions | 3b | C | ++ |
| ▪ Radiotherapy not feasible | 5 | D | ++ |
| ▪ In case of clinical complete response | | | |
| ▪ Inflammatory breast cancer (in case of pCR) | 2b | C | +/- |
| ▪ Multicentric lesions | 2b | C | +/- |
| ▪ cT4a-c breast cancer | 2b | B | +/- |

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# Neoadjuvant Systemic Therapy
# Timing of Diagnosis, Surgery and Radiotherapy

| | Oxford LoE | Oxford 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 surgery** | 2b | B | ++ |

# Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer



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| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| **Postmenopausal patients:** | | | |
| Who are inoperable and cannot / will not receive chemotherapy | 2a | B | + |
| Optimizes the option for breast conserving therapy | 1b | A | + |
| Aromatase inhibitors (for > 3 months) | 1a[a] | B | + |
| Aromatase inhibitor + lapatinib (HER2+ BC) | 2b | B | +/- |
| **Premenopausal patients** | | | |
| Who are inoperable and cannot / will not receive chemotherapy | 5 | C | + |
| Tamoxifen | 2b | C | + |
| Aromatase inhibitors + LHRHa | 1b | C | +/- |
| **Concurrent chemo-endocrine therapy** | 1b | A | - |
| **Prognostic score:** | | | |
| PEPI: pTN-Stage, 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)

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# Postneoadjuvant Therapy

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| **HR-positive (pCR and non-pCR)** | | | |
| ▪ Endocrine therapy according to menopausal status (see. ch. 10) | 1a | A | ++ |
| ▪ Capecitabine (in case of non-pCR) | 3b | C | +/- |
| **HER2-positive (in case of pCR)** | | | |
| ▪ Low-risk: Trastuzumab (to complete 12 months) | 2a | C | ++ |
| ▪ High-risk (N+): Trastuzumab + Pertuzumab (to complete 12 months) | 2b | C | + |
| **HER2-positive (in case of non-pCR)** | | | |
| ▪ T-DM1 | 1b | B | + |
| ▪ Neratinib after 1 year* Trastuzumab (HR-positive) | 3b | B | +/- |
| ▪ Trastuzumab + Pertuzumab (to complete 12 months) | 2b | C | +/- |
| **Triple negative (TNBC) (if non-pCR)** | | | |
| ▪ Capecitabine (up to 8 courses)** | 1b | B | + |

* in combination with standard endocrine therapy
** without platin based previous therapy

# Take Home Message - NST

- **Neoadjuvant systemic therapy offers an established treatment option for patients with early breast cancer if chemotherapy is indicated**
- **The pathologic response offers important prognostic information**
- **Surgical procedures after NST follows the same guidelines as compared to upfront surgery**
- **The options in axillary interventions follow a complex algorithm (see slide 16 of this chapter**
- **In case of non-pCR there is the option to improve prognosis by postneoadjuvant treatment in HER2+, TNBC or high-risk HR+ HER2- breast cancer by adapted postneaodjuvant therapy**
- **If postneoadjuvante endocrine therapy is indicated therapy is independend of the response to NST**