Neoadjuvant
(Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **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

Systematic review of published evidence
PUBMED 1999-2020
ASCO 1999-2019
SABCS 1999-2019
ECCO/ESMO 1999-2019
**Subtype-specific Strategies for Systemic Treatment**

**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  
  ++

---

**Systematic review of published evidence**

PUBMED 1999-2010
ASCO 1999-2019
SABCS 1999-2019
ECCO/ESMO 1999-2019
HER2+ Early Breast Cancer
Neo-/adjuvant and postneoadjuvant Therapy

<table>
<thead>
<tr>
<th>Adjuvant Therapy: low risk of recurrence</th>
<th>Neoadjuvant Therapy^3</th>
<th>Postneoadjuvant Therapy^4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezidivrisiko</td>
<td>Trastuzumab + Pertuzumab</td>
<td>Trastuzumab +/- Pertuzumab or T-DM1</td>
</tr>
<tr>
<td>• elderly or fragile patients</td>
<td>• Node-positive (cN+/pN+)</td>
<td>In case of pCR:</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>• Trastuzumab</td>
</tr>
<tr>
<td>• pT1, pNO</td>
<td>• cT ≥ 2</td>
<td>• Trastuzumab + Pertuzumab</td>
</tr>
<tr>
<td>Adjuvant Therapy: high risk of recurrence</td>
<td></td>
<td>- Node-positive prior NST</td>
</tr>
<tr>
<td>CHT + Trastuzumab + Pertuzumab^2</td>
<td></td>
<td>- Irrespective of ER-status</td>
</tr>
<tr>
<td>• Node-positive (pN+)</td>
<td></td>
<td>In case of non-pCR:</td>
</tr>
<tr>
<td>• Irrespective of ER-status^5</td>
<td></td>
<td>• T-DM1</td>
</tr>
</tbody>
</table>

Total duration of anti-HER2-therapy: 1 year

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)


Pathological complete response is associated with improved survival in all subgroups

4. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

Can achieve operability in primary inoperable tumors


Improved options for breast conserving surgery


Reduces the rate of lymphadenectomies


Allows individualization of therapy according to mid-course treatment effect

Allows individualization of post-neoadjuvant treatment

Inflammatory breast cancer

Inoperable breast cancer

Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation


If similar postoperative adjuvant chemotherapy is indicated


**Neoadjuvant Systemic Chemotherapy Response Prediction I**

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoEO2</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative hormone receptor status</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>ER+ and negative PgR-status</td>
<td>2a</td>
<td>B</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>1a</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>1b</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>

**Young age**

**cT1 / cT2 tumors o. N0 o. G3**

**Negative ER and PgR status**


**Triple negative breast cancer (TNBC)**


**Positive HER2 status**

the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145


Non-lobular tumor type


Early clinical response


**Multigene signature**


Ki-67

Tumour infiltrating lymphocytes

PIK3CA mutation
1. Loibl S, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol 2014: 32; 3212

**gBRCA mutation**


**HRD**


### Neoadjuvant Systemic Chemotherapy

#### Recommended Regimens and Schedules

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>Gr</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Standard protocols used in the adjuvant setting with a duration of at least 18 weeks*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxane followed by anthracycline</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Platinum in TNBC (irrespective of BRCA status)</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Nab-Paclitaxel weekly instead of Paclitaxel weekly</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* See chapter Adjuvant Chemotherapy

---

**Standard regimens used in the adjuvant setting with a duration of at least 18 weeks**


**AC or EC → D q3w or P q1w**

Taxane followed by anthracycline sequence


Platinum in TNBC (irrespective of BRCA status)


7. Sikov WM, Berry DA, Perou CM, et al: Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week
Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol, 2014


Nab-Paclitaxel weekly instead of Paclitaxel weekly


**Breast ultrasound**


---

**Neoadjuvant Systemic Therapy**

**Recommended Methods of Monitoring of Response**

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b B</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>2b B</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>2b B</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>2b B</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>2b B</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>5 D</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>3 C</td>
<td></td>
<td>+/-</td>
</tr>
</tbody>
</table>
Palpation

Mammography

MRI

PET(CT)

**Clip tumour region**


Trastuzumab in combination with chemotherapy


Eur J Cancer. 2016 Jul;62:62- 

Pertuzumab + Trastuzumab in combination with chemotherapy


4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)


Two anti-HER2 agents without chemotherapy

Anti-HER2 agent in combination with endocrine treatment
1. Rimawi MF, et al. SABCS 2014 (S6-02)
Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment


In case of response after 2 cycles of TAC in HR positive breast cancer consider 8 instead of 6 cycles of TAC

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

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>+/−</td>
</tr>
</tbody>
</table>

#### In case of no change:
- Completion of neoadjuvant chemotherapy (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 NST and proceed to surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

---

**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

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and...


DAC x 2 → NX x 4


In case of progressive disease:
Stop of NST and immediate surgery or radiotherapy


Additional adjuvant chemotherapy with non-cross-resistant regimen


Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies


6. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among...

**Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy**


Axillary intervention after PST


TAD (+SLNE) after PST, if pN1 (CNB prior to PST and ycN0


Mark previous tumor region


Surgery


<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clip tumor region before NST</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Appropriate surgery following NST</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>Microscopically clear margins</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Tumor resection according to most recent imaging result</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>

Microscopically clear margins

Tumor resection according to imaging result

Sentinel node biopsy (see chapter “Surgery”)
2. Boughey JC et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the
ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013: 310; 1455-1461


Verzicht auf operative Sanierung nach NACT

1. Yau C et al. SABCS 2019 (abs GS5-01)
2. Radovic M et al. SABCS 2019 (abs GS5-02)
3. Heil J et al. SABCS 2019 (abs GS5-03)
4. Tasulis M et al. SABCS 2019 (abs GS5-04)
5. Basik M et al. SABCS 2019 (abs GS5-05)
6. Vrancken Peeters MTFD et al. SABCS 2019 (abs GS5-06)
Positive margins after repeated excisions


Radiotherapy not feasible


In case of clinical complete response:

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margins after repeated excisions</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Radiotherapy not feasible</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>In case of clinical complete response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory breast cancer (in case of pCR)</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Multicentric lesions</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>cT4a-c breast cancer</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Inflammatory breast cancer in case of pCR


Multicentric lesions

cT4a-c breast cancer
Initiation of therapy after histologic diagnosis

Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)

Radiotherapy after surgery 2–3 months after surgery BCS
Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

<table>
<thead>
<tr>
<th>Postmenopausal patients:</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who are inoperable and cannot / will not receive chemotherapy</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Optimizes the option for breast conserving therapy</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Aromatase inhibitors (for &gt; 3 months)</td>
<td>1a</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Aromatase inhibitor + lapatinib (HER2+ BC)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Premenopausal patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Who are inoperable and cannot / will not receive chemotherapy</td>
<td>5</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Aromatase inhibitors + LHRHa</td>
<td>1b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

| Concurrent chemo-endocrine therapy                                                     | 1b         | A | -   |

| Prognostic score:                                                                      | 1b         | B | +   |
| PEPPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy |           |   |     |

Optimal duration of neoadjuvant endocrine therapy is unknown.
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

Postmenopausal patients:

Who are inoperable and cannot / will not receive chemotherapy


Optimizes the option for breast conserving therapy


Aromatase inhibitors (for > 3 months)


AI and fulvestrant


Concurrent chemo-endocrine therapy


Prognostic scores following NST


Statement ER and/or PgR positiv (pCR and non-pCR) Endocrine treatment according to menopausal status (s. Kap. 10)

Statement HER2 positive (after pCR): Low risk: Trastuzumab (to complete 12 mths)

Statement HER2 positive (after pCR): High risk (N+) Trastuzumab + Pertuzumab (to complete 12 mths)

<table>
<thead>
<tr>
<th>Statement</th>
<th>LoE</th>
<th>Grade</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR-positive (pCR and non-pCR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy according to menopausal status (see. ch. 10)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine (in case of non-pCR)</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>HER2-positive (in case of pCR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk: Trastuzumab (to complete 12 months)</td>
<td>2a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>High-risk (N+): Trastuzumab + Pertuzumab (to complete 12 months)</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td><strong>HER2-positive (in case of non-pCR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-DM1</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Neratinib after 1 year* Trastuzumab (HR-positive)</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab (to complete 12 months)</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Triple negative (TNBC) (if non-pCR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine (up to 8 courses)**</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

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

Statement HER2 positive (if non-pCR) T-DM1

Statement HER2 positive (if non-pCR) Neratinib (one year) after completing a year of adjuvant trastuzumab (if HR positive)

Statement HER2 positive (if non-pCR): Trastuzumab + Pertuzumab (to complete 12 mths)

Statement Tripel negativ (TNBC) (if non-pCR) Capecitabine (8 courses)
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 follow 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 postneoadjuvant therapy
- If postneoadjuvante endocrine therapy is indicated therapy is independend of the response to NST