Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Neoadjuvante
(Primäre) systemische Therapie
Neoadjuvante systemische Therapie

- **Versionen 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 1999-2019
ASCO 1999-2019
SABCS 1999-2019
ECCO/ESMO 1999-2019
### Subtyp-spezifische Strategien zur Systemtherapie

<table>
<thead>
<tr>
<th>AGO</th>
</tr>
</thead>
</table>

- **Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugt**
  - Endokrine Therapie ohne Chemotherapie
  - **HR+/HER2- mit „niedrigem Risiko”**
  - Konventionell dosierte AT-basierte Chemotherapie (q3w)
  - Dosisdichte Chemotherapie (inkl. weekly-Regime)
  - Anschließend endokrine Therapie
- **HR+/HER2- mit „hohem Risiko”**
- **HER2+**
  - Trastuzumab (plus Pertuzumab bei N+ oder NST)
  - Sequenzielles A/T-basiertes Regime mit simultaner Gabe von T + anti HER2-Th.
  - Anthracykin-freies, Platinhaltige Regime
  - Anthracykin-freies, Taxan-haltige Regime

- **Triple-negativ (TNBC)**
  - Konventionell dosierte AT-basierte Chemotherapie (q3w)
  - Dosisdichte sequenzielle A/T-basierte Chemotherapie (inkl. weekly Schemata)
  - Neoadjuvante Platin-haltige Chemotherapie

---

**Systematic review of published evidence**

- PUBMED 1999-2020
- ASCO 1999-2019
- SABCS 1999-2019
- ECCO/ESMO 1999-2019
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


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**


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
Palpation

Mammography

MRI

PET(-CT)

Clip tumour region
Trastuzumab in combination with chemotherapy


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)


Lapatinib in combination with chemotherapy


Lapatinib + Trastuzumab in combination with chemotherapy


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 DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC

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


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


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:
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 weeks after surgery BCS

Postmenopausal patients:

Who are inoperable and can / 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


### Postneoadjuvante Therapie

<table>
<thead>
<tr>
<th>HER positiv (pCR und non-pCR)</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endokrine Therapie nach Menopausenstatus (s. Kap. 10)</td>
<td>1a A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Capecitabin (bei non-pCR)</td>
<td>3b C</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

**HER2 positiv (bei pCR)**

- **Low risk: Trastuzumab (bis 12 Mon. komplett)**
  - 2a C ++

- **High risk (N+): Trastuzumab + Pertuzumab (bis 12 Mon. komplett)**
  - 2b C +

**HER2 positiv (bei non-pCR)**

- **T-DM1**
  - 1b B +

- **Neratinib nach 1 Jahr**
  - 3b B +/-

- **Trastuzumab + Pertuzumab (bis 12 Mon. komplett)**
  - 2b C +/-

**Triple negativ (TNBC) (bei non-pCR)**

- Capecitabin (bis zu 8 Kurse)**
  - 1b B +

* kombiniert mit Standard endokriner Therapie
** studienlage ohne platinbasierten Vortherapie

---

**Statement ER and/or PgR positiv (pCR und non-pCR):** Endokrine Therapie nach Menopausenstatus (s. Kap. 10)


etc.

---

**Statement HER2 positiv (bei pCR): Low risk: Trastuzumab (bis 12 Mon. komplett)**

Statement HER2 positiv (bei pCR): pN+ oder HR-: Trastuzumab + Pertuzumab (bis 12 Mon. komplett)

Statement HER2 positiv (bei non-pCR) T-DM1 (bis 12 Mon. anti-HER2-Therapie komplett)

Statement HER2 positiv (bei non-pCR) Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)

Statement Tripel negativ (TNBC) (bei non-pCR) Capecitabine (8 Kurse)
Die neoadjuvante systemische Therapie stellt eine etablierte Behandlungsform für Karzinome mit einer Indikation für eine Chemotherapie dar.

Das pathologische Ansprechen stellt eine wichtige prognostische Information dar.

Die operative Therapie der Brust nach Abschluss einer NST folgt den gleichen Kriterien wie bei primär operativem Vorgehen.

Die operativen Interventionen in der Axilla folgen einem komplexen Algorithmus (siehe Dia 16 in diesem Kapitel).

Bei non-pCR bestehen für das HER2+, TNBC oder high-risk HR+ HER2- Karzinom die Möglichkeit der Prognoseverbesserung durch eine adaptierte postneoadjuvante Therapie.

Die endokrine postneoadjuvante Therapie orientiert sich nicht am pathologischen Ansprechen.