Neoadjuvant (Primary) Systemic Therapy
Systematic review of published evidence
PUBMED 1999-2020
ASCO 1999-2020
SABCS 1999-2020
ECCO/ESMO 1999-2020
Subtype-specific Strategies for Systemic Treatment

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 (5xw)
  +
- Dose-dense chemotherapy (including weekly schedule)
  ++
- Followed by endocrine therapy
  ++

HER2+
- Trastuzumab (plus Pertuzumab in Nv or NACT)
  ++
  - Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy
    ++
  - Anthracycline-free chemotherapy + anti-HER2 therapy
    ++

Triple-negative (TNBC)
- Conventionally-dosed AT-based chemotherapy
  +
- Dose-dense chemotherapy (AD-based including weekly schedule)
  +
- Neoadjuvant platinum-containing chemotherapy
  +
- Neoadjuvant chemotherapy + ICPI (immune checkpoint-inhibitors)
  +/-

*Study participation recommended

Systematic review of published evidence
PUBMED 1999-2020
ASCO 1999-2020
SABCS 1999-2020
ECCO/ESMO 1999-2020


### Neoadjuvant Systemic Chemotherapy

#### Clinical Benefit

<table>
<thead>
<tr>
<th>Benefit</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leads to improvement of prognosis by individualization of post-neoadjuvant therapy</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Pathological complete response is associated with improved survival</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Can achieve operability in primary inoperable tumors</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Improved options for breast conserving surgery</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Decreases rate of axillary lymphadenectomies</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Allows individualization of therapy according to mid-course treatment effect</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

#### 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

5. EBCTCG. Long-term outcomes for neoad
8. 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
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant (Primary) Systemic Therapy

Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant...
systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508


If similar postoperative adjuvant chemotherapy is indicated
### General evidence


### Lobular cancer


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**Neoadjuvant Systemic Chemotherapy Response Prediction I**

<table>
<thead>
<tr>
<th>Factor</th>
<th>pCR* Probability</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>↑</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Negative hormone receptor status</td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Triple negative breast cancer</td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Positive HER2-status</td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Early clinical response</td>
<td>↑</td>
<td>1b</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lobular tumor type</td>
<td>↓</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Metaplastic tumor type</td>
<td>↓↓</td>
<td>4</td>
<td>C</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR.
See also chapter „Prognostic and predictive factors“
**Metaplastic breast cancer**


Multigene signature


3. Kuemmel S, Gluz O, Nitz U et al. Neoadjuvant nab-paclitaxel weekly versus dose-dense paclitaxel followed by dose-dense EC in high risk HR+/HER2- early BC by: Results from the neoadjuvant part of ADAPT HR+/HER2- trial. SABCS 2020; GS4-03.

**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

PDL-1-Status (TNBC):
Use of adjuvant standard regimens for NACT

Taxane followed by anthracycline sequence

Platinum in TNBC (irrespective of BRCA status)
1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from


Nab-Paclitaxel weekly instead of Paclitaxel weekly

**ICPi in combination with chemotherapy**


Breast ultrasound

Palpation
**Mammography**

**MRI**

**PET(-CT)**

**Clip pN+**


### Neoadjuvant Targeted Therapy in HER2 Positive Tumors

**Pertuzumab + Trastuzumab in combination with chemotherapy**

- Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)
  - LoE 2b
  - Grade B
  - AGO ++

- Trastuzumab in combination with standard polychemotherapy (low-risk)*
  - LoE 1b
  - Grade A
  - AGO +

- Anti-HER2 agents without chemotherapy
  - LoE 2b
  - Grade B
  - AGO +/-**

* Monochemotherapy and trastuzumab should preferably be used in the adjuvant setting
** Study participation recommended

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**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)
7. Hurvitz SA, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in...
patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2017. pii: S1470-2045(17)30716-7 [Epub ahead of print]


**Trastuzumab in combination with chemotherapy**


**Anti-HER2 agents without chemotherapy**


Neoadjuvant Chemotherapy
Treatment strategies based on clinical response

In case of early response
- Completion of neoadjuvant chemotherapy

In case of no change:
- Completion of neoadjuvant chemotherapy (NACT) followed by surgery
- Continuation of NACT 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 disease progression
- Re-evaluation of tumour biological factors
- Stop NACT and proceed to surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

Completin of neoadjuvant chemotherapy

In case of no change:
Completion of NACT, followed by surgery

Continuation of NST with non-cross-resistant regimen

AC or EC x 4 -> D x 4 or Pw x 12


DAC2x -> NX x 4


In case of progressive disease:

Stop of NACT 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


ypN0 (i+)
Mark previous tumor region

Surgery

Microscopically clear margins

Tumor resection according to imaging result
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
Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of therapy</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Delay of therapy (&gt; 60 days) associated with worse prognosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of surgery</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>4-8 weeks after last course of chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy within 2 months after surgery</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

Initiation of chemotherapy after histologic diagnosis

Time between surgery and last chemotherapy

Radiotherapy 2 mths after surgery BCS
1. Silva SB, Pereira AAL, Marta GN, de Barros Lima KML, de Freitas TB, Matutino ARB, de Azevedo Souza MCL, de Azevedo RGMV, de Viveiros PAH, da Silva Lima JM, Filassi JR, de Andrade Carvalho H, Piato JRM, Mano MS. Clinical impact of adjuvant radiation therapy
Neoadjuvant endocrine Therapy (NET)  
- Good clinical practice -

- Suitable for patients who are
  - inoperable
  - not able or not willing to undergo chemotherapy
- Limited data for premenopausal in contrast to postmenopausal patients is limited
- Optimal duration of NET is at least 4-6 months or until best response or until progression
- Choice of endocrine therapy is based on menopausal status
- NET for 2 up to 4 weeks is able to predict response to endocrine treatment by Ki-67 dynamics (prognostic / predictive evaluation)


Postmenopausal patients:
Aromatase inhibitors (for up to 6 months)


AI and fulvestrant

Concurrent chemo-endocrine therapy

Preoperative ET and Ki67 measurement:

Prognostic scores following NST


Statement ER and/or PgR positive (pCR and non-pCR) Endocrine Therapy after Menopausal Status (s. Kap. 10)

Statement Triple negative (TNBC) (in case of non-pCR)


Statement HER2 positiv (bei pCR):

Statement HER2 positiv (bei non-pCR):

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<table>
<thead>
<tr>
<th>pCR</th>
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<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk: Trastuzumab (to complete 12 mths)</td>
<td>2a</td>
<td>C</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>High-risk (C+N): Trastuzumab + Pertuzumab (to complete 12 mths)</td>
<td>2b</td>
<td>C</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Neratinib after 1 year Trastuzumab (HR-positive)*</td>
<td>2b</td>
<td>B</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>non-pCR</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>1b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Neratinib after 1 year* Trastuzumab (HR-positive)*</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab (to complete 12 mths)</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

* In combination with standard endocrine treatment.

Statement HER2 positiv (bei non-pCR):