Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Version 2002:**
  Costa

- **Versions 2003–2014:**
  Bauerfeind / Blohmer / Dall / Fersis / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Loibl / Lux / von Minckwitz / Müller / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2015:**
  Friedrich / Schneeweiss
Subtype-specific General Systemic Strategies

- **In case of indication for chemotherapy**, consider neoadjuvant approach

- **HR+/HER2- and “low risk”:**
  - Endocrine therapy without chemotherapy

- **HR+/HER2- and “high risk”**
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated in case of high tumor burden
  - Followed by endocrine therapy

- **HER2+**
  - Trastuzumab plus
    - Sequential A/T-based regimen with concurrent T + H
    - Anthracycline-free, carboplatin-cont. regimen
    - Dose dense & escalated in case of high tumor burden

- **TNBC**
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated
  - Plus Carboplatin in case of family history for BC/OC or gBRCA alteration
Neoadjuvant Systemic Chemotherapy
Clinical Benefit

- Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy
  
- Pathological complete response is associated with improved survival in particular subgroups
  
- Can achieve operability in primary inoperable tumors
  
- Improved options for breast conserving surgery
  
- Allows individualization of therapy according to mid-course treatment effect
  
- Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Pathological complete response is associated with improved survival in particular subgroups</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>Allows individualization of therapy according to mid-course treatment effect</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

* Study participation recommended
Neoadjuvant Systemic Chemotherapy

Indications

- 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

Oxford / AGO
LoE / GR

- Inflammatory breast cancer: 2b B ++
- Inoperable breast cancer: 1c A ++
- Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation: 1b B +
- If similar postoperative adjuvant chemotherapy is indicated: 1b A +
### Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>
## Neoadjuvant Systemic Therapy Response Prediction II

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene signature</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumour infiltrating lymphocytes</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

---

© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.
Guidelines Breast
Version 2015.1

www.ago-online.de

Further Information
References

FORSCHEN LEHREN HEILEN
## Neoadjuvant Systemic Chemotherapy

### Recommended Regimens and Schedules

- **Standard regimens used in the adjuvant setting with a duration of at least 18 weeks**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

- **AC or EC → D q3w or P q1w**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
</tr>
</tbody>
</table>

- **DAC**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
</tr>
</tbody>
</table>

- **AP → CMF**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
</tr>
</tbody>
</table>

- **Taxane followed by anthracycline sequence**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

- **Dose-dense regimen (e.g. E -P-CMF, E-P-C)**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
</tr>
</tbody>
</table>

- **Platinum in TNBC**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
</tr>
</tbody>
</table>

- **In case of family history of BC/OC or BRCA alteration**
  
<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
</tr>
</tbody>
</table>

*Study participation recommended*
# Superior Carboplatin Containing Regimens in the Neoadjuvant Setting

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Regimen</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sikov WM, et al. (JCO 2015)</td>
<td>CALGB 40603 Phase II</td>
<td>Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 6 q3w x4 – dd AC q2w x4</td>
<td>TNBC ± Cb: 54% vs 41% (ypT0/is ypN0)</td>
</tr>
<tr>
<td>von Minckwitz G, et al. (Lancet Oncol 2014)</td>
<td>Gepar Sixto Phase II</td>
<td>NPLD 20mg/m² qw x18 + Paclitaxel 80mg/m² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15mg/kg q3w x6</td>
<td>TNBC ± Cb: 53% vs. 37% (ypT0 ypN0)</td>
</tr>
<tr>
<td>Ando M, et al. (BCRT 2014)</td>
<td>Phase II</td>
<td>Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4</td>
<td>TNBC ± Cb: 61% vs. 26%</td>
</tr>
</tbody>
</table>
# Neoadjuvant Systemic Chemotherapy

## Recommended Methods of Monitoring of Response

- **Breast ultrasound**
  - Oxford / AGO LoE / GR: 2b B ++
- **Palpation**
  - Oxford / AGO LoE / GR: 2b B ++
- **Mammography**
  - Oxford / AGO LoE / GR: 2b B ++
- **MRI**
  - Oxford / AGO LoE / GR: 2b B +
- **PET(-CT)**
  - Oxford / AGO LoE / GR: 2b B +/-
- **Clip tumour region**
  - Oxford / AGO LoE / GR: 5 D ++
# Neoadjuvant Targeted Therapy in HER2 Positive Tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab in combination with chemotherapy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Lapatinib in combination with chemotherapy</td>
<td>1a</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab in combination with chemotherapy</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Pertuzumab + Trastuzumab in combination with chemotherapy</td>
<td>1a</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Two anti-HER2 agents without chemotherapy</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Anti-HER2 agent in combination with endocrine treatment</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Study participation recommended
Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Bevacizumab in combination with chemotherapy

- In hormone receptor positive BC
- In TNBC

Oxford / AGO LoE / GR

1b B -
1b B +/
Neoadjuvant Systemic Therapy

Procedures in Case of Early Response

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
# Neoadjuvant Systemic Therapy Procedures in Case of No Early Response

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 immediate surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Level of Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>D</td>
</tr>
</tbody>
</table>

* Study participation recommended
Local/Regional Procedure after Neoadjuvant Therapy

- Mark previous tumor region  
  Oxford / AGO LoE / GR  
  5 D ++

- Surgery  
  2b C ++

- Microscopically clear margins  
  5 D ++

- Tumor resection in the new margins  
  3b C +

- Sentinel node biopsy  
  (see chapter “Surgery”)
# Surgical Procedure of the Axilla Before or After NACT

## SLNB before or after NACT in cN0

<table>
<thead>
<tr>
<th>SLNB before NACT</th>
<th>SLNB after NACT</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2b B +/−</td>
</tr>
<tr>
<td>SLNB before NACT</td>
<td></td>
<td>2a B +/−</td>
</tr>
<tr>
<td>SLNB after NACT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Further surgical procedures depending on SLNB

<table>
<thead>
<tr>
<th>cN-Status (before NST)</th>
<th>pN-Status (before NST)</th>
<th>cN-Status (after NST)</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1a A +</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 B +/-</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) not analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2b B +</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SNB ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ycN+ (CNB/FNA)</td>
<td>2a B ++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ycN+ (CNB/FNA)</td>
<td>2b B ++</td>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Therapy
Indications for Mastectomy

- Positive margins after repeated excisions 3b C ++
- Radiotherapy not feasible 5 D ++
- In case of clinical complete response
  - Inflammatory breast cancer 2b C +
    - In case of pCR +/-
  - Multicentric lesions 2b C +/-
  - cT4a-c breast cancer 2b B +/-
Neoadjuvant Systemic Therapy
Timing of Surgery and Radiotherapy

- 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
Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

- Endocrine treatment in endocrine responsive disease  
  1a A ++
- Complete trastuzumab treatment for 1 year in HER2-positive disease  
  2b B ++
- In case of insufficient response
  - Further chemotherapy  
    3 C -
  - Experimental therapies in clinical trials  
    5 D +
Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

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

<table>
<thead>
<tr>
<th>Premenopausal patients</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who are inoperable and can / will not receive chemotherapy</td>
<td>5 C +</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b C +</td>
</tr>
<tr>
<td>Aromatase inhibitors + LHRH</td>
<td>1b C +/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concurrent chemo-endocrine therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A -</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b B +</td>
<td></td>
</tr>
</tbody>
</table>

Optimal duration of neoadjuvant endocrine therapy is unknown
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)
Neoadjuvant (Primary) Systemic Therapy (2/20 and 3/20)

Further information and references:

Systematic review of published evidence:
PUBMED 1999-2015
ASCO 1999-2015
SABCS 1999-2015
ECCO/ESMO 1999-2015
Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information and references:

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Pathological complete response is associated with improved survival in particular subgroups
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Can achieve operability in primary inoperable tumors**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Improved options for breast conserving surgery**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Allows individualization of therapy according to mid-course treatment effect**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery**
Abstimmungsergebnis der AGO-Empfehlungen: 9+, 14+/-, Rest Enthaltungen
Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information and references:

Inflammatory breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Inoperable breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

If similar postoperative adjuvant chemotherapy is indicated

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)**

**Further information and references:**

**Young age**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**cT1 / cT2 tumors o. N0 o. G3**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Negative ER and PgR status**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Triple negative breast cancer (TNBC)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Positive HER2 status**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Non-lobular tumor type**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Early clinical response**

Neoadjuvant Systemic chemotherapy - Response Prediction II (7/20)

Further information and references:

Multigene signature
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Ki-67
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Tumour infiltrating lymphocytes
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


PIK3CA mutation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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
**Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)**

*Further information and references:*

**Standard regimens used in the adjuvant setting with a duration of at least 18 weeks**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**AC or EC → D q3w or P q1w**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**DAC**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**AP → CMF**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Taxane followed by anthracycline sequence**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Dose-dense regimen (e.g. E-P-CMF, E-P-C)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Platinum in TNBC**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

in case of family history of BC/OC or BRCA alteration
Abstimmungsergebnis der AGO-Empfehlungen: 21+, 3+/-

2. Von Minckwitz et al. ASCO 2014 (abs 1005)
Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information and references:

Breast ultrasound
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Palpation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Mammography
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


MRI
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**PET(-CT)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Clip tumour region**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0
Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information and references:

Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

4. Pierga JY, et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. Breast Cancer Res Treat 2010: 122; 429-437

**Lapatinib in combination with chemotherapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Lapatinib + Trastuzumab in combination with chemotherapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Pertuzumab + Trastuzumab in combination with chemotherapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Two anti-HER2 agents without chemotherapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Anti-HER2 agent in combination with endocrine treatment**
Abstimmungsergebnis der AGO-Empfehlungen: 3+, 16+/-, 6-
1. Rimawi MF, et al. SABCS 2014 (S6-02)
Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)

Further information and references:

**Bevacizumab in combination with chemotherapy in hormone receptor positive**  
Abstimmungsergebnis der AGO-Empfehlungen: 13+/-, 17-


**Bevacizumab in combination with chemotherapy in TNBC**  
Abstimmungsergebnis der AGO-Empfehlungen: 2+/-, 13+/-, 9-

**Neoadjuvant Systemic Therapy Procedures in Case of Early Response (13/20)**

*Further information and references:*

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

*Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment*

Abstimmungsergebnis der AGO-Empfehlungen: 45/0


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

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response (14/20)

Further information and references:

In case of no change:
Completion of NST, followed by surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Continuation of NST with non-cross-resistant regimen
AC or EC x 4 → D x 4 or Pw x 12
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


DAC x 2 → NX x 4
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**In case of progressive disease:**

**Stop of NST and immediate surgery or radiotherapy**

Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Additional adjuvant chemotherapy with non-cross-resistant regimen**

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Local/Regional Procedure after Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

**Further information and references:**

**Mark previous tumor region**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Surgery**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Microscopically clear margins**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Tumor resection in the new margins**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Sentinel node biopsy (see chapter “Surgery”)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Neoadjuvant Systemic Therapy - Indications for Mastectomy (17/20)

Further information and references:

Positive margins after repeated excisions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Radiotherapy not feasible
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


In case of clinical complete response:
Inflammatory breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Multicentric lesions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

cT4a-c breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Neoadjuvant Systemic - Therapy Timing of Surgery and Radiotherapy (18/20)

Further information and references:

**Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Radiotherapy after surgery 2–3 weeks after surgery BCS**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment (19/20)

Further information:

Endocrine treatment in endocrine responsive disease
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Complete trastuzumab treatment for 1 year in HER2-positive disease
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

In case of insufficient response further chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Experimental therapies in clinical trials
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

No references
**Neoadjuvant Endocrine Therapy (20/20)**

*Further information and references:*

**Postmenopausal patients:**
*Who are inoperable and can / will not receive chemotherapy*
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


*Optimizes the option for breast conserving therapy*
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Aromatase inhibitors (for > 3 months)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Aromatase inhibitor + lapatinib (HER2+ BC)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Premenopausal patients:**
**Who are inoperable and can / will not receive chemotherapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Tamoxifen**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Aromatase inhibitors + LHRH**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Concurrent chemo-endocrine therapy**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0