Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Version 2002:**
  Costa

- **Versions 2003–2013:**
  Blohmer / Dall / Fersis / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Lux / von Minckwitz / Müller / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2014:**
  Bauerfeind / Loibl
<table>
<thead>
<tr>
<th>Subtype-specific Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
</tr>
<tr>
<td>- Trastuzumab plus</td>
</tr>
<tr>
<td>- Sequential AT-based regimen with concurrent T + H</td>
</tr>
<tr>
<td>- Anthracycline-free, carboplatin-containing regimen</td>
</tr>
<tr>
<td>- Dose dense &amp; escalated in case of high tumor burden</td>
</tr>
<tr>
<td>HR+/HER2- and &quot;low risk&quot;:</td>
</tr>
<tr>
<td>- Conventionally dosed AT-based chemotherapy</td>
</tr>
<tr>
<td>- Dose dense &amp; escalated in case of high tumor burden</td>
</tr>
<tr>
<td>- Followed by endocrine therapy</td>
</tr>
<tr>
<td>HR+/HER2- and &quot;high risk&quot;:</td>
</tr>
<tr>
<td>- Endocrine therapy without chemotherapy</td>
</tr>
<tr>
<td>TNBC</td>
</tr>
<tr>
<td>- Conventionally dosed AT-based chemotherapy</td>
</tr>
<tr>
<td>- Dose dense &amp; escalated</td>
</tr>
<tr>
<td>- In case of indication for chemotherapy, consider neoadjuvant approach</td>
</tr>
</tbody>
</table>

General Systemic Strategies
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

Oxford / AGO LoE / GR

1a A

1b A

1b A ++

1b A ++

1b B +*

* Study participation recommended
Neoadjuvant Systemic Chemotherapy

**Indications**

- **Inflammatory breast cancer**
  - Oxford / AGO LoE / GR: 2b B ++

- **Inoperable breast cancer**
  - Oxford / AGO LoE / GR: 1c A ++

- **Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**
  - Oxford / AGO LoE / GR: 1b B +

- **If similar postoperative adjuvant chemotherapy is indicated**
  - Oxford / AGO LoE / GR: 1b A +

- **TNBC**
  - Oxford / AGO LoE / GR: +

- **HER2 positive**
  - Oxford / AGO LoE / GR: 1b B +
# 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>
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</table>
## Neoadjuvant Systemic Chemotherapy 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>PAM50/Mammaprint</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>II</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>
Neoadjuvant Systemic Chemotherapy
Recommended Regimens and Schedules

- Standard regimens used in the adjuvant setting with a duration of at least 18 weeks
  1a A ++

- AC or EC $\rightarrow$ D q3w or P q1w
  2b A ++

- DAC
  2b B ++

- AP $\rightarrow$ CMF
  1b A +

- Taxane followed by anthracycline sequence
  2b B +

- Dose-dense regimen (e.g. E-P-CMF, E-P-C)
  1b B +*

- Capecitabine in combination with anthracycline and taxane
  1b B +/-

- Platinum in TNBC independent of BRCA-mutation
  2b B +*

Oxford / AGO
LoE / GR

*Study participation recommended
Possible Carboplatin Containing Regimen in the Neoadjuvant Setting

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Regimen</th>
<th>pCR rate ypT0/is, ypN0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sikov et al. (SABCS 2013)</td>
<td>CALGB 40603</td>
<td>Paclitaxel 80mg/m² weekly x 12 + Carboplatin AUC 6q3w x4 – dd AC (q2w)</td>
<td>49% 60% (+Bev)</td>
</tr>
<tr>
<td>von Minckwitz et al. (ASCO 2013)</td>
<td>Phase II</td>
<td>NPLD20mg/m² + Paclitaxel 80mg/m² + Carboplatin AUC 1.5mg/m² weekly x18</td>
<td>53% (+Bev)</td>
</tr>
<tr>
<td><strong>Negative study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alba et al. BCRT 2013</td>
<td>Phase II basal like</td>
<td>EC (90/600mg/m²)q3w x4 – Docetaxel 75mg/m² + Carboplatin AUC 6 q3w x 4</td>
<td>30%</td>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Chemotherapy
Recommended Methods of Monitoring of Response

- Breast ultrasound
- Palpation
- Mammography
- MRI
- PET(-CT)
- Clip tumour region

<table>
<thead>
<tr>
<th>Method</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast ultrasound</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Palpation</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>MRI</td>
<td>2b B +</td>
</tr>
<tr>
<td>PET(-CT)</td>
<td>1b D +/-</td>
</tr>
<tr>
<td>Clip tumour region</td>
<td>5 D ++</td>
</tr>
</tbody>
</table>
Neoadjuvant Targeted Therapy in HER2 Positive Tumors

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab in combination with chemotherapy</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Lapatinib in combination with chemotherapy</td>
<td>1b B -</td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab in combination with chemotherapy</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Pertuzumab + Trastuzumab in combination with chemotherapy</td>
<td>2b B +*</td>
</tr>
<tr>
<td>Two anti-HER2 agents without chemotherapy</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>

* Study participation recommended
Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Chemotherapy in combination with Bevacizumab

- In hormone receptor positive BC  
- In TNBC

Oxford / AGO
LoE / GR

2b 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

Oxford / AGO LoE / GR

1b A ++

2b C +
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

Oxford / AGO LoE / GR

In case of no change:
- 2b C ++
- 2b B +
- 1b B +

In case of progressive disease:
- 4 D ++*
- 4 D +/-*

* Study participation recommended
Local/Regional Procedure after Neoadjuvant Therapy

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

- Surgery
  - Oxford / AGO LoE / GR: 2b C ++

- Microscopically clear margins
  - Oxford / AGO LoE / GR: 5 D ++

- Tumor resection in the new margins
  - Oxford / AGO LoE / GR: 3b C +

- Sentinel node biopsy
  (see chapter “Surgery”)
  - Oxford / AGO LoE / GR: 5 D ++
Surgical Procedure of the Axilla Before or After NACT

<table>
<thead>
<tr>
<th>SLNB before or after NACT in cN0</th>
<th></th>
<th></th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB before NACT</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>SLNB after NACT</td>
<td>3</td>
<td>B</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>
<th></th>
<th>LoE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
<td>3</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) not analogue ACOZOG</td>
<td>ycN0</td>
<td>ALND</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SNB ALND</td>
<td>3</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ALND</td>
<td>2b</td>
<td>B</td>
<td>++</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
    - 3 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

---

**Oxford / AGO**
LoE / GR

4  C  ++

2b  B  ++
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

- Postmenopausal patients with endocrine-responsive breast cancers who are inoperable and can/will not receive chemotherapy
  
  - Optimizes the option for breast conserving therapy in postmenopausal patients with endocrine-responsive tumors
  
  - Aromatase inhibitors (for > 3 months)
  
  - Premenopausal patients with endocrine-responsive breast cancers who are inoperable and can/will not receive chemotherapy
    
    - Tamoxifen
    
    - Aromatase inhibitors + LHRH
  
  - Concurrent chemo-endocrine therapy
  
  - Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status

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:

Systematic review of published evidence:
PUBMED 1999-2012
ASCO 1999-2012
SABCS 1999-2012
ECCO/ESMO 1999-2012

Systematic review of national and international guidelines: St. Gallen, NIH, ASCO, German guidelines

References:

Selected review articles:
Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information:

Survival rates are similar after primary systemic (preoperative, neoadjuvant) therapy (NST) and adjuvant therapy. Pathological complete response (pCR) is associated with improved survival. In retrospective analyses of the German patient cohorts, this treatment effect is confined to specific subgroups in particular to patients with triple negative, HER2+ (non-luminal) and luminal B (HER2 negative) breast cancer. Achievement of pCR according to the most strict definition of no invasive and non-invasive tumor residues in the breast and axilla (ypT0 ypN0) predicts the most favorable overall survival.

Advantages of NST are
1. improved operability of primary inoperable tumors,
2. higher rate of breast conserving surgery,
3. selection of individualized therapy by early identification of treatment failures,
4. evaluation of short-term surrogate markers (clinical, pathologic, molecular) to predict long-term outcome, and
5. rapid evaluation of new drugs or treatment modalities.

Disadvantage of NST is
1. In one metaanalysis from 2005 an increased rate of loco-regional recurrences was suggested. However, this metaanalysis included trials where surgery was withheld in numerous patients.
References:

Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information:

Neoadjuvant systemic therapy (NST) is indicated in inoperable and inflammatory breast cancer, but also in operable breast cancer with tumor diameters of at least 2 centimeters.\textsuperscript{1-3} NST is a valid treatment option, if mastectomy seems necessary, but patient wishes breast conservation,\textsuperscript{3,4} and for all patient who would need adjuvant chemotherapy after adequate evaluation of radiological, histological and clinical prognostic factors.\textsuperscript{5} Patients may choose to receive systemic therapy before surgery to take advantage of the response assessment of the primary tumor as tumor response to NST is a surrogate for the effect of chemotherapy on micrometastases.\textsuperscript{6} Furthermore, a demonstrable response to NST may have a positive effect on patients compliance. NST may also be an option for patients who wish to delay surgery, e.g. in the second or third trimester of pregnancy.\textsuperscript{7}

It is especially indicated in TNBC and HER2+ breast cancer, because pCR correlates very well with the outcome in these subtypes.\textsuperscript{8,9}

References:

2. Buzdar AU. Cancer 110, 2394, 2007
Further information:

According to a metaanalysis including 3332 patients treated in 7 German neoadjuvant trials clinico-pathological factors predicting pCR following NST are younger age, smaller tumor size, non-lobular histology, higher grade, negative hormone receptor (HR) status, triple negative and HER2 positive status.\textsuperscript{1,2} Considering subgroups higher probability of pCR was associated with longer treatment in HR positive tumors, higher anthracycline doses in HR negative tumors, short-term higher-dose taxane- and anthracycline-based treatment in triple negative tumors, trastuzumab-containing treatment in HER2 positive tumors and the addition of capecitabine in all subtypes.\textsuperscript{1}

References:

**Neoadjuvant Systemic chemotherapy - Response Predictiong II (7/20)**

**Further information:**

Further predictive parameters are the presence of tumor-associated lymphocytes, and other proliferation marker like Ki-67 and topoisomerase IIα.\(^1\)\(^-\)\(^4\) The assessment of Ki-67 before therapy has prognostic and predictive impact.\(^5\)\(^,\)\(^6\) Although results of several gene expression profiling studies are promising, at the moment, none of these signatures has been proven to be of sufficient discriminatory power to be used in clinical setting.\(^7\)

It has been shown that TNBC subclassified by the Vanderbilt/Lehman signature into 7 subtypes has predictive information.\(^8\) It was previously shown that the androgen receptor positive TNBC have a lower rate of achieving a pCR.\(^9\) The luminal AR subtype is one of the 7 classified by Lehmann. In HER2 positive breast cancer, the absolute amount of ER seems to play a role in predicting response to neoadjuvant therapy.\(^10\) The \textit{PIK3CA} mutated HER2+ tumours achieve a significantly lower pCR rate than the wild-type tumours.\(^11\)\(^-\)\(^13\) Especially in patients receivin a dual anit-HER2 treatment.

**References:**

\(^3\)Denkert C, et al. SABCS 2013  
\(^4\)Loi S, et al. SABCS 2013  

Loibl S, Breast Cancer Res Treat, 2010


Gianni L, et al. SABCS 2011

Baselga J, ECC13, 2013

Loibl S, SABCS 2013
Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)

Further information:

Outside clinical trials the same regimens should be used for NST as in the adjuvant setting ie. anthracyclines and taxanes concurrently or sequentially for at least 6 cycles (18 weeks) or 6 months, respectively.¹ Trastuzumab should be provided to all patients with HER2 overexpressing breast cancer and no cardiac comorbidity.²,³ Recommended regimens are those used in the superior treatment arms of large randomized trials (NSABP B-27,⁴ GeparDuo,⁵ GeparTrio,⁶,⁷ ECTO⁸).

A short dose-dense chemotherapy regimen with epirubicin and paclitaxel increased pCR rate and survival as compared to four cycles of standard dose epirubicin plus paclitaxel.⁹ A sufficiently long NST with dose intensified epirubicin and paclitaxel followed by CMF, however, increased only pCR rate but not DFS as compared to standard treatment.¹⁰,¹¹ Nevertheless analogue to the adjuvant setting, the use of a standard dose intensified regimen as neoadjuvant treatment should be considered if the patients would most probably receive this regimen in the adjuvant setting. Several regimen from the adjuvant setting and the neoadjuvant setting can be used.

Several studies have examined the use of capecitabine in the neoadjuvant setting with conflicting results.¹²-¹⁴ One metaanalysis of the German neoadjuvant trials point to the fact that capecitabine might play a role in NST but further prospective trials are needed.¹⁵

Platinum salts, have recently been shown in large prospectively randomized trials (the German GeparSixto study and the American CALGB 40603 study¹⁶,¹⁷ to increase pCR rates when given as part of the neoadjuvant chemotherapy, supporting the previous data from mainly small, non-randomized trials¹⁸-²¹. The study from Alba et al. combining Carboplatin with docetaxel (75mg/m²) compared to docetaxel 100mg/m² could not demonstrate superiority for the carboplatin arm. However, it has not been shown that this is specific platinum effect and not merely the effect of an alkylating agent.

References:

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information:

Monitoring during treatment must include breast examination before each cycle. The frequency and nature of imaging assessment during chemotherapy is controversial. Minimal requirements for the surgeon include clinical examination, mammogram, ultrasound, and in selected cases MRI. The response measured by breast ultrasound after 2 cycles of NST is a good predictor of later pCR. Various studies describe a good prediction of pCR if the breast MRI shows a good response in size of the tumor and reduction in volume and in contrast agent dynamic. However, the accuracy of MRI is not adequate to obviate either the need for staging by sentinel node biopsy or the need for complete axillary dissection in women determined to be node positive prior to NST. FDG-PET does not provide an accurate assessment of residual tumour after primary chemotherapy of breast cancer and is therefore not recommended outside clinical trials.

References:

Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information:

Several studies have examined the use of trastuzumab in combination with chemotherapy for patients with HER2 positive breast cancer in the neoadjuvant setting.\(^1-6\) The results of randomized trials demonstrated that, compared to chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy significantly increased pathologic complete response rate.\(^1-5\) Improvements in disease-free, event-free and overall survival were also reported.\(^1-5\) The achievement of pCR with chemotherapy and trastuzumab was associated with improved disease-free survival, distant disease-free survival and overall survival.\(^2,3,6-9\) The use of lapatinib instead of trastuzumab can not be recommended, although efficacy can be seen in HER2 positive tumors.\(^10,11\)

The combination of chemotherapy with trastuzumab and lapatinib or pertuzumab can significantly increase the pathologic complete response rate, but should preferably be used in clinical studies in the neoadjuvant setting until further results are available, although the combination of trastuzumab and pertuzumab has been licensed by the FDA for neoadjuvant therapy.\(^11-14\) Chemotherapy-free regimens combining 2 anti-HER2 agents were also active.\(^15,16\) Subcutaneous trastuzumab, has a pharmacokinetic profile and efficacy non-inferior to standard intravenous administration, and therefore offers a valid treatment alternative.\(^17\)

References:

Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)

Further information:

Three large randomized phase III studies showed a higher pCR rate after combination of chemotherapy and bevacizumab than with chemotherapy alone in patients with HER2 negative breast cancer in the neoadjuvant setting. In the German GeparQuinto trial, while no effect of bevacizumab was seen in hormone receptor (HR) positive patients,1 bevacizumab significantly increased the pCR rate in the triple negative subgroup.1,2 In the NSABP B40 trial, however, the effect of bevacizumab was seen predominantly in HR positive breast cancer.3 This controversial results cannot be explained for now. The CALGB study is the 3rd trial showing an increased pCR by adding bevacizumab to chemotherapy.4 Long term data need to be awaited before the recommendation for neoadjuvant bevacizumab can be granted.

References:

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

Further information:

Early response following 2 to 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound is associated with higher pCR rates at surgery.\textsuperscript{1-3} In case of early response NST should be completed as planned.\textsuperscript{4} In patients responding to 2 cycles of TAC, however, continuation of treatment with additional 6 instead of 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective, unplanned subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer.\textsuperscript{5}

References:

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

*Further information:*

In case of no change following 2 two 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound alternative strategies should be discussed. Completion of NST as planned is associated with a clinical response in around 50% of patients. The pCR rate, however, is only 2-6%.\(^1\,^2\) Following 4 cycles of an anthracycline-containing regimen the switch to taxanes is recommended.\(^3\) Survival in an unselected group of patients, however, is not improved.\(^4\) The addition of everolimus to paclitaxel is not justified.\(^5\) In case of no response following 2 cycles of TAC, however, the switch to 4 cycles of vinorelbine plus capecitabine (NX) instead of continuation with 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer.\(^6\)

In case of progressive disease immediate surgery or primary radiotherapy is recommended.\(^7\) Patients who have extensive residual cancer after a full course anthracycline and taxane containing NST remain at high risk for relapse, in particular patients with grade 3 and hormone receptor negative breast cancer.\(^8\) Those patients should be referred to participation in postneoadjuvant clinical trials.\(^7\)

*References*

Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

Further information:

Precise documentation of tumor location before, during and at the end of NST is necessary. Surgery is an integral part of primary breast cancer treatment following NST. The aim of surgery is to completely remove invasive and non-invasive breast cancer residues after NST and to obtain clear margins at pathology examination. No compromise should be made in surgical margins to obtain better cosmetic results. Under these circumstances excision within new tumor margins might be feasible according to current data. Thus far, studies evaluating sentinel node biopsy after NST have been inconsistent with regard to feasibility and efficacy. Therefore, it is not recommended outside of clinical trials, see also chapter surgery.1-4

References:

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

Further information:

Breast conserving surgery (BCS) should not be considered if negative margins are not achievable even after repetitive excisions, in case of widespread DCIS or microcalcifications, in case of inflammatory breast cancer or if adjuvant radiotherapy is not feasible.\(^1\)\(^-\)\(^3\) In cases with cT4a-c tumors or multicentric lesions (lesions in different quadrant) BCS is also not recommended.\(^1\)\(^-\)\(^5\) However, if a clinical complete response is achieved following NST, BCS should be evaluated within controlled clinical trials.

References:

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

Further information:

It is unknown whether preoperative radiotherapy following NST achieved similar results as radiotherapy following NST and surgery. Preoperative radiotherapy might result in higher rates of breast conservation without compromising cosmetic result. However, preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with NST and do not replace adequate surgery which should be performed after leucocyte nadir around 2 to 4 weeks following last cycle of chemotherapy. Adjuvant radiotherapy after NST should be administered according to the same recommendations made for those patients who do not receive NST. Even in patients with pCR following NST whole breast irradiation is indicated after breast-conserving surgery. If surgery can be omitted after pCR has still be to confirmed.

References:

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

**Further information:**

Postneoadjuvant therapy is indicated in patients at high risk of relapse after neoadjuvant therapy.\(^1\) The NATAN study using a bisphosphonate in unselected women with residual cancer was not successful.\(^2\) Currently several trials have started investigating palbociclib in patients at very high risk after neoadjuvant therapy with luminal type breast cancer.\(^3\) The Katherine study investigates the use of T-DM1 instead of trastuzumab after PST.\(^4\)

**References**

\(^1\) Mittendorf et al. *J Clin Oncol* 2011

\(^2\) von Minckwitz et al. *Cancer Res* 2013, SABCS abstract


Neoadjuvant Endocrine Therapy (20/20)

Further information:

NST with aromatase inhibitor represents an option for postmenopausal patients with highly endocrine responsive breast cancer, which can improve breast conservation rate.\(^1\)\(^-\)\(^5\) However, chemotherapy is still widely used in this setting despite small studies showing little advantage over an endocrine approach.\(^3\) The lack of a practice standard reflects the absence of a phase III trial definitively comparing neoadjuvant endocrine therapy with neoadjuvant chemotherapy. Neoadjuvant endocrine therapy might be reasonable for postmenopausal patients with hormone receptor positive breast cancer who are inoperable and for whom it is desirable to avoid certain chemotherapy related adverse events. According to prospective data from randomized trials and systemic review, aromatase inhibitors are more active and better tolerated than tamoxifen.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\) All 3 third generation aromatase inhibitors have similar activity.\(^6\) Current data support a duration of at least 3 months, but do not support the use of concurrent preoperative chemotherapy.\(^5\)\(^,\)\(^7\) The achievement of pCR is not a suitable surrogate endpoint for survival in luminal A type and HER2+ luminal B type breast cancer.\(^8\) Patients with pathologically node-negative T1 or T2 disease with a fully suppressed Ki67 level and persistent estrogen receptor expression after completion of NST have a very low risk of relapse.\(^9\) A small study in premopausal women comparing ARI plus GnRH with Tam + GnRH demonstrate a superiority for the ARI.\(^10\)

References:

10. XX Lancet Oncol 2011 (Japanese group)