

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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## Neoadjuvant (Primary) Systemic Therapy

# Neoadjuvant Systemic Therapy

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- **Versions 2002–2017:**  
**Bauerfeind / Blohmer / Costa / Dall / Fersis /  
Friedrich / Göhring / Harbeck / Heinrich / Huober /  
Jackisch / Kaufmann / Liedtke / Lux /  
von Minckwitz / Müller / Mundhenke / Nitz /  
Schneeweiss / Schütz / Solomayer**
- **Version 2018:**  
**Loibl / Untch**

# 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

+

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++

**HER2+**

- Trastuzumab (plus Pertuzumab neoadjuvant at high risk)
  - Sequential A/T-based regimen with concurrent T + anti Her 2 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

+

++

+

# Dose dense Paclitaxel

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| Schedule   | ED [mg/m <sup>2</sup> ] | Cycles | Cumulative dose | mg/m <sup>2</sup> /week |
|------------|-------------------------|--------|-----------------|-------------------------|
| EC-Pac q3w | 175                     | 4      | 700             | 58,33                   |
| ddEC-ddPac | 175                     | 4      | 700             | 87,5                    |
| ddEC-Pw    | 80                      | 12     | 960             | 80                      |

# Neoadjuvant Systemic Chemotherapy

## Clinical Benefit

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|  | Oxford |    |     |
|--|--------|----|-----|
|  | LoE    | GR | AGO |
| <ul style="list-style-type: none"> <li>Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)</li> </ul> | 1a     | A  |     |
| <ul style="list-style-type: none"> <li>Pathological complete response is associated with improved survival</li> </ul>  | 1b     | A  |     |
| <ul style="list-style-type: none"> <li>Can achieve operability in primary inoperable tumors</li> </ul>   | 1b     | A  |     |
| <ul style="list-style-type: none"> <li>Improved options for breast conserving surgery</li> </ul>   | 1b     | A  |     |
| <ul style="list-style-type: none"> <li>Decreases rate of axillary lymph node dissection</li> </ul>   | 3b     | C  |     |
| <ul style="list-style-type: none"> <li>Allows individualization of therapy according to mid-course treatment effect</li> </ul>   | 1b     | B  |     |
| <ul style="list-style-type: none"> <li>Allows individualization of post-neoadjuvant treatment*</li> </ul>  | 1b     | B  |     |

\* Study participation recommended

# Neoadjuvant Systemic Chemotherapy - Indications

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- **Inflammatory breast cancer**
- **Inoperable breast cancer**
- **Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**
- **If similar postoperative adjuvant chemotherapy is indicated**
- **To allow a risk adapted postoperative therapy**

| Oxford    |          |           |
|-----------|----------|-----------|
| LoE       | GR       | AGO       |
| <b>2b</b> | <b>B</b> | <b>++</b> |
| <b>1c</b> | <b>A</b> | <b>++</b> |
| <b>1b</b> | <b>B</b> | <b>++</b> |
| <b>1b</b> | <b>A</b> | <b>+</b>  |
| <b>1b</b> | <b>A</b> | <b>++</b> |

# Neoadjuvant Systemic Chemotherapy Response Prediction I

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| Factor                             | LoE <sub>Ox2</sub><br>001 | CTS | GR | AGO |
|------------------------------------|---------------------------|-----|----|-----|
| ▪ Young age                        | 1a                        | B   | A  | +   |
| ▪ cT1 / cT2 tumors o. N0 o. G3     | 1a                        | B   | A  | ++  |
| ▪ Negative hormone receptor status | 1a                        | B   | A  | ++  |
| ▪ ER+ und negativer PgR-Status     | 2a                        | B   | B  | ++  |
| ▪ Triple negative breast cancer    | 1a                        | B   | A  | ++  |
| ▪ Positive HER2 status             | 1a                        | B   | A  | ++  |
| ▪ Non-lobular tumor type           | 1a                        | B   | A  | +   |
| ▪ Early clinical response          | 1b                        | B   | A  | +   |

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## Response Prediction II

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| Factor                                       | LoE <sub>2009</sub> | CTS | GR | AGO |
|--|---------------------|-----|----|-----|
| ▪ <b>Multigene signatures</b>                | III                 | C   | B  | +/- |
| ▪ <b>Ki-67</b>                               | I                   | B   | A  | +   |
| ▪ <b>Tumor infiltrating lymphocytes*</b>     | I                   | B   | B  | +   |
| ▪ <b>PIK3CA</b> mutation in HER2 positive BC | I                   | B   | B  | +/- |
| ▪ <b>gBRCA</b> in TNBC                       | II                  | B   | B  | +   |
| ▪ <b>Homologous recombination deficiency</b> | IV                  | C   | C  | +/- |

\* defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front  
(> 50% lymphocytes of stromal area)



# Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules



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- **Standard protocols used in the adjuvant setting with a duration of at least 18 weeks\***
  
- **Taxane followed by anthracycline**
- **Platinum in TNBC (irrespective of BRCA status)**
- **Nab-Paclitaxel weekly instead of Paclitaxel weekly**

|  | Oxford    |          |           |
|--|-----------|----------|-----------|
|  | LoE       | GR       | AGO       |
|  | <b>1a</b> | <b>A</b> | <b>++</b> |
|  | <b>1a</b> | <b>A</b> | <b>+</b>  |
|  | <b>2b</b> | <b>B</b> | <b>+</b>  |
|  | <b>1b</b> | <b>B</b> | <b>+</b>  |

\* See chapter Adjuvant Chemotherapy

# Neoadjuvant Systemic Therapy

## Recommended Methods of Monitoring of Response

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- **Breast ultrasound**
- **Palpation**
- **Mammography**
- **MRI**
- **PET(-CT)**
- **Clip tumor region**
- **Clip placement in pN+**

| Oxford |    |     |
|--------|----|-----|
| LoE    | GR | AGO |
| 2b     | B  | ++  |
| 2b     | B  | ++  |
| 2b     | B  | ++  |
| 2b     | B  | +   |
| 2b     | B  | +/- |
| 5      | D  | ++  |
| 3      | C  | +/- |

# Neoadjuvant Targeted Therapy in HER2 Positive Tumors



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- **Trastuzumab in combination with chemotherapy**
- **Pertuzumab + trastuzumab in combination with chemotherapy**
- **Two anti-HER2 agents without chemotherapy**

| Oxford |    |     |
|--------|----|-----|
| LoE    | GR | AGO |
| 1b     | A  | ++  |
| 2b     | B  | ++  |
| 2b     | B  | +/- |

# Neoadjuvant Systemic Therapy Procedures in Case of Early Response

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

- **Complete all chemotherapy before surgery i.e.  $\geq 18$   
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**

|    | Oxford |    |     |
|----|--------|----|-----|
|    | LoE    | GR | AGO |
| 1b | A      | ++ |     |
| 2b | C      | +  |     |

# Neoadjuvant Systemic Therapy Procedures in Case of No Early Response



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## 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 progressive disease:

- **Stop of NACT and surgery or radiotherapy**
- **Additional adjuvant chemotherapy with non cross-resistant regimen**

|   | Oxford |    |     |
|---|--------|----|-----|
|   | LoE    | GR | AGO |
| Completion of neoadjuvant chemotherapy (NACT) followed by surgery | 2b     | C  | ++  |
| Continuation of NACT with non cross-resistant regimen             | 2b     | B  | +   |
| AC or EC x 4 → D x 4 or Pw x 12                                   | 2b     | B  | +   |
| DAC x 2 → NX x 4  | 1b     | B  | +   |
| Stop of NACT and surgery or radiotherapy                          | 4      | D  | ++  |
| Additional adjuvant chemotherapy with non cross-resistant regimen | 4      | D  | +/- |

# Neoadjuvant Systemic Therapy

## Loco-regional Surgery



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- **Clip previous tumor region during surgery**
- **Appropriate surgery following NACT**
- **Microscopically clear margins**
- **Tumor resection according to most recent imaging result**

| Oxford |    |     |
|--------|----|-----|
| LoE    | GR | AGO |
| 5      | D  | ++  |
| 2b     | C  | ++  |
| 2      | B  | ++  |
| 2      | B  | +   |

# Axillary Surgery and NACT

| SLNB before or after NACT in cN0                     |  |                          |                                    |    |   |     |
|--|--|--------------------------|------------------------------------|----|---|-----|
| SLNB before NACT                                     |  |                          |                                    | 2b | B | +/- |
| SLNB after NACT                                      |  |                          |                                    | 2b | B | +   |
| Further surgical procedures depending on SLNB status |  |                          |                                    |    |   |     |
| cN-Status<br>(before NACT)                           | pN-Status<br>(before NACT)             | N-Status<br>(after NACT) | Surgical Procedure<br>(after NACT) |    |   |     |
| cN0  | pN0(sn)                                | -                        | Nihil                              | 1a | A | +   |
| cN0  | pN+(sn) according to<br>ACOSOG Z0011   | ycN0                     | Nihil                              | 5  | D | +   |
|  |  |                          | Re-SN only                         | 2b | B | -   |
|  |  |                          | ALND                               | 3  | B | -   |
| cN0  | pN+(sn) different from<br>ACOSOG Z0011 | ycN0                     | Re-SN only                         | 2b | B | -   |
|  |  |                          | ALND                               | 2b | B | +   |
|  |  |                          | Axillary XRT                       | 2b | B | +   |
| cN0  | Not done                               | ypN0(sn)                 | SN only                            | 2b | B | +   |
|  |  |                          | ALND                               | 2b | B | -   |
|  |  | ypN1(sn)                 | ALND                               | 2b | B | +   |
|  |  |                          | Axillary RT                        | 5  | B | +   |
| cN+  | pN+ (CNB)                              | ycN0                     | SN only                            | 2b | B | +/- |
|  |  |                          | TAD including SN                   | 3b | C | +   |
|  |  |                          | ALND                               | 2b | B | +/- |
| cN+  | pN+ (CNB)                              | ypN1 (CNB)               | ALND                               | 2B | B | ++  |

# Neoadjuvant Systemic Therapy

## Indications for Mastectomy

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- **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**

| Oxford    |          |            |
|-----------|----------|------------|
| LoE       | GR       | AGO        |
| <b>3b</b> | <b>C</b> | <b>++</b>  |
| <b>5</b>  | <b>D</b> | <b>++</b>  |
| <b>2b</b> | <b>C</b> | <b>+/-</b> |
| <b>2b</b> | <b>C</b> | <b>+/-</b> |
| <b>2b</b> | <b>B</b> | <b>+/-</b> |



# Neoadjuvant Systemic Therapy

## Timing of Diagnosis, Surgery and Radiotherapy

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|  | Oxford    |          |           |
|--|-----------|----------|-----------|
|  | LoE       | GR       | AGO       |
| <b>Initiation of therapy</b>   |           |          |           |
| Necessary delay of therapy does not impact prognosis<br>(even if > 4 weeks)        | <b>2b</b> | <b>B</b> |           |
| <b>Surgery</b>   |           |          |           |
| After nadir of leucocyte count<br>(2 to 4 weeks after last course of chemotherapy) | <b>2b</b> | <b>B</b> | <b>++</b> |
| <b>Radiotherapy within 2–3 months after BCS</b>                                    | <b>2b</b> | <b>B</b> | <b>++</b> |

# Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer



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|  | Oxford |    |     |
|--|--------|----|-----|
|  | LoE    | GR | AGO |

|  |                 |   |     |
|--|-----------------|---|-----|
| <ul style="list-style-type: none"> <li>■ <b>Postmenopausal patients:</b> <ul style="list-style-type: none"> <li>■ Who are inoperable and cannot / will not receive chemotherapy</li> <li>■ Optimizes the option for breast conserving therapy</li> <li>■ Aromatase inhibitors (for &gt; 3 months)</li> <li>■ Aromatase inhibitor + lapatinib (HER2+ BC)</li> </ul> </li> </ul> | 2a              | B | +   |
|  | 1b              | A | +   |
|  | 1a <sup>a</sup> | B | +   |
|  | 2b              | B | +/- |
| <ul style="list-style-type: none"> <li>■ <b>Premenopausal patients</b> <ul style="list-style-type: none"> <li>■ Who are inoperable and cannot / will not receive chemotherapy</li> <li>■ Tamoxifen</li> <li>■ Aromatase inhibitors + LHRHa</li> </ul> </li> </ul>  | 5               | C | +   |
|  | 2b              | C | +   |
|  | 1b              | C | +/- |
| <ul style="list-style-type: none"> <li>■ <b>Concurrent chemo-endocrine therapy</b></li> </ul>  | 1b              | A | -   |
| <ul style="list-style-type: none"> <li>■ <b>Prognostic score:</b> <ul style="list-style-type: none"> <li>■ PEPI: pTN-Stadium, ER expression and Ki-67 expression after neoadjuvant endocrine therapy</li> </ul> </li> </ul>  | 1b              | B | +   |

<sup>a</sup> Optimal duration of neoadjuvant endocrine therapy is unknown.  
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

# Postneoadjuvant Therapy

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FORSCHEN  
LEHREN  
HEILEN

|   | Oxford |    |     |
|---|--------|----|-----|
|   | LoE    | GR | AGO |
| <b><u>HR positive (pCR and non-pCR)*</u></b>                              |        |    |     |
| ▪ Endocrine Therapy according to Menopausal Status (see. Ch. 10)          | 1a     | A  | ++  |
| ▪ Capecitabine (if non-pCR)   | 3b     | C  | +/- |
| <b><u>HER2 positive(after pCR)</u></b>                                    |        |    |     |
| ▪ Low risk: Trastuzumab (to complete 12 months)                           | 2a     | C  | ++  |
| ▪ High risk (eg HR-/N+): Trastuzumab + Pertuzumab (to complete 12 months) | 2b     | C  | +   |
| <b><u>HER2 positive (if non-pCR)</u></b>                                  |        |    |     |
| ▪ T-DM1 (to complete 14 doses of anti-HER2-Therapy)                       | 1b     | B  | +   |
| ▪ Neratinib after 1 year Trastuzumab (only if HR-positive)                | 4      | C  | +/- |
| ▪ Trastuzumab + Pertuzumab (to complete 12 months)                        | 2b     | C  | +/- |
| <b><u>Tripelnegative (TNBC) (if non-pCR)</u></b>                          |        |    |     |
| ▪ Capecitabine (up to 8 courses)  | 1b     | B  | +   |

\*Study participation recommended