Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **Versions 2002–2022:**

- **Version 2023:**
  Gluz / Witzel

Data bases screened
A Prognostic Factor is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

A Predictive Factor is associated with the probability of the effect of a given therapy.

Definition of Prognosis and Prediction

“Low absolute risk implies low absolute benefit”

## Early Breast Cancer (M0) – eBC
### Prognostic Factors I

<table>
<thead>
<tr>
<th>Factor</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size - pT</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Axillary lymph node status - pN</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Histological tumor type (mucinous, tubular etc.)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Grade (Elston &amp; Ellis) - G</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Age</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Histologically proven peritumoral lymphatic vessel and vascular invasion (L1 V1)</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>pCR after NACT* in (luminal-B-like, HER2+, TN)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Increased risk of recurrence in invasive-lobular BC, cT3/4, N+</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m²)</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Margins (resection status) - R0 / R1</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>

* NACT = Neoadjuvant Chemotherapy

### General references

### Tumor size

### Lymph node status

**Histological type (mucinous, tubular etc.)**

**Tumor grade (Elston & Ellis)**

**Age**

**Histologically proven lymph and/or blood vessel invasion**

**pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer**

**Increased risk of recurrence in invasive-lobular BC, cT3/4, N+**

**Obesity (BMI > 30 kg/m²)**

**Resection status (R0 / R1)**
Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
ER/PR

HER2

Ki-67


Post-treatment Ki-67


7. Wolff AC, Hammond ME, Hicks DG, et al.: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer:


Early Breast Cancer (M0) - eBC
Prognostic Factors III

Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)
(*Should only be used in the context of clinico-pathological criteria (e.g. tumor size, number involved lymph nodes, grade, Ki67) for therapeutic decision making)


MammaPrint®


**Oncotype DX®**


**EndoPredict®**


Prosigna®


7. Lænkholm AV, Jensen MB, Eriksen JO et al. The ability of PAM50 risk of recurrence score to predict 10-year distant recurrence in


Breast Cancer Index 


IHC-4 Score


PREDICT (https://breast.predict.nhs.uk/)

Lobular Score:

CTS Clinical Treatment Score

CPS-EG Score
**Early Breast Cancer (M0) - eBC**

**Prognostic Factors IV**

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tumor cells (DTC, in bone marrow)</td>
<td>1a</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Circulating tumor cells (CTC, in blood, Cell Search®)</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>CTC before NACT (regarding OS, DDFS, LRFI)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>3a</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Validated clinical data only available for this assay

**DTC**


**DTC and radiation**


**CTC**


**Therapy decision based on CTCs**

**Cell-free DNA**
Head to head comparisons


Endopredict


MammaPrint


Oncotype DX


12. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-


**Prosigna (ROR / PAM50)**


3. Jensen MB, Lænholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-


Breast Cancer Index


Head to head comparisons


Endopredict


**MammaPrint**


**Oncotype DX**


12. Penault-Llorca F, Filleron T, Asselain B, et al. The 21-gene Recurrence Score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-


**Prosigna (ROR / PAM50)**


3. Jensen MB, Lænholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-


Breast Cancer Index


## Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

<table>
<thead>
<tr>
<th></th>
<th>TailorX</th>
<th>RxPONDER</th>
<th>PlanB</th>
<th>ADAPT</th>
<th>MINDACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>median 7.5 years</td>
<td>median 5.3 years</td>
<td>5-year DFS</td>
<td>median 30 months</td>
<td>median 8.7 years</td>
</tr>
<tr>
<td>Trial design (biomarker question)</td>
<td>pN0, Randomization RS 11–25 (v-CTX)</td>
<td>pN0, Randomization RS 0-5 (v-CTX)</td>
<td>Prospective ODX testing, ET alone in RS 0-1 (pN=1)</td>
<td>Non-inferiority (DFS) ET alone: RS 0-11 vs RS 12-25/ET response</td>
<td>Prospectively defined 5y DMFS threshold for ET alone</td>
</tr>
<tr>
<td>Percentage clinically defined low-risk group</td>
<td>66.1%/47.2% (59.2%, adj online)</td>
<td>all 1-3 involved lymph nodes</td>
<td>all clinical CTX indication (pN=0)</td>
<td>all clinical chemotherapy (CTX) indication (pN=0)</td>
<td>33% (90.8%, adj online)</td>
</tr>
<tr>
<td>Percentage high clinical and low genomic risk (clinical CTX indication)</td>
<td>16.7% (RS 0–10)</td>
<td>40.6% (RS 0–10)</td>
<td>25.0% (RS 0–11)</td>
<td>ET trial (pN=0) all RS 0-25, low genomic risk with ET alone</td>
<td>28.2% (high clinical/low genomic risk)</td>
</tr>
<tr>
<td>Test failure rate</td>
<td>n.r.</td>
<td>n.r.</td>
<td>2.0%</td>
<td>n.r.</td>
<td>2.9% (fresh frozen)</td>
</tr>
<tr>
<td>Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)</td>
<td>69.5% (RS 11–25)</td>
<td>57.2% (RS 14–24)</td>
<td>69.4% (RS 12–25)</td>
<td>Reduced only RS 0-11 (37.8%) or RS 12-25/ET response (62.1%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Percentage genomically high-risk group (only for Oncotype DX)</td>
<td>14.3% (RS ≥ 26)</td>
<td>n.a.</td>
<td>24.3% (RS ≥ 26)</td>
<td>n.a.</td>
<td>27.0% (high clinical and high genomic risk)</td>
</tr>
<tr>
<td>12-year follow-up reported</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### TailorX

### RxPONDER

### PlanB

**ADAPT**


**MINDACT**


**Several tests**

Adjuvant Endocrine Therapy
Predictive Factors for DFS

Therapy
- Endocrine therapy
- Extended endocrine therapy (EAT)
- Tamoxifen
- Ovarian ablation or suppression
- Aromatase inhibitors vs. tamoxifen

Factor
- ER / PR status [%]
- IHC staining intensity (ER/PR)
- Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*
- Breast Cancer Index® Mammaprint
- CYP2D6-polymorphism
- Menopausal status
- Menopausal status
- ER / PR / HER2 as single factors
- Invasive-lobular breast cancer
- Ki-67 high
- Obesity (BMI > 30 kg/m²)

LoE       GR       AGO
1a A ++
1a A -
1b A +
2b B +/-
2b B -
1c A ++
1c A -
2b B +
2b B +/-
2b B +/-

General publications

Endocrine therapy

**EAT**

**Amenorrhoea**

**Body Mass Index**


CYP2D6


Ki-67 Bestimmung nach kurzer präoperativer endokriner Therapie


3. Ellis MJ, Suman VJ, Hoog J et al. Ki-67 Proliferation Index as a tool for chemotherapy decision during and after neoadjuvant aromatase inhibitor treatment of breast cancer: Results from the American College of Surgeons Oncology Group Z1031 Trial

### Adjuvant Chemotherapy and Targeted Therapy

#### Predictive Factors for DFS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant Chemotherapy</strong></td>
<td>70-Gene-signature (MammaPrint®)</td>
<td>1b A +</td>
</tr>
<tr>
<td></td>
<td>21-Gene-signature (Oncotype DX RS®)</td>
<td>1b A +</td>
</tr>
<tr>
<td></td>
<td>EPclin (Endopredict®)</td>
<td>2b B +</td>
</tr>
<tr>
<td></td>
<td>PAM-50 (Prosigna®)</td>
<td>2b B +</td>
</tr>
<tr>
<td></td>
<td>Histological type (lobular vs. NST)</td>
<td>2b B -</td>
</tr>
<tr>
<td></td>
<td>TIL’s in TNBC</td>
<td>2b B +/-</td>
</tr>
<tr>
<td><strong>Anti-HER2-Therapy</strong></td>
<td>HER2 (IHC, ISH)</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>PARP-Inhibitors</strong></td>
<td>gBRCA1/Mutation (HER2 neg.)</td>
<td>1a A +</td>
</tr>
</tbody>
</table>

*Consider decision according to age/menopausal status, prospective evidence available for MammaPrint and OncotypeDX only (see next slide)

#### 70-Gene-Signature (MammaPrint®)
2. Cardoso F, van 't Veer L, Poncet C, et al. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. ASCO 2020, #506

#### OncotypeDX
3. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2020, GS3-00
(0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial. SABCS 2020, GS4-04.

**EPclin (EndoPredict®)**

**PAM-50 (Prosigna®)**

**Histological type:**

**Anti-HER2 therapy**
see evidence in chapter “Chemotherapy and targeted therapy”

**PARPi**


3. Kalinsky KM, Barlow WE, Gralow JR et al. Abstract GS2-07: Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) ≤ 25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG S1007 (RxPONDER). Cancer Research 2022; 82: GS2-07-GS02-07.


5. Gluz O, Nitz U, Christgen M et al. Prognostic impact of recurrence score, endocrine response and clinical-pathological factors in high-
risk luminal breast cancer: Results from the WSG-ADAPT HR+/HER2- chemotherapy trial. Journal of Clinical Oncology 2021; 39: 504-504.

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

<table>
<thead>
<tr>
<th>Factor</th>
<th>pCR* Probability</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>↑</td>
<td>1a A</td>
</tr>
<tr>
<td>Obesity</td>
<td>↓</td>
<td>2a B</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>↑↑</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Negative hormone receptor status</td>
<td>↑↑</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Triple negative breast cancer</td>
<td>↑↑</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Positive HER2-status</td>
<td>↑↑</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>↑</td>
<td>1b A</td>
</tr>
<tr>
<td>Lobular tumor type</td>
<td>↓</td>
<td>1a A</td>
</tr>
<tr>
<td>Metaplastic tumor type</td>
<td>↓</td>
<td>4 C</td>
</tr>
</tbody>
</table>

Key:
- **↑**: High (↑) or very high (↑↑) probability to reach pCR.
- **↓**: Low (↓) or very low (↓↓) probability to reach pCR.
- **LoE**: Level of Evidence (A: high, B: moderate, C: low).
- **GR**: Grade of Recommendation (+: favorable, ±: equivocal, –: unfavorable).
- **AGO**: Grade of Agreement (+: high, ±: moderate, –: low).

General evidence

Body mass index
**Lobular cancer**

**Metaplastic breast cancer**
### Neoadjuvant Systemic Chemotherapy (NACT)

**Predictive Factors for pCR II**

<table>
<thead>
<tr>
<th>Factor</th>
<th>pCR* Probability</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression profiles (gene signatures) (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, Breast Cancer IndexSM)</td>
<td>↑</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>↑</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes**</td>
<td>↑</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation (for HER2-positive BC)</td>
<td>↑</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>gBRCA-mutation (for the effect of chemotherapy)</td>
<td>↑</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>gBRCA-mutation (for the effect of platinum)</td>
<td>↔</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* High (↑) or very high (↑↑) probability of pCR, low (↓) or very low (↓↓) probability of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

---

**TIL**


**PIK3CA**


gBRCA bei TNBC

CTC
Cell-free DNA


### Treatment of Metastatic Breast Cancer

#### Predictive Factors for response

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td>ER / PR (prim. tumor, better: metastasis)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Response to prior therapy</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Autocrine receptor mutation (ESR1)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Alpelisib</td>
<td>PIK3CA mutation (prim. tumor, metastases, plasma)</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Trastuzumab Deruxtecan</td>
<td>HER2-low or HER2-positive</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Response to prior therapy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Anti-HER2-therapy</td>
<td>HER2 (prim. tumor, better: metastasis)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Checkpoint-Inhibitors</td>
<td>PD-L1 positivity* (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>PARP-Inhibitors</td>
<td>gBRCA1/2-mutation</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Bone modifying drugs</td>
<td>Bone metastasis</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>

# see chapter „pathology”

### Endocrine therapy


### Endocrine therapy - ESR1:


### Alpelisib

Chemotherapy

Anti-HER2-Therapy

Checkpoint-Inhibitors


PARP-Inhibitors


Bone modifying drugs


**CTC monitoring (any therapy)**


BRCA 1/2:


PIK3CA:


HER2-Mutation:

ESR1:

NTRK:
MSI:
FDA approval across tumor entities (23.5.17): see full prescribing information for pembrolizumab

PALB2:
Head to head comparisons


Endopredict


MammaPrint


Oncotype DX


17. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2020, GS3-00.

Prosigna (ROR / PAM50)


**Breast Cancer Index**


**PARPi**

NGS in breast cancer:


## Joint Consensus Recommendations of AMP, ACMG, ASCO and CAP for Reporting Genetic Variants in Cancer

<table>
<thead>
<tr>
<th>Tier</th>
<th>LoE</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>A.1</td>
<td>Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of cancer</td>
</tr>
<tr>
<td></td>
<td>A.2</td>
<td>Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field</td>
</tr>
<tr>
<td>Tier 2</td>
<td>C.1</td>
<td>Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor</td>
</tr>
<tr>
<td></td>
<td>C.2</td>
<td>Biomarkers that serve as inclusion criteria for clinical trials</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Biomarkers that show plausible therapeutic significance based on preclinical studies</td>
</tr>
<tr>
<td>Tier 3</td>
<td></td>
<td>Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases. No convincing published evidence or cancer association</td>
</tr>
<tr>
<td>Tier 4</td>
<td></td>
<td>Observed at significant allele frequency in the general or specific subpopulation Databases. No existing published evidence of cancer association</td>
</tr>
</tbody>
</table>

### Treatment Recommendations for genetic variants

