Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **Versions 2002–2023:**
  Costa / Fasching / Fersis / Friedrichs / Gerber / Gluz / Göhring / Harbeck /
  Jackisch / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Mundhenke /
  Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon /
  Solomayer / Thill / Thomssen / Untch / Witzel / Wöckel

- **Version 2024:**
  Thill / Friedrich / Kreipe

Data bases screened
Definition

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”

<table>
<thead>
<tr>
<th>Quality Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biological hypothesis</td>
</tr>
<tr>
<td>• Simple and standardized assessment method, quality assurance (QA) of the test</td>
</tr>
<tr>
<td>• Prospectively planned statistical evaluation (primary goal)</td>
</tr>
<tr>
<td>• Validation of clinical significance according to</td>
</tr>
<tr>
<td>- „Oxford Level of Evidence (LoEOx2001)” criteria and „Grades of Recommendation (GR)”</td>
</tr>
<tr>
<td>- „Grades of Recommendation (GR)” as well as modified LoE criteria for the use in archived specimen (LoE2009) and category of tumor marker study (CTS)</td>
</tr>
<tr>
<td>• Clinical relevance for treatment decisions</td>
</tr>
</tbody>
</table>
Prognostic Factors for an Ipsilateral Recurrence after DCIS 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection margins</td>
<td>1a</td>
</tr>
<tr>
<td>Age</td>
<td>1a</td>
</tr>
<tr>
<td>Size</td>
<td>1a</td>
</tr>
<tr>
<td>Grade</td>
<td>1a</td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td>1a</td>
</tr>
<tr>
<td>Method of diagnosis</td>
<td>1a</td>
</tr>
<tr>
<td>Focality</td>
<td>1a</td>
</tr>
<tr>
<td>HER2-overexpression</td>
<td>1a</td>
</tr>
<tr>
<td>ER / PR (positive vs. negative)</td>
<td>1a</td>
</tr>
</tbody>
</table>

#See chapter “DCIS”

Diagnostische Methode

Fokalität

(mod.) Van Nuys Prognose Index und MSKCC Nomogramm


Palpables DCIS
Palpabel + COX-2+p16+Ki-67+
Palpabel + ER-, HER2, +Ki-67+

HER2-Überexpression
ER/PgR (positiv vs. negativ)

DCIS-Score


2. Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, et al. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)


DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)

Familiäre Karzinombelastung, Menopausenstatus, BMI und Brustdichte

Kontralaterales Mammakarzinom
Molecular Subtyping


Diagnostische Methode

Fokalität

(mod.) Van Nuys Prognose Index, MSKCC Nomogramm und DCISonRT


Palpables DCIS
Palpabel + COX-2+p16+Ki-67+
Pulpabel + ER-, HER2, +Ki-67+
HER2-Überexpression
ER/PgR (positiv vs. negativ)

DCIS-Score


2. Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, et al. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)


**DCISionRT:**

**DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom**

**Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)**

**Familiäre Karzinombelastung, Menopausenstatus, BMI und Brustdichte**

Kontralaterales Mammakarzinom


Molecular Profile

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)
1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82


Resection status (R0 / R1)


Early Breast Cancer (M0) - eBC
Prognostic Factors II

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PR</td>
</tr>
<tr>
<td>HER2 (IHC, ISH)</td>
</tr>
<tr>
<td>ER / PR / HER2 / Ki-67 to assess the intrinsic type with regards to tumor histology and biology</td>
</tr>
<tr>
<td>Proliferation markers</td>
</tr>
<tr>
<td>Ki-67 before, during, or after treatment</td>
</tr>
<tr>
<td>Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PR</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>HER2 (IHC, ISH)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>ER / PR / HER2 / Ki-67 to assess the intrinsic type with regards to tumor histology and biology</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Ki-67 before, during, or after treatment</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* Biomarker and Multi Gene Expression test should be evaluated on core needle biopsy prior endocrine therapy

ER/PR

HER2
HER2 low vs. HER2 0:

Ki-67
patients with ER-positive/HER2-negative early breast cancer: a systematic review and meta-analysis. Eur J Cancer. 2023 Nov;194:113358

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:


Predictive pathology of endocrine responsiveness

- Immunohistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if ≥ 1%, low positivity ≥ 1% to 10%; PR positive if ≥10%)
- Detection of endocrine responsiveness by Ki-67 decrease to < 10% after 3-4 weeks of preoperative endocrine therapy in primary breast cancer
- Detection of secondary, i.e. acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue

ASCO/CAP Guideline for ER- and PR-testing


IHC-testing for ER-positivity


IHC Scores


Monoclonal Antibodies for ER-Testing


ER low (ER 1%-10%)


Primary endocrine resistance


Secondary endocrine resistance (ESR1 mutation)


Gene expression profiles (GEP; multigene assays, gene signatures)

(*Should only be used in the context of clinical-pathological criteria (e.g. tumor size, number involved lymph nodes, grade, Ki67) for therapeutic decision making)


MammaPrint®


3. Mittempergher L, Delahaye LJM, Witteveen AT et al. MammaPrint and BluePrint Molecular Diagnostics Using Targeted RNA Next-


Oncotype DX®


**EndoPredict**

**Prosigna**


**IHC-4 Score**


**PREDICT** ([https://breast.predict.nhs.uk/](https://breast.predict.nhs.uk/))


**HER2DX**


3. Villacampa G, Tung NM, Pernas S, et al. Association of HER2DX with pathological complete response and survival outcomes in

**Lobular Score:**

**CTS Clinical Treatment Score**

**CPS-EG Score**

RCB
### DTC


### DTC and radiation


### CTC


---

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

* Validated clinical data only available for this assay

Therapy decision based on CTCs

Cell-free DNA/ctDNA:
2. Janni W et al., Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer, SABCS 2023, #PS06-06.
Head to head comparisons


Endopredict


MammaPrint


**Oncotype DX**


Prosigna (ROR / PAM50)


Breast Cancer Index


**Head to head comparisons**


**Endopredict**


MammaPrint


**Oncotype DX**


Prosigna (ROR / PAM50)


Breast Cancer Index


**RxPONDER**

**Plan B**

**ADAPT**

**MINDACT**

**Several tests**
## Adjuvant Endocrine Therapy

### Predictive Factors for DFS

<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 status [%]</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>• IHC staining intensity (ER/PR)</td>
<td>1a</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>• Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Extended endocrine therapy (EAT)</td>
<td>• Breast Cancer Index* MammaPrint</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>• CYP2D6-polymorphism</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian ablation or suppression</td>
<td>• Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Aromatase inhibitors vs. tamoxifen</td>
<td>• ER / PR / HER2 as single factors</td>
<td>1c</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>• Invasive-lobular breast cancer</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>• Ki-67 high</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>• Obesity (BMI &gt; 30 kg/m²)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

### General publications


### Endocrine therapy


4. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay


EAT


Amenorrhoea


Body Mass Index
1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82


CYP2D6


Ki-67 Bestimmung nach kurzer präoperativer endokriner Therapie


Adjuvant Chemotherapy and Targeted Therapy
Predictive Factors for DFS

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

OncotypeDX
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


EPclin (EndoPredict®)


PAM-50 (Prosigna®)


Histological type:

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

PARPi
4. 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.

### General evidence


### Neoadjuvant Systemic Chemotherapy (NACT)

#### Predictive Factors for pCR 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><strong>Young age</strong></td>
<td>↑</td>
<td></td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>↓</td>
<td>2a</td>
<td>B</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><strong>Negative hormone receptor status</strong></td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Triple negative breast cancer</strong></td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Positive HER2-status</strong></td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Early clinical response</strong></td>
<td>↑</td>
<td>1b</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Lobular tumor type</strong></td>
<td>↓</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Metaplastic tumor type</strong></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“
Body mass index

Lobular cancer

Metaplastic breast cancer
TIL


**PIK3CA**


gBRCA bei TNBC

PAM50 neoadjuvant:

Blueprint:
4. Pellicane JV, Beitsch PD, Rock DT, et al. ; NBRST Investigators Group. Combined 70- and 80-gene signatures identify tumors with genomically luminal biology responsive to neoadjuvant endocrine therapy and are prognostic of 5-year outcome in early-


**HER2DX:**


Metastatic Breast Cancer (mBC)
Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search®)</td>
<td>1a A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>1b B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Early response assessment (3w)</td>
<td>1b A</td>
<td>-*</td>
<td></td>
</tr>
<tr>
<td>Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype</td>
<td>1b A</td>
<td>-*</td>
<td></td>
</tr>
<tr>
<td>Cell-free DNA (cfDNA in blood)</td>
<td>2a A</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

* Study participation recommended

CTC
8. Munoz-Arcos LS, Nicolò E, Serafini MS, et al. Latest advances in clinical studies of circulating tumor cells in early and

Cell-free DNA/ctDNA:
Endocrine therapy


Endocrine therapy - ESR1:

Alpelisib

Capivasertib
2. Hopcroft L, Wigmore EM, Williamson SC (2023) Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. NPJ Breast Cancer 9(1):64. doi:10.1038/s41523-023-00571-w

Chemotherapy

Anti-HER2-Therapy

Checkpoint-Inhibitors


PARP-Inhibitors


Bone modifying drugs


CTC monitoring (any therapy)

BRCA 1/2:


**PIK3CA:**


**AKT1/PTEN:**

2. Hopcroft L, Wigmore EM, Williamson SC (2023) Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. NPJ Breast Cancer 9(1):64. doi:10.1038/s41523-023-00571-w

**HER2-Mutation:**

**ESR1:**


**NTRK:**


**MSI:**
1. 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
1. Bartlett JMS, Sgroi DC, Treuner K et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast


PARPi

**Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC**

<table>
<thead>
<tr>
<th>Diagnostic Tool*</th>
<th>Outcome</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence from studies with other cancer patients („tumor-agnostic testing“)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, …)</td>
<td>Efficacy of diverse therapies</td>
<td>4</td>
<td>D</td>
<td>+/-**</td>
</tr>
<tr>
<td>Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)</td>
<td>Efficacy of diverse therapies, prognosis</td>
<td>3a</td>
<td>C</td>
<td>+/-**</td>
</tr>
<tr>
<td>Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)</td>
<td>Efficacy of evaluated drugs</td>
<td>1b</td>
<td>B</td>
<td>+/-**</td>
</tr>
</tbody>
</table>

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE
** Participation in clinical trials or structured registries recommended

**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>Tier 1</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>Tier 1</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>Tier 2</td>
<td>C.2</td>
<td>Biomarkers that serve as inclusion criteria for clinical trials</td>
</tr>
<tr>
<td>Tier 2</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