Prognostische und prädiktive Faktoren
Prognostische und prädiktive Faktoren

- **Versionen 2002–2023:**

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

Data bases screened
Definition

Prognostische Faktoren
Dienen der Vorhersage des wahrscheinlichen weiteren Krankheitsverlaufs (z. B. krankheitsfreies oder progressionsfreies Überleben, Gesamtüberleben). Die Vorhersage kann durch die Therapie beeinflusst werden.

Prädiktive Faktoren
Dienen der Vorhersage eines wahrscheinlichen Therapieeffektes.

Definition of Prognosis and Prediction
“Low absolute risk implies low absolute benefit”


© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.
Guidelines Breast Version 2024.0D

www.ago-online.de
Prognostische Faktoren für das Auftreten eines ipsilateralen Rezidivs nach DCIS 1

- Resektionsränder  1a
- Alter  1a
- Größe  1a
- Grading  1a
- Komedonekrose  1a
- Diagnostische Methode  1a
- Fokalität  1a
- HER2-Überexpression  1a
- ER / PR (positiv vs. negativ)  1a

s. auch Kapitel „Ductales Carcinoma in situ“

Diagnostische Methode


Fokalität


(mod.) Van Nuys Prognose Index und MSKCC Nomogramm


Palpables DCIS
Palpable + COX-2+p16+Ki-67+
Palpable + 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


**Palpable DCIS**
- Palpable + COX-2+p16+Ki-67+
- Palpable + 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
1. Alaeikhanehshir S, Engelhardt EG, van Duijnhoven FH, et al. The impact of patient characteristics and lifestyle factors on the risk of
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)


Frühes Mammakarzinom (M0) – eBC Prognosefaktoren II

Oxford

<table>
<thead>
<tr>
<th>Faktor</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 zur Abschätzung des intrinsischen Typs unter Berücksichtigung der Tumorphysiologie und -biologie</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>▪ Proliferationsmarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Ki-67 vor, während oder nach der Behandlung</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>▪ Neu-Bestimmung Ki-67 nach kurzer, präoperativer endokriner Therapie (2 Wochen) (ypT und ypN)*</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

*Biomarkertestung und Genexpressionstest sollten an Stanze vor Therapie bestimmt werden

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:


Prädiktive Pathologie der endokrinen Responsivität

- Immunhistochemische Detektion des Östrogen- und Progesteronrezeptors am Paraffinschnitt mit Angabe des Prozentsatzes positiver Tumorzellkerne (ER positiv bei ≥ 1%; niedrig positiv bei ≥1% bis 10%, PR positiv bei ≥10%)  
  Oxford  
  LoE GR AGO  
  1a A ++

- Nachweis endokriner Responsivität durch Ki67 Abfall auf ≤10% nach 3-4 wöchiger präoperativer endokriner Therapie bei Erstdiagnose  
  Oxford  
  LoE GR AGO  
  1b A +

- Nachweis sekundärer (unter endokriner Therapie erworbener) endokriner Resistenz durch Untersuchung der aktivierenden ESR1 Mutation in der Liquid Biopsy oder den Metastasen  
  Oxford  
  LoE GR AGO  
  1b A +

s. auch Kapitel „Pathologie“

ASCO/CAP Guideline for ER- and PR-testing


IHC-testing for ER-positivity


IHC Scores


immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

**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 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®


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


**EndoPredict**

**Prosigna**


IHC-4 Score


PREDICT (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


**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**


event rates. SABCS 2022, GS 1-05

Prosigna (ROR / PAM50)

Breast Cancer Index
TailorX

RxPONDER

Plan B

**ADAPT**

**MINDACT**

**Several tests**
**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


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.


Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR I

Faktor | pCR* | Oxford | LoE | GR | AGO
--- | --- | --- | --- | --- | ---
Junges Alter | ↑ | 1a | A | +
Adipositas | ↓ | 2a | B | +
ct1 / ct2-Tumoren o. N0 o. G3 | ↑↑ | 1a | A | ++
Negativer ER- und PR-Status | ↑↑ | 1a | A | ++
Triple negative (TNBC) | ↑↑ | 1a | A | ++
Positiver HER2-Status | ↑↑ | 1a | A | ++
Frühes klinisches Ansprechen | ↑ | 1b | A | +
Invasives lobuläres Karzinom | ↓ | 1a | A | +
Metaplastisches Karzinom | ↓↓ | 4 | C | +

* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR

Siehe auch Kapitel „Prognostische und prädiktive Faktoren“

General evidence
**Body mass index**

**Lobular cancer**

**Metaplastic breast cancer**
Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR II

<table>
<thead>
<tr>
<th>Faktor</th>
<th>pCR*</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genexpressions-Profile (Gensignaturen) (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index®)</td>
<td>↑</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>HER2DX (27 Gene, Ansprechen auf Trastuzumab/Pertuzumab)</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-infiltrierende Lymphozyten**</td>
<td>↑</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA Mutation (für HER2-positives MaCa)</td>
<td>↑</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>gBRCA Mutation (für Effekt der Chemotherapie)</td>
<td>↑↑</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>gBRCA Mutation (für Platin-Effekt)</td>
<td>↔</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Hohe (↑) oder sehr hohe (↑↑) Wahrscheinlichkeit einer pCR, niedrigere (↓) oder sehr niedrige (↓↓) Wahrscheinlichkeit einer pCR
** Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionfront
(Stroma besteht mit > 50 % aus Lymphozyten)

TIL


gBRCA bei TNBC


PAM50 neoadjuvant:


Blueprint:


HER2DX:
1. Guarneri V, Bras-Maristany F, Dieci MV, et al. HER2DX genomic test in HER2-positive/hormone receptor-
positive breast cancertreated with neoadjuvant trastuzumab and pertuzumab: A correlative analysis from the PerELISA trial. EBioMedicine. 2022 Nov;85:104320.


CTC


**Cell-free DNA/ctDNA:**


Metastasiertes Mammakarzinom (mBC) Marker zur Indikationsstellung

<table>
<thead>
<tr>
<th>Therapie</th>
<th>Faktor</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endokrine Therapie</td>
<td>ER / PR (Primärtumor, besser Metastase)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Ansprechen auf vorherige Therapie</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>• Elacestrant</td>
<td>autokrine Rezeptormutation (ESR1) (Metastase, Plasma)</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>• Alpelisib</td>
<td>PIK3CA Mutation (Primärtumor, Metastase, Plasma)</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>• Capivasertib</td>
<td>PIK3CA, AKT1, PTEN Alterationen (Primärtumor, Metastase, Plasma)</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>• Trastuzumab Deruxtecan</td>
<td>HER2-low oder HER2-positiv</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>• Chemotherapie</td>
<td>Ansprechen auf vorherige Therapie</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>• Anti-HER2- Therapie</td>
<td>HER2 (Primärtumor, besser Metastase)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>• Checkpoint-Inhibitoren</td>
<td>PD-L1 Positivität* (IC, CPS) in TNBC (Primärtumor oder Metastase)</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>MSI/TMB</td>
<td>3</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>• PARP-Inhibitoren</td>
<td>gBRCA1/2-Mutation</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>sBRCA1/2 / gPALB2</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

Endocrine therapy


Endocrine therapy - ESR1:

5. Berger F, Marce M, Delaloge S, et al.; PADA-1 investigators Randomised, open-label, multicentric phase III trial to evaluate the

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)


Mutationsdiagnostik* bei mBC: „Precision medicine“ für zielgerichtete Therapien

<table>
<thead>
<tr>
<th>Alteriertes Gen</th>
<th>Therapierelevanz</th>
<th>Genregion</th>
<th>Ausgangsmaterial</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1, BRCA2</td>
<td>Olaparib, Talazoparib</td>
<td>Alle Exons</td>
<td>Keimbahn: Blutzellen, Somatisch: Gewebe</td>
<td>1b A ++</td>
</tr>
<tr>
<td></td>
<td>Olaparib</td>
<td></td>
<td>Keimbahn: Blutzellen</td>
<td>2b B +</td>
</tr>
<tr>
<td>PALB2</td>
<td>Olaparib</td>
<td></td>
<td>Keimbahn: Blutzellen</td>
<td>2b B +</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Alpelisib</td>
<td>Exon 7, 9 und 20</td>
<td>Primärtumor, Metastasen, Plasma</td>
<td>1b A ++</td>
</tr>
<tr>
<td>AKT1, PTEN,</td>
<td>Capivasertib</td>
<td></td>
<td>Primärtumor, Metastasen, Plasma</td>
<td>1b A +</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>HER2-Mutation</td>
<td>Kinase- und extrazelluläre Domänen; S310, L755, V777, Y772_A775dup</td>
<td>Primärtumor, Metastasen, Plasma; insbes. lobuläres CA</td>
<td>4 C +/-</td>
</tr>
<tr>
<td>(unabh. vom</td>
<td>HER2-Status)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR1</td>
<td>Resistenz gegenüber AI</td>
<td>Exon 4, 7 und 8</td>
<td>Metastasen, Plasma</td>
<td>2b B +</td>
</tr>
<tr>
<td></td>
<td>Ansprechen auf Elacestrant</td>
<td></td>
<td>Metastasen, Plasma</td>
<td>1b B ++</td>
</tr>
<tr>
<td>NTRK Genfusion</td>
<td>Larotrectinib, Entrectinib</td>
<td>Fusions- und Splicevarianten</td>
<td>Tumor, bei sekretor. MammaCa</td>
<td>2a B +</td>
</tr>
<tr>
<td>MSI</td>
<td>Pembrolizumab</td>
<td>Mikrosatelliten-Instabilität</td>
<td>Gewebe</td>
<td>2a B +</td>
</tr>
</tbody>
</table>

* idealerweise Paneldiagnostik  # siehe auch Kapitel Pathologie

BRCA 1/2:


**PIK3CA:**


7. Papaxoinis G, Kotoula V, Alexopoulou Z, et al. Significance of PIK3CA Mutations in Patients with Early Breast Cancer Treated with


**AKT1/PTEN:**

1. Turner NC, Oliveira M, Howell S, et al. (2022) Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone

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


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