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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Prognostische und prädiktive Faktoren



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## Prognostische und prädiktive Faktoren

- **Versionen 2002–2019:**  
Costa / Fasching / Fersis / Friedrichs / Gerber / Göhring / Harbeck / Janni /  
Kolberg-Liedtke / Loibl / Lück / Mundhenke / Nitz / Rody / Schaller /  
Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thill /  
Thomssen / Witzel / Wöckel
  
- **Version 2020:**  
Kreipe / Thomssen

### Data bases screened

Pubmed 2008 - 2019, ASCO 2003 – 2019, SABCS 2003 – 2019, Cochrane data base (n.d.)

### Guidelines screened

St.Gallen/Vienna 2019: Burstein HJ, Curigliano G, Loibl S et al.; Members of the St. Gallen International Consensus Panel on the Primary Therapy of Early Breast Cancer 2019. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019 Oct 1;30(10):1541-1557.

ABC4: Cardoso F, Senkus E, Costa A et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)<sup>†</sup>. Ann Oncol. 2018 Aug 1;29(8):1634-1657.


ABC5 Original Slide Set After Voting – pre-publication – Jan. 2020 (personal communication)

NCCN 2019: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. NCCN Evidence Blocks™. Version 3.2019 – September 6, 2019. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast\\_blocks.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf). Download Jan 19, 2020.

ASCO 2016: Harris LN, Ismaila N, McShane LM et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.

Clark GM et al. Prognostic and predictive factors. In: Diseases of the breast, 2nd edition: Seiten 489-514. Harris JR, Lippmann ME, Morrow M, Osborne CK (Hrsg). Lippincott-Raven Publishers, Philadelphia 2000.

Harbeck N, Penault-Llorca F, Cortes J et al. Breast cancer. Nat Rev Dis Primers. 2019 Sep 23;5(1):66.



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## Definition


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

**Prädiktive Faktoren** dienen der Vorhersage eines wahrscheinlichen Therapieeffektes.

### Definition of Prognosis and Prediction

Hayes DF, Bast RC, Desch CE et al.:Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996 Oct 16;88(20):1456-66.

McGuire WL, Clark GM. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med. 1992 Jun 25;326(26):1756-61.



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# “Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

Peto, R., Davies, C., Godwin, J., et al. 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379, 432–444.

Nielsen T, Jensen B, et al High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B, SABCS 2015S1-08



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## Quality Criteria

- **Biological hypothesis**
- **Simple and standardized assessment method, quality assurance (QA) of the test**
- **Prospectively planned statistical evaluation (primary goal)**
- **Validation of clinical significance according to**
  - „Oxford Level of Evidence (LoEOx2001)“ criteria and „Grades of Recommendation (GR)“
  - „Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE2009) and category of tumor marker study (CTS)
- **Clinical relevance for treatment decisions**

<sup>1</sup> Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009  
<sup>2</sup> Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011  
<sup>3</sup> McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.

Hayes DF, Bast RC, Desch CE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.

McGuire WL, Clark GM. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med. 1992 Jun 25;326(26):1756-61.

Jeremy Howick, Iain Chalmers, Paul Glasziou, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.

McShane LM, Altman DG, Sauerbrei W et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072. Available:

McShane LM, Hayes DF (2012) Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 30 (34): 4223–4232.

Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 101 (21): 1446–1452.

Frühes Mammakarzinom (M0) - eBC Prognosefaktoren I			
Faktor	Oxford		
	LoE	GR	AGO
▪ Tumorgröße - pT	1a	A	++
▪ Lymphknotenstatus - pN	1a	A	++
▪ Histologischer Typ (muzinös, tubulär etc.)	2b	B	++
▪ Grading (Elston & Ellis) – G	2a	B	++
▪ Alter	2a	B	++
▪ Histologisch nachgewiesener Einbruch in Lymph- und/oder Blutgefäße (L1, V1)	1b	B	++
▪ pCR nach NACT* bei (Lum B-like, HER2+, TN)	1a	A	++
▪ Erhöhtes Rezidivrisiko bei initial invas.-lob. Typ, cT3/4, N+	2a <sup>a</sup>	B	+/-
▪ Übergewicht (BMI > 30 kg/m <sup>2</sup> )	1b	B	+
▪ Resektionsstatus – R0 / R1	1a	A	+

\* NACT = Neoadjuvante Chemotherapie

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2. Harris LN, Ismaila N, McShane LM et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
3. Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
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Tumor size    LoE 1a    A    AGO++

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.

2. Balic M, Thomssen C, Würtle R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.

Lymphknotenstatus      LoE 1a      A      AGO ++

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Balic M, Thomssen C, Würtle R et al. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2019 Apr;14(2):103-110.

Histological type (mucinous, tubular etc.)      LoE 2b      B      AGO ++

1. Dieci MV, Orvieto E, Dominici M. Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. Oncologist. 2014 Aug;19(8):805-13.
2. Horlings HM, Weigelt B, Anderson EM et al. Genomic profiling of histological special types of breast cancer. Breast Cancer Res Treat. 2013 Nov;142(2):257-69.
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Grading (Elston & Ellis)      LoE 2a      B      AGO ++

1. Thomas JS, Kerr GR, Jack WJ et al. Histological grading of invasive breast carcinoma--a simplification of existing methods in a large conservation series with long-term follow-up. Histopathology. 2009 Dec;55(6):724-31.
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association. J Clin Pathol. 2018 Aug;71(8):680-686.

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#### Age LoE 2a B AGO ++

1. Johnson HM, Irish W, Muzaffar M et al. Quantifying the relationship between age at diagnosis and breast cancer-specific mortality. Breast Cancer Res Treat. 2019 Oct;177(3):713-722
2. Liu YR, Jiang YZ, Yu KD et al. Different patterns in the prognostic value of age for breast cancer-specific mortality depending on hormone receptor status: a SEER population-based analysis. Ann Surg Oncol. 2015 Apr;22(4):1102-10.
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#### Histologically proven lymph and/or blood vessel invasion LoE 1b B AGO ++

1. Ryu YJ, Kang SJ, Cho JS et al. Lymphovascular invasion can be better than pathologic complete response to predict prognosis in breast cancer treated with neoadjuvant chemotherapy. Medicine (Baltimore). 2018 Jul;97(30):e11647

#### pCR after NACT\* in Luminal B-like, HER2 and TN Breast Cancer ; LoE 1aA AGO ++

1. Nekljudova V, Loibl S, von Minckwitz G et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). Contemp Clin Trials. 2018 Aug;71:194-198.
2. Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol. 2015 May;22(5):1441-6.
3. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72.
4. Increased risk of recurrence in invasive-lobular BC, cT3/4, N+ LoE 2a B AGO +/-

5. Huober J, Schneeweiss A, Blohmer J-U, et al. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy – Results of a pooled analysis based on the GBG meta-database, SABCS 2018; P2-08-01
6. Thomas M, Kelly ED, Abraham J et al. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. Semin Oncol. 2019 Apr;46(2):121-132.

Obesity (BMI > 30 kg/m<sup>2</sup>)      LoE 1b B AGO +

1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914.
2. Xia X, Chen W, Li J et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480.
3. Houssami, N., et al., The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014. 21(3): p. 717-30.

Resection status (R0 / R1)      LoE 1a A AGO +

1. Harris LN, Ismaila N, McShane LM et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
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Frühes Mammakarzinom (M0) – eBC Prognosefaktoren II			
Faktor	Oxford		AGO
	LoE	GR	
▪ ER / PgR	2a	B	++
▪ HER2 (IHC, ISH)	2b	B	++
▪ ER / PgR / HER2 / Ki-67 zur Abschätzung des molekularen Typs	2b	B	++
▪ uPA / PAI-1 (Femtelle® ELISA) in N0	1a	A	+
▪ Proliferationsmarker			
▪ Ki-67 vor, während oder nach der Behandlung	1a	B	+

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## ER/PR

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## HER2

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2. Slamon, D.J., Clark, G.M., Wong, S.G. et al. 1987. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235, 177–182.
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### uPA/PAI-1

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2. Jänicke, F., Prechtel, A., Thomssen, C., et al. 2001. Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. *J. Natl. Cancer Inst.* 93, 913–920.
3. Look, M.P., van Putten, W.L.J., Duffy, M.J., et al. 2002. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. *J. Natl. Cancer Inst.* 94, 116–128.
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### Ki-67

1. Cheang, M.C.U., Chia, S.K., Voduc, D. et al.: 2009. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J. Natl. Cancer Inst.* 101, 736–750. doi:10.1093/jnci/djp082.
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#### Post-treatment Ki-67

1. Dowsett M, Smith IE, Ebbs SR, et al: Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer. Journal of the National Cancer Institute 99:167-170, 2007
2. Ellis MJ, Tao Y, Luo J, et al: Outcome Prediction for Estrogen Receptor-Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics. J. Natl. Cancer Inst. 100:1380-1388, 2008
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## Reproducibility

- **ER/PR: concordance central vs local is high (97%; Plan B, SABCs 2014)**
- **Grading: concordance central vs local is 68% (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6% (ASCO /CAP JCO 2013)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)**
- **Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)**

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2013, 31(31):3997-4013.



Faktor	Oxford		
	LoE	GR	AGO
■ Genexpressionsprofile (GEP; Multigene Assays, Gensignaturen)			
■ MammaPrint® (N0-1)	1b	A	+
■ Oncotype DX® (N0-1, HR+, HER2-)	1b	A	+
■ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	+
■ Prosigna® (N0-1, HR+, HER2 -)	2b	B	+
■ Breast Cancer Index <sup>SM</sup> (N0-1, HR+ HER2-)	2b	B	+/-*
■ CTS Clinical Treatment Score**	2b	B	+
■ Disseminierte Tumorzellen (DTC, im Knochenmark)	1a	A	+/-
■ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®) §	1b	A	+/-
■ CTC vor NACT (in Bezug auf OS, DFS, LRFI)	1b	B	+/-
■ Therapieentscheidungen basierend auf CTC-Phänotypen	3a	C	-
■ Cell-free DNA (cfDNA, im Blut, für DFS, PFS, OS)	2b <sup>a</sup>	B	+/-
* Sollte nur bei ausgewählten Patientinnen angewandt werden, wenn alle anderen Kriterien keine Therapieentscheidung zulassen, ** Abschätzung des Spätrezidiv-Risikos; § Validierte klinische Daten nur verfügbar für diesen Assay			

### Genexpressionsprofile (GEP; Multigene Assays, Gensignaturen)

(\*Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making)

### MammaPrint® (N0-1) LoE 1b A AGO+\*

1. Slembrouck L, Darrigues L, Laurent C et al. Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and Blueprint® Kit at University Hospitals Leuven and Curie Institute Paris. Transl Oncol. 2019 Dec;12(12):1557-1565.
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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1D</p> <p>www.ago-online.de FORSCHEN LEHREN HEILEN</p>					
	70 gene signature (MammaPrint®) §	21 gene Recurrence score (Oncotype DX®) §	8 gene signature (Endopredict®) §	PAM 50 (Prosigna®) §	Breast Cancer Index <sup>SM</sup> (BCI) §
<b>Provider</b>	Agendia	Genomic Health	Sividon (Myriad)	NanoString	Biotheranostics
<b>Type of assay</b>	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
<b>Type of tissue</b>	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
<b>Technique</b>	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
<b>Central lab</b>	yes	yes	no	no	yes
<b>Indication and population studied</b>	prognostic N-/+, < 70 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated	Prognostic pT1-3pNo – pN1 ER+ / HER2- Endocrine treated
<b>Risk classes</b>	Low - high	RS (Low – intermediate – high)	Low - high	ROR (Low – inter- mediate – high), molecular types	Low - high
<b>Clinical Validation</b>	yes	yes	yes	yes	Yes
<b>Registration</b>	FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMI)» CE-Mark (fresh tissue and FFPE)	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance	Service Mark (SM)

§ Validated clinical data only available for this assay

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	70 gene signature (MammaPrint®) §	21 gene Recurrence score (Oncotype DX®) §	8 gene signature (Endopredict®) §	PAM 50 (Prosigna®) §	Breast Cancer Index <sup>SM</sup> (BCI)
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown	EAT after 5 yrs
Prospective- retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%)	ABCSG 6 (19%) ABCSG 8 (36%) GEICAM-9906 (45%) ATAC (10%)	MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%)	Ma JCO 2006 Jansen JCO 2007 Jerevall BRCT 2008 Bartlett AnnOnc 2019
Prospective evidence	MINDACT (N0, N1) (5- year DFS, OS)	TAILORx (9-year DFS, OS), N0, low- risk, S<11, intermediate risk RS ≤ 25, high risk RS ≥ 26) PlanB (N0, highrisk/N+) (5-year DFS, OS)	–	–	–
§ Validated clinical data only available for this assay					

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# Prospektiv randomisierte Studien

## (Oncotype DX [TAILORx, PlanB], MammaPrint [MINDACT])

Die Prognose in der Niedrigrisiko-Gruppe ist für beide Tests hervorragend  
(ca. 94% 5-Jahres DFS mit adjuvanter endokriner Therapie)

	TailorX	PlanB	MINDACT
Nachbeobachtungszeit	Median 90 Mo	5-J-DFS	Median 60 Mo
Anteil klinisch definierte Niedrigrisikogruppe	6615 von 9427 (70.2%, adj-onl)	Chemotherapie-Indikation war Einschlusskriterium	3336 von 6693 (49,8%, adj-onl)
Anteil klinisch hohes, genomisch niedriges Risiko (klinisch für Chemotherapie geeignet)	16,7% (RS 0–10)	15,3% (RS 0–11)	23,2% (high clinical / low genomic risk)
Test failure rate	n.r.	2,9%	26% (fresh frozen tissue)
Anteil intermediäre Risikogruppe (gilt nur für Oncotype DX)	69,1% (RS 11–25)	60,4% (RS 12–25)	n.a.
Anteil high risk Risikogruppe (gilt nur für Oncotype DX)	14,3% (RS ≥ 26)	24,3% (RS ≥ 26)	27,0% (high clinical + high genomic risk)
10-Jahres-Follow-Up	---	---	---

### Mammaprint

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<div>  <h2>Adjuvante Endokrine Therapie</h2> <h3>Prädiktive Faktoren für DFS</h3> </div>					
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2020.1D  www.ago-online.de FORSCHEN LEHREN HEILEN		Therapie	Faktor	Oxford	
				LoE	GR AGO
		• Endokrine Therapie	ER/PgR Status [%]	1a	A ++
			IHC Färbeintensität (ER/PgR)	1a	A -
		• Erweiterte endokrine Therapie (EAT)	Breast Cancer Index <sup>SM</sup> (5 J. Let (MA.17) bzw. 5 J. Tam (aTTOM) nach 5 J. Tam)	2b	B +
		• Tamoxifen	CYP2D6 Polymorphismus	2b	B -
		• Ovarieller Ablation oder Funktionsunterdrückung	Menopausenstatus	1c	A ++
		• Aromataseinhibitoren vs. Tamoxifen	Menopausenstatus	1c	A ++
			ER / PgR / HER2 als Einzelmarker	1c	A -
			Invasives lobuläres MammaCa	2b	B +
			Ki-67 hoch	2b	B +/-
			Übergewicht (BMI > 30 kg/m <sup>2</sup> )	2b	B +/-

1. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95
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receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011 Aug 27;378(9793):771-84

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12. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. *Sci Rep*. 2014 Dec 15;4:7480. doi: 10.1038/srep07480.

#### CYP2D6

1. Bezerra LS, Santos-Veloso MAO, Bezerra Junior NDS, et al. Impacts of Cytochrome P450 2D6 (CYP2D6) Genetic Polymorphism in Tamoxifen Therapy for Breast Cancer. *Rev Bras Ginecol Obstet*. 2018 Dec;40(12):794-799.
2. Brooks JD, Comen EA, Reiner AS, et al; WECARE Study collaborative group, Malone KE, Bernstein JL. CYP2D6 phenotype, tamoxifen, and risk of contralateral breast cancer in the WECARE Study. *Breast Cancer Res*. 2018 Dec 10;20(1):149.
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## Adjuvante Chemo- und zielgerichtete Therapie

### Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford		
		LoE	GR	AGO
■ Adjuvante Chemotherapie	uPA / PAI-1 (ELISA, Femtelle®)	1a	A	+/-
	70-Gen-Signature (Mammaprint)	1b	A	+
	21-Gen-Recurrence-Score (Oncotype DX®)	1b	A	+
	EPclin (EndoPredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
■ Anti-HER2-Therapie	HER2 (IHC, ISH)	1a	A	++

#### uPA/PAI-1

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#### 70-Gen-Signatur (Mammaprint®)

1. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. 2016;375(8):717-729.

### OncotypeDX


1. Paik, S., Tang, G., Shak, S., et al. 2006. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J. Clin. Oncol.* 24, 3726–3734.
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### EPclin (EndoPredict®)

1. Sestak I, Martín M, Dubsky P et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019 Jul;176(2):377-386.

### PAM-50 (Prosigna®)

1. Prat A, Galván P, Jimenez B et al. Prediction of Response to Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay. *Clin Cancer Res.* 2016 Feb 1;22(3):560-6.
2. Jensen MB, Lænkholm AV, Nielsen TO et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. *Breast Cancer Res.* 2018 Jul 27;20(1):79.

<div>  <h2>Neoadjuvante Chemotherapie (NACT)</h2> <h3>Prädiktive Faktoren für pCR I</h3> </div>				
Faktor	pCR* Wahrscheinlichkeit	Oxford		
		LoE	GR	AGO
▪ Junges Alter	↑	1a	A	+
▪ cT1 / cT2-Tumoren o. N0 o. G3	↑↑	1a	A	++
▪ Negativer ER- und PgR-Status	↑↑	1a	A	++
▪ Tripelnegatives MammaCa (TNBC)	↑↑	1a	A	++
▪ Positiver HER2-Status	↑↑	1a	A	++
▪ Frühes klinisches Ansprechen	↑	1b	A	+
▪ Invasives lobuläres Karzinom	↓	1a	A	+
▪ Metaplastisches Karzinom	↓↓	4	C	+

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

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384: 164-72.
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#### Lobular cancer

1. Loibl S, Volz C, Mau C, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular

breast carcinoma. *Breast Cancer Res Treat* 2014;144: 153-62.

#### Metaplastic breast cancer

1. McMullen ER, Zoumberos NA, Kleer CG. Metaplastic Breast Carcinoma: Update on Histopathology and Molecular Alterations. *Arch Pathol Lab Med*. 2019 Dec;143(12):1492-1496.
2. Tzanninis IG, Kotteas EA, Ntanasis-Stathopoulos I et al. Management and Outcomes in Metaplastic Breast Cancer. *Clin Breast Cancer*. 2016 Dec;16(6):437-443.
3. Al-Hilli Z, Choong G, Keeney MG, et al. Metaplastic breast cancer has a poor response to neoadjuvant systemic therapy. *Breast Cancer Res Treat*. 2019;176(3):709–716.

<div>  <h2>Neoadjuvante Chemotherapie (NACT)</h2> <h3>Prädiktive Faktoren für pCR II</h3> </div>				
Faktor	pCR* Wahrscheinlichkeit	Oxford		
		LoE	GR	AGO
▪ Genexpressions-Profil (Gensignaturen) (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, Breast Cancer Index <sup>SM</sup> )	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor-infiltrierende Lymphozyten**	↑	2a	B	+
▪ PIK3CA Mutation (für HER2-positives MaCa)	↑	2a	B	+/-
▪ gBRCA Mutation (für Effekt der Chemotherapie)	↑	2b	B	+
▪ gBRCA Mutation (für Platin-Effekt)	↔	2b	B	+/-

\* 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 Invasionsfront (Stroma besteht mit > 50% aus Lymphozyten)

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## TIL

- Denkert, C., Loibl, S., Noske, A., et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. 2010. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.
- Denkert C, von Minckwitz G, Brase JC, et al. Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. J Clin Oncol. 2014 Dec 22. pii: JCO.2014.58.1967.
- Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, et al. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat. 2014 Dec;148(3):467-76
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- Mao Y, Qu Q, Zhang Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PLoS One. 2014 Dec 12;9(12)
- Tung NM, Winer EP. Tumor-Infiltrating Lymphocytes and Response to Platinum in Triple-Negative Breast Cancer. J Clin Oncol. 2015 Jan 5. pii: JCO.2014.59.6031.



## 7. Denkert et al, SABCS 2016

### PIK3CA

1. Loibl S, von Minckwitz G, Schneeweiss A, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. *J Clin Oncol*. 2014 Oct
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### gBRCA bei TNBC

1. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant

chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347.

Metastasiertes Mammakarzinom (mBC) Prognosefaktoren			
Faktor	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ Zirkulierende Tumorzellen (CTC im Blut, Cell Search®) <ul style="list-style-type: none"> <li>■ Prognose</li> <li>■ Frühes Therapieansprechen (3 Wo.)</li> </ul> </li> <li>■ Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen</li> <li>■ Cell-free DNA (cfDNA/ctDNA im Blut)</li> </ul>	1a  1b  1b  2a	A  B  A  A	+  +  -*  +/-
* Studienteilnahme empfohlen			

- Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017 Feb;31:244-259.

## CTC

- Bidard FC, Peeters DJ, Fehm T, et al. 2014. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol. 2014 Apr;15(4):406-14.
- Cristofanilli, M., Budd, G.T., Ellis, M.J., et al. 2004. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N. Engl. J. Med. 351, 781–791. doi:10.1056/NEJMoa040766.
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- Giuliano, M., Giordano, A., Jackson, S., et al. 2011. Circulating tumor cells as prognostic and predictive markers in metastatic breast cancer patients receiving first-line systemic treatment. Breast Cancer Res. 13, R67. doi:10.1186/bcr2907.
- Smerage JB, Barlow WE, Hortobagyi GN, et al. 2014. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014 Nov, 1;32(31):3483-9

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7. Jauch SF, Riethdorf S, Sprick MR, et al. Sustained prognostic impact of circulating tumor cell status and kinetics upon further progression of metastatic breast cancer. *Breast Cancer Res Treat.* 2018 Oct 1. doi: 10.1007/s10549-018-4972-y. [Epub ahead of print] PMID: 30276763

#### Cell-free DNA

1. Cheng J, Holland-Letz T, Wallwiener M, et al. Circulating free DNA integrity and concentration as independent prognostic markers in metastatic breast cancer. *Breast Cancer Res Treat.* 2018 May;169(1):69-82.
2. Yang J, Cheng L, Zhang J, et al. Predictive value of circulating cell-free DNA in the survival of breast cancer patients: A systemic review and meta-analysis. *Medicine (Baltimore).* 2018 Jul 97(28):e11417.
3. Zill OA, Banks KC, Fairclough SR, et al. The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients. *Clin Cancer Res.* 2018 Aug 1;24(15):3528-3538.

<div>  <div> <b>Metastasiertes Mammakarzinoms (mBC)</b>  <b>Prädiktive Faktoren für Ansprechen</b> </div> </div>					
Therapie	Faktor	Oxford			
		LoE	GR	AGO	
▪ Endokrine Therapie	ER/PR (Primärtumor, besser Metastase)	1a	A	++	
	Ansprechen auf vorherige Therapie	2b	B	++	
	autokrine Rezeptormutation (ESR1)	2b	B	+	
▪ Chemotherapie	Ansprechen auf vorherige Therapie	1b	A	++	
▪ Anti-HER2- Therapie	HER2 (Primärtumor, besser Metastase)	1a	A	++	
▪ Immun-Checkpoint-Inhibitoren (Atezolizumab)	PD-L1 IC Positivität <sup>#</sup> beim TNBC (Primärtumor oder Metastase)	1b	B	+	
▪ PARP-Inhibitoren	gBRCA1/2-Mutation	1a	A	++	
▪ Bone modifying drugs	Knochenmetastasen	1a	A	++	
▪ Beliebige Therapie	CTC monitoring	1b	A	++	
* In klinischen Studien					
<sup>#</sup> ≥1% bestimmt auf Immunzellen (IC) mit SP142 (siehe Kapitel „Pathologie“)					

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## Endocrine therapy

ER/PR (Primärtumor, besser Metastase)

Campbell FC, Blamey RW, Elston CW, et al. Quantitative oestradiol receptor values in primary breast cancer and response of metastases to endocrine therapy. *Lancet*. 1981;2(8259):1317–1319.

## Chemotherapy

### Response to prior therapy

Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)<sup>†</sup>. *Ann Oncol*. 2018;29(8):1634–1657.

## Anti-HER2-Therapy

HER2 (primary, better: metastasis)

Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of

efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19(10):2587–2595.

#### Checkpoint-Inhibitoren

Atezolizumab, PDL-1 expression on IC in TNBC (primary or metastasis)

Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018 Nov 29;379(22):2108-2121.

#### PARP-Inhibitoren

gBRCA-mutations

Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. 2017;377(6):523-533.

Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med*. 2018;379(8):753-763.

#### Bone modifying drugs

Aktas B, Kasimir-Bauer S, Lehmann N, et al.: Validity of bone marker measurements for monitoring response to bisphosphonate therapy with zoledronic acid in metastatic breast cancer. *Oncol Rep*. 2013;30(1):441–447.


Loftus LS, Edwards-Bennett S, Sokol GH. Systemic therapy for bone metastases. *Cancer Control*. 2012;19(2):145–153.

Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. *J Natl Cancer Inst*. 2012;104(14):1059–1067.

#### CTC monitoring (any therapy)

Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol. 2014;15:406-14.

Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014;32(31):3483-9.

<div>  <b>Mutationsdiagnostik bei mBC:</b>  <b>„Precision medicine“ für zielgerichtete Therapien</b> </div>						
Alteriertes Gen	Therapierelevanz	Genregion	Ausgangsmaterial	Oxford		AGO
				LOE	GR	
BRCA1, BRCA2	PARP Inhibitor	Alle Exons	Keimbahn: Blutzellen Somatisch: Gewebe	1b 2b	A B	++ +/-
PIK3CA	Alpelisib	Exon 7,9 und 20	Primärtumor, Metastasen, Plasma	1b	A	+
HER2-Mutation (unabh. vom HER2-Status)	Neratinib, Lapatinib	Kinase- und extrazelluläre Domänen; S310, L755, V777, Y772_A775dup	Primärtumor, Metastasen, Plasma	4	C	+/-
ESR1	Resistenz gegenüber AI	Exon 4,7 und 8	Metastasen, Plasma	2b	B	+/-
NTRK Genfusion	Larotrectinib, Entrectinib	Fusions- und Spleißvarianten	Tumorgewebe, ins. Sekretor. MammaCa	2a	B	+
MSI	Pembrolizumab	Mikrosatelliten- Instabilität	Gewebe	2a	B	+

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#### BRCA 1/2:

1. Robson M, Im SA, Senkus E et al. (2017) Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 377:523-533. doi: 10.1056/NEJMoa1706450
2. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. (2015) Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50. doi: 10.1200/JCO.2014.56.2728.

#### PIK3CA:

1. André F, Ciruelos E, Rubovszky G, Campone M et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 380:1929-1940. doi: 10.1056/NEJMoa1813904

#### HER2-Mutation:

1. Hyman DM, Piha-Paul SA, Won H, et al. (2018) HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature 554:189-194. doi: 10.1038/nature25475.



2. Ma CX, Bose R, Gao F, et al. (2017) Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. Clin Cancer Res. 23:5687-5695. doi: 10.1158/1078-0432.CCR-17-0900.

#### ESR1:


1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. Cancer 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
3. Fribbens C, O'Leary B, Kilburn L et al. (2016) Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol. 34:2961-8. doi: 10.1200/JCO.2016.67.3061

#### NTRK:

1. Cocco E, Scaltriti M, Drilon A (2018) NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 15(:731-747. doi: 10.1038/s41571-018-0113-0.

#### MSI:

FDA Zulassung entitätsübergreifend (23.5.17): Full prescribing information for pembrolizumab is available at:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/125514s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf)



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# Therapierelevante Mutationsdiagnostik beim Mammakarzinom („actionable“)

Therapie*	Faktor	Oxford		
		LoE	GR	AGO
Aus Studien bei anderen Karzinomen („tumoragnostische Testung“)				
■ Companion Diagnostics Mutations bei Therapien für andere Karzinome (z.B. BRAF, FGFR1, ...)	Effektivität verschiedener Medikamente	4	D	+/-**
■ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, lokale „hand selected„ Panels)	Effektivität verschiedener Medikamente, Prognose	3a	C	+/-**

\* Bestimmungsmethode somatischer Veränderungen nicht bewertet. Prinzipiell möglich aus Tumorfrischmaterial, Paraffin-Gewebe, zirkulierenden Nukleinsäuren

\*\* Teilnahme an Studien oder strukturierten Programmen empfohlen

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