Guidelines Breast
Version 2021.1D

FORSCHEN
LEHREN
HEILEN

Prognostische und prädiktive Faktoren

Data bases screened

Pubmed 2008 - 2012, ASCO 2003 – 2012, SABCS 2003 – 2012, Cochrane data base (n.d.)

Guidelines screened

1. 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.
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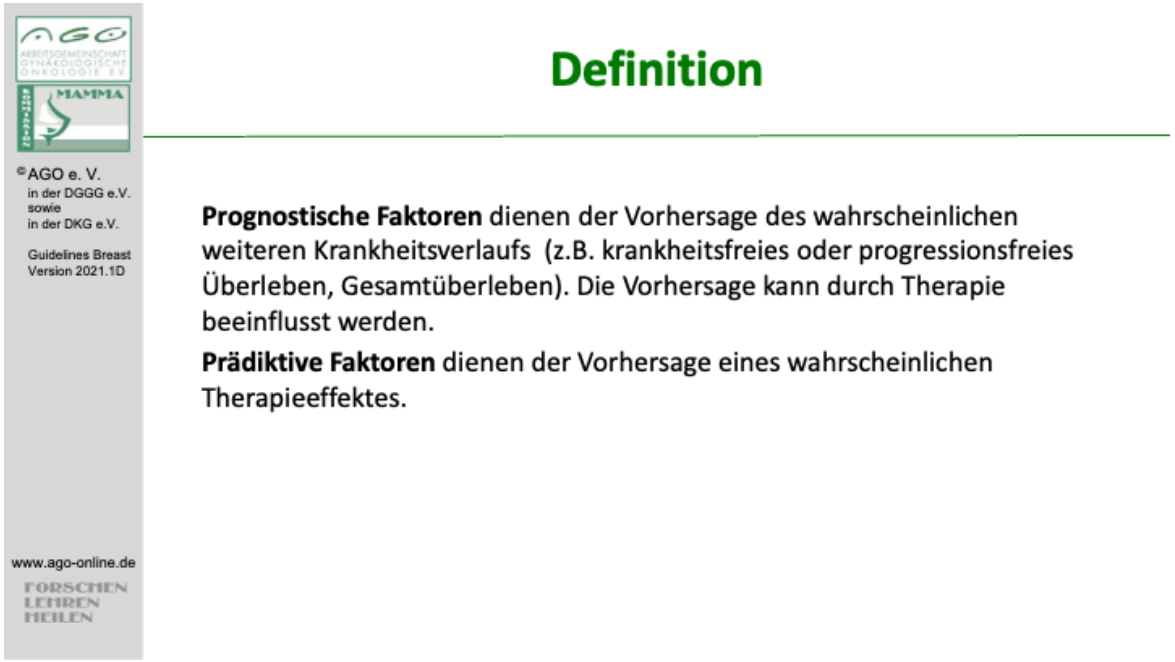

Definition of Prognosis and Prediction

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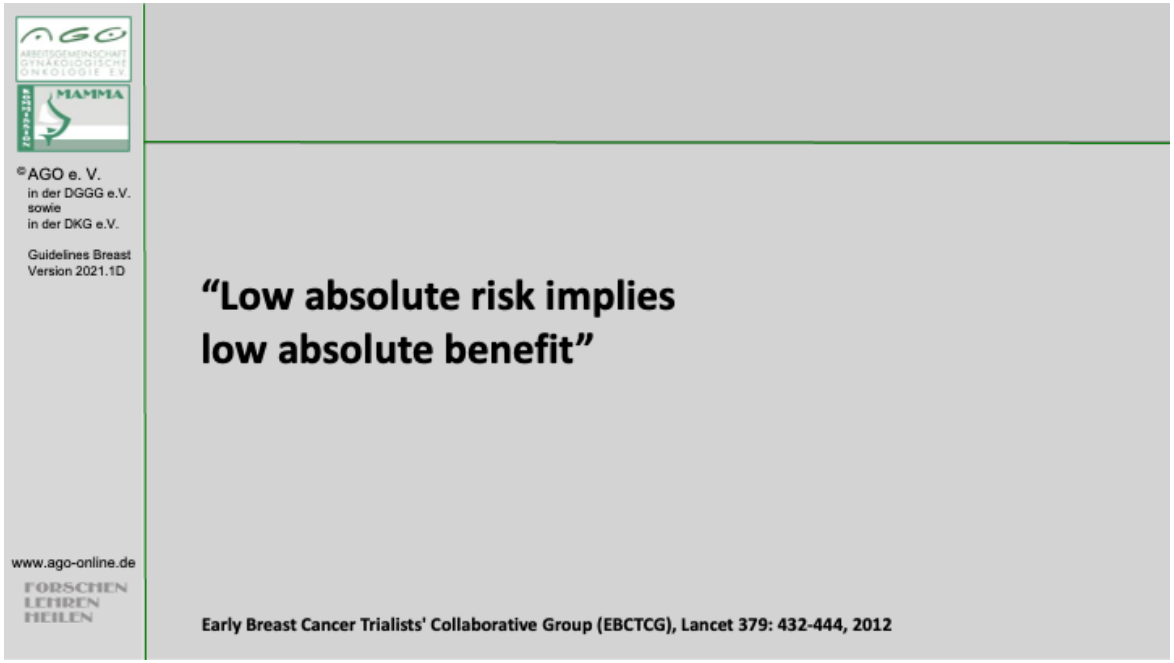

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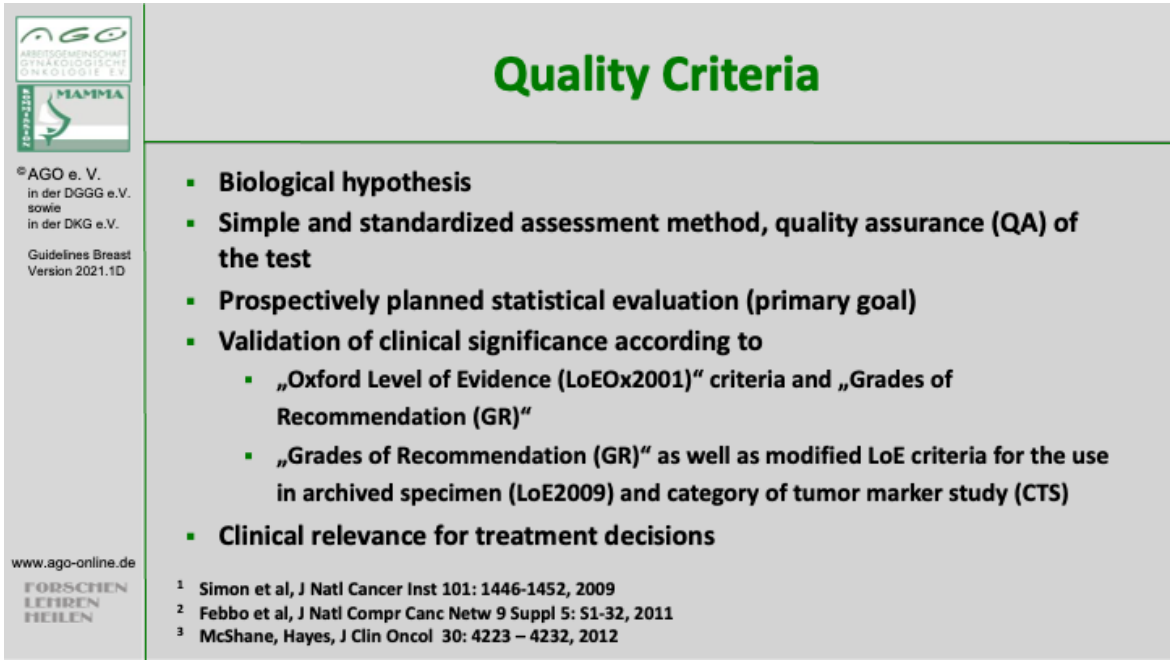

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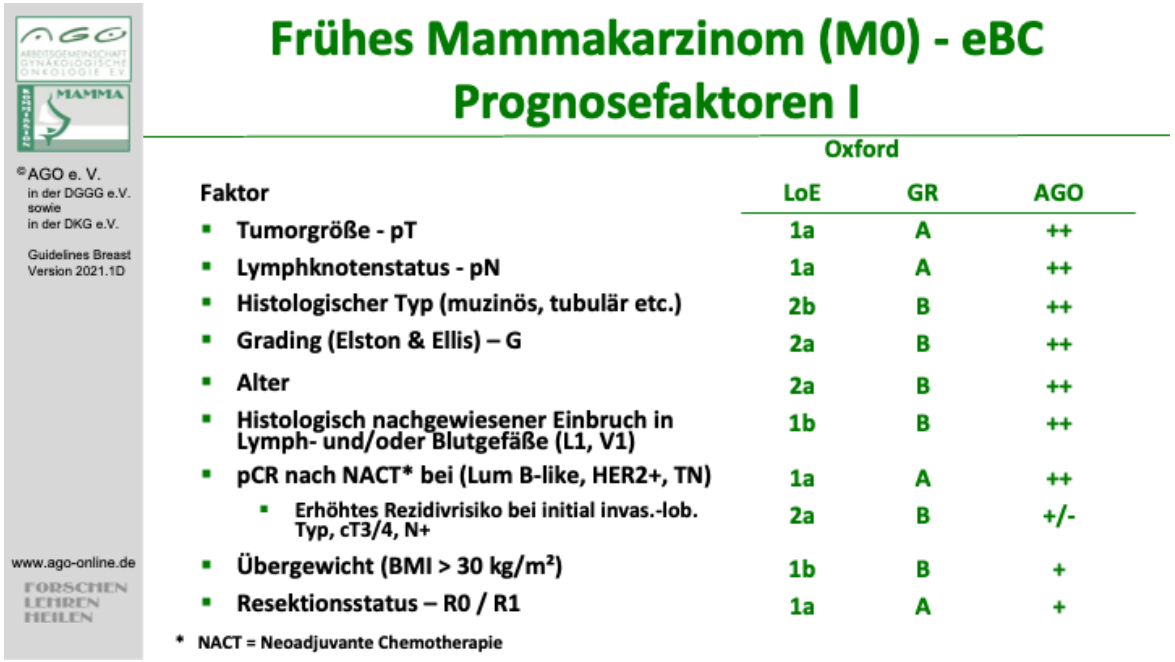

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Tumor size

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.
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Lymph node status

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Histological type (mucinous, tubular etc.)

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Tumor grade (Elston & Ellis)

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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Age

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Histologically proven lymph and/or blood vessel invasion

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

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

1. 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
2. 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^2)

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treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014. 21(3): p. 717-30.

Resection status (R0 / R1)

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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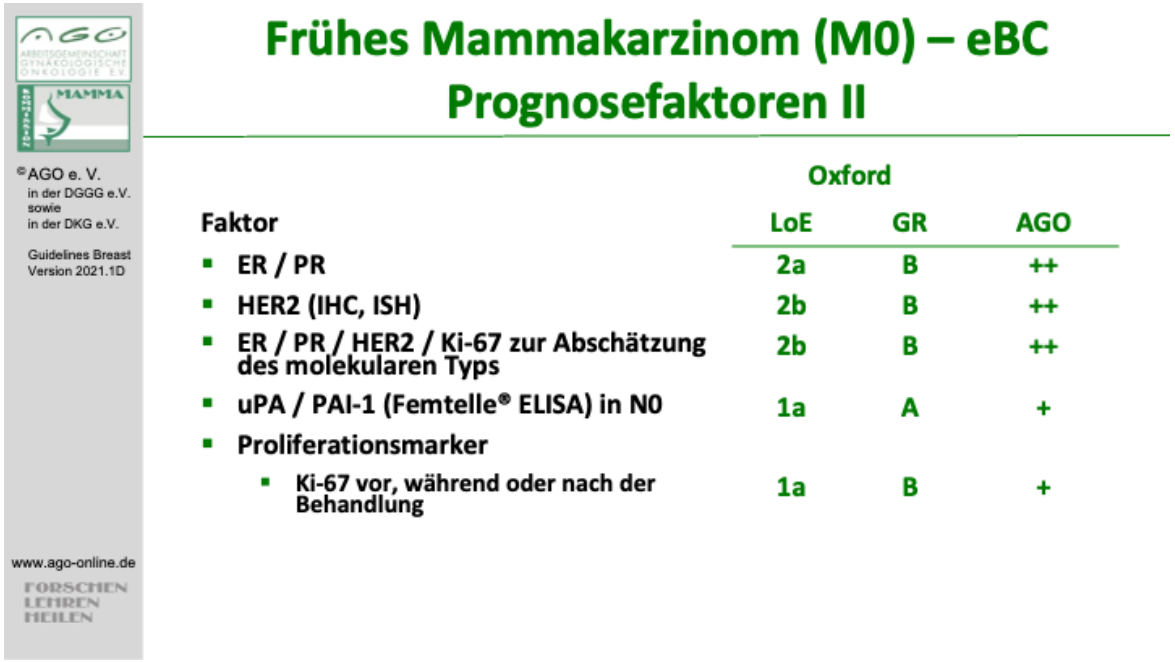

Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren II

Faktor	Oxford LoE	Oxford GR	AGO
▪ ER / PR	2a	B	++
▪ HER2 (IHC, ISH)	2b	B	++
▪ ER / PR / 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	+

ER/PR

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HER2

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uPA/PAI-1

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<u>Ki-67</u>

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<u>Post-treatment Ki-67</u>

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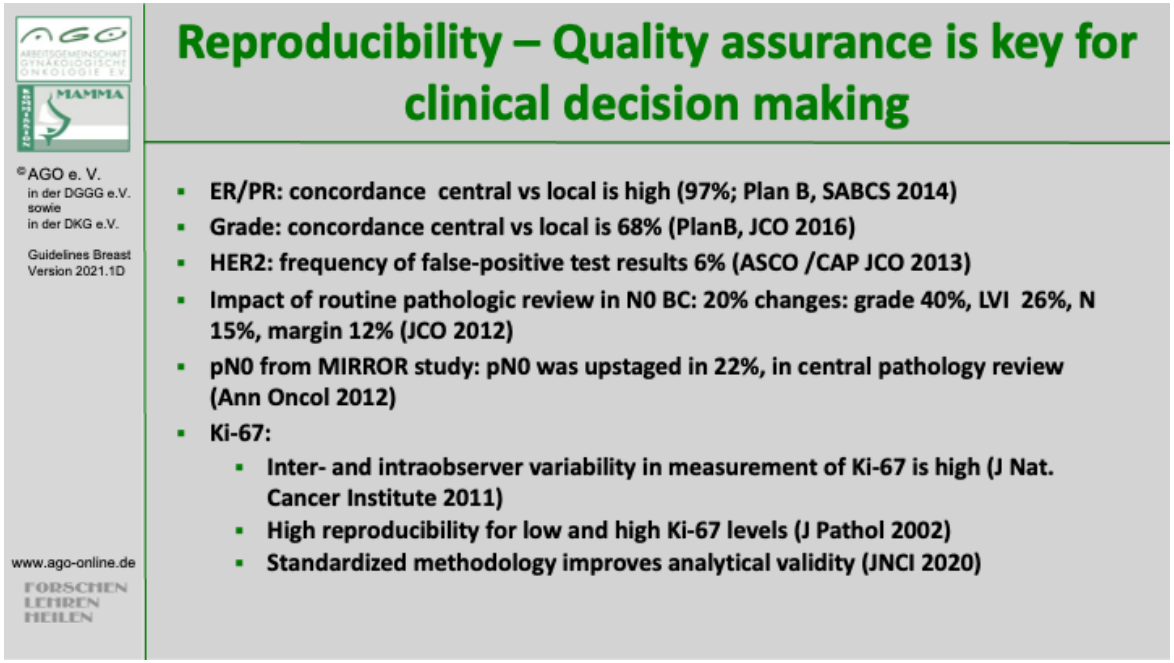

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Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)

(*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®

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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Oncotype DX®

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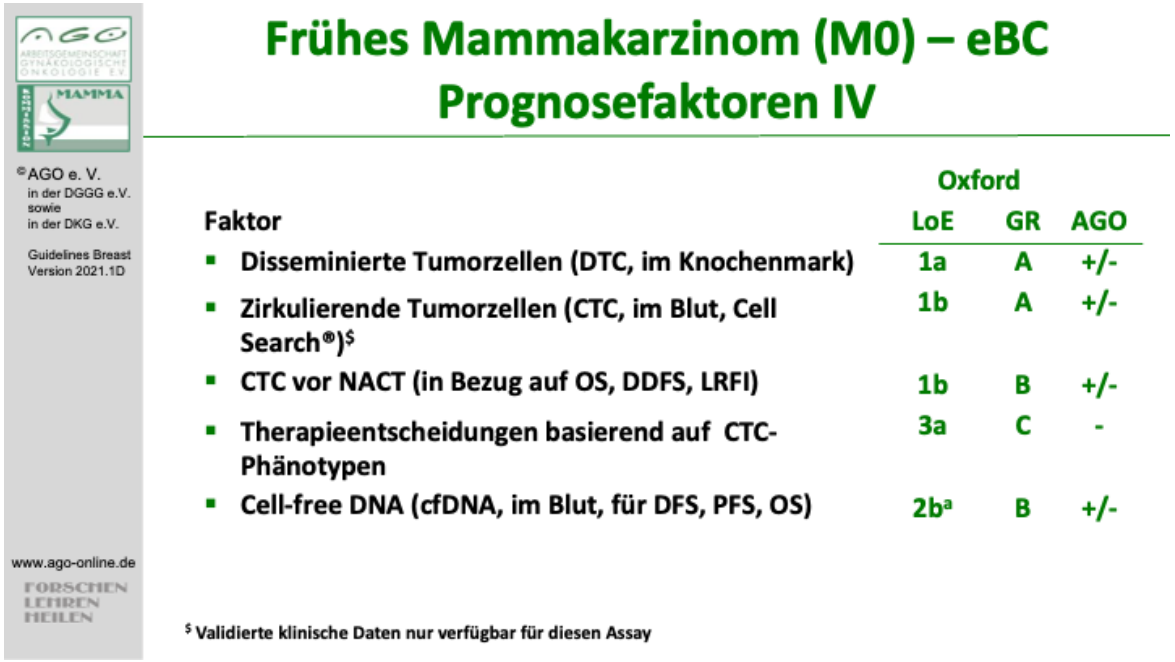

Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren IV

Faktor	Oxford LoE	Oxford GR	AGO
▪ Disseminierte Tumorzellen (DTC, im Knochenmark)	1a	A	+/-
▪ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®)$	1b	A	+/-
▪ CTC vor NACT (in Bezug auf OS, DDFS, LRFI)	1b	B	+/-
▪ Therapieentscheidungen basierend auf CTC-Phänotypen	3a	C	-
▪ Cell-free DNA (cfDNA, im Blut, für DFS, PFS, OS)	2b[a]	B	+/-

$ Validierte klinische Daten nur verfügbar für diesen Assay

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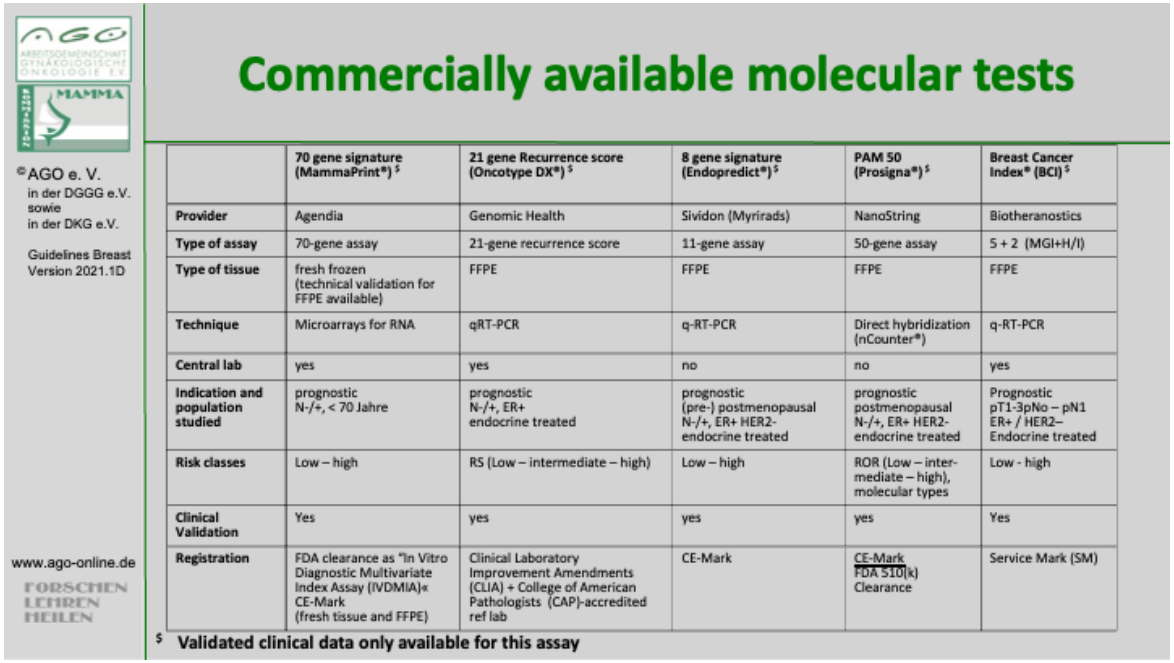

Commercially available molecular tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI) $
Provider	Agendia	Genomic Health	Sividon (Myrirads)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
Central lab	yes	yes	no	no	yes
Indication and population studied	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
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – inter-mediate – high), molecular types	Low - high
Clinical Validation	Yes	yes	yes	yes	Yes
Registration	FDA clearance as "In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« 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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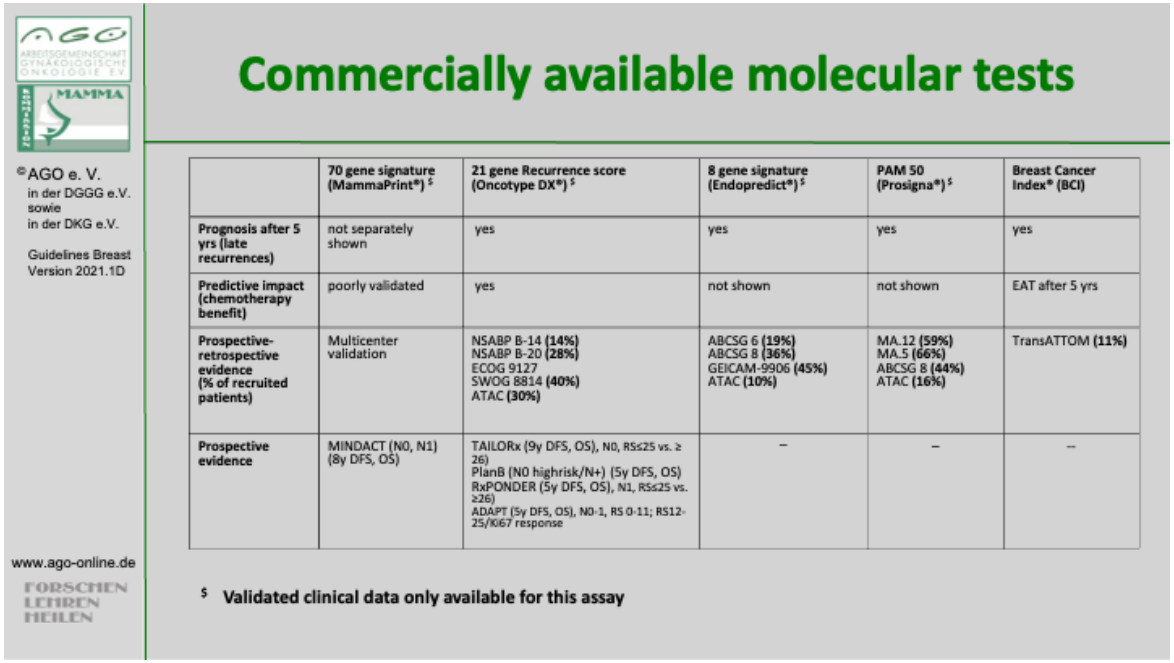

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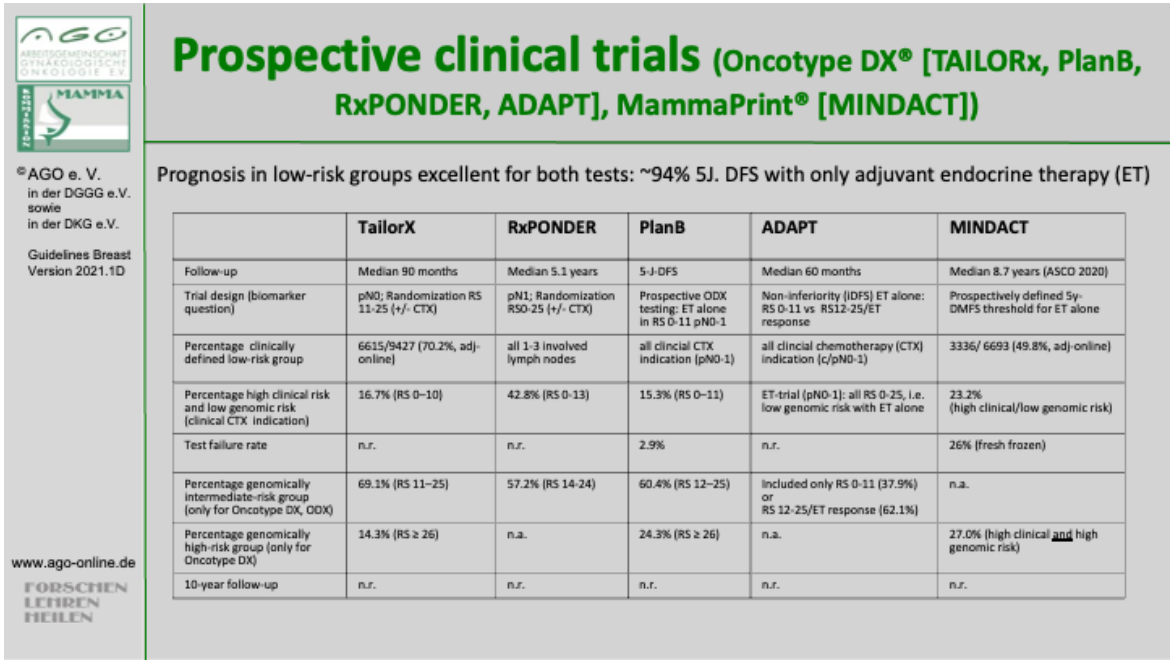

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	Median 90 months	Median 5.1 years	5-J-DFS	Median 60 months	Median 8.7 years (ASCO 2020)
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (IDFS) ET alone: RS 0-11 vs RS12-25/ET response	Prospectively defined 5y-DMFS threshold for ET alone
Percentage clinically defined low-risk group	6615/9427 (70.2%, adj-online)	all 1-3 involved lymph nodes	all clincial CTX indication (pN0-1)	all clincial chemotherapy (CTX) indication (c/pN0-1)	3336/ 6693 (49.8%, adj-online)
Percentage high clinical risk and low genomic risk (clinical CTX indication)	16.7% (RS 0–10)	42.8% (RS 0-13)	15.3% (RS 0–11)	ET-trial (pN0-1): all RS 0-25, i.e. low genomic risk with ET alone	23.2% (high clinical/low genomic risk)
Test failure rate	n.r.	n.r.	2.9%	n.r.	26% (fresh frozen)
Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)	69.1% (RS 11–25)	57.2% (RS 14-24)	60.4% (RS 12–25)	included only RS 0-11 (37.9%) or RS 12-25/ET response (62.1%)	n.a.
Percentage genomically high-risk group (only for Oncotype DX)	14.3% (RS ≥ 26)	n.a.	24.3% (RS ≥ 26)	n.a.	27.0% (high clinical and high genomic risk)
10-year follow-up	n.r.	n.r.	n.r.	n.r.	n.r.

Mammaprint

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Several tests

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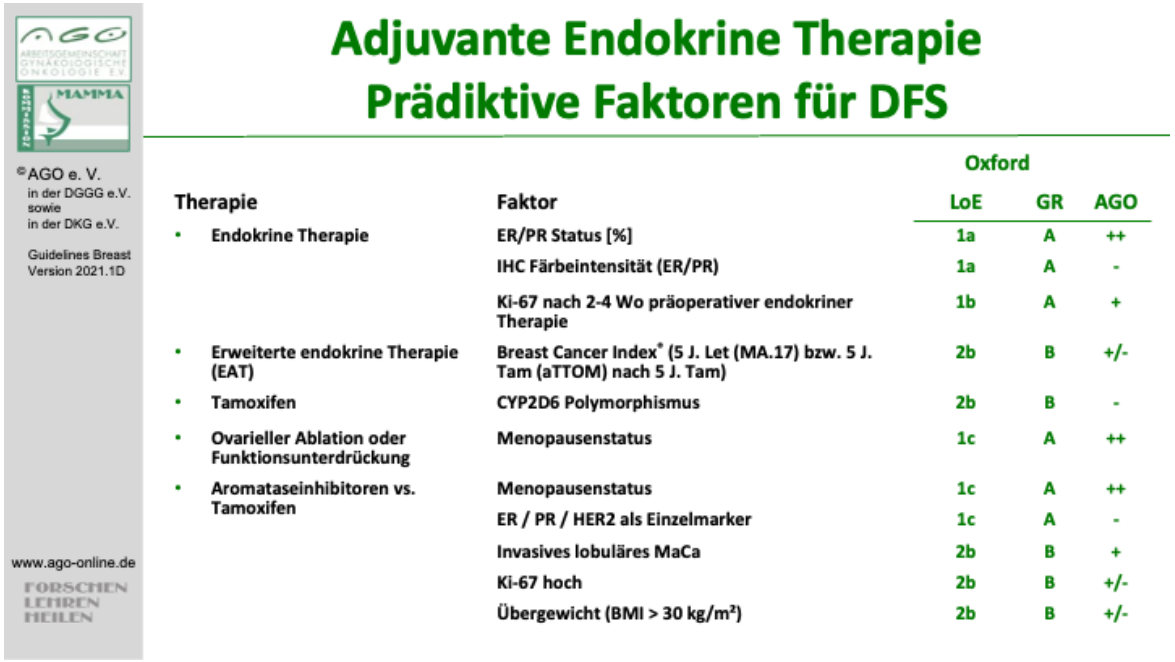

Adjuvante Endokrine Therapie
Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford LoE	Oxford GR	Oxford AGO
• Endokrine Therapie	ER/PR Status [%]	1a	A	++
	IHC Färbeintensität (ER/PR)	1a	A	-
	Ki-67 nach 2-4 Wo präoperativer endokriner Therapie	1b	A	+
• Erweiterte endokrine Therapie (EAT)	Breast Cancer Index® (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 / PR / HER2 als Einzelmarker	1c	A	-
	Invasives lobuläres MaCa	2b	B	+
	Ki-67 hoch	2b	B	+/-
	Übergewicht (BMI > 30 kg/m²)	2b	B	+/-

General publications

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3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone 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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5. Thürliman B et al: Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat. 2009; 113:137-44
6. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017 Apr 1;35(10):1061-1069.
7. Dowsett M, Ellis MJ, Dixon JM, et al. Evidence-based guidelines for managing patients with primary ER+ HER2- breast cancer deferred from surgery due to the COVID-19 pandemic. Breast Cancer. 2020 Jun 8;6:21.
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EAT

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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
2. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab. 2011 May;96(5):1336-43.

Body Mass Index

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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. 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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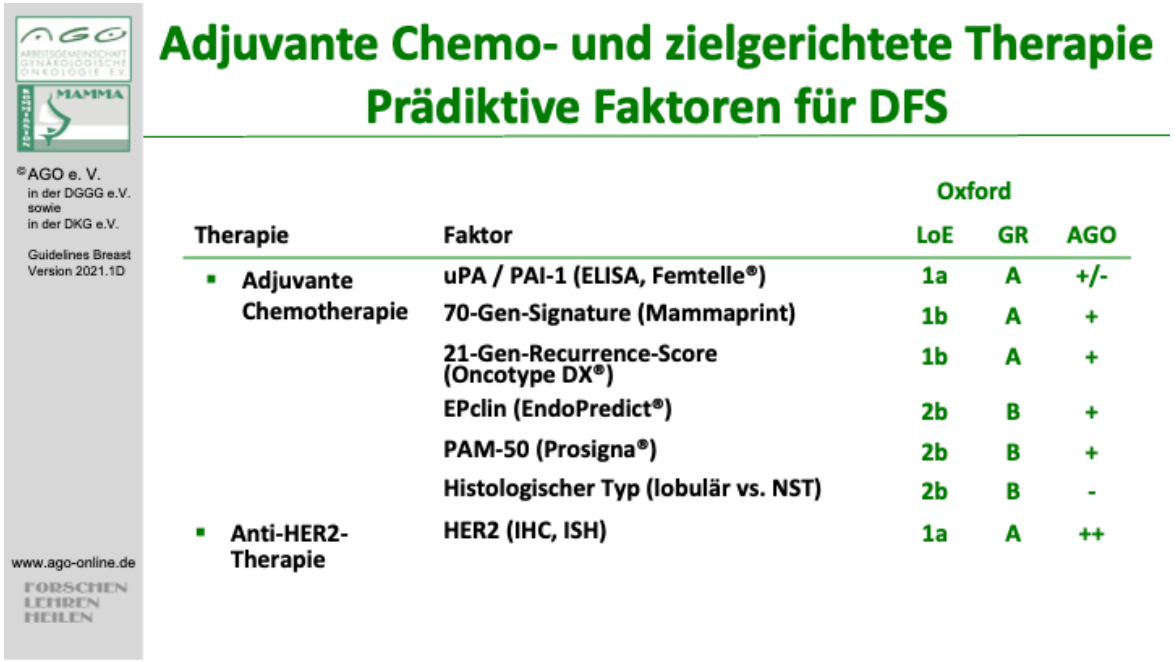

Adjuvante Chemo- und zielgerichtete Therapie
Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford LoE	Oxford 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	+
	Histologischer Typ (lobulär vs. NST)	2b	B	-
▪ Anti-HER2-Therapie	HER2 (IHC, ISH)	1a	A	++

uPA/PAI-1

1. Harbeck N, Kates RE, Look MP, et al. Enhanced benefit from adjuvant systemic chemotherapy in breast cancer patients classified high-risk according to uPA and PAI-1 (n=3,424). Cancer Res 62 (16): 4617-22, 2002.
2. Harbeck N, Schmitt M, Meisner C, et al. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. Eur J Cancer. 2013 May;49(8):1825-35.
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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.
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

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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.
2. Sparano JA, Gray RJ, Makower DF, et al. Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial [published online ahead of print, 2019 Sep 30]. *JAMA Oncol*. 2019;e194794.
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4. Harbeck N, Gluz O, Kuemmel S, et al. Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (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®)

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®)

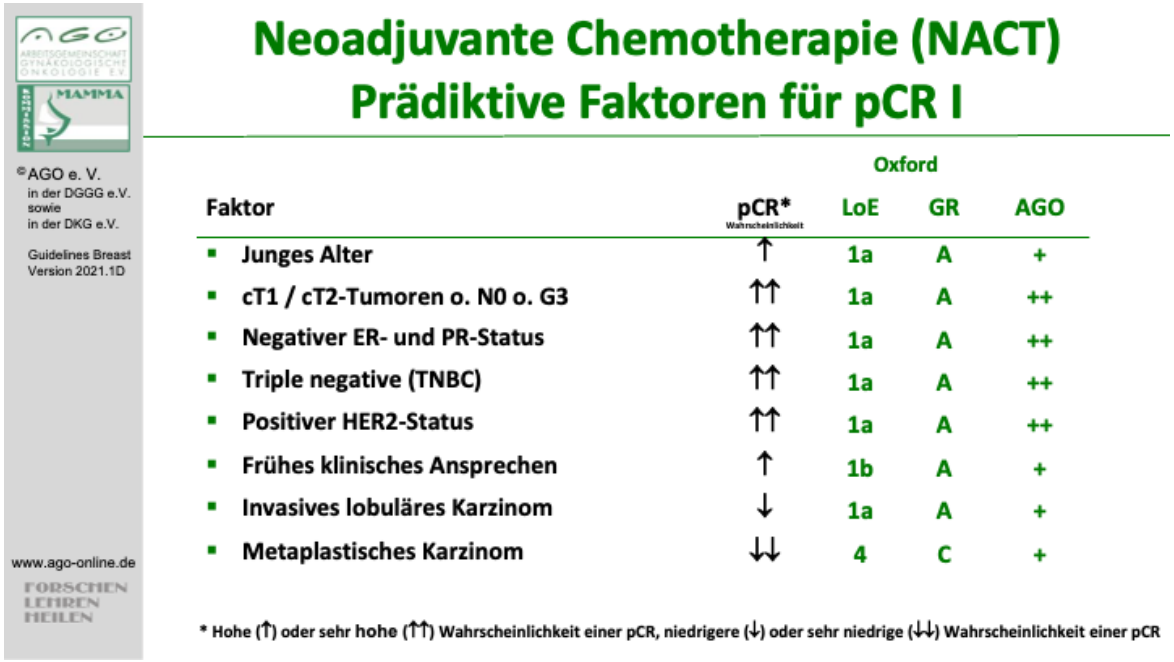
1. Prat A, Galván P, Jimenez B et al. Prediction of Response to Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay. Clin Cancer Res. 2016 Feb 1;22(3):560-6.
2. Jensen MB, Lænkholm AV, Nielsen TO et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based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

Histological type:

1. De Nonneville A, Jauffret C, Goncalves A. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit Breast Cancer Res Treat. 2019 Jun;175(2):379-387.
2. Fu R, Yang J, Wang H et al.: A nomogram for determining the disease-specific survival in invasive lobular carcinoma of the breast: A population study. Medicine (Baltimore). 2020 Oct 23;99(43):e22807.

Anti-HER2 therapy

see evidence in chapter “Chemotherapy and targeted therapy”



Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR I

Faktor	pCR* Wahrscheinlichkeit	Oxford LoE	Oxford GR	AGO
Junges Alter	↑	1a	A	+
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

General evidence

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.
2. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 2013;24: 2978-84.
3. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res Treat 2017.
4. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366: 299-309.
5. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30: 1796-804.

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.

Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR II

Faktor	pCR* Wahrscheinlichkeit	Oxford LoE	Oxford GR	Oxford AGO
▪ Genexpressions-Profile (Gensignaturen) (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	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)

TIL

1.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.

2.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.

3.Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, et al. The prognostic value of tumor-infiltrating

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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3.Pogue-Geile KL, Song N, Jeong JH, et al: Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial. Clin Oncol. 2015 Jan 5. pii: JCO.2014.56.2439

4.Sueta A, Yamamoto Y, Yamamoto-Ibusuki M, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PLoS One. 2014 Dec 26;9(12):e116054.

5.Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016 Aug;27(8):1519-25.

6.Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2019 Jan 9. doi: 10.1093/annonc/mdy536. [Epub ahead of print]

7.Fan H, Li C, Xiang Q, et al. PIK3CA mutations and their response to neoadjuvant treatment in early breast cancer: A systematic review and meta-analysis. Thorac Cancer. 2018 May;9(5):571-579.

8.Zardavas D, Te Marvelde L, Milne RL, et al. Tumor PIK3CA Genotype and Prognosis in Early-Stage Breast Cancer: A Pooled Analysis of Individual Patient Data. J Clin Oncol. 2018 Apr 1;36(10):981-990.

<u>gBRCA bei TNBC</u>

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	Oxford GR	AGO
▪ Zirkulierende Tumorzellen (CTC im Blut, Cell Search®)			
▪ Prognose	1a	A	+
▪ Frühes Therapieansprechen (3 Wo.)	1b	B	+
▪ Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen	1b	A	-*
▪ Cell-free DNA (cfDNA/ctDNA im Blut)	2a	A	+/-

* Studienteilnahme empfohlen

1. 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

1. 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.
2. Cristofanilli, M., Budd, G.T., Ellis, M.J., et al. 2004. Circulating tumor cells, disease progression,

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.

Metastasiertes Mammakarzinoms (mBC)
Prädiktive Faktoren für Ansprechen

Therapie	Faktor	Oxford LoE	Oxford GR	AGO
▪ Endokrine Therapie	ER/PR (Primärtumor, besser Metastase)	1a	A	++
	Ansprechen auf vorherige Therapie	2b	B	++
	autokrine Rezeptormutation (ESR1)	2b	B	+
▪ Alpelisib	PIK3CA Mutation (Primärtumor, Metastase, Plasma)	1b	A	++
▪ Chemotherapie	Ansprechen auf vorherige Therapie	1b	A	++
▪ Anti-HER2- Therapie	HER2 (Primärtumor, besser Metastase)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitoren	gBRCA1/2-Mutation	1a	A	++
▪ Bone modifying drugs	Knochenmetastasen	1a	A	++
▪ Beliebige Therapie	CTC monitoring	1b	A	+*

* In klinischen Studien; # Siehe auch Kapitel „Pathologie“

+Endocrine therapy

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.

Endocrine therapy - 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

Anti-HER2-Therapy

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-Inhibitors

1.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.

2.Cortes J, Cescon DW, Rugo HS et al.: KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828.

PARP-Inhibitors

1.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.

2.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

1.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.

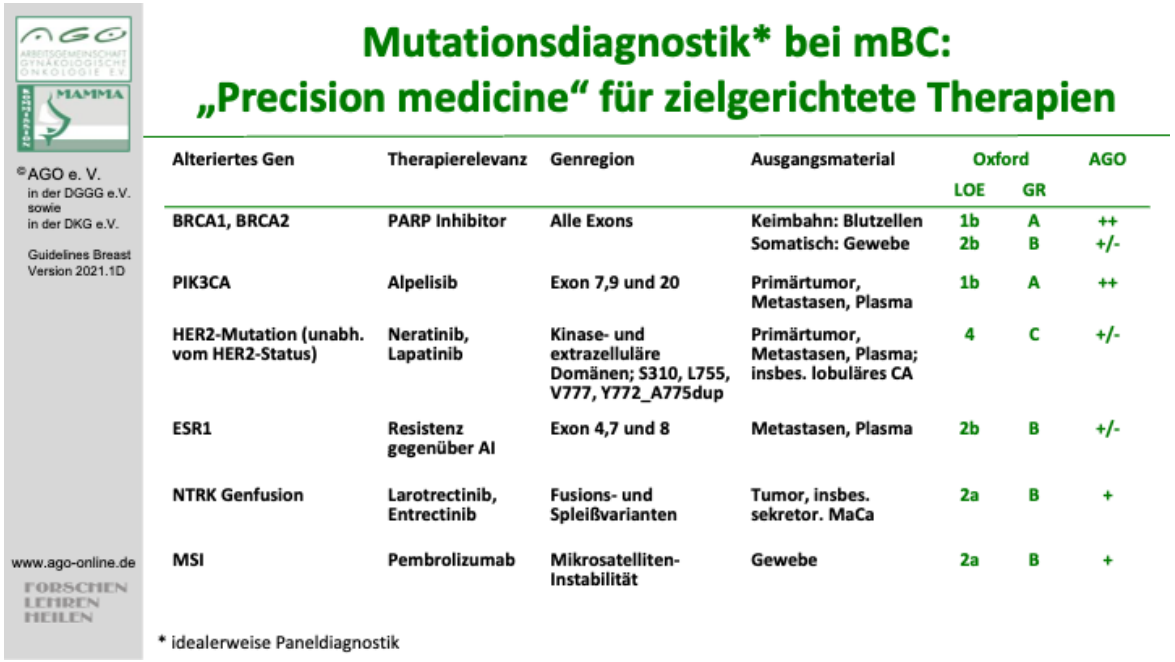
2.Loftus LS, Edwards-Bennett S, Sokol GH. Systemic therapy for bone metastases. *Cancer Control*. 2012;19(2):145–153.

3.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)

1.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.

2.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.



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

Alteriertes Gen	Therapierelevanz	Genregion	Ausgangsmaterial	Oxford		AGO
				LOE	GR	
BRCA1, BRCA2	PARP Inhibitor	Alle Exons	Keimbahn: Blutzellen	1b	A	++
			Somatisch: Gewebe	2b	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; insbes. lobuläres CA	4	C	+/-
ESR1	Resistenz gegenüber AI	Exon 4,7 und 8	Metastasen, Plasma	2b	B	+/-
NTRK Genfusion	Larotrectinib, Entrectinib	Fusions- und Spleißvarianten	Tumor, insbes. sekretor. MaCa	2a	B	+
MSI	Pembrolizumab	Mikrosatelliten-Instabilität	Gewebe	2a	B	+

* idealerweise Paneldiagnostik

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:

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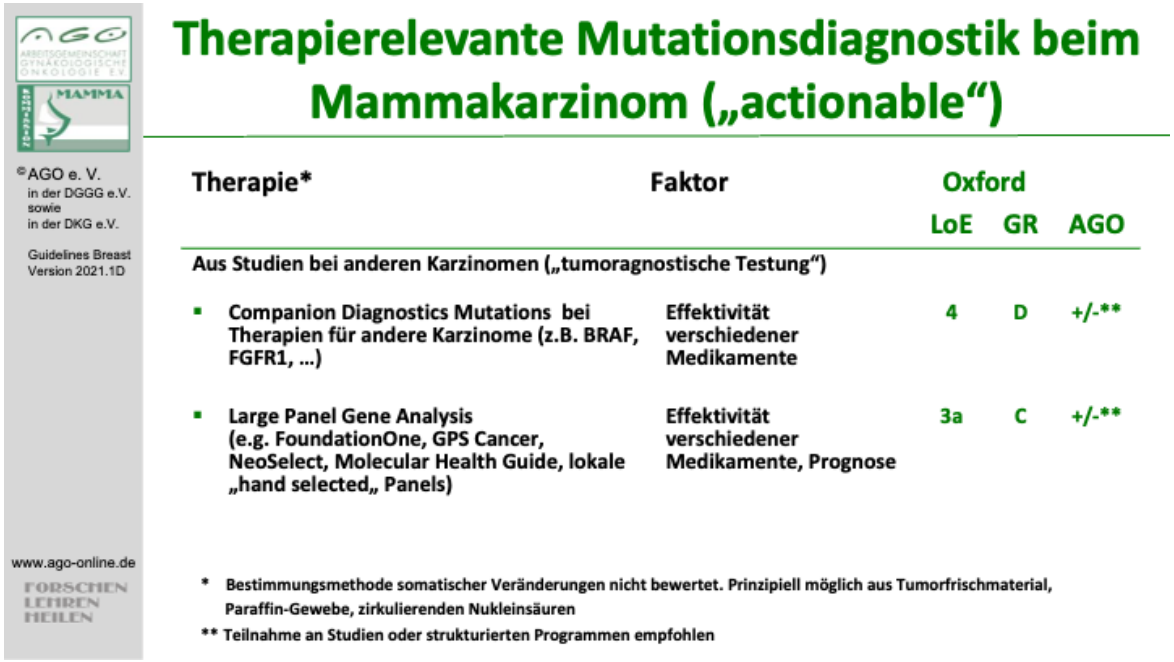
MSI:

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



Therapierelevante Mutationsdiagnostik beim Mammakarzinom („actionable“)

Therapie*	Faktor	Oxford LoE	Oxford 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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