Guidelines Breast
Version 2024.1D

FORSCHEN
LEHREN
HEILEN

Prognostische und prädiktive Faktoren

Prognostische und prädiktive Faktoren

- **Versionen 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

Pubmed 2008 - 2023, ASCO 2017-2023, SABCS 2003 – 2023, ESMO 2023, Cochrane data base (n.d.)

Definition

Prognostische Faktoren

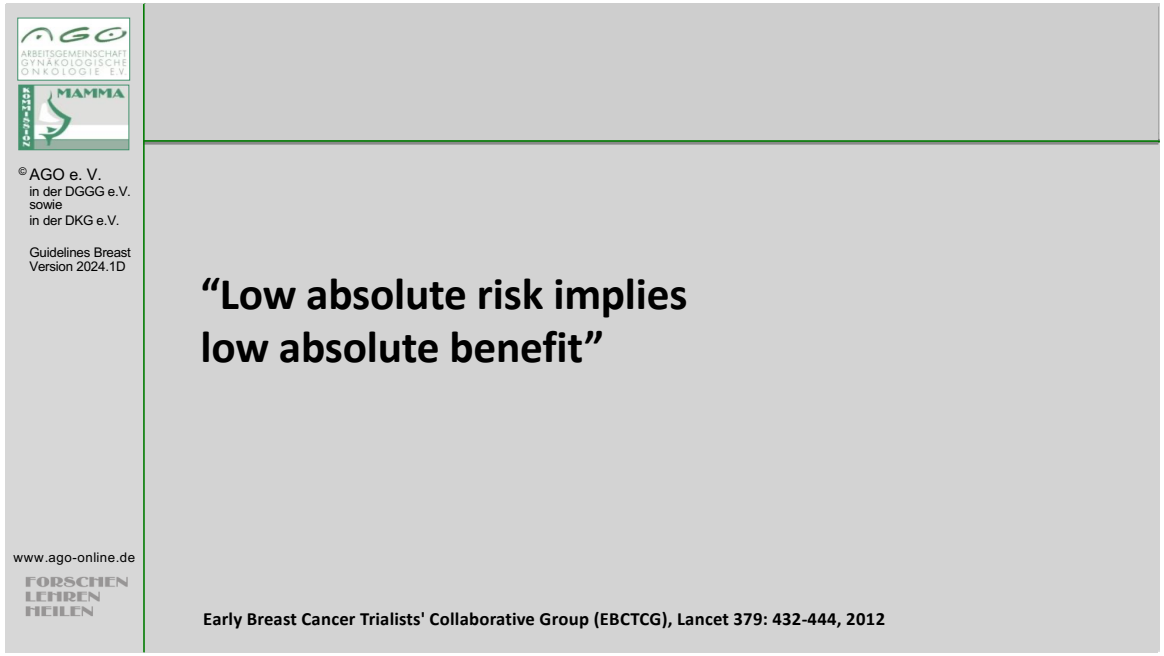
Dienen der Vorhersage des wahrscheinlichen weiteren Krankheitsverlaufs
(z. B. krankheitsfreies oder progressionsfreies Überleben, Gesamtüberleben).
Die Vorhersage kann durch die Therapie beeinflusst werden.

Prädiktive Faktoren

Dienen der Vorhersage eines wahrscheinlichen Therapieeffektes.

<u>Definition of Prognosis and Prediction</u>

1. 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.
2. 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.



1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012
2. 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.
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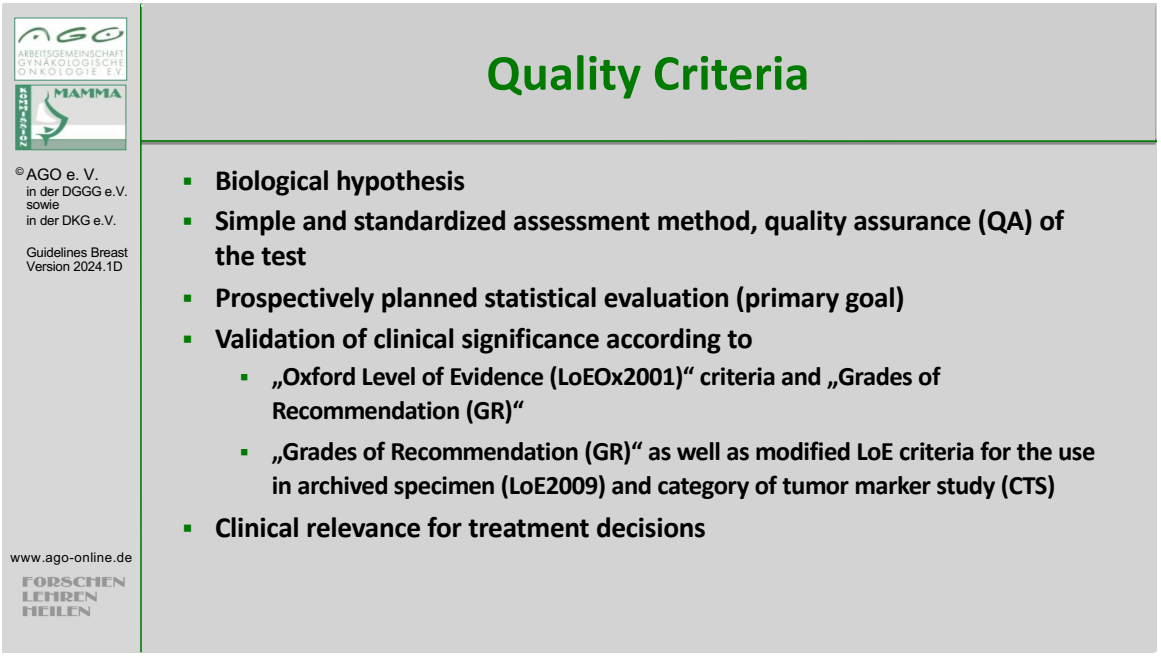

1. Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
2. Hayes DF, Bast RC, Desch CE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.
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4. McShane LM, Altman DG, Sauerbrei W et al. (2005) Reporting recommendations for tumor marker prognostic studies. J. Clin. Oncol. 23 (36): 9067–9072.
5. 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.
6. 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.

Prognostische Faktoren für das Auftreten eines ipsilateralen Rezidivs nach DCIS I

	LoE
▪ **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“

1. Visser LL, Elshof LE, Schaapveld M et al. Clinicopathological Risk Factors for an Invasive Breast Cancer recurrence after Ductal Carcinoma In Situ-A Nested Case-Control Study. Clin Cancer Res. 2018 Aug 1;24(15):3593-3601.
2. Rakovitch E, Gray R, Baehner FL et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat. 2018 Jun;169(2):359-369
3. Cutuli B: Ductal carcinoma in situ in 2019: Diagnosis, treatment, prognosis. Presse Med. 2019 Oct;48(10):1112-1122
4. Badve SS, Gökmen-Polar: Ductal carcinoma in situ of breast: update 2019. Pathology. 2019 Oct;51(6):563-569.
5. Van Bockstal MR, Agahozo MC, Koppert LB: A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2020 Mar 1;146(5):1189-1197
6. Solin LJ: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33
7. Giannakeas V, Sopik V, Narod SA. Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer. JAMA Netw Open. 2020 Sep; 3(9): e2017124. Published online 2020 Sep 16. doi: 10.1001/jamanetworkopen.2020.17124
8. Groen EJ, Hudecek J, Mulder L, et al. Prognostic value of histopathological DCIS features in a large-scale international interrater reliability study. Breast Cancer Res Treat. 2020; 183(3): 759–770. Published online 2020 Jul 30. doi: 10.1007/s10549-020-05816-x

Diagnostische Methode

1. Park HS, Park S, Cho J, et al. Risk predictors of underestimation and the need for sentinel node biopsy in patients diagnosed with ductal carcinoma in situ by preoperative needle biopsy. J Surg Oncol. 2013 Mar;107(4):388-92. doi: 10.1002/jso.23273. Epub 2012 Sep 24.
2. Schulz S, Sinn P, Golatta M, et al. Prediction of underestimated invasiveness in patients with ductal carcinoma in situ of the breast on percutaneous biopsy as rationale for recommending concurrent sentinel lymph node biopsy. Breast. 2013 Aug;22(4):537-42.
3. Elshof LE, Schmidt MK, Rutgers EJ, et al. Cause-specific Mortality in a Population-based Cohort of 9799 Women Treated for Ductal Carcinoma In Situ. Ann Surg. 2017 Apr 3. doi: 10.1097/SLA.0000000000002239. [Epub ahead of print]
4. Punglia RS, Jiang W, Lipsitz SR, et al. Clinical risk score to predict likelihood of recurrence after ductal carcinoma in situ treated with breast-conserving surgery. Breast Cancer Res Treat. 2017 Oct 28. doi: 10.1007/s10549-017-4553-5. [Epub ahead of print]

Fokalität

1. Meijnen P, Bartelink H. Multifocal ductal carcinoma in situ of the breast: A contraindication for breast-conserving treatment? J Clin Oncol 2007;25:5548–5549
2. Rakovitch E, Pignol JP, Hanna W, et al. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. J Clin Oncol 2007;25:5591–5596

(mod.) Van Nuys Prognose Index und MSKCC Nomogramm

1. Lagios MD, Page DL, Silverstein MJ. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006;24:3809-11
2. Rudloff U, Jacks LM, Goldberg JL, et al. Nomogram for predicting the risk of local recuurence after breast conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010; 28(23): 3762-9
3. Van Zee KJ, Patil S. Validation of a nomogram for predicting risk of local recurrence for ductal carcinoma in situ. J Clin Oncol 2012; 30(25): 3143-4.
4. Sweldens C, Peeters S, van Limbergen E, et al. Öocal relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the Memorial Sloan-Kettering Cancer Center DCIS nomogram. Cancer J 2014; 20(1): 1-7.
5. Lei RY, Carter DL, Antell AG, et al. A Comparison of Predicted Ipsilateral Tumor Recurrence Risks in Patients With Ductal Carcinoma in

Situ of the Breast After Breast-Conserving Surgery by Breast Radiation Oncologists, the Van Nuys Prognostic Index, the Memorial Sloan Kettering Cancer Center DCIS Nomogram, and the 12-Gene DCIS Score Assay. Adv Radiat Oncol 2020;6(2):100607.

6. Grimm LJ , Rahbar H , Abdelmalak M, et al: Ductal Carcinoma in Situ: State-of-the-Art Review. Radiology. 2021 Dec 21;211839. doi: 10.1148/radiol.211839. Online ahead of print.
7. Wärnberg F, Karlsson P, Holmberg E, et al: Prognostic Risk Assessment and Prediction of Radiotherapy Benefit for Women with Ductal Carcinoma In Situ (DCIS) of the Breast, in a Randomized Clinical Trial (SweDCIS). Cancers 2021, 13,6103

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

1. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst. 2013 May 15;105(10):701-10.
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)
3. Rakovitch E, Nofech-Mozes S, Hanna W et al. A large prospectively-designed study of the DCIS score. Predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. SABCS 2015. S5-04
4. Wood WC, Alvarado M, Buchholz DJ, et al. The current clinical value of the DCIS Score. Oncology (Williston Park). 2014 May;28 Suppl 2:C2, 1-8, C3.
5. O'Keefe TJ, Blair SL, Hosseini A et al. HER2-Overexpressing Ductal Carcinoma In Situ Associated with Increased Risk of Ipsilateral Invasive Recurrence, Receptor Discordance with Recurrence. Cancer Prev Res (Phila). 2020 Sep;13(9):761-772. doi: 10.1158/1940-6207.CAPR-20-0024.
6. Lazzeroni M, DeCensi A, Guerrieri-Gonzaga A et al. Prognostic and predictive value of cell cycle progression (CCP) score in ductal carcinoma in situ of the breast. Mod Pathol. 2020 Jun;33(6):1065-1077. doi: 10.1038/s41379-020-0452-0.
7. Hwang KT , Suh YJ, PARK CH, et al: Hormone Receptor Subtype in Ductal Carcinoma in Situ: Prognostic and Predictive Roles of the Progesterone Receptor. The Oncologist 2021;26:e1939–e1950

DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

1. Eng-Wong J, JP Costantino et al. The Impact of Systemic Therapy Following Ductal Carcinoma In Situ. J Natl Cancer Inst Monogr 2010; 41: 200 – 203
2. Ryan R, Tawfik O, Jensen RA, Anant S. Current Approaches to Diagnosis and Treatment of Ductal Carcinoma In Situ and Future Directions. Prog Mol Biol Transl Sci. 2017;151:33-80.

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

1. Noh JM, Lee J, Choi DH, et al. HER-2 overexpression is not associated with increased ipsilateral breast tumor recurrence in DCIS treated with breast-conserving surgery followed by radiotherapy. Breast. 2013 Oct;22(5):894-7.
2. Solin LJ.: Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions. Curr Oncol Rep. 2019 Mar 5;21(4):33. doi: 10.1007/s11912-019-0777-3.
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4. Van Bockstal MR, Agahozo MC, Koppert LB, et al. A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer. 2019 Apr 24. doi: 10.1002/ijc.32362. [Epub ahead of print]
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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 an ipsilateral event after a primary DCIS: A systematic review. Breast. 2020 Apr; 50: 95–103. Published online 2020 Feb 19. doi: 10.1016/j.breast.2020.02.006

Kontralaterales Mammakarzinom

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Molecular Subtyping

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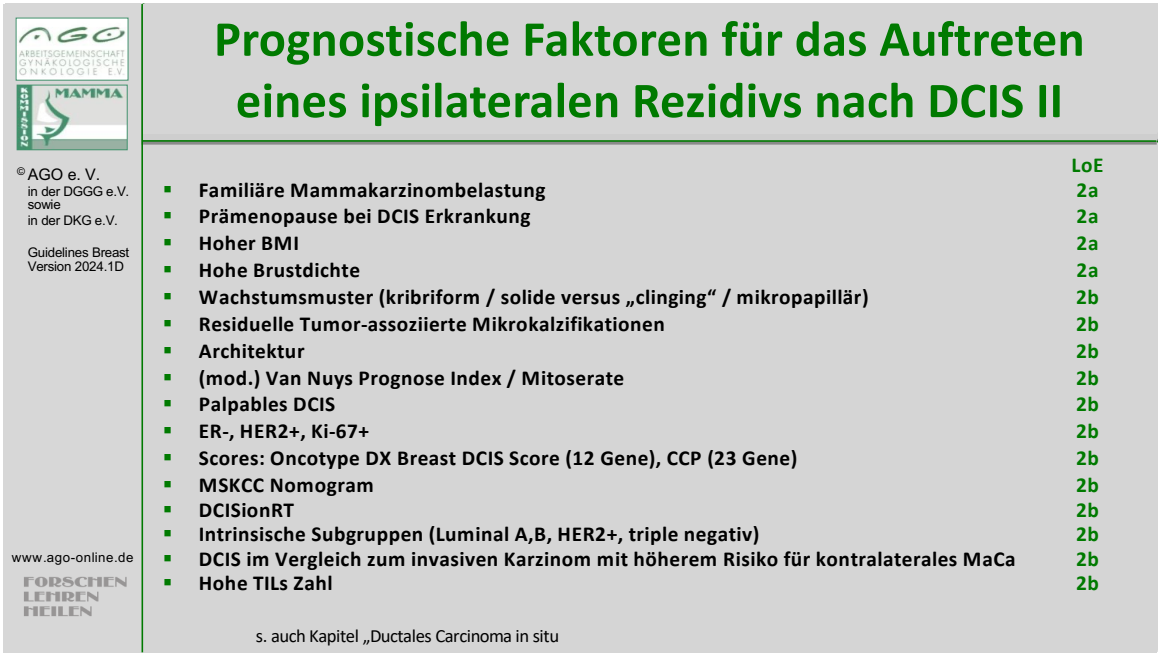

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DCISionRT:

1. Weinmann S, Leo MC, Francisco M, et al. Validation of a Ductal Carcinoma *In Situ* Biomarker Profile for Risk of Recurrence after Breast-Conserving Surgery with and without Radiotherapy. Clin Cancer Res. 2020 Aug 1;26(15):4054-4063.
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Molecular Profile

1. Nofech-Mozes S, Hanna W, Rakovitch E. Molecular Evaluation of Breast Ductal Carcinoma in Situ with Oncotype DX DCIS. Am J Pathol. 2018 Dec 31. pii: S0002-9440(18)30581-9
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3. Tumour-infiltrating lymphocytes add prognostic information for patients with low-risk DCIS: findings from the SweDCIS randomised radiotherapy trial. Schiza A, Thurfjell V, Stenmark Tullberg A; Eur J Cancer. 2022 Jun; 168:128-137
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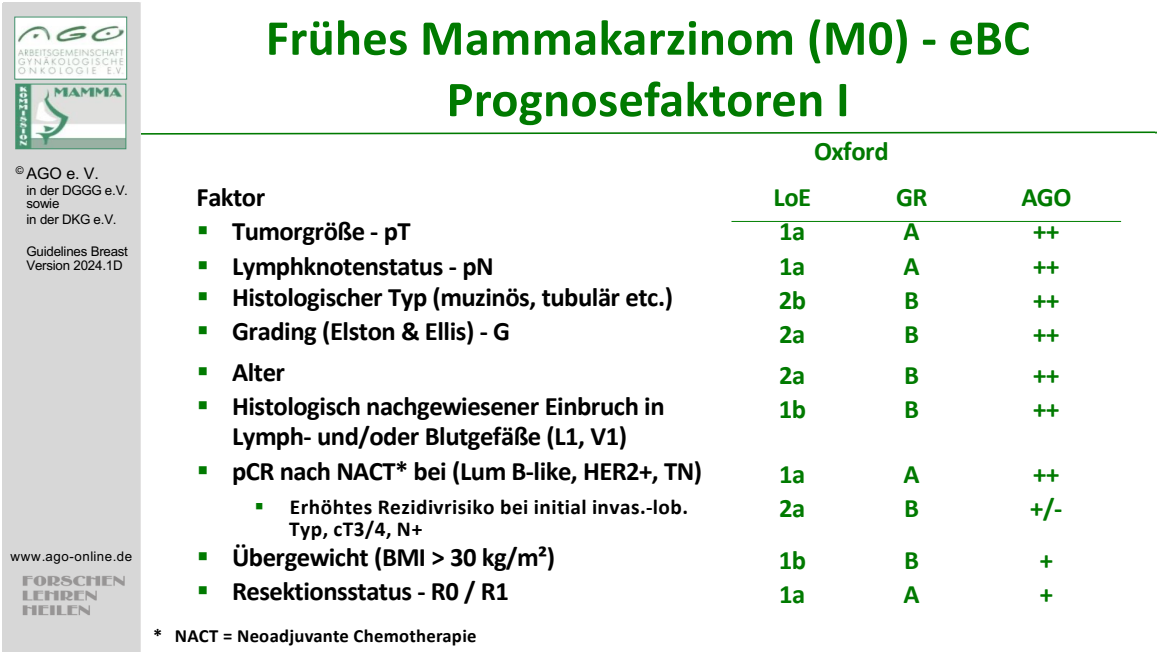

Frühes Mammakarzinom (M0) - eBC
Prognosefaktoren I

Faktor	Oxford LoE	Oxford GR	Oxford 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	B	+/-
▪ Übergewicht (BMI > 30 kg/m²)	1b	B	+
▪ Resektionsstatus - R0 / R1	1a	A	+

* NACT = Neoadjuvante Chemotherapie

General references

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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3. Balic M, Thomssen C, Würstlein R et al. St. Gallen/Vienna 2023: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. Breast Care (Basel). 2023 Apr;18(3):213-222.

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.
2. Balic M, Thomssen C, Würstlein 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.

Lymph node status

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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Histological type (mucinous, tubular etc.)

1. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010 Jun;4(3):192-208
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Tumor grade (Elston & Ellis)

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. Rakha EA, Aleskandarani M, Toss MS et al. Breast cancer histologic grading using digital microscopy: concordance and outcome association. J Clin Pathol. 2018 Aug;71(8):680-686.
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Age

1. Brandt J, Garne JP, Tengrup I et al. Age at diagnosis in relation to survival following breast cancer: a cohort study. World J Surg Oncol. 2015 Feb 7;13:33.

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

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
2. Lin Y, Zhang Y, Fang H et al. Survival and clinicopathological significance of blood vessel invasion in operable breast cancer: a systematic review and meta-analysis. Jpn J Clin Oncol. 2023 Jan 6;53(1):35-45.
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pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer

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 Jul 12;384(9938):164-72.
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. 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.

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

1. 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.
2. Van Baelen K, Geukens T, Maetens M et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol. 2022 Aug;33(8):769-785. Erratum in: Ann Oncol. 2022 Dec 16; PMID: 35605746.

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

follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914.
2. Nguyen HL, Geukens T, Maetens M, et al. Obesity-associated changes in molecular biology of primary breast cancer. Nat Commun. 2023 Jul 21;14(1):4418.
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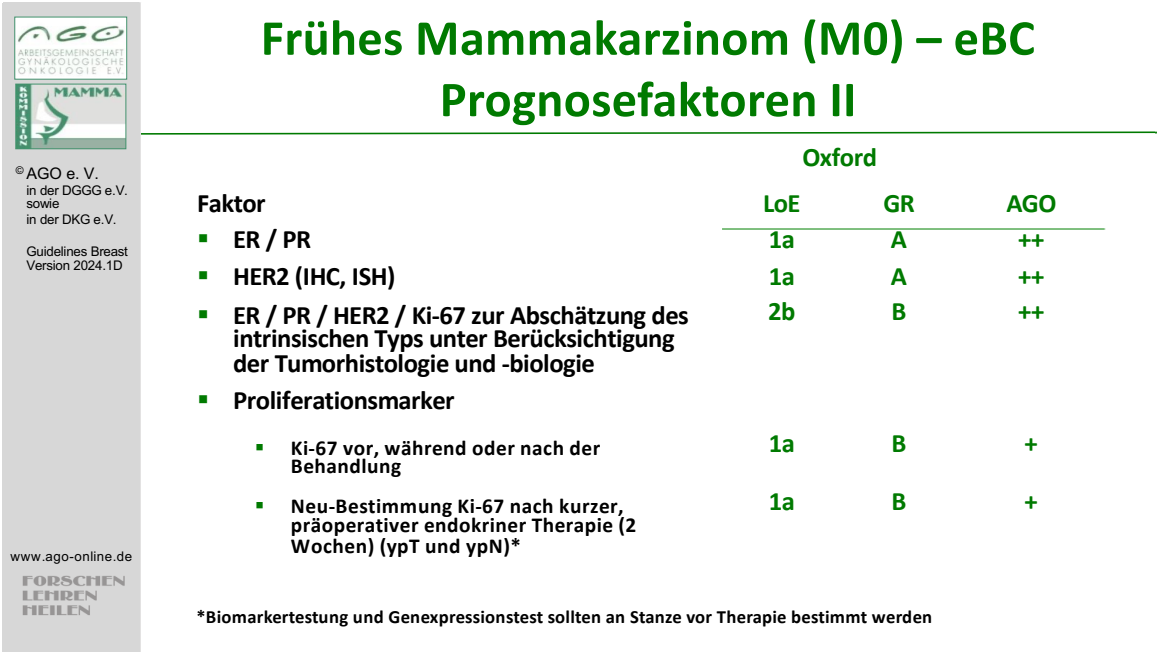
4. Chen H, Yuan M, Quan X, et al. The relationship between central obesity and risk of breast cancer: a dose-response meta-analysis of 7,989,315 women. Front Nutr. 2023 Nov 9;10:1236393.

Resection status (R0 / R1)

1. 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): 717-30.
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.



Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren II

Faktor	Oxford LoE	Oxford GR	AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2 / Ki-67 zur Abschätzung des intrinsischen Typs unter Berücksichtigung der Tumorhistologie und -biologie	2b	B	++
▪ Proliferationsmarker			
▪ Ki-67 vor, während oder nach der Behandlung	1a	B	+
▪ Neu-Bestimmung Ki-67 nach kurzer, präoperativer endokriner Therapie (2 Wochen) (ypT und ypN)*	1a	B	+

*Biomarkertestung und Genexpressionstest sollten an Stanze vor Therapie bestimmt werden

ER/PR

1. Allison KH, Hammond MEH, Dowsett M et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020 Apr 20;38(12):1346-1366
2. Allison KH, Hammond MEH, Dowsett M et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020 May;144(5):545-563
3. Jorns JM. Breast Cancer Biomarkers: Challenges in Routine Estrogen Receptor, Progesterone Receptor, and HER2/neu Evaluation. Arch Pathol Lab Med. 2019 Dec;143(12):1444-1449

HER2

1. Ross JS, Slodkowska EA, Symmans WF et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14, 320–368
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HER2 low vs. HER2 0:

1. Zhang H, Katerji H, Turner BM, Audet al. HER2-low breast cancers: incidence, HER2 staining patterns, clinicopathologic features, MammaPrint and BluePrint genomic profiles. Mod Pathol. 2022 Aug;35(8):1075-1082
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Ki-67

1. de Azambuja E, Cardoso F, de Castro G Jr, et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer. 2007 May 21;96(10):1504-13
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3. Nitz U, Gluz O, Huober J et al. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. Ann Oncol. 2017 Nov 1;28(11):2899
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5. 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
6. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol. 2020 Nov;21(11):1443-1454
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8. Gluz O, Nitz UA, Christgen M, et al. Impact of age, recurrence score (RS) and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Analysis of ADAPT and ADAPTcycle trials. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089
9. Martins-Branco D, Nader-Marta G, Molinelli C et al. Ki-67 index after neoadjuvant endocrine therapy as a prognostic biomarker in

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

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 2007: 99:167-170
2. DeCensi A, Guerrieri-Gonzaga A, Gandini S, et al. Prognostic significance of Ki-67 labeling index after short-term presurgical tamoxifen in women with ER-positive breast cancer. Annals Oncol 2011 Mar;22(3):582-7
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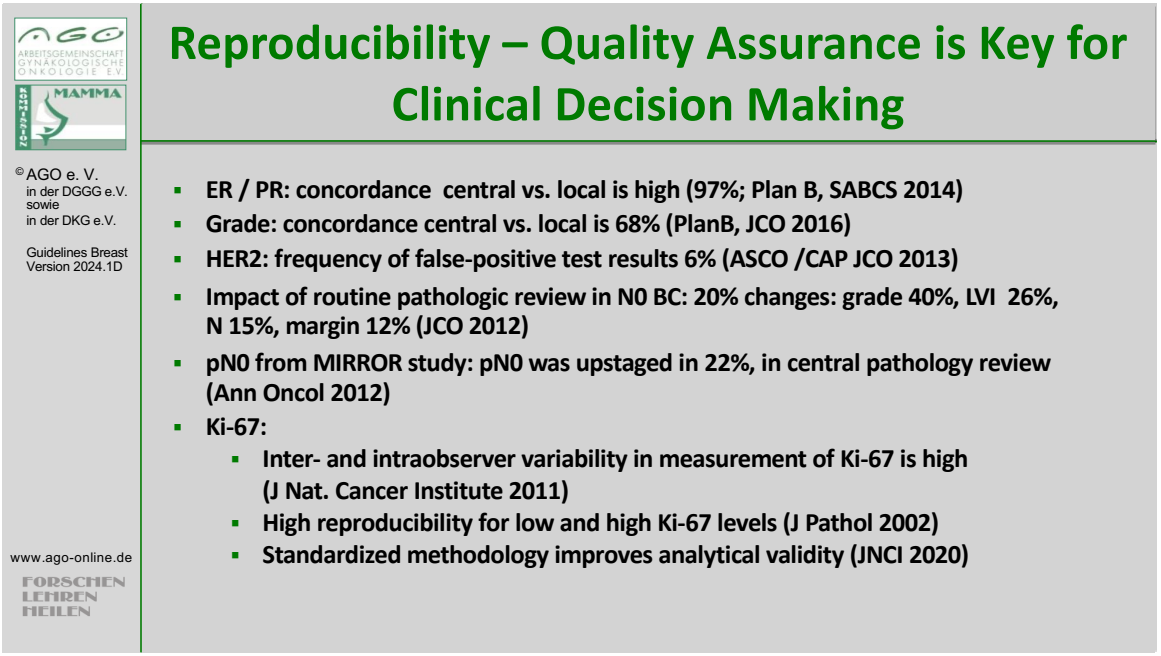

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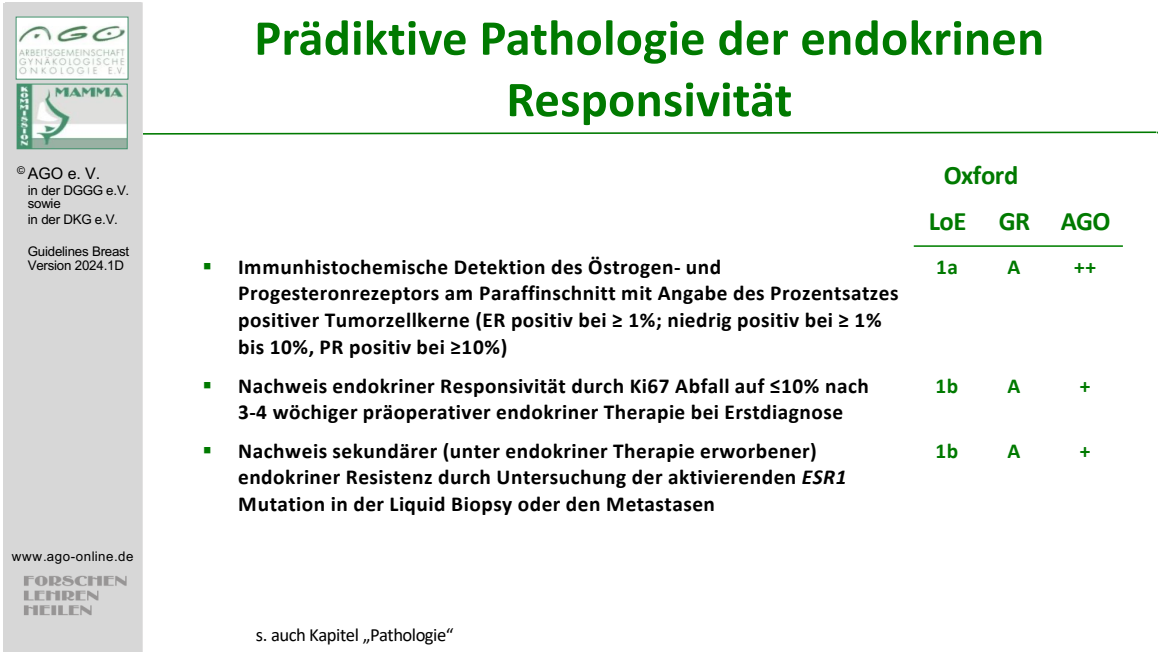

ASCO/CAP Guideline for ER- and PR-testing

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IHC-testing for ER-positivity

1. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017;75:284-298. doi:10.1016/j.ejca.2017.01.017.
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<u>IHC Scores</u>

1. Allred, D. C., Harvey, J. M., Berardo, M., et al. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Modern Pathology, 11(2), 155–168.

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

Monoclonal Antibodies for ER-Testing

1. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival.J Clin Oncol. 2006 Dec 20;24(36):5637-44.

ER low (ER 1%-10%)

1. Deyarmin, B. et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. Annals of Surgical Oncology 20, 87–93 (2013).

2. Prabhu, J. S. et al. A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors. Journal of Cancer 5, 156–165 (2014).

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Primary endocrine resistence

1. Tryfonidis K, Zardavas D, Katzenellenbogen BS, Piccart M. Endocrine treatment in breast cancer: Cure, resistance and beyond.Cancer Treat Rev. 2016 Nov;50:68-81. doi: 10.1016/j.ctrv.2016.08.008

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Secondary endocrine resistence (*ESR1* mutation)

1. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, Mouret-Reynier MA, Sohn JH, Taylor D, Harnden KK, Khong H, Kocsis J, Dalenc F, Dillon PM, Babu S, Waters S, Deleu I, García Sáenz JA, Bria E, Cazzaniga M, Lu J, Aftimos P, Cortés J, Liu S, Tonini G, Laurent D, Habboubi N, Conlan MG, Bardia A. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial.J Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338.
2. Wong NZH, Yap DWT, Ong RJM, Zhao JJ, Chan YH, Tey JCS, Sundar R, Lim JSJ, Dawood SS. Efficacy of Oral SERDs in the treatment of ER+, HER2 - metastatic breast cancer, a stratified analysis of the ESR1 wild type and mutant subgroups. Ann Oncol. 2023 Oct 21:S0923-7534(23)04328-4. doi: 10.1016/j.annonc.2023.10.122.
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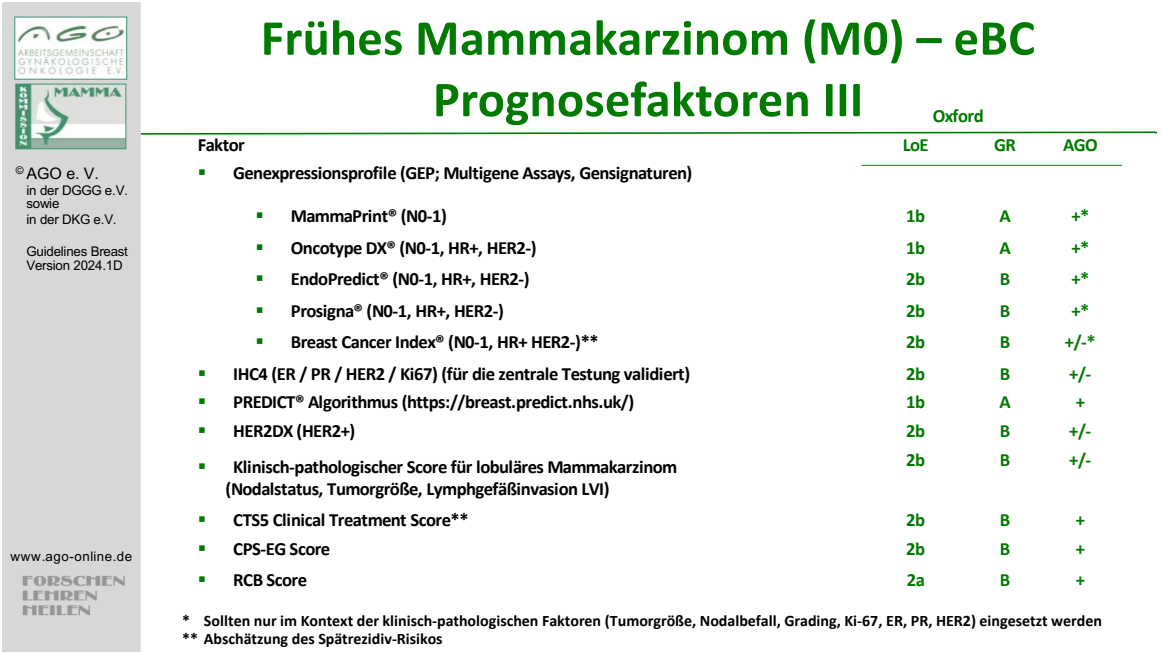

Frühes Mammakarzinom (M0) – eBC
Prognosefaktoren III

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® (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ IHC4 (ER / PR / HER2 / Ki67) (für die zentrale Testung validiert)	2b	B	+/-
▪ PREDICT® Algorithmus (https://breast.predict.nhs.uk/)	1b	A	+
▪ HER2DX (HER2+)	2b	B	+/-
▪ Klinisch-pathologischer Score für lobuläres Mammakarzinom (Nodalstatus, Tumorgröße, Lymphgefäßinvasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+
▪ RCB Score	2a	B	+

* Sollten nur im Kontext der klinisch-pathologischen Faktoren (Tumorgröße, Nodalbefall, Grading, Ki-67, ER, PR, HER2) eingesetzt werden
** Abschätzung des Spätrezidiv-Risikos

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)

1. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2022 Jun 1;40(16):1816-1837. doi: 10.1200/JCO.22.00069. Epub 2022 Apr 19. Erratum in: J Clin Oncol. 2022 Aug 1;40(22):2514. Lemij AA, Baltussen JC, de Glas NA, et al. Gene expression signatures in older patients with breast cancer: A systematic review. Crit Rev Oncol Hematol. 2023 Jan;181:103884.

MammaPrint®

1. Cardoso F, van't Veer LJ et al.; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29.
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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, ctDNA im Blut, prognostisch für DFS, PFS, DDFS, OS)	2a	B	+/-

* Validierte klinische Daten nur verfügbar für diesen Assay

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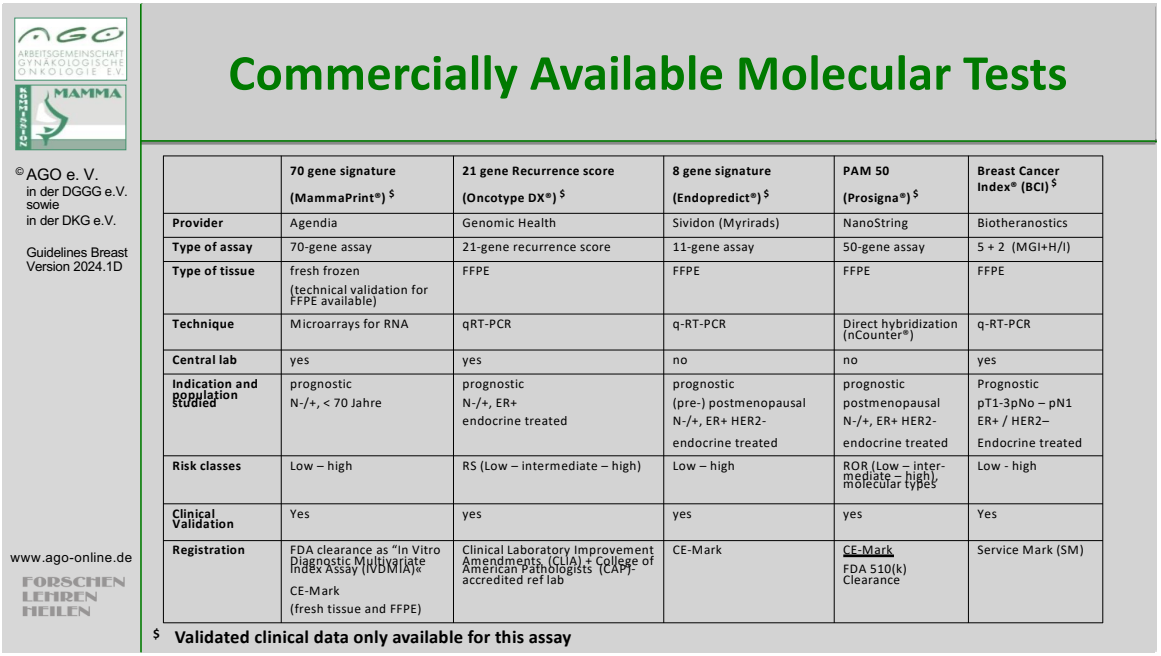

Commercially Available Molecular Tests

	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 – intermediate – 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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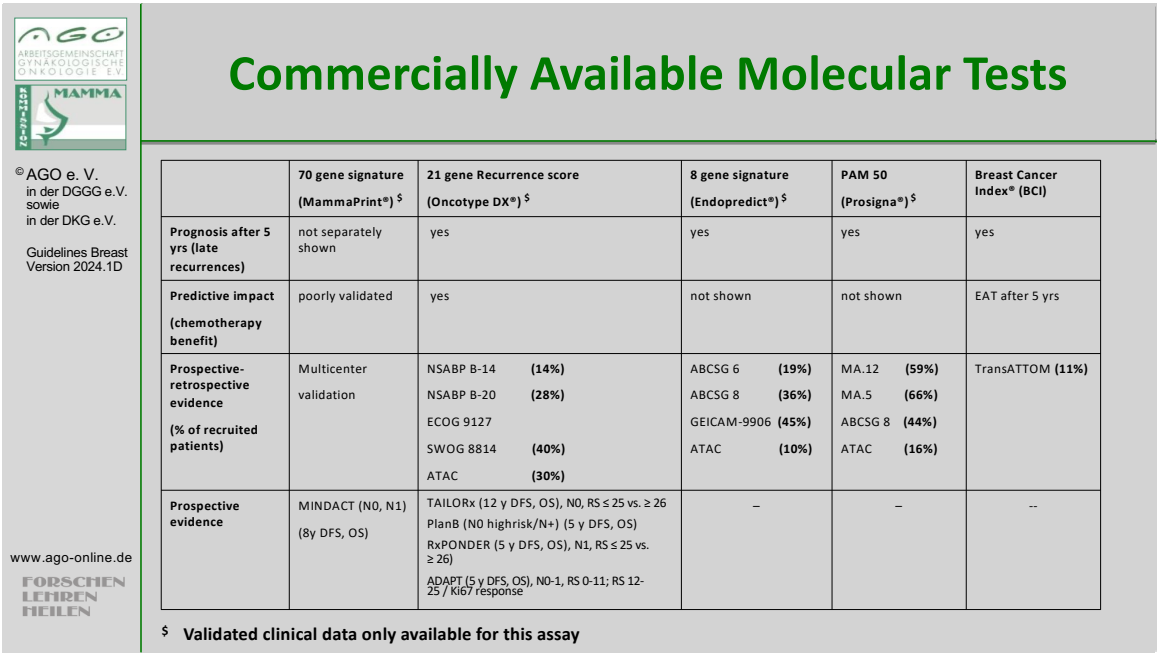

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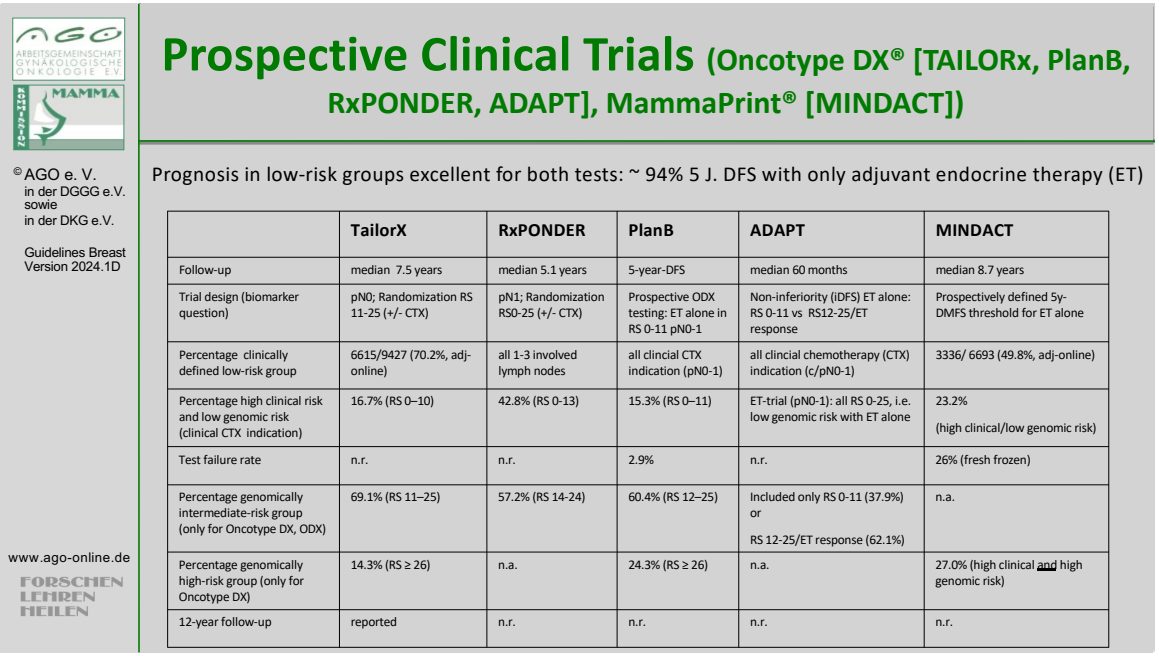

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	median 7.5 years	median 5.1 years	5-year-DFS	median 60 months	median 8.7 years
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (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)
12-year follow-up	reported	n.r.	n.r.	n.r.	n.r.

TailorX

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MINDACT

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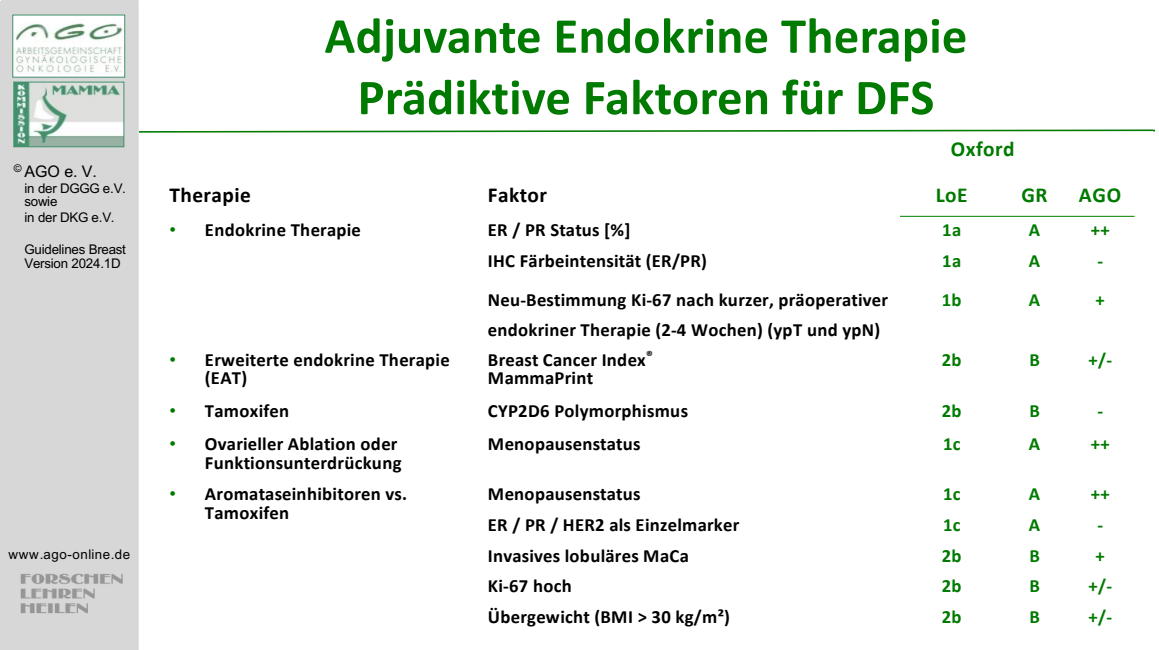

Adjuvante Endokrine Therapie
Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford LoE	Oxford GR	Oxford AGO
• Endokrine Therapie	ER / PR Status [%]	1a	A	++
	IHC Färbeintensität (ER/PR)	1a	A	-
	Neu-Bestimmung Ki-67 nach kurzer, präoperativer endokriner Therapie (2-4 Wochen) (ypT und ypN)	1b	A	+
• Erweiterte endokrine Therapie (EAT)	Breast Cancer Index® MammaPrint	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	+/-

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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.
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Adjuvante Chemo- und zielgerichtete Therapie
Prädiktive Faktoren für DFS

Therapie	Faktor	Oxford LoE	Oxford GR	AGO
▪ Adjuvante Chemotherapie	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	-
	TIL´s bei TNBC	2b	B	+/-
▪ Anti-HER2-Therapie	HER2 (IHC, ISH)	1a	A	++
▪ PARP-Inhibitor	*gBRCA1/2* Mutation (HER2 neg.)	1a	A	+

*Entscheidung nach Alter/Menopausenstatus zu erwägen, prospektive Evidenz nur für Mammaprint und OncotypeDX verfügbar (siehe nächste Folie)

70-Gene-Signature (Mammaprint®)

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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
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Anti-HER2 therapy

see evidence in chapter "Chemotherapy and targeted therapy"

PARPi

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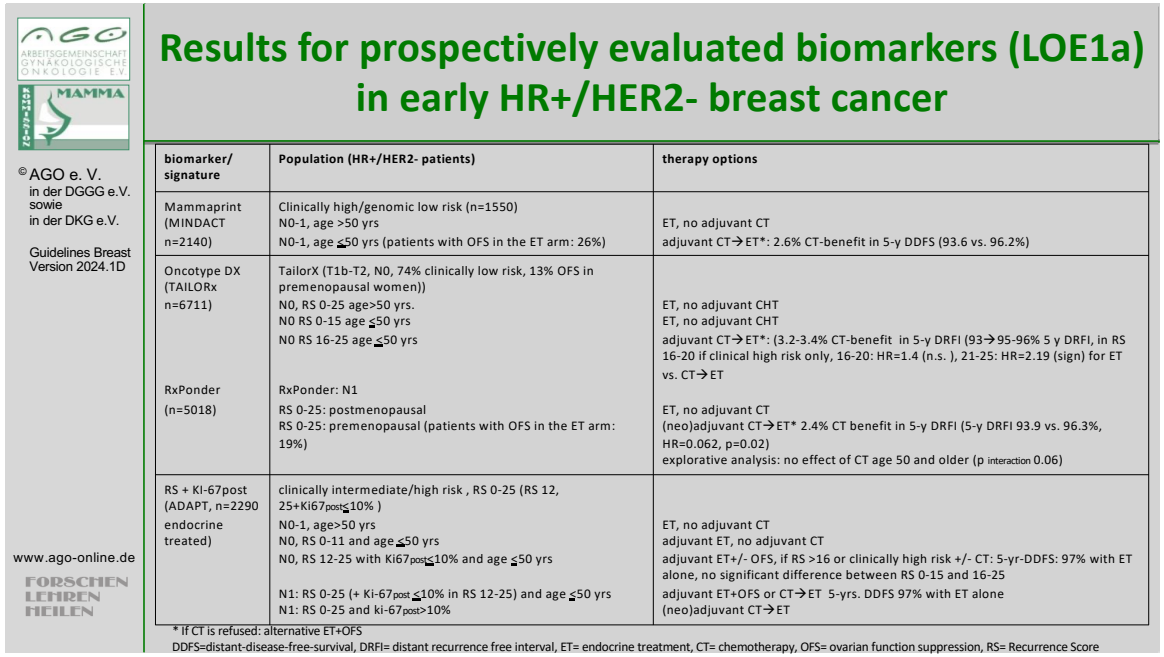

Results for prospectively evaluated biomarkers (LOE1a) in early HR+/HER2- breast cancer

biomarker/ signature	Population (HR+/HER2- patients)	therapy options
Mammaprint (MINDACT n=2140)	Clinically high/genomic low risk (n=1550) N0-1, age >50 yrs N0-1, age ≤50 yrs (patients with OFS in the ET arm: 26%)	 ET, no adjuvant CT adjuvant CT→ET*: 2.6% CT-benefit in 5-y DDFS (93.6 vs. 96.2%)
Oncotype DX (TAILORx n=6711)	TailorX (T1b-T2, N0, 74% clinically low risk, 13% OFS in premenopausal women)) N0, RS 0-25 age>50 yrs. N0 RS 0-15 age ≤50 yrs N0 RS 16-25 age ≤50 yrs	 ET, no adjuvant CHT ET, no adjuvant CHT adjuvant CT→ET*: (3.2-3.4% CT-benefit in 5-y DRFI (93→95-96% 5 y DRFI, in RS 16-20 if clinical high risk only, 16-20: HR=1.4 (n.s.), 21-25: HR=2.19 (sign) for ET vs. CT→ET
RxPonder (n=5018)	RxPonder: N1 RS 0-25: postmenopausal RS 0-25: premenopausal (patients with OFS in the ET arm: 19%)	 ET, no adjuvant CT (neo)adjuvant CT→ET* 2.4% CT benefit in 5-y DRFI (5-y DRFI 93.9 vs. 96.3%, HR=0.062, p=0.02) explorative analysis: no effect of CT age 50 and older ($p_{interaction}$ 0.06)
RS + KI-67post (ADAPT, n=2290 endocrine treated)	clinically intermediate/high risk , RS 0-25 (RS 12, 25+$Ki67_{post}$≤10%) N0-1, age>50 yrs N0, RS 0-11 and age ≤50 yrs N0, RS 12-25 with $Ki67_{post}$≤10% and age ≤50 yrs N1: RS 0-25 (+ $Ki\text{-}67_{post}$ ≤10% in RS 12-25) and age ≤50 yrs N1: RS 0-25 and $ki\text{-}67_{post}$>10%	 ET, no adjuvant CT adjuvant ET, no adjuvant CT adjuvant ET+/- OFS, if RS >16 or clinically high risk +/- CT: 5-yr-DDFS: 97% with ET alone, no significant difference between RS 0-15 and 16-25 adjuvant ET+OFS or CT→ET 5-yrs. DDFS 97% with ET alone (neo)adjuvant CT→ET

* If CT is refused: alternative ET+OFS

DDFS=distant-disease-free-survival, DRFI= distant recurrence free interval, ET= endocrine treatment, CT= chemotherapy, OFS= ovarian function suppression, RS= Recurrence Score

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Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR I

Faktor	pCR* Wahrscheinlichkeit	Oxford LoE	Oxford GR	Oxford 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

1. 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.
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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.

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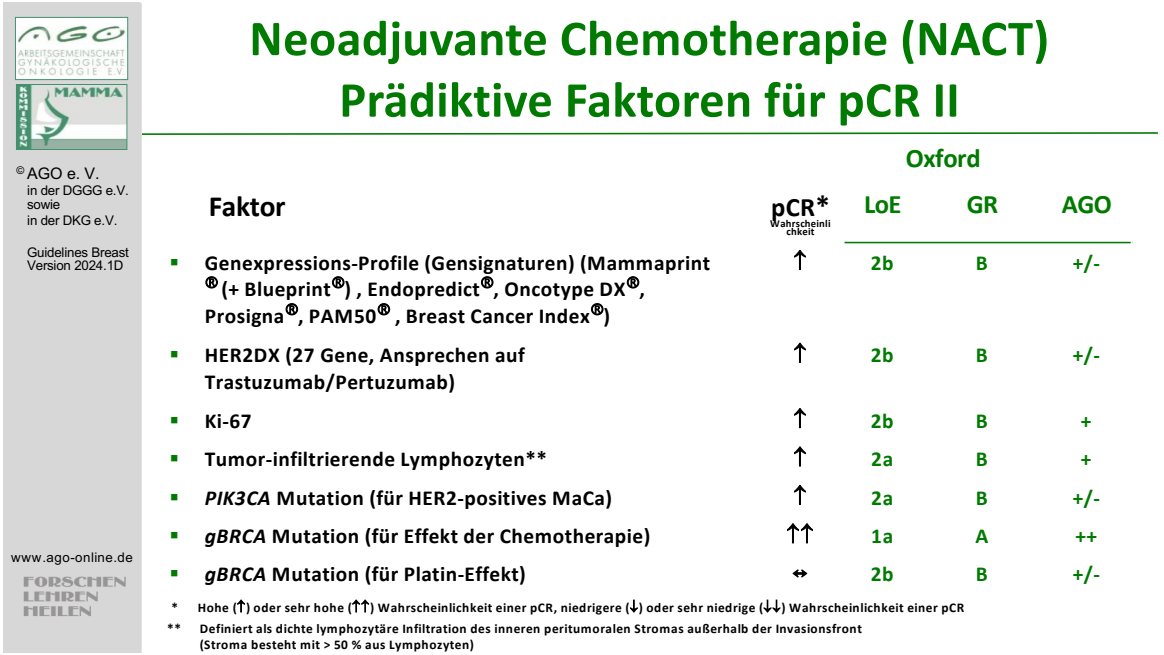

Neoadjuvante Chemotherapie (NACT)
Prädiktive Faktoren für pCR II

Faktor	pCR* Wahrscheinlichkeit	Oxford LoE	Oxford GR	Oxford AGO
▪ Genexpressions-Profile (Gensignaturen) (Mammaprint®(+ Blueprint®) , Endopredict®, Oncotype DX®, Prosigna®, PAM50® , Breast Cancer Index®)	↑	2b	B	+/-
▪ HER2DX (27 Gene, Ansprechen auf Trastuzumab/Pertuzumab)	↑	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)	↑↑	1a	A	++
▪ *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

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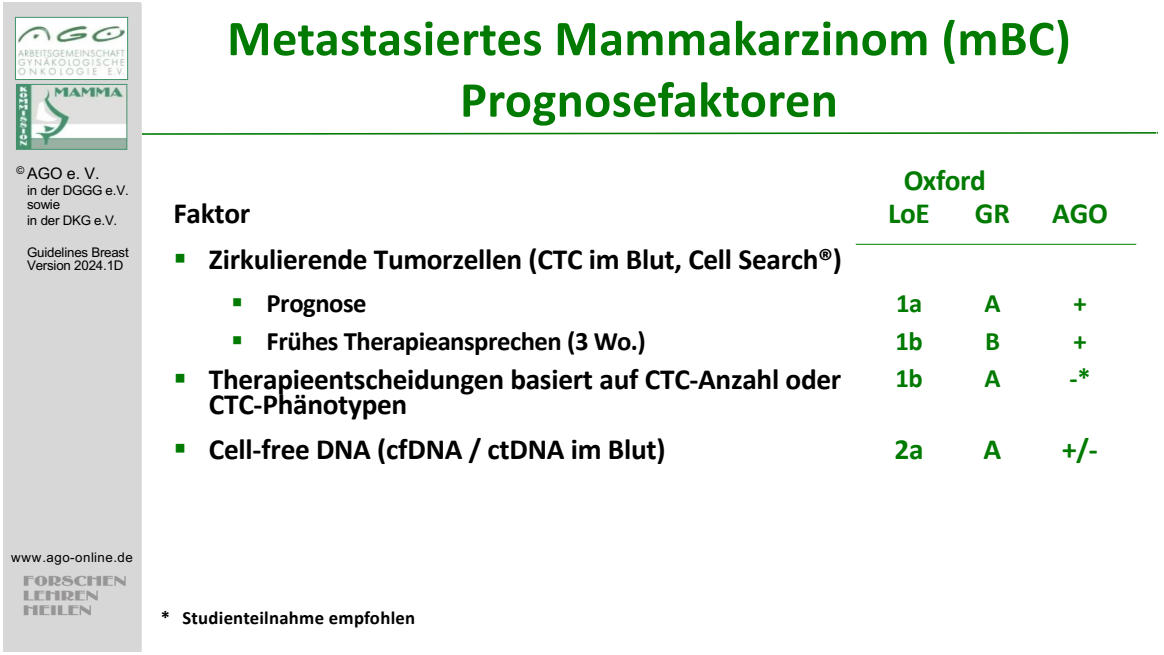

Metastasiertes Mammakarzinom (mBC)
Prognosefaktoren

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

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Metastasiertes Mammakarzinom (mBC)
Marker zur Indikationsstellung

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

Endocrine therapy

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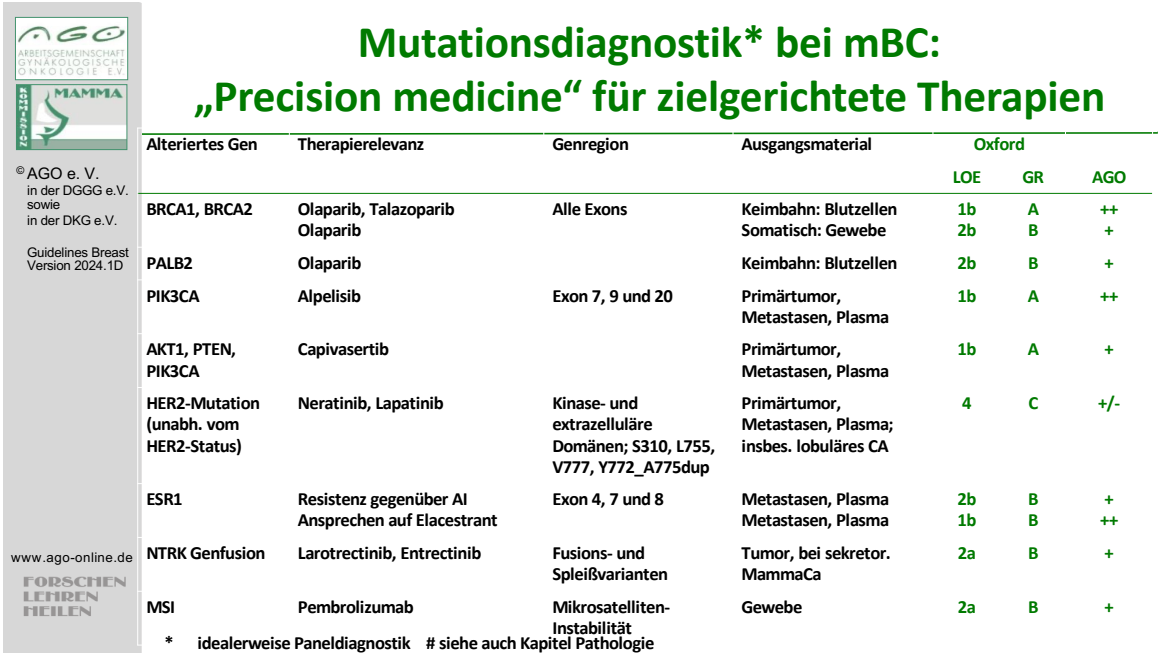

Mutationsdiagnostik* bei mBC: „Precision medicine“ für zielgerichtete Therapien

Alteriertes Gen	Therapierelevanz	Genregion	Ausgangsmaterial	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	Alle Exons	Keimbahn: Blutzellen Somatisch: Gewebe	1b 2b	A B	++ +
PALB2	Olaparib		Keimbahn: Blutzellen	2b	B	+
PIK3CA	Alpelisib	Exon 7, 9 und 20	Primärtumor, Metastasen, Plasma	1b	A	++
AKT1, PTEN, PIK3CA	Capivasertib		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 Ansprechen auf Elacestrant	Exon 4, 7 und 8	Metastasen, Plasma Metastasen, Plasma	2b 1b	B B	+ ++
NTRK Genfusion	Larotrectinib, Entrectinib	Fusions- und Spleißvarianten	Tumor, bei sekretor. MammaCa	2a	B	+
MSI	Pembrolizumab	Mikrosatelliten-Instabilität	Gewebe	2a	B	+

* idealerweise Paneldiagnostik # siehe auch Kapitel Pathologie

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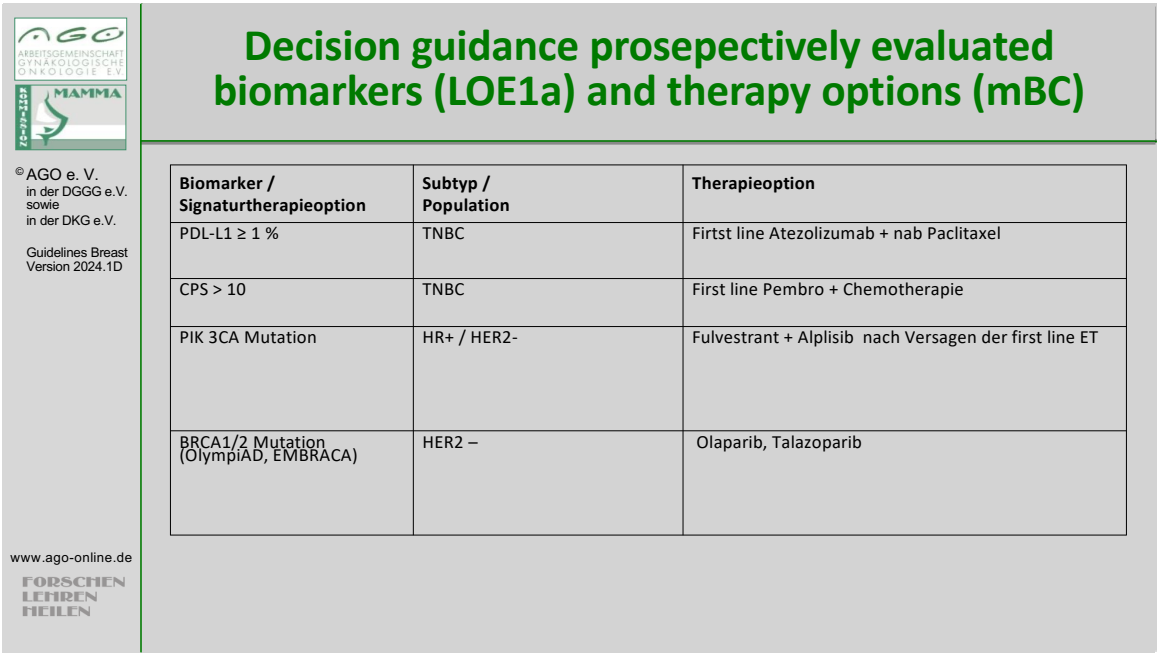

Decision guidance prosepectively evaluated biomarkers (LOE1a) and therapy options (mBC)

Biomarker / Signaturtherapieoption	Subtyp / Population	Therapieoption
PDL-L1 ≥ 1 %	TNBC	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TNBC	First line Pembro + Chemotherapie
PIK 3CA Mutation	HR+ / HER2-	Fulvestrant + Alplisib nach Versagen der first line ET
BRCA1/2 Mutation (OlympiAD, EMBRACA)	HER2 –	Olaparib, Talazoparib

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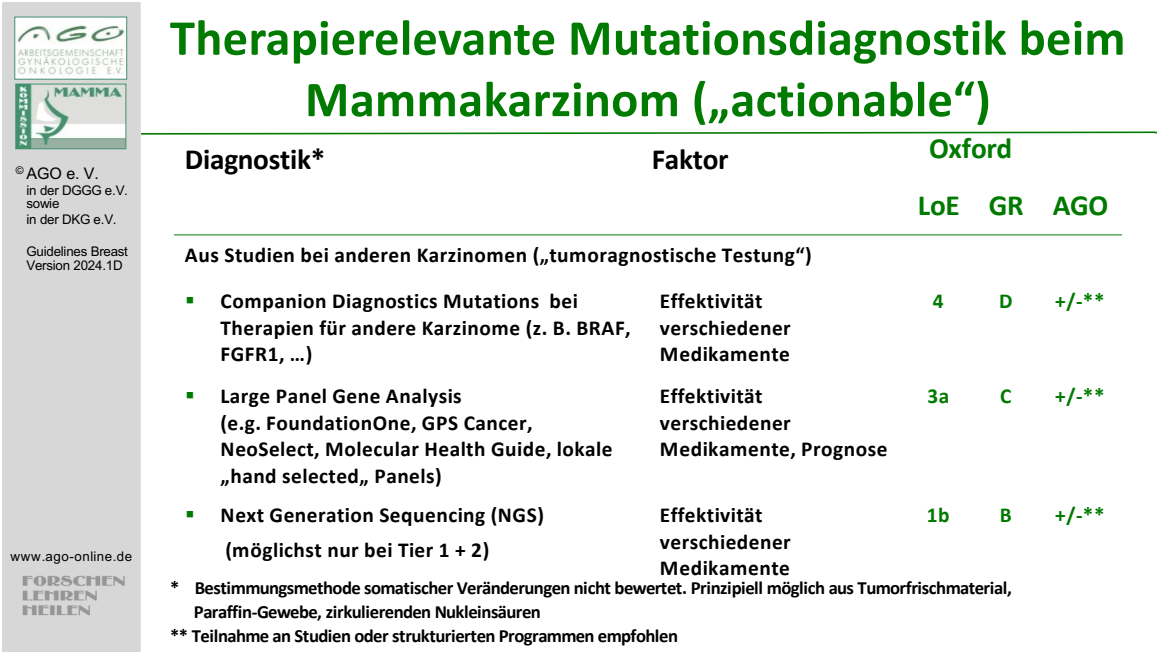

Therapierelevante Mutationsdiagnostik beim Mammakarzinom („actionable“)

Guidelines Breast
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HEILEN

Diagnostik*	Faktor	Oxford LoE	Oxford GR	Oxford 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	+/-**
▪ Next Generation Sequencing (NGS) (möglichst nur bei Tier 1 + 2)	Effektivität verschiedener Medikamente	1b	B	+/-**

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

** Teilnahme an Studien oder strukturierten Programmen empfohlen

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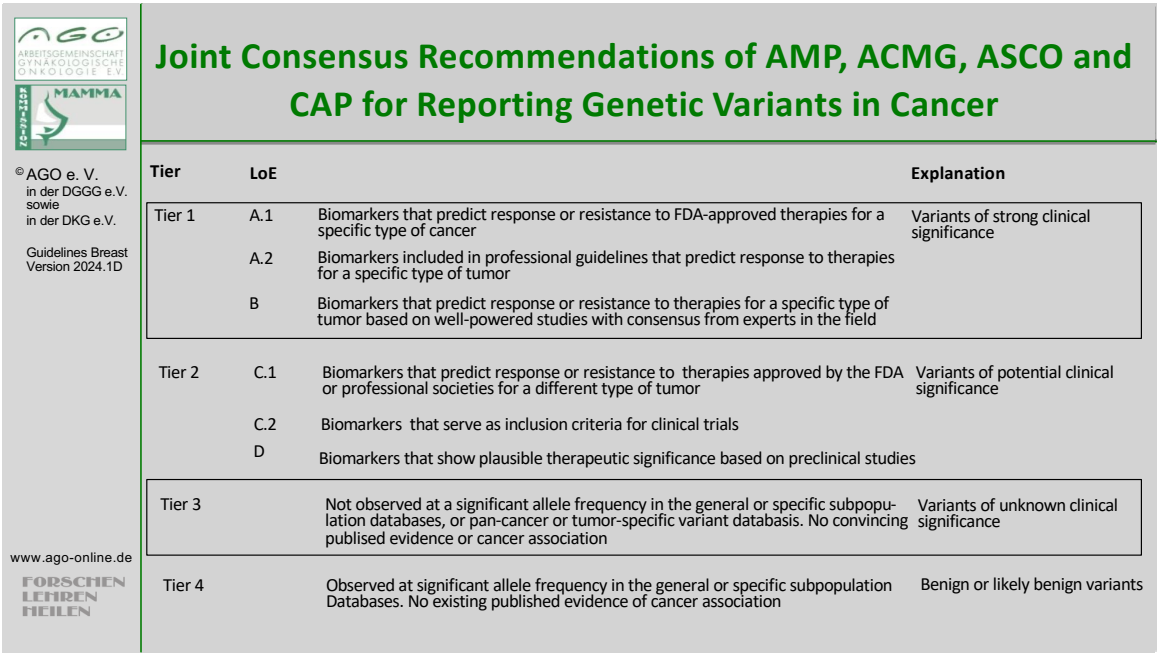

Treatment Recommendations for genetic variants

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