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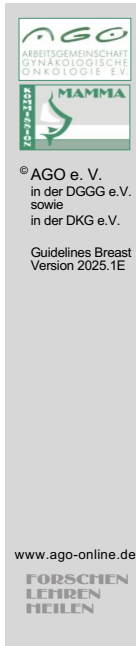
Guidelines Breast
Version 2025.1E

FORSCHEN
LEHREN
HEILEN

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Prognostic and Predictive Factors

Prognostic and Predictive Factors



- **Versionen 2002–2024:**

Costa / Fasching / Fersis / Friedrich/ 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 2025:**

Fehm / Stickeler

Data bases screened

Pubmed 2008 - 2024, ASCO 2017-2024, SABCS 2003 – 2024, ESMO 2024, Cochrane data base (n.d.)

Definition



A **Prognostic Factors** is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

A **Predictive Factor** is associated with the probability of the effect of a given therapy.

Definition of Prognosis and Prediction

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.



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“Low absolute risk implies low absolute benefit”

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

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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Quality Criteria for selection of prognostic/predictive markers

- **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**

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.
3. 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.
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.

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	<u>LoE</u>
▪ Resection margins	1a
▪ Age	1a
▪ Size	1a
▪ Grade	1a
▪ Comedo necrosis	1a
▪ Method of diagnosis	1a
▪ Focality	1a
▪ HER2-overexpression	1a
▪ ER / PR (positive vs. negative)	1a

#see chapter „DCIS“

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.
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4. Badve SS, Gökmen-Polar: Ductal carcinoma in situ of breast: update 2019. Pathology. 2019 Oct;51(6):563-569.
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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.
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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
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(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
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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)
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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.
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Familiäre Karzinombelastung, Menopausenstatus, BMI und Brustdichte

1. Alaeikhaneshir 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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Early Breast Cancer (M0) – eBC

clinical/histopathological Prognostic Factors I

Faktor	Oxford		
	LoE	GR	AGO
▪ Tumor size - pT	1a	A	++
▪ Axillarx lymph node status - pN	1a	A	++
▪ Histological tumor typ (mucinous, tubular etc.)	2b	B	++
▪ Grade(Elston & Ellis) - G	2a	B	++
▪ Histologically proven peritumoral lymphatic vessel and vascular invasion (L1, V1)	1b	B	++
▪ pCR after NACT* in (luminal B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invasive-lobular BC, cT3/4, N+	2a	B	+/-
▪ Margins (resection status) – R0/R1	1a	A	+
▪ Obesity (BMI > 30 kg/m ²)	1b	B	+
▪ Age	2a	B	++

* NACT = Neoadjuvant Chemotherapy

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, Würtle 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

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Lymph node status

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Histological type (mucinous, tubular etc.)

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Tumor grade (Elston & Ellis)

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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

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pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer

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

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Obesity (BMI > 30 kg/m²)

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Age

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Early Breast Cancer (M0) - eBC Histopathological Prognostic Factors II

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

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

ER/PR

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HER2

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Med. 2023 Sep 1;147(9):993-1000

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Ki-67

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

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Reproducibility – Quality Assurance is Key for Clinical Decision Making

- **ER / PR: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grade: 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: grade 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)**
- **Ki67:**
 - **Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)**
 - **High reproducibility for low and high Ki67 levels (J Pathol 2002)**
 - **Standardized methodology improves analytical validity (JNCI 2020)**

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Predictive pathology of endocrine responsiveness

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Immunohistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if $\geq 1\%$, low positivity $\geq 1\%$ to 10%; PR positive if $\geq 10\%$) 	1a	A	++
<ul style="list-style-type: none"> Detection of endocrine responsiveness by Ki-67 decrease to $\leq 10\%$ after 3-4 weeks of preoperative endocrine therapy in primary breast cancer 	1b	A	+
<ul style="list-style-type: none"> Detection of secondary, i.e. acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue 	1b	A	+

see chapter „Pathology“

ASCO/CAP Guideline for ER- and PR-testing

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IHC-testing for ER-positivity

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IHC Scores

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Monoclonal Antibodies for ER-Testing

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ER low (ER 1%-10%)

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Primary endocrine resistance

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Secondary endocrine resistance (*ESR1* mutation)

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Early Breast Cancer (M0) - eBC Prognostic Factors III

Factor	Oxford		
	LoE	GR	AGO
▪ Gene expression profiles (GEP, multigene assays, gene signatures)			
▪ 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 SM (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ IHC4 (ER / PR / HER2 / Ki-67) (validated for central testing)	2b	B	+/-
▪ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
▪ HER2DX (HER2+)	2b	B	+/-
▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+
▪ RCB Score	2a	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)

** Estimation of late recurrence

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)

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MammaPrint®

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Oncotype DX®

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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 (Myriad)	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 (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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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)
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%)	TransATTOM (11%)
Prospective evidence	MINDACT (N0, N1) (8y DFS, OS)	TAILORx (12 y DFS, OS), N0, RS ≤ 25 vs. ≥ 26 PlanB (N0 highrisk/N+) (5 y DFS, OS) RxPONDER (5 y DFS, OS), N1, RS ≤ 25 vs. ≥ 26 ADAPT (5 y DFS, OS), N0-1, RS 0-11; RS 12-25 / Ki67 response	–	–	–

‡ Validated clinical data only available for this assay

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Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

	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 clinical CTX indication (pN0-1)	all clinical 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.

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Early breast cancer (M0) – CTCs / ct-DNA prognosis and prediction

	Oxford		
	LoE	GR	AGO
Prognosis before treatment			
▪ Disseminated tumor cells (DTC)	1a	A	+/-
▪ Circulating tumor cells (CTC, Cell Search®)*	1a	A	+/-
▪ ct-DNA	1a	A	+/-
Prognosis after treatment (surgery +/- chemo)			
▪ DTCs	1b	A	+/-
▪ CTCs	1b	A	+/-
▪ ct-DNA	1b	A	+/-
Post(neo)adjuvant treatment decisions based on			
▪ CTC-positivity	3a	C	-
▪ ct-DNA positivity	5	D	-**
▪ Mutations detected by ct-DNA	5	D	-**

* Validated clinical data only available for this assay; ** Study participation recommended

DTC before treatment

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ct-DNA – prognostic relevance after surgery +/- chemotherapy

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Clinical studies on post-(neo)adjuvant therapy decisions in the case of post-therapeutic ctDNA positivity in early breast cancer (EBC)

Name of the study	NCT number	Phase	Inclusion criteria	Experimental arm
ARTEMIS	04803539	II	Triple negative, Stage II-III	Capecitabine + Camrelizumab + Apatinib
PERSEVERE	04849364	II	Triple negative non PCR	Depending on mutation + Capecitabin
KAN-HER	05388149	II	HER2 positive, 2-6 cycle T-DM1	Neratinib (in addition to T-DM1)
ASPRIA	04434040	II	triple negative non PCR	Atezolizumab + Sacituzumab Govitecan

Modified from Tegeler CM et al. Cancers 2024

Tegeler CM, Hartkopf AD, Banys-Paluchowski M, et al. . Circulating Tumor DNA in Early and Metastatic Breast Cance-Current Role and What Is Coming Next. Cancers (Basel). 2024 Nov 22;16(23):3919. doi: 10.3390/cancers16233919. PMID: 39682108; PMCID: PMC11640659.

Predictive Factors: Adjuvant Endocrine Therapy

Therapy	Factor	Oxford		
		LoE	GR	AGO
▪ Endocrine therapy	▪ ER / PR status [%]	1a	A	++
	▪ IHC staining intensity (ER/PR)	1a	A	-
	▪ Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks)	1b	A	+
	▪ Recurrence Score 12-25 and Ki-67 decrease below <=10% after short preoperative endocrine therapy	1b	B	+
	▪ Breast Cancer Index [*] MammaPrint	2b	B	+/-
▪ Extended endocrine therapy (EAT)	▪ CYP2D6-polymorphism	2b	B	-
▪ Tamoxifen	▪ Menopausal status	1c	A	++
▪ Ovarian ablation or suppression	▪ Menopausal status	1c	A	++
▪ Aromatase inhibitors vs. tamoxifen	▪ ER / PR / HER2 as single factors	1c	A	-
	▪ Invasiv-lobular breast cancer	2b	B	+
	▪ Ki-67 high	2b	B	+/-
	▪ Obesity (BMI > 30 kg/m ²)	2b	B	+/-

General publications

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1. Dowsett M, Torsten O, A´Hern R et al. Assessemnt of Ki-67 in Breast Cancer: Recommendations from the International Ki67 Breast Cancer Working Group. J Natl Cancer Inst 2011;103:1656-1664
2. Kim HJ, Noh WC, Lee ES et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in premenopausal patients with estrogen receptor positive and HER2-negative lymph-node positive breast cancer. Breast Cancer Res 202;22(1):54-59.
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EAT

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Predictive Factors: (Neo-)Adjuvant Chemotherapy and Targeted Therapy

Therapy	Factor	Oxford		
		LoE	G R	AGO
▪ Adjuvant Chemotherapy	70-Gene-signature (Mammaprint®)	1b	A	+
	21-Gene-signature (Oncotype DX RS®)	1b	A	+
	EPclin (Endopredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
	Histological type (lobular vs. NST)	2b	B	-
▪ Anti-HER2-Therapy	TIL's in TNBC	1a	A	+/-
	HER2 (IHC, ISH)	1a	A	++
▪ PARP-Inhibitors	gBRCA1/Mutation (HER2 neg.)	1a	A	++

*Consider decision according to age/menopausal status, prospective evidence available for Mammaprint and OncotypeDX only (see next slide)

70-Gene-Signature (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.
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OncotypeDX

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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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EPclin (EndoPredict®)

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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.
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Histological type:

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TiLs:

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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+Ki67post≤10%) N0-1, age>50 yrs N0, RS 0-11 and age ≤50 yrs N0, RS 12-25 with Ki67post≤10% and age ≤50 yrs N1: RS 0-25 (+ Ki-67post≤10% in RS 12-25) and age ≤50 yrs N1: RS 0-25 and ki-67post>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

1. Sparano JA, Gray RJ, Ravdin PM et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. *New England Journal of Medicine* 2019; 380: 2395-2405.
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epirubicin plus cyclophosphamide in high-risk HR+/HER2- early breast cancer: results from the neoadjuvant part of the WSG-ADAPT-HR+/HER2- trial. *Ann Oncol*. 2023 Jun;34(6):531-542.

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Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR I

Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR

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Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®(+ Blueprint®), Endopredict® Oncotype DX®, Prosigna®, PAM50®, Breast Cancer Index SM)	↑	2b	B	+/-
▪ HER2DX (27 genes, response to trastuzumab/pertuzumab)	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	1a	A	+
▪ PIK3CA mutation (for HER2-positive BC)	↓	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-
▪ PD-L1 expression (TNBC)	↑	1b	A	+/-

* High (↑) or very high (↑↑) probability of pCR, low (↓) or very low (↓↓) probability of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

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Metastatic breast cancer (M1) – CTCs / ct-DNA Prognosis and prediction

	Oxford		
	LoE	GR	AGO
Prognosis			
▪ Circulating tumor cells (CTC, Cell Search®)	1a	A	+
▪ ct-DNA	1a	A	+
Early therapy response (after 2-3 weeks of treatment)			
▪ CTCs	1a	A	+
▪ ct-DNA	2a	B	+
Therapy decisions based on			
▪ Dynamics of CTC numbers	1b	A	-*
▪ Phenotype of CTCs	2b	B	-/+*
▪ ct-DNA-dynamics	5	D	-*
▪ <i>ESR1</i> -monitoring	2b	B	+/-*
▪ Using ct-DNA to indicate approved mutation based treatments (e.g. <i>ESR1</i> , <i>PIK3CA</i>)	1a	A	++**

*Study participation recommended; **Note the approval text!

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Treatment of Metastatic Breast Cancer

Markers to determine treatment indications

Therapy	Factor	Oxford		
		LoE	GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (<i>ESR1</i>) (metastases, plasma)	1b	B	++
▪ Alpelisib / Inavolisib	<i>PIK3CA</i> mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	<i>PIK3CA</i> , <i>AKT1</i> , <i>PTEN</i> alterations (primary tumor, metastases, plasma)	1b	A	+
▪ Trastuzumab Deruxtecan	HER2-low/-pos. (prim. tumor, better: metastasis)	1b	A	++
	HER2-ultralow (prim. tumor, better: metastasis)	2b	B	+/-
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity ^a (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	<i>gBRCA1/2</i> -mutation	1a	A	++
	<i>sBRCA1/2/gPALB2</i>	2b	B	+

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Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies

Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	All exons	Germline: Blood cells	1b	A	++
			Somatic: Tissue	2b	B	+
PALB2	Olaparib		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib / Inavolisib	Exons 7, 9 and 20	Primary tumor, metastases, plasma	1b	A	++
AKT1, PTEN, PIK3CA	Capivasertib		Primary tumor, metastases, plasma	1b	A	+
HER2-mutation (Independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI Response to Elacestrant	Exons 4, 7 and 8	Metastases, plasma	2b	B	+
			Metastases, plasma	1b	B	++
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics # see chapter „pathology“

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A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

	ESCAT evidence tier	Clinical value class	Clinical implication
Ready for routine use	I: alteration-drug match is associated with improved outcome in clinical trials	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved	Clinical trials to be discussed with patients
	IV: pre-clinical evidence of actionability	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018 Sep 1;29(9):1895-1902. doi: 10.1093/annonc/mdy263. PMID: 30137196; PMCID: PMC6158764.