Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2023.1E

FORSCHEN
LEHREN
HEILEN

Prognostic and Predictive Factors

Prognostic and Predictive Factors

- **Versions 2002–2022:**
  Costa / Fasching / Fersis / Friedrichs / Gerber / Göhring / Harbeck / Jackisch / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thill / Thomssen / Untch / Witzel / Wöckel

- **Version 2023:**
  Gluz / Witzel

Data bases screened

Pubmed 2008 - 2022, ASCO 2017-2022, SABCS 2003 – 2022, ESMO 2022, 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

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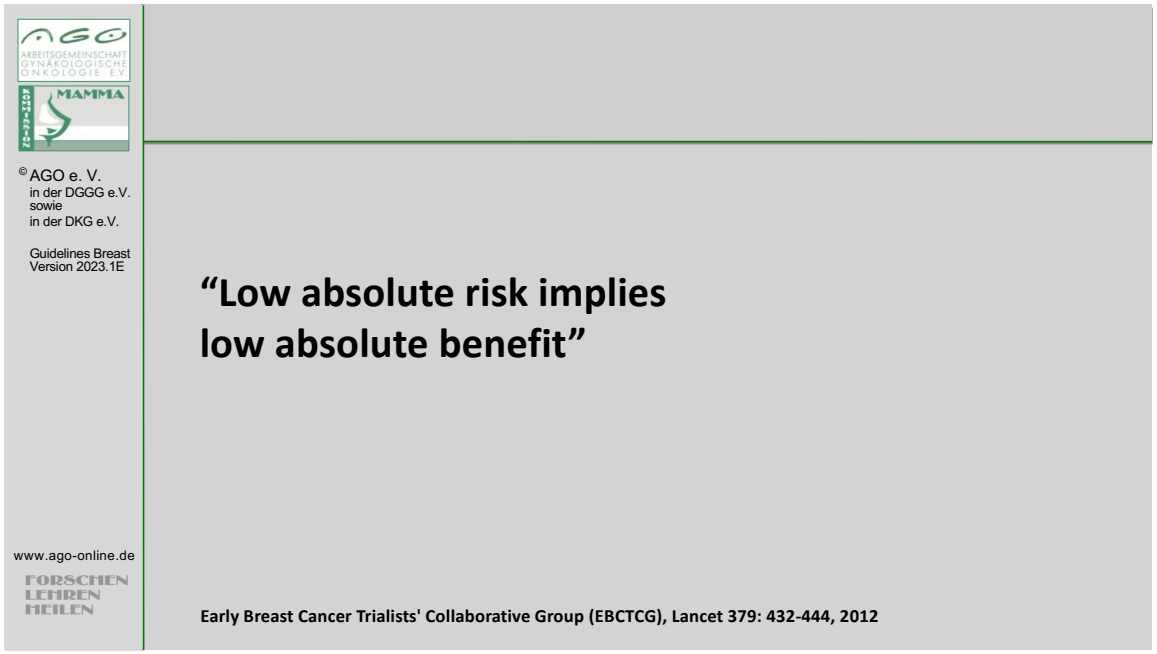

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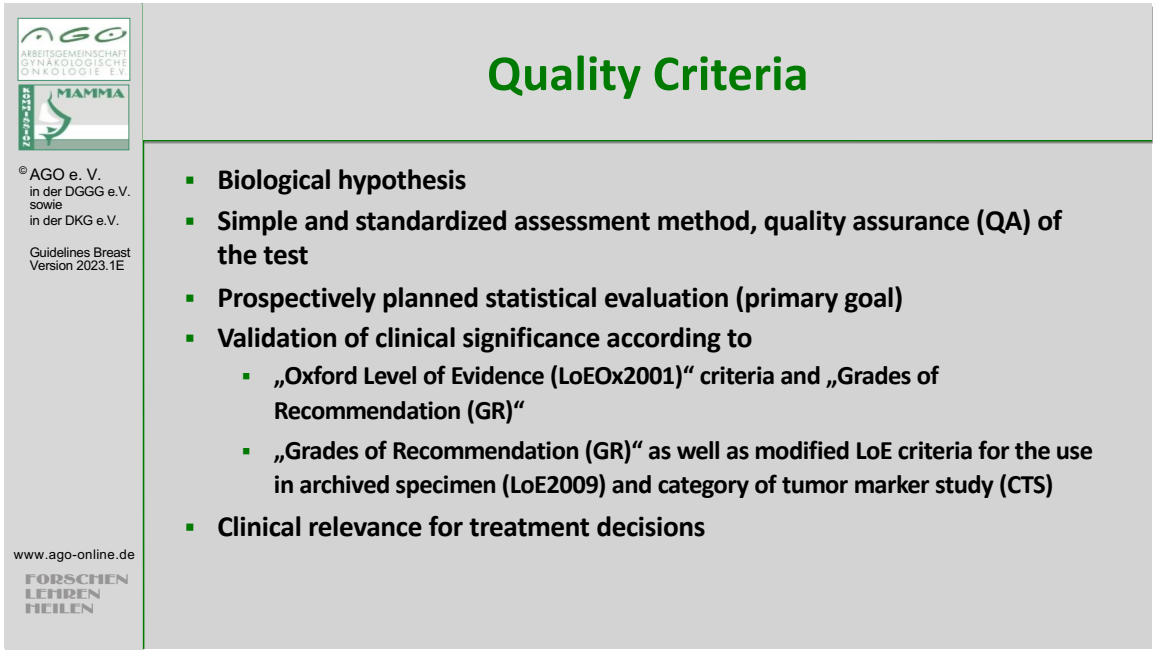

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Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE$_{Ox2001}$	Oxford GR	AGO
▪ Tumor size - pT	1a	A	++
▪ Axillary lymph node status - pN	1a	A	++
▪ Histological tumor type (mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis) - G	2a	B	++
▪ Age	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	+/-
▪ Obesity (BMI > 30 kg/m²)	1b	B	+
▪ Margins (resection status) - R0 / R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

General references

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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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Age

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Histologically proven lymph and/or blood vessel invasion

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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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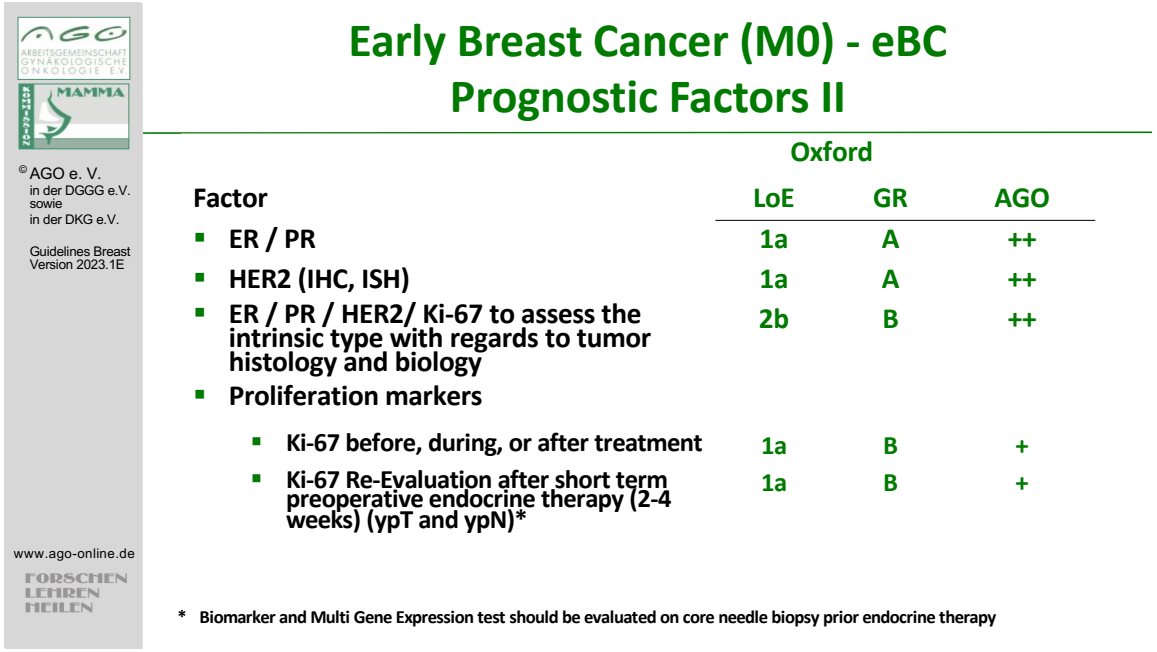

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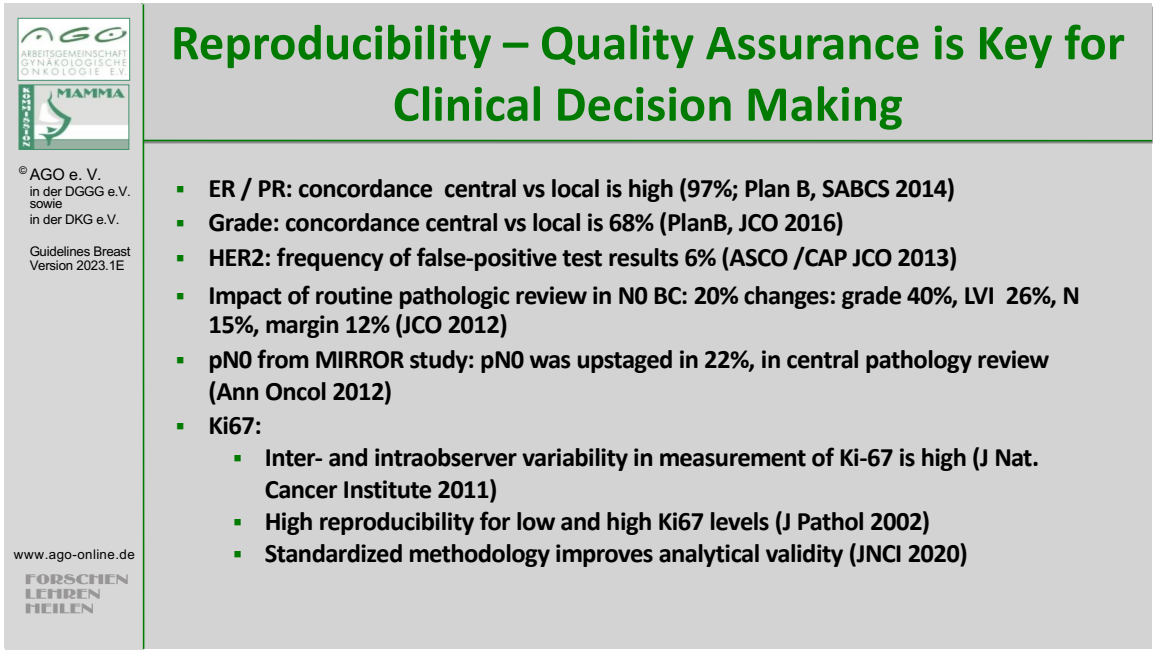

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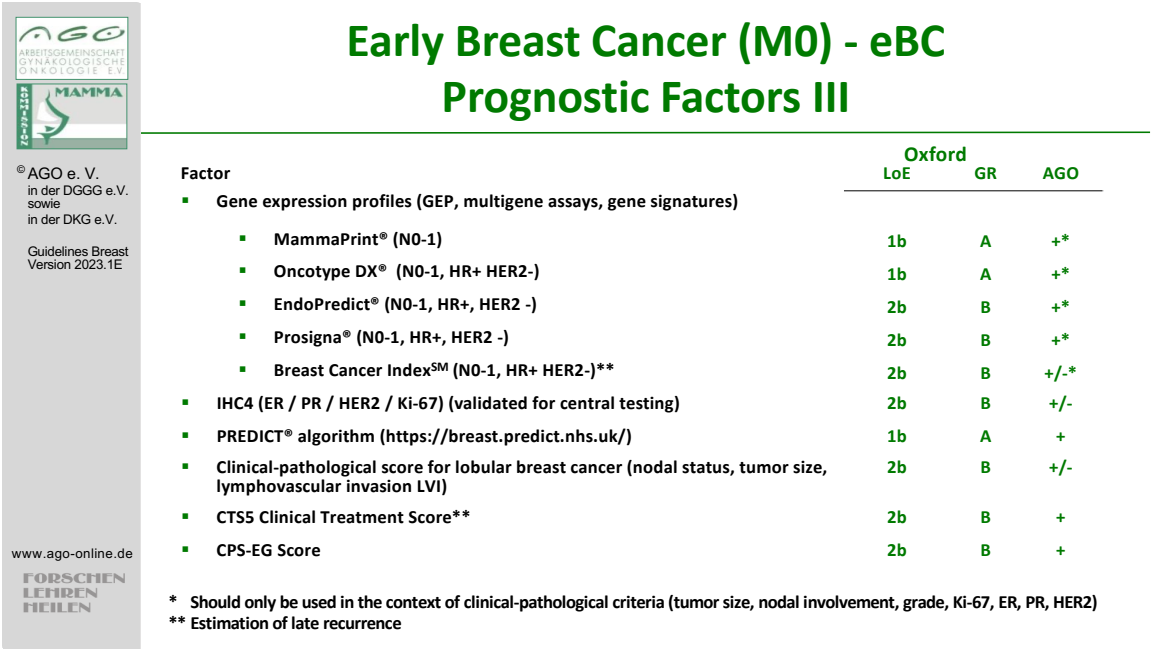

Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	Oxford LoE	Oxford 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	+
▪ 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	+

* 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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EndoPredict®

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Prosigna®

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Breast Cancer Index®

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Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®)*	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)	2a	B	+/-

* Validated clinical data only available for this assay

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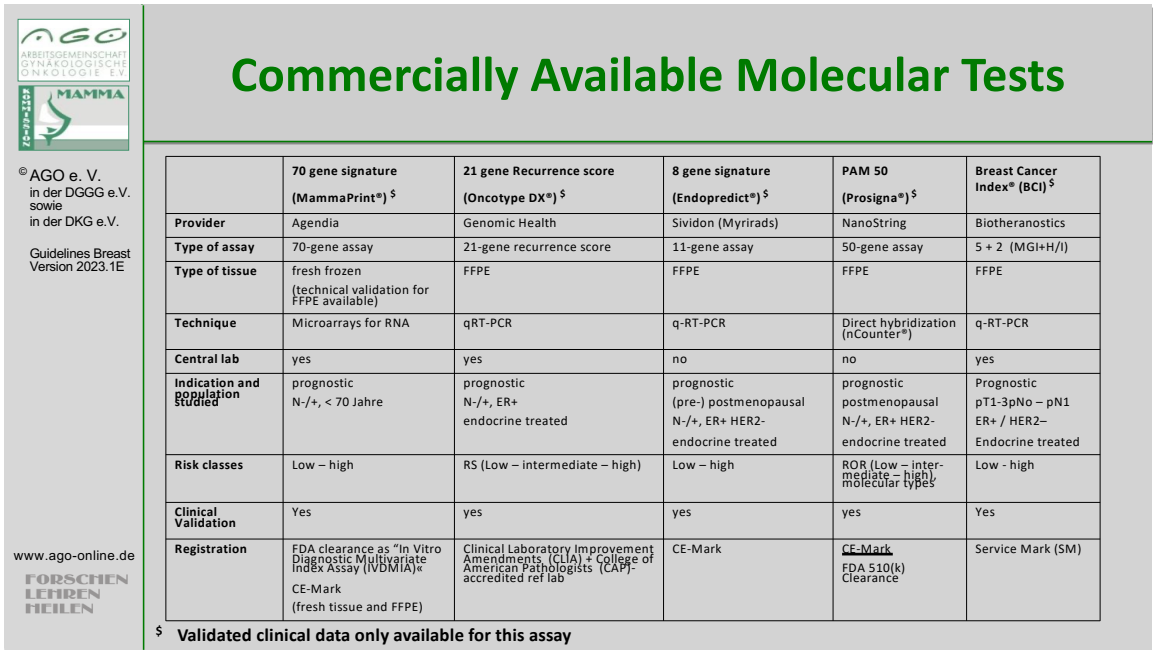

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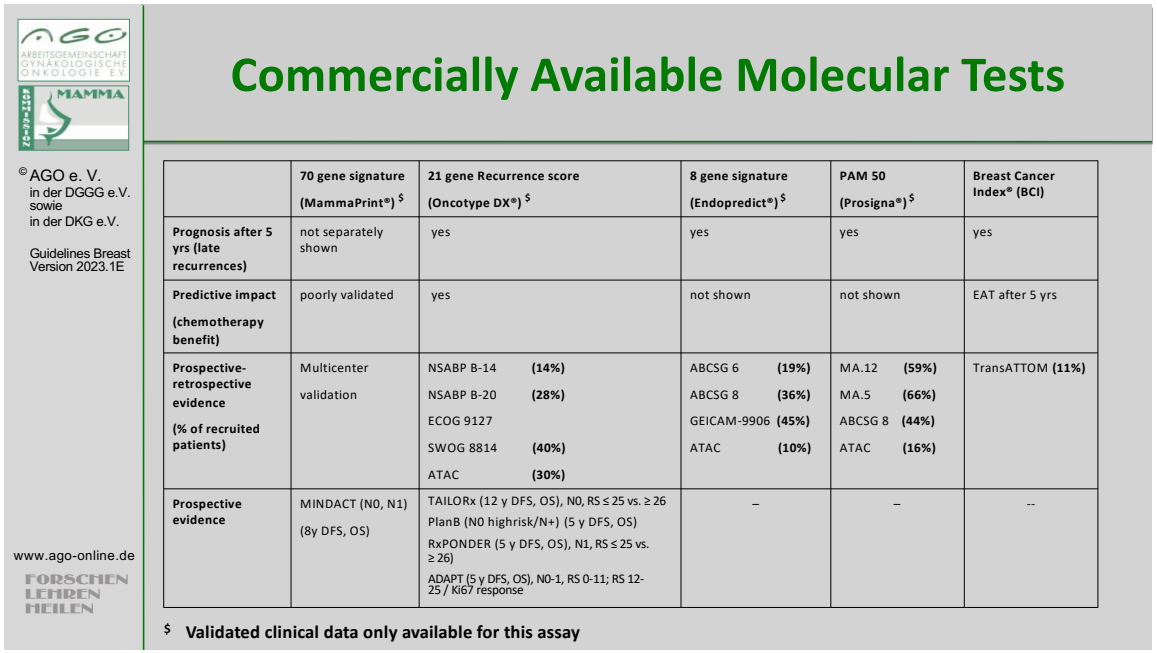

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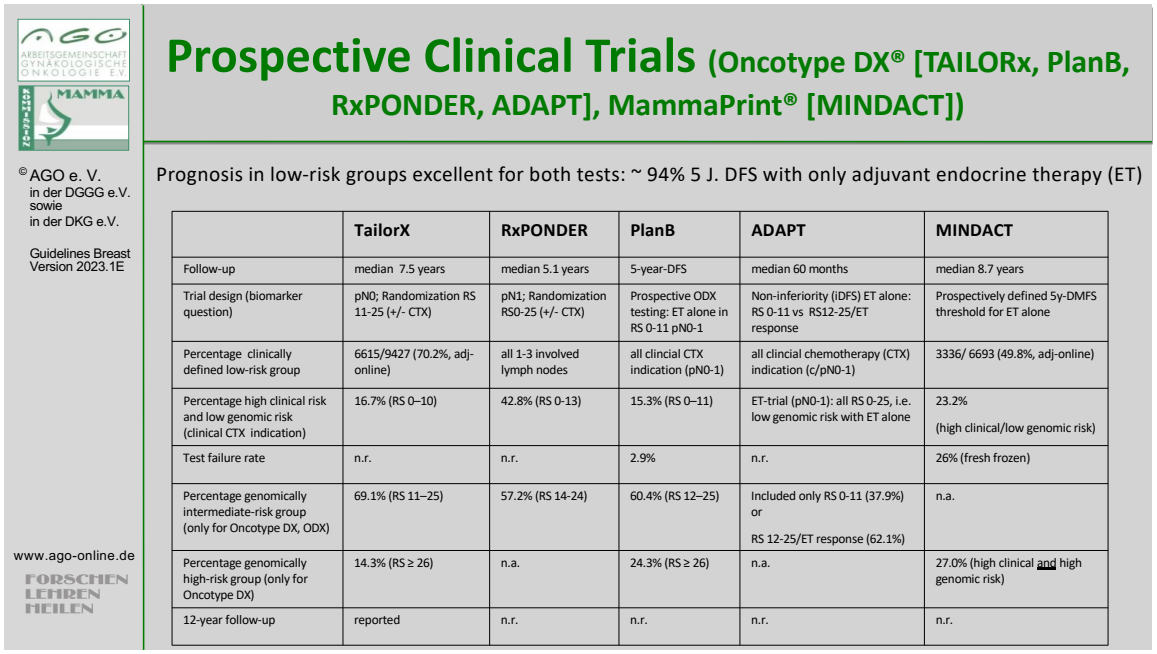

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	median 7.5 years	median 5.1 years	5-year-DFS	median 60 months	median 8.7 years
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority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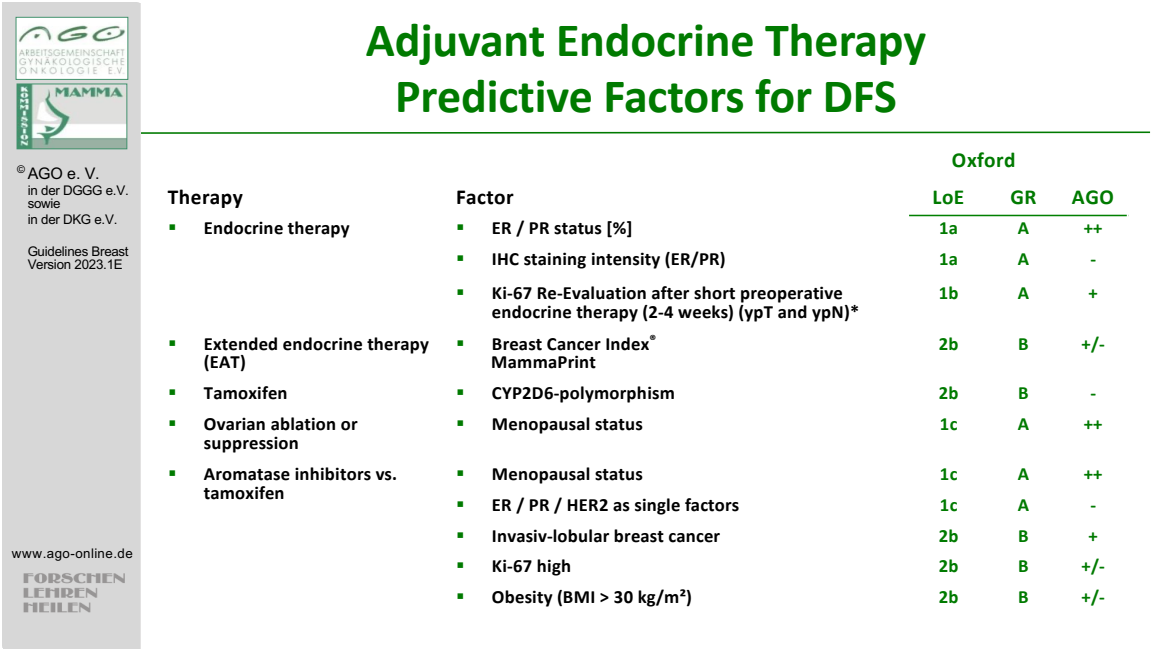

Adjuvant Endocrine Therapy
Predictive Factors for DFS

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) (ypT and ypN)*	1b	A	+
▪ Extended endocrine therapy (EAT)	▪ Breast Cancer Index® MammaPrint	2b	B	+/-
▪ Tamoxifen	▪ CYP2D6-polymorphism	2b	B	-
▪ Ovarian ablation or suppression	▪ Menopausal status	1c	A	++
▪ Aromatase inhibitors vs. tamoxifen	▪ Menopausal status	1c	A	++
	▪ ER / PR / HER2 as single factors	1c	A	-
	▪ Invasiv-lobular breast cancer	2b	B	+
	▪ Ki-67 high	2b	B	+/-
	▪ Obesity (BMI > 30 kg/m²)	2b	B	+/-

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Adjuvant Chemotherapy and Targeted Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	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	-
	TIL´s in TNBC	2b	B	+/-
▪ Anti-HER2-Therapy	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®)

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OncotypeDX

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EPclin (EndoPredict®)

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PAM-50 (Prosigna®)

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Anti-HER2 therapy

see evidence in chapter “Chemotherapy and targeted therapy”

PARPi

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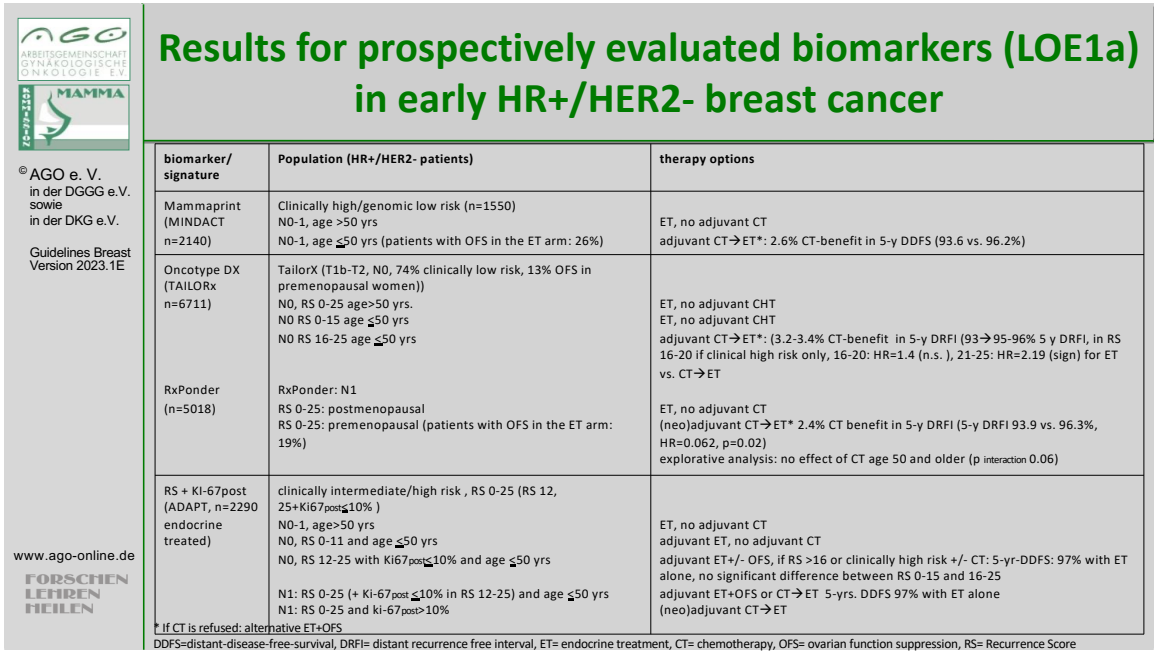

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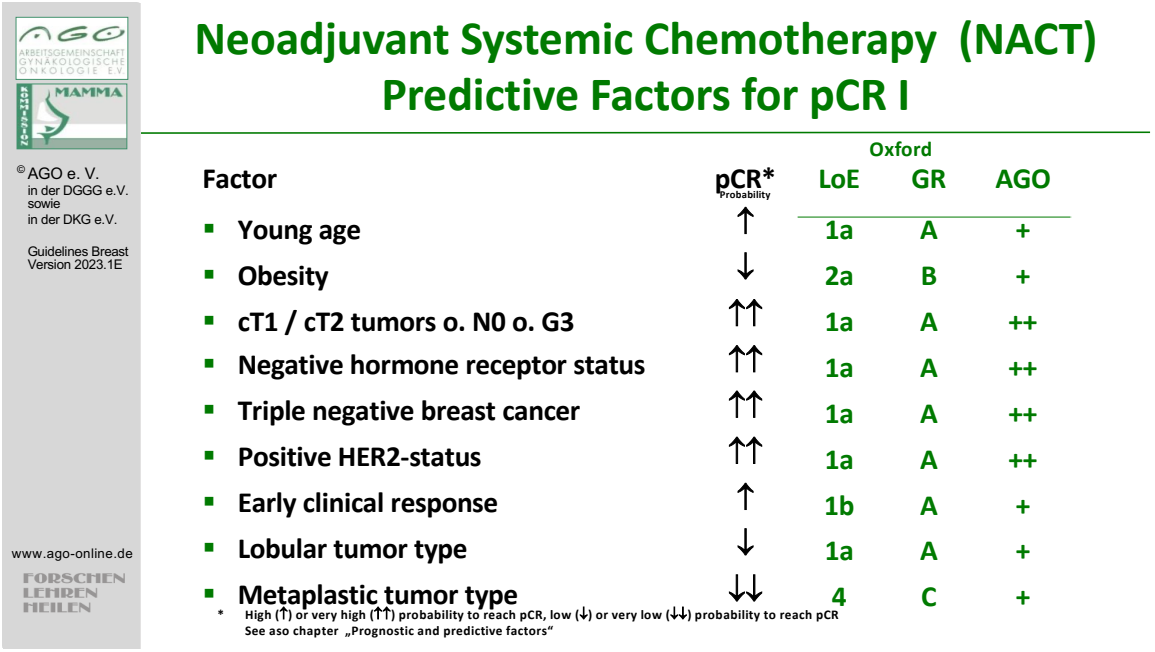

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford 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
See aso chapter „Prognostic and predictive factors"

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Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *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	+/-

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

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

TIL

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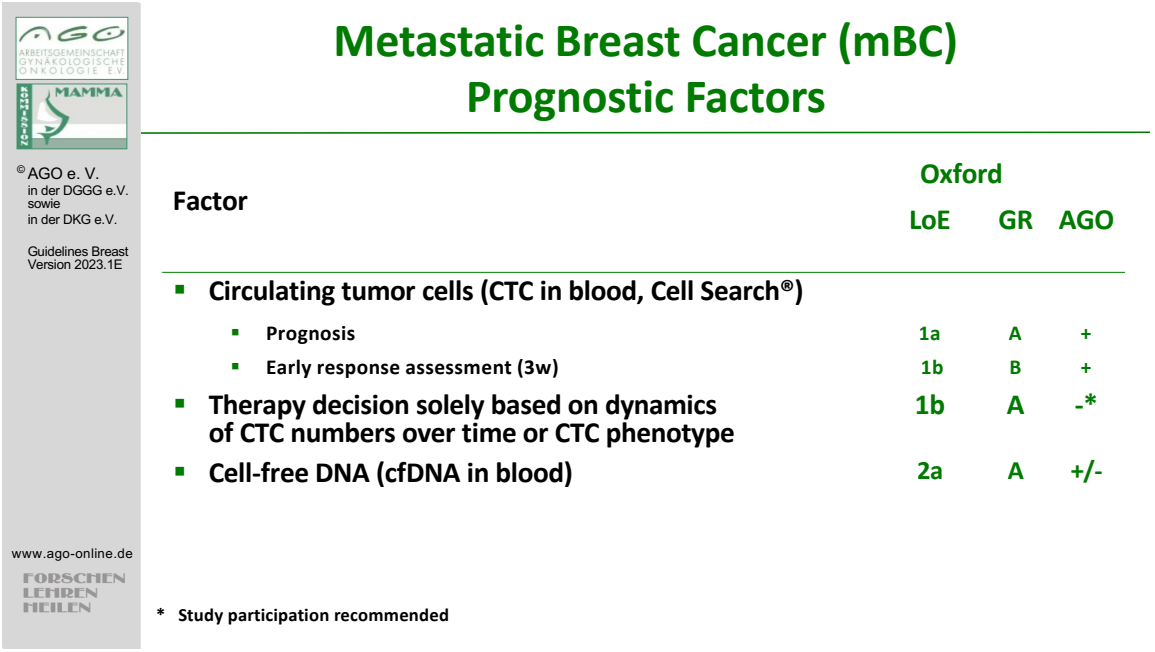

Metastatic Breast Cancer (mBC)
Prognostic Factors

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ **Circulating tumor cells (CTC in blood, Cell Search®)**			
▪ Prognosis	1a	A	+
▪ Early response assessment (3w)	1b	B	+
▪ **Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype**	**1b**	**A**	**-***
▪ **Cell-free DNA (cfDNA in blood)**	**2a**	**A**	**+/-**

* Study participation recommended

CTC

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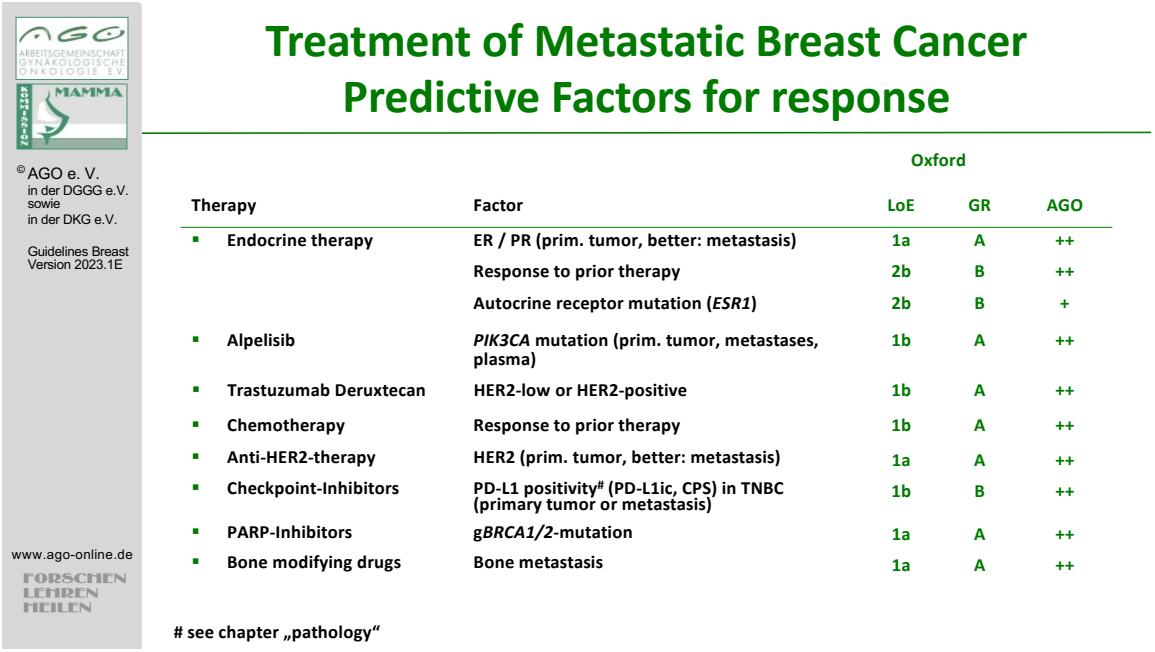

Treatment of Metastatic Breast Cancer
Predictive Factors for response

Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (*ESR1*)	2b	B	+
▪ Alpelisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Trastuzumab Deruxtecan	HER2-low or HER2-positive	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	g*BRCA1/2*-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++

see chapter „pathology“

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<u>CTC monitoring (any therapy)</u>

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

Altered genes	Therapeutic relevance	Gene region	Material	Oxford LOE	Oxford GR	Oxford AGO
BRCA1, BRCA2	Olaparib, Talazoparib Olaparib	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +/-
PALB2	Olaparib		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7, 9 and 20	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 oral SERDs	Exons 4, 7 and 8	Metastases, plasma Metastases, plasma	2b 1b	B 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

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

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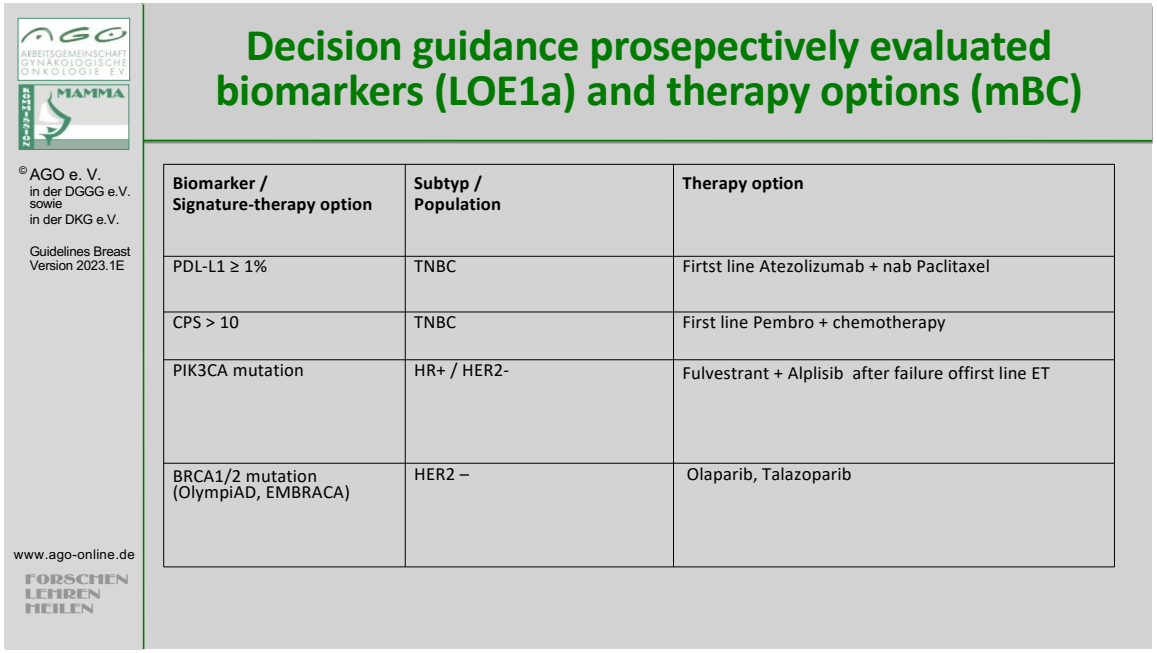

Biomarker / Signature-therapy option	Subtyp / Population	Therapy option
PDL-L1 ≥ 1%	TNBC	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TNBC	First line Pembro + chemotherapy
PIK3CA mutation	HR+ / HER2-	Fulvestrant + Alplisib after failure offirst line ET
BRCA1/2 mutation (OlympiAD, EMBRACA)	HER2 –	Olaparib, Talazoparib

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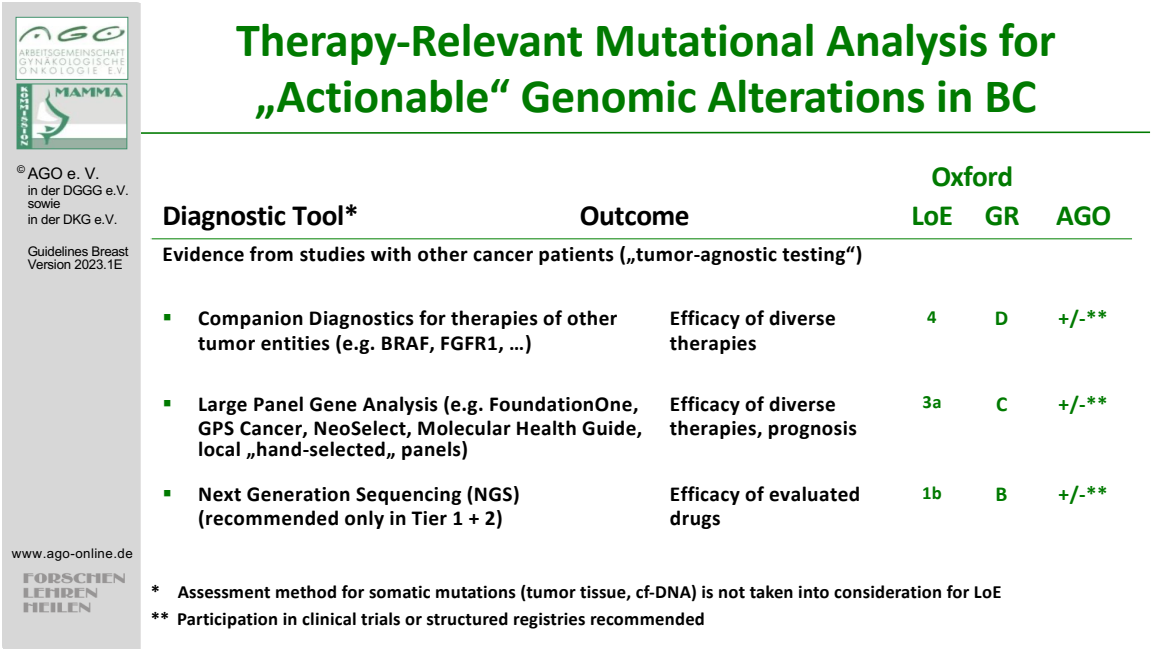

Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC

Diagnostic Tool*	Outcome	Oxford LoE	Oxford GR	AGO
Evidence from studies with other cancer patients („tumor-agnostic testing“)				
▪ Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, …)	Efficacy of diverse therapies	4	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)	Efficacy of diverse therapies, prognosis	3a	C	+/-**
▪ Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)	Efficacy of evaluated drugs	1b	B	+/-**

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended

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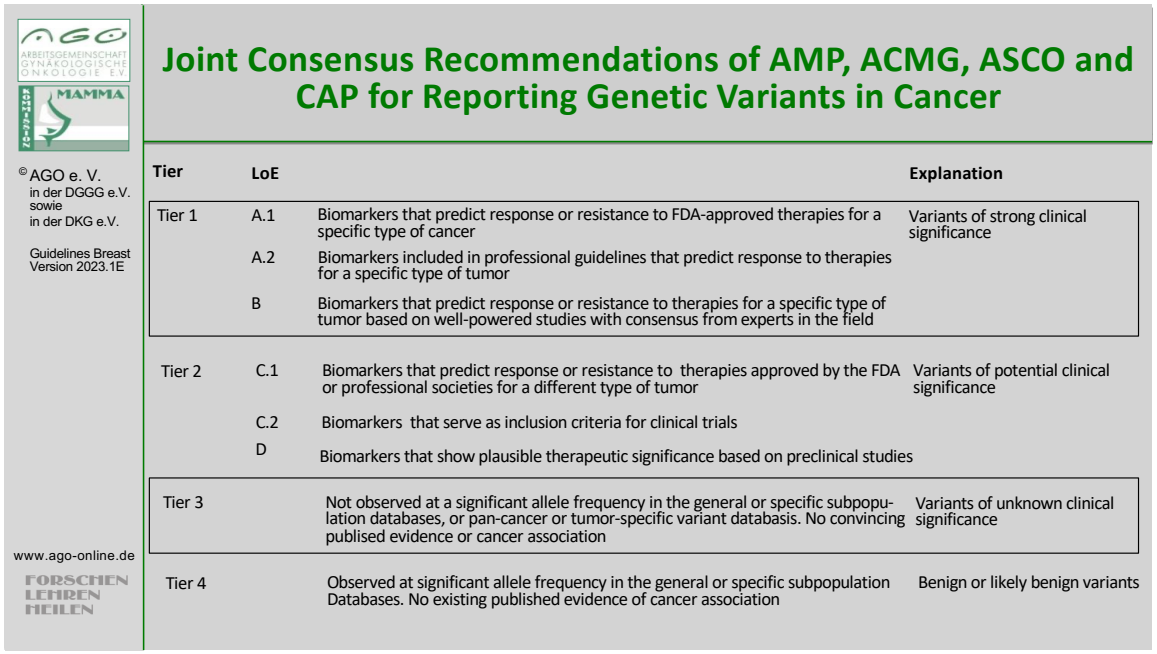

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