Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Prognostic and Predictive Factors

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Prognostic and Predictive Factors

- **Versions 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

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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.

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“Low absolute risk implies low absolute benefit”

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

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Quality Criteria

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

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in der DKG e.V.

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Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	LoE
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“

Prognostic Factors for an Ipsilateral Recurrence after DCIS II

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	LoE
Hereditary breast cancer risk	2a
Premenopausal at time of DCIS diagnosis	2a
High BMI	2a
High breast density	2a
Growth pattern (cribriform / solid versus „clinging“ / micro-papillary)	2b
Residual tumor-associated microcalcifications	2b
Architecture	2b
(modified) Van Nuys Prognostic Index/ mitotic rate	2b
Palpable DCIS	2b
ER-, HER2+, Ki-67+	2b
Scores: DCIS, Oncotype DX Breast DCIS Score (12 genes); CCP (23 genes)	2b
MSKCC Nomogram	2b
▪ DCISionRT	2b
Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b
DCIS compared to invasive carcinoma with higher risk of contralateral BC	2b
High number of TILs	2b

#see chapter „DCIS“

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

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Early Breast Cancer (M0) - eBC
Prognostic Factors II

Factor	Oxford LoE	Oxford GR	Oxford 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

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
▪ Immunhistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue; scored as percentage of positive tumor cell nuclei (ER positive if ≥ 1%, low positivity ≥ 1% to 10%; PR positive if ≥10%)	1a	A	++
▪ Detection of endocrine responsiveness by Ki-67 decrease to ≤ 10% after 3-4 weeks of preoperative endocrine therapy in primary breast cancer	1b	A	+
▪ 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“

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Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	Oxford LoE	Oxford GR	Oxford 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

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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, ctDNA in blood, prognostic for DFS, PFS, DDFS, OS)	2a	B	+/-

* Validated clinical data only available for this assay

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI) $
Provider	Agendia	Genomic Health	Sividon (Myrirads)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
Central lab	yes	yes	no	no	yes
Indication and population studied	prognostic N-/+, < 70 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated	Prognostic pT1-3pNo – pN1 ER+ / HER2– Endocrine treated
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – inter-mediate – high), molecular types	Low - high
Clinical Validation	Yes	yes	yes	yes	Yes
Registration	FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« CE-Mark (fresh tissue and FFPE)	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance	Service Mark (SM)

$ **Validated clinical data only available for this assay**

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Commercially Available Molecular Tests

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	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**

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

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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 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.

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Adjuvant Endocrine Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	Oxford 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)

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

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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-67_{post} ≤10% in RS 12-25) and age ≤50 yrs N1: RS 0-25 and ki-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

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford 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®(+ 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**	↑	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)

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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

Treatment of Metastatic Breast Cancer
Markers for Indication

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Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
▪ Elacestrant	Autocrine receptor mutation (*ESR1*) (metastases, plasma)	1b	B	++
▪ Alpelisib	*PIK3CA* mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Capivasertib	*PIK3CA, AKT1, PTEN* alterations (primary 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# (IC, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
	MSI/TMB	3	C	+
▪ PARP-Inhibitors	g*BRCA1/2*-mutation	1a	A	++
	sBRCA1/2/gPALB2	2b	B	+

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

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Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	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	++
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 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 # see chapter „pathology“

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

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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

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

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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

Joint Consensus Recommendations of AMP, ACMG, ASCO and CAP for Reporting Genetic Variants in Cancer

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Tier	LoE		Explanation
Tier 1	A.1	Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of cancer	Variants of strong clinical significance
	A.2	Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor	
	B	Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	
Tier 2	C.1	Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor	Variants of potential clinical significance
	C.2	Biomarkers that serve as inclusion criteria for clinical trials	
	D	Biomarkers that show plausible therapeutic significance based on preclinical studies	
Tier 3		Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databasis. No convincing publised evidence or cancer association	Variants of unknown clinical significance
Tier 4		Observed at significant allele frequency in the general or specific subpopulation Databases. No existing published evidence of cancer association	Benign or likely benign variants