

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Prognostic and Predictive Factors

Prognostic and Predictive Factors

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- **Versionen 2002–2024:**

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- **Version 2025:**

Fehm / Stickeler

Definition

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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”**

Quality Criteria for selection of prognostic/predictive markers

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- **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**

Prognostic Factors for an Ipsilateral Recurrence after DCIS I

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	<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“

Prognostic Factors for an Ipsilateral Recurrence after DCIS II

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

LoE

2a

2a

2a

2a

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

2b

#see chapter „DCIS“

Early Breast Cancer (M0) – eBC

clinical/histopathological Prognostic Factors I

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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

Early Breast Cancer (M0) - eBC

Histopathological Prognostic Factors II

Oxford

Factor

- ER / PR
- HER2 (IHC, ISH)
- ER / PR / HER2/ Ki-67 to assess the intrinsic type with regards to tumor histology and biology
- Proliferation markers
 - Ki-67 before, during, or after treatment
 - Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*

LoE

GR

AGO

1a

A

++

1a

A

++

2b

B

++

1a

B

+

1a

B

+

Reproducibility – Quality Assurance is Key for Clinical Decision Making

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- **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)**

Predictive pathology of endocrine responsiveness



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	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“

Early Breast Cancer (M0) - eBC

Prognostic Factors III

Oxford

Factor	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Gene expression profiles (GEP, multigene assays, gene signatures) <ul style="list-style-type: none"> ▪ MammaPrint® (N0-1) ▪ Oncotype DX® (N0-1, HR+ HER2-) ▪ EndoPredict® (N0-1, HR+, HER2 -) ▪ Prosigna® (N0-1, HR+, HER2 -) ▪ Breast Cancer IndexSM (N0-1, HR+ HER2-)** ▪ IHC4 (ER / PR / HER2 / Ki-67) (validated for central testing) ▪ PREDICT® algorithm (https://breast.predict.nhs.uk/) ▪ HER2DX (HER2+) ▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI) ▪ CTS5 Clinical Treatment Score** ▪ CPS-EG Score ▪ RCB Score 	<ul style="list-style-type: none"> 1b 1b 2b 2b 2b 2b 1b 2b 2b 2b 2b 2a 	<ul style="list-style-type: none"> A A B B B B A B B B B B 	<ul style="list-style-type: none"> +* +* +* +* +/-* +/- + +/- +/- + + +

* 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

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) §
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 (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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	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])

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 <u>and</u> 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

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Prognosis before treatment

- Disseminated tumor cells (DTC)
- Circulating tumor cells (CTC, Cell Search®)*
- ct-DNA

Prognosis after treatment (surgery +/- chemo)

- DTCs
- CTCs
- ct-DNA

Post(neo)adjuvant treatment decisions based on

- CTC-positivity
- ct-DNA positivity
- Mutations detected by ct-DNA

	Oxford		
	LoE	GR	AGO
	1a	A	+/-
	1a	A	+/-
	1a	A	+/-
	1b	A	+/-
	1b	A	+/-
	1b	A	+/-
	3a	C	-
	5	D	-**
	5	D	-**

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



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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

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Modified from Tegeler CM et al. Cancers 2024

Predictive Factors: Adjuvant Endocrine Therapy

Therapy	Factor	Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Endocrine therapy ▪ Extended endocrine therapy (EAT) ▪ Tamoxifen ▪ Ovarian ablation or suppression ▪ Aromatase inhibitors vs. tamoxifen 	<ul style="list-style-type: none"> ▪ ER / PR status [%] ▪ IHC staining intensity (ER/PR) ▪ Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) ▪ Recurrence Score 12-25 and Ki-67 decrease below <=10% after short preoperative endocrine therapy ▪ Breast Cancer Index[®] MammaPrint ▪ CYP2D6-polymorphism ▪ Menopausal status ▪ Menopausal status ▪ ER / PR / HER2 as single factors ▪ Invasiv-lobular breast cancer ▪ Ki-67 high ▪ Obesity (BMI > 30 kg/m²) 	<ul style="list-style-type: none"> 1a 1a 1b 1b 2b 2b 1c 1c 1c 2b 2b 2b 	<ul style="list-style-type: none"> A A A B B A A A B B B 	<ul style="list-style-type: none"> ++ - + + +/- - ++ - + +/- +/-

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



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Therapy	Factor	Oxford		
		LoE	G R	AGO
<ul style="list-style-type: none"> 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	1a	A	+/-
<ul style="list-style-type: none"> Anti-HER2-Therapy 	HER2 (IHC, ISH)	1a	A	++
<ul style="list-style-type: none"> 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

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

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Neoadjuvant Systemic Chemotherapy (NACT)

Predictive Factors for pCR I



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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

Neoadjuvant Systemic Chemotherapy (NACT)

Predictive Factors for pCR II



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Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> Gene expression profiles (gene signatures) (Mammaprint[®] (+ Blueprint[®]), Endopredict[®] Oncotype DX[®], Prosigna[®], PAM50[®], Breast Cancer IndexSM) 	↑	2b	B	+/-
<ul style="list-style-type: none"> HER2DX (27 genes, response to trastuzumab/pertuzumab) 	↑	2b	B	+/-
<ul style="list-style-type: none"> Ki-67 	↑	2b	B	+
<ul style="list-style-type: none"> Tumor infiltrating lymphocytes** 	↑	1a	A	+
<ul style="list-style-type: none"> PIK3CA mutation (for HER2-positive BC) 	↓	2a	B	+/-
<ul style="list-style-type: none"> gBRCA-mutation (for the effect of chemotherapy) 	↑	2b	B	+
<ul style="list-style-type: none"> gBRCA-mutation (for the effect of platinum) 	↔	2b	B	+/-
<ul style="list-style-type: none"> 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)

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



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Prognosis

- Circulating tumor cells (CTC, Cell Search®)
- ct-DNA

Early therapy response (after 2-3 weeks of treatment)

- CTCs
- ct-DNA

Therapy decisions based on

- Dynamics of CTC numbers
- Phenotype of CTCs
- ct-DNA-dynamics
- *ESR1*-monitoring
- Using ct-DNA to indicate approved mutation based treatments (e.g. *ESR1*, *PIK3CA*)

Oxford

LoE	GR	AGO
1a	A	+
1a	A	+
1a	A	+
2a	B	+
1b	A	-*
2b	B	-/+*
5	D	-*
2b	B	+/-*
1a	A	++**

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

Treatment of Metastatic Breast Cancer

Markers to determine treatment indications



Oxford

Therapy	Factor	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 [#] (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

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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	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“

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



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	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

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