



AGO Breast Panel Recommendations for the use of treatment-relevant biomarkers in early and advanced breast cancer—2026 Update

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ABSTRACT

Biomarkers are integral to modern breast cancer management by providing essential information for prognosis and treatment selection. This review presents the 2026 update of the recommendations of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group, AGO) on therapy-relevant prognostic and predictive biomarkers. The recommendations are based on a structured evaluation of the most recent and clinically relevant evidence using the AGO grading system to support decision-making in routine clinical practice.

1. Introduction

In modern breast cancer (BC) treatment, biomarkers are increasingly used to guide therapeutic decision-making. Prognostic biomarkers provide information on the risk of recurrence, disease progression, or death and are independent of the administered treatment. Nevertheless, prognostic information is therapeutically relevant, as it is essential to estimate an absolute treatment benefit, thereby assessing the need for a (potentially toxic) oncologic therapy (“Who requires therapy?”). In contrast, predictive markers forecast the likelihood of response to a given treatment and are therefore used to also determine relative therapy efficacy (“Does a therapy work?”). Many biomarkers have both prognostic and predictive value.

The following overview summarizes the recommendations of the Breast Expert Panel of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO; German Gynecological Oncology Group) regarding therapy-relevant prognostic and predictive biomarkers, which are updated annually. This update is based on a structured evaluation algorithm. The most recent and clinically relevant publications are systematically reviewed, and the strength of each recommendation is defined using the 5-level AGO rating system, which provides recommendations for use in clinical practice (Table 1). The focus is on clinically relevant recommendations and those associated with approved therapeutic consequences.

2. Patient characteristics, tumor stage, and histopathologic factors

Age (AGO ++), menopausal status (AGO ++), body mass index (BMI, AGO +), concomitant medications, physical and psychological comorbidities, performance status, as well as the patient's preferences are key factors in determining an optimal treatment strategy [1,2].

Table 1
AGO recommendation levels.

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restrictions, and should be performed
+	This investigation or therapeutic intervention has limited benefit for patients and can be performed
+/-	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge, a general recommendation cannot be given
-	This investigation or therapeutic intervention can be of disadvantage to patients and might not be performed
--	This investigation or therapeutic intervention is of clear disadvantage to patients and should be avoided or omitted in any case

In early BC (eBC), local tumor extent in the breast (T stage, AGO ++), involvement of ipsilateral lymph nodes (N category, AGO ++), and resectability (R category, AGO +) determine the risk of disease recurrence and distant metastasis [3,4]. Moreover, (y)TNM staging after neoadjuvant systemic therapy (NAT) is used to assess treatment response and thereby allows further refinement of prognosis. In particular, pathological complete response (pCR) in the breast and lymph nodes (AGO ++), as well as the CPS-EG score (AGO +), are used to guide postneoadjuvant systemic treatment [5–7]. Table 2 summarizes treatment relevant biomarkers and their clinical implications in patients with eBC.

Histopathologic prognostic factors include histology (AGO ++), tumor grade according to Elston and Ellis (AGO ++), as well as multiple immunohistochemical markers, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which are discussed in the next chapter [1,8,9]. Various online prognostic tools (e.g., PREDICT, CTS-5) integrate multiple prognostic factors to estimate recurrence risk (AGO +) [10,11].

The presence of distant metastases (M stage) distinguishes a curative from a non-curative treatment setting, which is associated with fundamentally different therapeutic objectives (AGO ++). In metastatic BC (mBC), overall survival is determined by tumor burden, the pattern of metastatic involvement (e.g. cerebral, visceral, non-visceral, bone-only), and the time point of metastatic occurrence (de novo versus secondary metastatic disease) [12]. Moreover, disease-free interval as well as the number and duration of response to prior treatment lines are important for guiding therapeutic decisions and estimating overall survival. For ER/PR-positive BC, endocrine-sensitive and endocrine-resistant disease are defined according to the timing of relapse and disease progression. Primary endocrine resistance is defined as relapse within the first 2 years of adjuvant endocrine treatment or disease progression within the first 6 months of first-line endocrine treatment for mBC. Secondary (acquired) endocrine resistance is defined as relapse while on adjuvant endocrine treatment after the first 2 years, relapse within 12 months after completion of adjuvant endocrine treatment, or disease progression after 6 months of endocrine treatment for mBC [12].

3. Immunohistochemical markers

In clinical practice, BC subtyping is based on the assessment of hormone receptors (HR), namely the estrogen receptor (ER) and progesterone receptor (PR), as well as the human epidermal growth factor receptor 2 (HER2) status [13]. This classification defines the subtypes HR-positive/HER2-negative (often referred to as luminal-like BC), HER2-positive/HR-positive as well as HER2-positive/ER-negative, and

Table 2
Treatment-relevant biomarker in early breast cancer.

Population	Biomarker	Consequence
All patients	Menopausal status (AGO ++)	Type of Endocrine treatment
All patients	Disease staging and pathological assessment (AGO ++)	Use and intensity of chemotherapy Intensity of endocrine treatment Use and intensity of radiotherapy Use of Ribociclib ^a / Abemaciclib ^b Use and intensity of HER2-directed treatment ^c Use of Pembrolizumab ^d Use of Olaparib ^e
All patients	ER, PR, HER2, (dynamic) Ki67 (AGO ++)	Endocrine treatment (if HR+) ^f Chemotherapy (if high risk) Ribociclib (if intermediate-high risk HR+/HER2-) ^g Abemaciclib (if high risk HR+/HER2-) ^b HER2-directed treatment (if HER2+) ^c Pembrolizumab (if high risk TNBC) ^d
HR+/HER2- AND NO-1 AND therapeutic relevance	Gene expression arrays (AGO +)	Chemotherapy (if high risk) ^g Ribociclib (if high risk) ^a Olaparib (if high risk) ^e
family history OR therapeutic relevance	gBRCA1, gBRCA2 (AGO ++)	

^a Three years of adjuvant ribociclib is indicated in patients with ≥ 1 positive lymph node or in node-negative patients with T2 disease and high-risk tumor biology (Ki-67 > 20%, grade 3, or a high-risk gene expression signature), or with T3 disease.

^b Two years of adjuvant abemaciclib is indicated in patients with ≥ 4 positive lymph nodes or in patients with 1–3 positive lymph nodes and either grade 3 disease or a tumor size ≥ 5 cm.

^c In stage II–III HER2-positive disease, NAT combined with dual HER2 blockade (trastuzumab and pertuzumab) is the preferred treatment option. Patients achieving pCR should continue trastuzumab for a total duration of 1 year, combined with pertuzumab in case of initial node-positive disease. T-DM1 is indicated for patients who do not achieve pCR. Neratinib may be considered in patients with HR+/HER2+ disease.

^d Pembrolizumab is indicated in patients with stage II–III TNBC in combination with neoadjuvant chemotherapy (taxane plus carboplatin followed by AC/EC), irrespective of PD-L1 status, and should be continued after surgery for an additional 9 cycles.

^e Olaparib is indicated in patients with germline BRCA1 or BRCA2 mutations and triple-negative disease with residual invasive disease after neoadjuvant chemotherapy or stage II–III disease treated with adjuvant chemotherapy. In HR+/HER2-disease, olaparib is indicated in patients with a CPS-EG score ≥ 3 after neoadjuvant chemotherapy or ≥ 4 positive lymph nodes if treated with adjuvant chemotherapy.

^f The benefit of endocrine therapy in tumors with low ER expression (1–10%) is uncertain.

^g Gene expression assays should be interpreted in conjunction with established clinicopathological risk factors.

triple-negative BC (TNBC), which determine prognosis and treatment algorithms. Of note, intrinsic subtypes (i.e., luminal A, luminal B, HER2-enriched, and basal-like) may overlap with these histopathologic subtypes but are defined on a molecular basis (gene expression patterns, e.g., the PAM50 assay) and can therefore only be approximated using classical immunohistochemistochemical staining [1]. As HR and HER2 status may change during the course of disease, histological reassessment of recurrent or metastatic lesions should be performed whenever feasible (AGO ++). [14,15].

The ER/PR status is of prognostic relevance (AGO ++). [16,17],

predictive of response to endocrine therapy (AGO ++). [18,19] and, when negative or low positive, is associated with better response to NAT (AGO ++). [20]. Classification of a carcinoma as ER- or PR-positive requires at least 1% positive tumor cell nuclei. As there is limited data on benefit from endocrine therapy in tumors with 1–10% positive cells, these tumors should be reported as “ER Low Positive” and considered separately in treatment planning (AGO ++). Interpretation of immunohistochemical staining results should follow the guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) [21].

HER2 testing should also follow the recommendations of the ASCO/CAP guidelines [22]. The HER2 status is considered positive when immunohistochemical staining yields a score of 3+, defined by intense, complete circumferential membrane staining in more than 10% of invasive tumor cells. In cases with a score of 2+ (weak to moderate complete membrane staining in >10% of invasive tumor cells), additional in situ hybridization (CISH, SISH, or FISH) is required (AGO ++). [22]. Tumors with a score of 3+ or 2+ with positive in situ hybridization are classified as HER2-positive. HER2-positive tumors respond to HER2-targeted therapies, including trastuzumab, pertuzumab, tucatinib, neratinib, lapatinib, and HER2-directed antibody–drug conjugates (ADCs), such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (AGO ++). HER2 status is also associated with prognosis (AGO ++). and response to NAT (AGO ++). [23]. In metastatic breast cancer (MBC), the ADC trastuzumab deruxtecan is effective also in tumors with low (1+ or HER2 2+ with ISH-negative) and ultralow (HER2 0 with faint membrane staining) HER2 expression (AGO ++). [24–26].

Ki-67 is a proliferation marker that correlates with pCR rates following NAT (AGO +). [27,28]. Due to its prognostic properties, it is used as a decision aid for or against (neo)adjuvant chemotherapy in HR-positive/HER2-negative EBC. Endocrine response can be assessed by analyzing changes in Ki-67 expression after a short course (2–4 weeks) of preoperative endocrine induction treatment (AGO +). [29]. A decrease to <10%, in conjunction with other prognostic factors like gene expression markers supports decision-making regarding (neo)adjuvant chemotherapy [30].

The programmed death ligand 1 (PD-L1) is an immune checkpoint molecule that binds to its receptor PD-1, thereby suppressing T-cell activity [31]. PD-L1 is expressed by tumor cells as well as by lymphocytes within the tumor microenvironment. Immune checkpoint inhibitors block the PD-1/PD-L1 interaction, thereby restoring antitumor immune activity. PD-L1 assessment in metastatic TNBC is predictive of response to the checkpoint inhibitors pembrolizumab and atezolizumab [32,33]. Importantly, assay methods and cutoffs are indication- and drug-specific. Pembrolizumab is approved in combination with chemotherapy for metastatic breast cancer patients with a combined positive score (CPS) ≥ 10 (AGO ++), whereas atezolizumab is used in tumors with an immune cell score (IC score) ≥ 1 . Importantly, the 22C3 combined positive score used for pembrolizumab and the SP142 immune-cell score used for atezolizumab are not interchangeable, as they identify only partially overlapping patient populations [34]. Substitution of one assay for the other is not validated and may therefore result in inappropriate patient selection. For NAT of TNBC, pembrolizumab is approved regardless of PD-L1 expression [35].

4. Gene expression signatures

Several prognostic gene expression signatures are commercially available (Table 3). In Germany, Oncotype DX (AGO +), EndoPredict (AGO +), Prosigna (AGO +), and MammaPrint (AGO +) are commonly used in clinical practice. All these genomic assays integrate the activity of multiple genes into a prognostic score and are applied in HR-positive/HER2-negative EBC to support chemotherapy decision making. While Oncotype DX, MammaPrint, and, most recently, Prosigna have been validated for treatment decision-making in prospective randomized controlled phase III trials (TAILORx/RxPONDER, MINDACT, and

Table 3

Gene expression signatures.

Gene expression profiles (GEP, multigene assays, gene signatures)	AGO
MammaPrint® (N0-1)	+ ^a
Oncotype DX® (N0-1, HR + HER2-)	+ ^a
EndoPredict® (N0-1, HR+, HER2 -)	+ ^a
Prosigna® (N0-1, HR+, HER2 -)	+ ^a
Breast Cancer Index SM (N0-1, HR + HER2-) ^b	+/- ^b

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

^b Estimation of late recurrence.

OPTIMA, respectively), evidence supporting EndoPredict is derived primarily from retrospective analyses of prospective cohorts [36–42]. Patients with invasive EBC of at least grade 2 and at least 20 mm tumor size may additionally be treated with the CDK4/6 inhibitor ribociclib in case of a high-risk genomic assay [43]. Gene expression signatures should always be assessed on untreated tumor tissue (i.e., on core biopsies in the case of endocrine induction therapy) and should be interpreted in the context of established clinical-pathological criteria (menopausal status, tumor size, lymph node involvement, grade, Ki-67, ER, PR, HER2).

5. Treatment-relevant germline alterations

Therapy-relevant germline alterations in cancer predisposition genes are inherited in an autosomal dominant manner. As these mutations are present in all somatic cells, nucleated peripheral blood cells are used for detection. Pathogenic germline mutations in BRCA1, BRCA2, and PALB2 (gBRCA1, gBRCA2, and gPALB2 mutations) not only increase the risk of developing BC (and other malignancies) but are also predictive of response to systemic therapies, particularly PARP inhibitors (Table 4). The presence of a gBRCA1 or gBRCA2 mutation also increases the likelihood of achieving pCR after neoadjuvant chemotherapy,

Table 4

Clinically relevant germline alterations in early and metastatic breast cancer.

Subtype	Marker	Timepoint of assessment ^a	Therapeutic consequence
Early breast cancer			
HR+/HER2-	gBRCA1 (AGO++) gBRCA2 (AGO++)	after neoadjuvant chemotherapy with non-pCR and CPSEG≥3 or adjuvant chemotherapy and at least pN2	Olaparib, 1year adjuvant in combination with endocrine therapy (AGO++)
TNBC	gBRCA1 (AGO++) gBRCA2 (AGO++)	after neoadjuvant chemotherapy with non-pCR or adjuvant chemotherapy and at least pN1 or pT2	Olaparib, 1year adjuvant (AGO++)
Metastatic/advanced breast cancer			
HR+/HER2-	gBRCA1 (AGO++) gBRCA2 (AGO++) gPALB2 (AGO++)	after 1st-Line ET-based treatment simultaneously to BRCA testing	Olaparib or Talazoparib until disease progression (AGO++) Olaparib until disease progression (AGO+) ^b
TNBC	gBRCA1 (AGO++) gBRCA2 (AGO++) gPALB2 (AGO++)	from 1st line treatment on simultaneously to BRCA testing	Olaparib or Talazoparib until disease progression (AGO++) Olaparib until disease progression (AGO+) ^b

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; BRCA1/2, breast cancer1/2 gene; germline (g), HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PALB2, partner and localizer of BRCA2; TNBC, triple negative breast cancer.

^a Patients who meet the criteria for an increased familial risk are tested at any time point, regardless of tumor biology or treatment setting.

^b not approved.

irrespective of whether carboplatin is included (AGO +) [44]. Therefore, testing for gBRCA1/2 (AGO ++) and gPALB2 (AGO +) alterations is indicated whenever the results may inform systemic treatment decisions, regardless of the familial cancer risk.

In patients with a gBRCA1 or gBRCA2 mutation, one year of (post-neo-)adjuvant olaparib is indicated in HER2-negative EBC with an increased risk of recurrence (AGO ++) [45]. Risk stratification follows the inclusion criteria of the OlympiA trial: In HR-positive/HER2-negative disease after neoadjuvant chemotherapy, absence of pCR and a CPS-EG score ≥3, or after adjuvant chemotherapy with at least four pathologically involved lymph nodes (≥pN2); in TNBC after NAT in the absence of pCR, or after adjuvant chemotherapy with lymph node involvement (≥pN2) or a tumor size ≥2 cm (≥pT2).

In MBC, gBRCA1/2 or gPALB2 mutations are detected in approximately 6% of patients, independent of family history [46]. In HER2-negative disease, poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib (OlympiAD trial) and talazoparib (EMBRACA trial) are recommended (HR-: AGO ++/HR + AGO +) [47,48]. Although PARP inhibitors are not approved for gPALB2 mutations, their use is supported by compelling data from a single-arm phase II study (AGO +) [49]. There is also no formal approval for PARP inhibitors in the presence of somatic BRCA1 or BRCA2 mutations (sBRCA1, sBRCA2); however, treatment may be considered on an individual basis, for example after a recommendation of a molecular tumor board (AGO ± for olaparib) [49].

In Germany, any licensed physician may initiate germline genetic testing after obtaining written informed consent in accordance with the Genetic Diagnostics Act (GenDG), provided that the test result is required as a predictive factor for treatment determination. In these cases, additional certification in genetic counseling is not required. If a pathogenic mutation is identified, the patient should subsequently receive formal genetic counseling by a physician with appropriate training.

6. Somatic alterations

Somatic genetic alterations arise during tumorigenesis or tumor progression and are therefore restricted to tumor cells; some may occur early in the course of disease, whereas others emerge at later stages or are induced by treatment pressure. Many treatment-relevant alterations affect signal transduction pathways regulating proliferation and differentiation and are particularly relevant for the management of endocrine-resistant HR-positive/HER2-negative MBC [50,51].

The PI3K (phosphatidylinositol 3-kinase)/AKT/PTEN (phosphatase and tensin homolog) signaling pathway regulates cell growth, survival, and metabolic processes. The PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene encodes a catalytic subunit of PI3K, a key component of this pathway. Therapy-relevant PIK3CA mutations are present in approximately 35–40% of HR-positive/HER2-negative tumors [52]. These are frequently hotspot mutations (especially E542K, E545K, H1047R and H1047L) that remain stable throughout disease progression [53]. Given the high concordance across disease stages, primary tumor tissue, metastatic tissue, or liquid biopsy (ctDNA analysis) may be used for testing. However, as mutations can sometimes also be acquired, current tumor tissue or ctDNA should be preferred whenever possible.

The following PI3K inhibitors are approved for use in HR-positive/HER2-negative MBC with PIK3CA mutations:

–Inavolisib in combination with palbociclib and fulvestrant as first-line therapy in patients with endocrine resistance (recurrence during or within 12 months after adjuvant endocrine therapy), based on the INAVO-120 trial (AGO ++) [54].

–Alpelisib (not available in Germany) in combination with fulvestrant after prior endocrine therapy from second-line treatment onward, based on the SOLAR-1 trial (AGO ±) [55].

Accordingly, mutation status should be known no later than after first-line therapy; in endocrine-resistant patients, already at the time of diagnosis of distant disease (AGO ++).

Activation of the PI3K/AKT/PTEN pathway may also occur through AKT mutations or loss of the inhibitory tumor suppressor PTEN, observed in approximately 2–3% and 5–10% of patients with MBC, respectively [56]. Again, high concordance between primary and metastatic lesions has been demonstrated. Like PIK3CA, AKT alterations can be detected using ctDNA. However, due to the lower sensitivity of ctDNA-based assays for PTEN deletions, tumor tissue should preferably be used for PTEN assessment. Based on the CAPitello-291 trial, the only recently approved AKT inhibitor is capivasertib, which is used in combination with fulvestrant in patients with disease progression under endocrine therapy and alterations in the PI3K/AKT/PTEN pathway (AGO +) [57]. Therefore, PIK3CA, AKT, and PTEN status should be determined no later than at the start of second-line therapy (AGO +).

Under the selective pressure of endocrine therapy, mutations may arise in the ESR1 gene which encodes the estrogen receptor. These mutations typically affect the ligand-binding domain (especially D538G, Y537S, Y537N, Y537C, and E380) and result in ligand-independent receptor activation [58]. While ESR1 mutations are rare in untreated tumors, they are detected in approximately 20–40% of endocrine-pretreated MBC [59]. Therefore, to accurately capture current mutation status, testing should not be performed on archived tissue. Instead, liquid biopsy (ctDNA analysis) represents an optimal approach to assess current mutation status and to address tumor heterogeneity across metastatic sites to track resistance against aromatase inhibitors (AGO ++) [60–62]. As a previously negative result may no longer reflect the current tumor biology, ctDNA based ESR1 testing should be considered at each disease progression during endocrine-based treatment.

Oral selective estrogen receptor degraders (SERDs) can overcome endocrine resistance driven by ESR1 mutations. The oral SERDs elacestrant (EMERALD trial) and imlunestrant (EMBER-3 trial) are approved as monotherapy for the treatment of HR-positive/HER2-negative MBC with ESR1 mutations after resistance to prior endocrine therapy (AGO +) [63,64]. The benefit from elacestrant appears to be more pronounced in patients with longer prior exposure to CDK4/6 inhibitor therapy, particularly ≥ 12 months. The oral SERD giredestrant, has demonstrated increased efficacy when combined with everolimus also in ESR1 wild-type HR-positive/HER2-negative MBC [65].

In patients with metastatic breast cancer lacking standard therapeutic options, evaluation of additional molecular targets using extended NGS panels may be considered within the framework of a

multidisciplinary molecular tumor board. The European Society of Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) defines six levels of clinical evidence for molecular targets according to their implications for patient management [66]. Additional treatment options with ESCAT level I-II evidence are listed in Table 5 and include olaparib in patients with somatic BRCA mutations, checkpoint inhibitors in patients with microsatellite instability (MSI) or high tumor mutational burden (TMB) (AGO +), neurotrophic tyrosine receptor kinase (NTRK) inhibitors in patients with NTRK gene fusions (AGO +), and tyrosine kinase inhibitors in patients with HER2 mutations (AGO +/-) [12].

7. Circulating biomarkers

As part of tumor progression, individual tumor cells may enter the bloodstream. Moreover, tumor-specific molecules may be released into the circulation, particularly during tumor growth and disease progression. Circulating tumor DNA (ctDNA) consists of tumor-derived DNA fragments present in blood plasma. In principle, two main approaches to detect ctDNA detection are used: tumor-informed and tumor-uninformed (tumor-agnostic) assays [67]. Tumor-informed ctDNA assays are based on prior sequencing of the individual patient's tumor tissue to identify tumor-specific somatic mutations that are then tracked in the plasma. Tumor-informed approaches are mainly investigated in EBC for minimal residual disease (MRD) detection and early relapse monitoring (AGO +/-) [68–71]. Currently, these assays should be offered only within clinical trials, such as the SURVIVE study, which investigates the use of ctDNA monitoring to tailor surveillance strategies [72].

Tumor-uninformed (tumor-agnostic) ctDNA assays do not require prior knowledge of the tumor's genomic profile and instead screen plasma for predefined panels of common alterations [73]. In breast cancer (BC), these assays are primarily used in the metastatic setting to identify actionable somatic alterations (e.g., in PIK3CA, ESR1, and AKT1) that guide treatment selection or to monitor the emergence of ESR1 mutations during endocrine therapy (AGO ++) [64,74,75]. The randomized phase III PADA-1 and SERENA-6 trials demonstrated that an early switch from an aromatase inhibitor to a selective estrogen receptor degrader (SERD), while maintaining CDK4/6 inhibition, delays disease progression in patients with HR-positive, HER2-negative breast cancer who develop ctDNA-detected ESR1 mutations before radiographic progression [61,75].

Table 5
Treatment relevant mutation diagnostic in metastatic breast cancer.

Altered genes	Therapeutic relevance	Gene region	Material	AGO
BRCA1, BRCA2	Olaparib, Talazoparib	All exons	Germline: Blood cells	++
	Olaparib		Somatic: Primary tumor, metastases	+
PALB2	Olaparib		Germline: Blood cells	+
PIK3CA	Alpelisib	Exons 7, 9, 20	Primary tumor, metastases, ctDNA	++
	Inavolisib			
AKT1, PTEN, PIK3CA	Capivasertib		Primary tumor, metastases, ctDNA	+
ESR1	Resistance against AI Elacestrant, Imlunestrant, Giredestrant	Exons 4, 7, 8	Metastases, ctDNA	+
				++
NTRK gene fusion	Larotrectinib, Entrectinib, Reprotectinib	Fusion- and splice variants	Primary tumor, metastases, particulary secretory BC	+
MSI	Pembrolizumab	Microsatellite-instability	Primary tumor, metastases	+
TMB	Checkpoint-Inhibitors	Tumor mutational burden	Primary tumor, metastases	+
HER2-mutations	Tyrosin Kinase Inhibitors	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases	+/-

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; AI, aromatase inhibitor; BC, breast cancer; BRCA1/2, breast cancer1/2 gene; ctDNA, circulating tumor deoxyribonucleic acid; ESR1, estrogen receptor alpha gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localizer of BRCA2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, MSI, microsatellite-instability.

8. Conclusion

A thorough understanding of prognostic and predictive biomarkers and the appropriate timing of their assessment is essential for selecting an optimal treatment strategy. With an increasing number of targeted therapies, accurate prognostic evaluation and prediction of treatment response are increasingly important for identifying patients who derive maximal therapy response while avoiding unnecessary toxicity. To capture dynamic changes in tumor biology and biomarker status, longitudinal molecular assessment through re-biopsy of residual or recurrent disease and/or repeated liquid biopsy should be considered whenever feasible, particularly when changes in biomarker status are likely to influence treatment selection. Continued research into biomarkers and their integration into therapeutic decisions will further refine risk stratification and therapeutic personalization in the era of precision medicine.

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