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magazine of european medical oncology

Molecular profiling leading to personalized treatment in breast cancer

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Summary With the development of various targeted therapies in breast cancer, detection of biomarkers for predicting treatment efficacy gains importance. With the definition of intrinsic subtypes, breast cancer has paved the way for personalized treatment. Already known and recently recognized targets play an important role both in metastatic and early breast cancer. As a result, early molecular profiling is becoming a part of early diagnostic work-up. Notwithstanding, further treatment targets and agents are needed, particularly in the most aggressive subtype encompassing heterogenous diseases under the group of triple negative breast cancer.

Keywords Molecular signature · Targeted therapy · Biomarkers · Breast cancer · Next generation sequencing

Breast cancer is the most common tumor in women and the second most common cause for cancer-related death in women [1]. During the last decades, various treatment targets have been defined and have enabled efficient therapeutic strategies in breast cancer (BC). In order to offer the most suitable treatment, molecular profiling for already established biomarkers is needed. Various technologies have been established, covering a wide range of recognized targets along with potential further biomarkers, such as next generation sequencing (NGS) or ribonucleic acid(RNA)-based profiling or analyzing specific targets with polymerase chain reaction (PCR) based assays. In addition, well-preserved tumor tissue for testing is important. Defining treatment targets enables the administration of efficient agents beyond chemotherapy.

Intrinsic subtypes and role of prognostic tests

The classical stratification into the four subgroups luminal A, luminal B, human epidermal growth factor receptor 2 positive (HER2+) and triple negative is still crucial in the treatment of breast cancer. In addition to definition of the subtype, in hormone receptor positive (HR+), HER2– BC the estimation of risk for recurrence is important for treatment decisions. Several tools dealing with gene signatures have been developed to date. One of the signatures, PAM 50, estimates the intrinsic subtype by the gene signature and provides additional prognostic information [2]. Oncotype includes 21 genes for the prediction of the recurrence risk and enables the stratification into three groups: low, intermediate and high risk [3]. Sparrano et al. randomized 6711 patients with HR+, HER2–, lymph node negative (N–) breast cancer with an intermediate recurrence score of 11–25 between chemotherapy plus endocrine treatment and endocrine treatment alone in a prospective trial. In the total cohort no benefit from adding adjuvant chemotherapy in intermediate risk patients was shown. Nonetheless, women ≤ 50 years old with a recurrence score of 16–25 receiving chemotherapy in combination with endocrine

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therapy were more likely to show a benefit in disease-free survival (DFS) [4].

Challenging the definition of intrinsic subtypes

HER2 low

The transmembrane tyrosine kinase receptor HER2 represents a well-established treatment target. HER2 positivity is defined by the American Society of Clinical Oncology/College of American Pathologist as immunohistochemistry (IHC)+++ [5]. In tissues with IHC++, meaning a weak to moderate membrane staining in >10% of tumor cells, a reflex in situ hybridization (ISH) is recommended [5]. If tissue is IHC 0 or IHC+, the result is HER2 negative (HER2–) [5]. However, HER2 low is IHC+ or IHC++ with a negative ISH result.

Due to the development of antibody–drug conjugates (ADCs), HER2 low has reached a new significance. ADC trastzumab–deruxtecan (T-Dx) shows effectiveness in HER2+, HER2 low and also in HER2 heterogeneous BC by the bystander killing effect [6–8]. The phase III trial was presented at ESMO 2021 and a significantly longer DFS and overall survival (OS) compared to trastuzumab-emtansine (T-DM1) in second line was detected in HER2+ mBC patients [9]. Phase III trials are ongoing in HER2 low patients.

Another second-generation antibody conjugate targeting HER2 is SYD958, called trastuzumab duocarmazine, with an ongoing phase III study TULIP, which showed promising results in the first analysis presented at ESMO 2021[10]. It showed efficacy in heavily pretreated, HER2+, HER2 low, and T-DM1 resistant breast cancers in a phase I trial [11].

HER2 mutations

Beyond HER2 low BC, ERB2 mutations remain a treatment challenge. HER2 mutations function as driver mutations in tumors without an amplification of HER2 too [12]. Tyrosine kinase inhibitors, such as HER2 targeting neratinib are able to directly inhibit intracellular signaling and have demonstrated their efficacy in HER2 mutations [13].

HER3

As HER2 needs another member of the ERB family to build heterodimers for signaling, human epidermal growth factor receptor 3 (HER3) plays a role in HER2+ breast cancers. HER3 appears to be a part of an escape mechanism in HER2 targeting treatments. As a result, HER3 and its mechanisms in signaling have been widely studied. There is evidence that HER3 is essential for the HER2 driven phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) pathway by binding heterodimers with HER2 [14]. The ADC patritumab deruxtecan which specifically binds to HER3 is under evaluation [15]. Patritumab deruxtecan showed efficacy and tolerability in a phase 1 study including 21 pretreated metastatic breast cancer patients [16]. This ADC showed also promising results in a phase 1 study in nonsmall cell lung cancer, especially in patients with higher HER3 expression [17]. However, targeting HER3 in breast cancer is still a future goal and needs to be studied further.

TNBC

TNBC lacking estrogen receptor (ER)–, progesteron receptor (PR)–, and HER2 remains a treatment challenge. As shown by Burstein et al. and others, TNBC is a heterogeneous disease. Burstein et al. defined 4 TNBC subtypes using a PAM50 gene signature: luminal androgen receptor (LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS) and basal-like immune activated (BLIA) [18]. Androgen-receptor (AR) might represent a treatment target, as AR– inhibitors were studied in AR expressing TNBC and showed clinical response [19]. The recently developed ADC sacituzumab–govitecan, targeting the antithrophoblast cell–surface antigen 2 (TROP2) has shown promising results in heavily pretreated patients with TNBC [20]. Further studies in triple negative and also HER2-BC are ongoing. To date, no selection by TROP2 expression is needed due to the bystander killing effect, but the efficacy is clearly correlated with the level of TROP2 expression.

Potential of liquid biopsy

Over the last decade, an increasing number of technologies to comprehensively analyze circulating deoxyribonucleic acid (DNA) and particularly the tumor fraction have evolved and now various possibilities for mutation testing are provided [21–23]. The phase 2a plasmaMATCH trial selected patients for specific treatment based on detection of mutations in circulating tumor DNA. The sensitivity and specificity in the circulating tumor DNA were comparable with mutation testing in tumor tissue for protein kinase B 1 (AKT1), HER2, and phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) mutations [21]. This trial paved the way for future personalized oncology approaches.

Another example in endocrine therapy-resistant breast cancers is the acquired estrogen receptor 1 (ESR1) mutation [24, 25]. The detection of ESR1 mutation in plasma after progression on aromatase inhibitor could be used for endocrine treatment decision [23]. Fulvestrant has shown efficacy in ESR1-mutated breast cancer [23] and clinical trials are now testing the hypothesis in larger patient cohorts.

Table 1 Therapeutic agents and their targets

Target	Setting	Therapeutic agent
Germline mBCRA1/2	Adjuvant, palliative	PARP inhibitors
HER2	Neoadjuvant, adjuvant, palliative	Trastuzumab, pertuzumab, neratinib, lapatinib, tucatinib, T-DM1, T-Dx
HER2 mutations	Palliative	Neratinib, lapatinib, tucatinib
HER2 low/HER2 heterogeneity	In development palliative	T-Dx
HR	Neoadjuvant, adjuvant, palliative	SERM, AI
PIK3CA	Palliative	Alpelisib
PD-L1/CPS	Palliative, neoadjuvant?	Atezolizumab, pembrolizumab
PTEN, AKT	Palliative?	AKT inhibitors?
TROP2?	Palliative	Sacituzumab–govitecan

HER2 Human epidermal growth factor receptor 2, *HR* hormone receptor, *PIK3CA* phosphoinositide-3-kinase, catalytic, alpha polypeptide, *PD-L1* Programmed death-ligand 1, *CPS* combined positive score, *PTEN* phosphatase and tensin homolog, *AKT* protein kinase B, *TROP2* antithrophoblast cell–surface antigen 2, *T-DM1* trastuzumab–emtansine, *T-Dx* trastuzumab–deruxtecan, *SERM* selective estrogen receptor modulators, *AI* aromatase inhibitors

Biomarkers with therapeutic relevance

Besides the well-known HR and HER2 status, which became relevant during the 1990s, more biomarkers have gained therapeutic importance (Table 1).

PIK3CA mutation

The establishment of alpelisib in the therapy algorithm of PIK3CA-mutated metastatic HR+, HER2– BC requires testing for this mutation [26]. Although the PIK3CA mutation is an early mutation, an acquired PIK3CA mutation may occur under CDK4/6 inhibitor treatment associated with resistance to these drugs [24]. While the SOLAR trial demonstrated efficacy of alpelisib particularly in PIK3CA-mutated patients [27], in the BYlieve trial alpelisib showed a significant impact on progression free survival (PFS) after progress on CDK4/6 [22]. In this trial, PIK3CA mutation testing was done by NGS or PCR in circulating DNA in addition to tumor tissue [22].

PI3K/AKT pathway

Changes in the PI3K/AKT pathway like phosphatase and tensin homolog (PTEN) loss or hyperactivated AKT represent potentially useful treatment targets [28]. The PI3K/AKT signaling pathway plays an important role in breast cancer. PTEN possesses an inhibiting role, whereas AKT holds an activating function. The AKT inhibitors capivasertib and ipatasertib showed promising results in the phase II trials LOTUS and FAKTION [29, 30]. However, the phase III trial IPATunity130 with ipatasertib in combination with paclitaxel in metastatic TNBC (mTNBC) failed to confirm its benefit [31]. A biomarker analysis of the IPATunity130 is planned and may provide additional information about the subgroups. However, the first results of the phase III trial analyzing capivasertib in this setting are not yet available.

BRCA 1/2 mutation

In HER2– disease, PARP inhibitors represent an active agent in germline-mutated BRreat CAncer gene (BRCA1/2) mBC [32, 33]. In mBC PARP inhibitors significantly prolong PFS [32, 33]. No significant impact in overall survival (OS) has been be detected. In ovarian cancer these agents are effective in both germline and somatic mutations [34]. However, the role of somatic BRCA1/2 mutations or "BRCAness" in BC is not fully clarified to this date. In the GeparOLA trial, for example, germline and somatic BRCA1/2 and additional mutations leading to homologous recombinant deficiency were included [35]. The effect of olaparib as an additional neoadjuvant agent was superior only in germline-mutated BRCA1/2 patients in the HR+ and in the <40 years subgroups [35]. Another trial including germline mutations, somatic mutations, BRCA1/2 methylation status and BRCA 1/2 messenger RNA (mRNA) analyzing the effect of carboplatin versus docetaxel in metastatic setting showed an effect of carboplatin solely in the germline-mutated cohort [36]. Nonetheless, only a small number of patients revealed a germline mutation in this study. The significance of somatic BRCA1/2 mutations or a "BRCAness type" for treatment in BC has not yet been confirmed. Further studies are needed, and one of the trials is the ABCSG45 neoadjuvant phase II study evaluating the combination of carboplatin and olaparib versus standard neoadjuvant chemotherapy in patients with "BRCAness". Germline BCRA1/2 mutation testing is becoming an imperative for TNBC and high-risk hormone receptor positive BC patients in the adjuvant setting based on the adjuvant OlympiaD trial. Administration of olaparib for 1 year after finishing adjuvant/neoadjuvant treatment in high risk germline-mutated BRCA1/2 patients leads to an improved invasive disease-free survival (iDFS) [37].

PD-L1 and CPS score

A clinically established biomarker beyond germline BRCA1/2 mutation status for treatment decision in TNBC is the programmed death-ligand 1 (PD-L1) status [38, 39]. In mTNBC the addition of atezolizumab to nab–paclitaxel significantly prolonged PFS and improved median OS in PD-L1 positive patients [38]. PD-L1 positivity was defined as PD-L1 expression in immune cells that covers ≥1% of the tumor and was assessed using the SP142 PD-L1 immunohistochemical assay (Ventana) [38]. In the KEYNOTE-355, the addition of pembrolizumab improved PFS in patients with a combined positive score (CPS) ≥10 [39]. In contrast, the role of the PD-L1 status in the neoadjuvant setting is less prominent, since the benefit of pembrolizumab or atezolizumab was shown independently from the PD-L1 status [40, 41].

To sum up, with the development of novel targeted therapies, molecular profiling is gaining in importance. Whereas an increasing number of molecularly driven clinical trials is becoming available, it is increasingly difficult for clinical trials to represent the heterogeneity of breast cancer biology. Nevertheless, in today's clinical practice biomarker testing, it is a prerequisite to adequately treat breast cancer patients. Analysis of established biomarkers in BC is essential for all patients where treatment is available. Currently, it is still recommended to perform biopsies of new lesions in metastatic patients. The hope is that with the increasing number of studies, cell free DNA based mutation testing will demonstrate its reliability and robustness and at least partially replace the more invasive tissue testing. With the available novel technologies, the hope is to identify an increasing number of treatment targets and agents which are urgently needed especially for TNBC.

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