CHAPTER 02

Metastatic Breast Cancer, Diagnosis and Cutting-Edge Therapeutics Approaches

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SUMMARY

Cancer has emerged as a critical global health concern, impacting millions of lives worldwide. It is a lethal disorder that poses severe health consequences as it involves the uncontrolled growth of abnormal cells which leads to the formation of tumor (TUM). Its severity escalates as these malignant cells invade nearby tissues and organs, disrupting their normal functions. Metastatic breast cancer (MBC) which is also categorized as stage IV breast cancer (BC), is an advanced and serious form of cancer. In this stage cancer cells from the original TUM in the breast possess the ability to migrate to other parts of the body such as bones, liver, lungs and brain. The spread of cancer cells is facilitated through the bloodstream or lymphatic system. MBC is considered incurable, and treatment focuses on managing symptoms, improving quality of life and prolonging survival. Common symptoms include bone pain, shortness of breath and fatigue. Despite advancements in treatment, the prognosis for MBC remains challenging. Therefore, this chapter provides a detailed overview of the complex processes related to the diagnosis and treatment of MBC. This chapter also investigates associated challenges during early phase of detection, explores evolving diagnostic methods and emphasizes the crucial role of selective medicine in MBC treatments. Furthermore, this chapter also examines the cutting-edge therapeutic approaches involved in the amelioration of MBC.

INTRODUCTION

Breast cancer (BC) related deaths have shown a consistent increase over the past few decades. Nevertheless, metastatic BC continues to pose a notable health challenge in the 21st century, emerging as a top-notch cause of mortalities among women globally (Li et al., 2016; 2019). The term "metastasis (MTSTs)" denotes the process in which cells migrate from the primary site of origin. This term originates from the Greek words "meta" (displacement) and "stasis" (localization) (Martinez-Perez et al., 2019; Hossain et al., 2022). The process of MTSTs encompasses different cancer-specific behaviors, such as migration and invasion (Palmirotta et al., 2018). Despite advancements in our understanding of cancer biology, denoted by the development of novel biomarkers and targeted therapies, the survival rates for individuals with metastatic BC have not seen remarkable improvement (Belpomme et al., 2007; Li et al., 2016).

In recent years, most developed nations have witnessed a decline in the proportion of patients presenting with metastatic BC, primarily attributed to advancements in initial-stage disease treatment (Cardoso et al., 2018). However, a substantial percentage, approximately 6-10%, still presents with the metastatic disorder at the time of diagnosis. Furthermore, around 30% of individuals primarily spotted with earlier-stage BC ultimately experience advanced or metastatic disease (Li et al., 2016). Approximately 21% of individuals showed a survival rate of 5-years. The primary objective of treatment in such cases is focused on palliating the disease, with high survivability as well as minimum drug toxicity (Wilkinson & Gathani, 2022).

The process of MBC treatment has become increasingly intricate, providing physicians a variety of chemotherapeutic agents suitable for patients with hormone-insensitive formation of tumors (TUMs) (Redig & McAllister, 2013). Anthracycline and taxane-based regimens are currently favored as the first-line treatment for symptomatic MBC patients, based on their efficacy in randomized clinical studies (Pantel & Alix-Panabières, 2019). The growing global utilization of adjuvant chemotherapy further complicates the selection of agents for metastatic environments (Yancik et al., 2001). Therefore, this chapter aims to explore metastatic BC, diagnosis and cutting-edge therapeutic approaches.

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MORPHOLOGICAL AND MOLECULAR CLASSIFICATION OF MBC

The MBC classification in clinical settings is based on the morphological characteristics of TUMs, leading to distinct types. These include infiltrating ductal carcinoma of various special types i.e., infiltrating tubular, lobular, medullary, adenoid and mucinous cystic carcinoma (Schlumpf et al., 2004). Further sub-classification involves assessing histological grade, which considers factors i.e., mitotic count, nuclear pleomorphism and cellular differentiation. Smaller size tubular carcinomas are commonly correlated with earlier stage appearance compared to infiltrating ductal carcinomas (Li et al., 2019).

BC TUMs are also classified into different 5 subtypes (STs) on the basis of the expression of estrogen and progesterone receptors (ER/PR) and HER2 oncogenic factors (Lynce et al., 2017). ER related positive TUMs are the most common and low grade reported factor unlike ER related negative TUMs (Xiong et al., 2018). The ER/PR related positive STs incorporate Luminal A as well as B while ER related negative subgroups comprises of HER2 STs, basal-like STs as well as normal-like STs, demonstrating an altered expression of gene profile (Gupta et al., 2018; Mann et al., 2019; Mao et al., 2021).

It is reported that HER2 possesses the capability to induce remarkable minor results as compared to the normal as well as luminal-like groups. These STs are connected with more progressive stages at performance and a higher proportion of stem cell-like cells, contributing to their aggressive clinical behavior (Mihailov et al., 2024). Approximately 20% of breast TUMs overexpress the Her2 oncogene and PR negativity among all ER-positive TUMs independently predicts Her2 positivity. TUMs lacking expression of ER, PR and Her2 are termed triple-negative BCs (TNBC), accounting for approximately 15% of BCs (Narod, 2010). TNBCs are often larger, grade III TUMs with an aggressive phenotype and poorer outcome, with a higher incidence in younger women, African American women and those with mutated BRCA1 (Mego et al., 2010; Mihailov et al., 2024).

Beside these STs, there is a distinct form known as inflammatory BC (IBC), clinically and biologically different from other types. IBC is characterized by TUM emboli in dermal lymphatic channels, generalized breast tenderness and typically presents at a progressive stage. Most IBC patients have axillary lymph node involvement at diagnosis and around 35% exhibit distant metastases (Nathanson et al., 2023). Elevated Her2 levels are found in nearly 50% of IBC cases, contributing to the greater proportion of metastases at appearance. The most effective nature of IBC can be attributed to its great angioinvasive and angiogenic properties, along with elevated expression of pro-angiogenic elements and genes correlated with the basal-like phenotype, vascular function and immune response. Genes involved in cell migration and invasion i.e., integrin VASP and ARNT are also up surged in IBC (Jin et al., 2023).

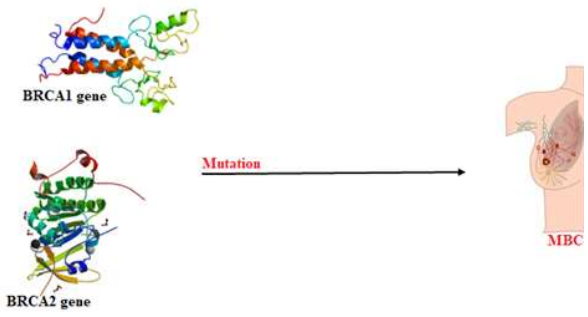

Fig 1. Illustration of BRCA1 and BRCA2 genes

GENETIC AND EPIGENETIC FACTORS THAT INFLUENCE TUMOR BEHAVIOR

Understanding the epigenetic traits associated with BC is essential for cancer prevention in different levels (Wang & Wu, 2020; Venetis et al., 2023). Firstly, it aids in recognizing risk factors and their processes, secondly, it establishes markers for early disorder detection and thirdly, it helps in identifying markers for disease progression and drug resistance (de Visser & Joyce, 2023). Micro-RNA miR-21 has been recognized as a key player in regulating TUM progression by modulating the expression of several genes, encompassing RAB6A. MiR-21's oncogenic effect is thought to involve the regulation of the TUM suppressor gene PTEN, which is often down-surged in various BCs. Elevated levels of miR-21 have been associated with advanced stage presentation and poor survival in BC (Wang et al., 2017; Ensenyat-Mendez et al., 2021).

Other micro-RNAs have shown higher levels in the serum of BC patients, particularly those with metastases (Ma et al., 2015). Additionally, miR-195 levels in blood were found to be elevated in BC patients, decreasing to normal levels after TUM resection (Iqbal & Iqbal, 2014). Epigenetic studies have revealed that different types of BC STs exhibit distinct LINE-1 methylation profiles, and silencing of the estrogen receptor as well as inactivation of BRCA1 and BRCA2 can occur through methylation along with other epigenetic mechanisms (Raeeszadeh-Sarmazdeh et al., 2020) Fig. 1. The frequency of these epigenetic alterations can vary among BC cases. For instance, RASSF1A was hypermethylated in 65–85% of breast TUMs. A meta-analysis indicated that hypermethylation of the BRCA1 gene is a high-risk factor for developing BC (Amini et al., 2012; van den Hurk et al., 2022).

While dominant gene mutations are present in only a small number of BCs, common mutations are found in BRCA genes. Single-nucleotide polymorphisms (SNPs) likely explain the heterogeneous nature of BC and individual differences in TUM behavior (Lamouille et al., 2014). The matrix metalloproteinase family is a relevant gene family showing such genetic variations. SNPs associated with high expression of MMP-1 correlate with advanced TUM stage, while those leading to elevated MMP-8 expression act as TUM suppressors (Fares et al., 2020). Conversely, SNPs causing down-regulation of MMP-8 enhance BC MTSTs. Breast TUMs resulting from genetically transmitted abnormalities, including TP53 mutations, tend to cluster in a younger age

group (45 years) and exhibit a more aggressive phenotype (Fares et al., 2020).

DIAGNOSTIC TECHNIQUES

Imaging

MBC is a prevalent malignancy affecting females worldwide, emphasizing the critical importance of early detection and continuous monitoring in therapy (Linder & Schiska, 2015). These facets play a pivotal role in recognizing risk factors, early disease markers and monitoring disease progression and drug resistance (Manca et al., 2016). Diagnosis comprises monitoring patients through imaging techniques or observing symptoms i.e., pain or palpable masses. Vigilant monitoring of healthy subjects has proven beneficial in detecting minor TUMs that may lead to BC progression (Agrawal et al., 2020) Fig. 2 illustrates the most significant BC staging techniques.

Imaging methods have emerged as effective tools for BC detection and to monitor the response of various sorts of anti-cancerous drugs. Mammography, acknowledged as the gold standard, provides high sensitivity and specificity, cost-effectiveness and sufficient tolerance (Bourgeois et al., 2013). However, limitations i.e., pain, anxiety, false alarms and radiation risks prompt the exploration of improved techniques (Gomez-Perez et al., 2016). Ultrasound (US), the most effective imaging method, is useful in diagnosing and analyzing breast pathology. Its reported benefits comprise the absence of high sensitivity as well as ionizing radiation. Certain technological approaches incorporating US contrast as well as elastography additionally contribute to the intervention of BC (Gomez-Perez et al., 2016).

Recent studies have been undertaken for the assessment of angiogenesis of breast TUM using 3-D contrast-enhanced US as well as dynamic contrast MRI recognition systems displayed better results of these approaches in the evaluation of angiogenesis of TUM (Jacklyn et al., 2017; Mann et al., 2019). MRI is reported as the most diagnostic method that serves a fundamental role in different treatment aspects including MTSTs assessment, therapy response monitoring as well as TUM recurrence investigation (Ming et al., 2020). While aforementioned imaging approaches possess certain limitations incorporating sensitivity problems leading radiologists to reveal novel approaches (Orel & Schnall, 2001). Numerous contrast agents particularly gadolinium-based structures for MRI as well as mammography, respectively, are suggested to enhance diagnostic image sensitivity as well as enhance the quality factor of molecular processes at the molecular and cellular levels (Eisenbrey et al., 2016). Single-photon emission computed tomography (SPECT) and Positron emission tomography (PET) are other imaging techniques that employ radioactive isotopes releasing position and are reported as the most effective diagnostic approach in BC patients. Besides, various investigations have demonstrated the potent use of SPECT and PET in patients suffering from BC individuals with bone MTSTs (Jacklyn et al., 2017; Oza et al., 2021), similarly, Fig 3. illustrates the intercommunication between cardiac and BC biomarkers.

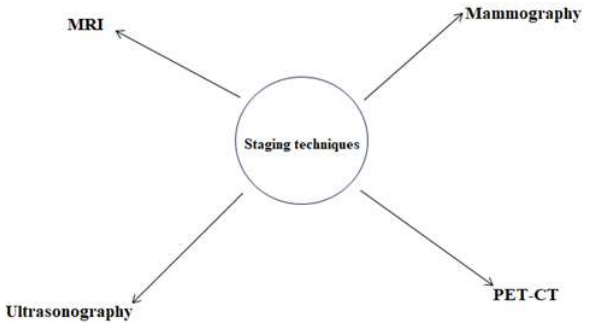

Fig 2. Most significant imaging modalities commonly used for BC staging

Biomarkers

The application of certain imaging approaches is limited by high cost and specificity. For the management of these problems, the arrival of novel biomarkers has become essential for the mitigation of drawbacks linked with the aforementioned imaging technologies (Tekade & Sun, 2017). The use of certain biomarkers that possess the ability to diagnose MBC is reported as crucial in current times. Numerous biomarkers act as necessary elements in enhancing our knowledge of the molecular mechanisms involved in the pathogenesis of BC and also facilitate the generation of novel therapeutic approaches and modulation of treatment response (Sanz-Garcia et al., 2022; Cuccaro et al., 2023).

Numerous investigations have reported potential diagnostic markers for the detection and monitoring of BC. These factors include different mRNAs, enzymes as well as certain proteins (Rani et al., 2019). HER2 is reported as a substantial proteinaceous element that serves as a crucial factor in the regulation of cellular growth as well as differentiation via certain signal transduction processes (Luque et al., 2021). Furthermore, it is also reported that the increased concentration of HER2 is examined in certain individuals suffering from BC which enables it as a substantial predictive factor for BC (Al-Mahmood et al., 2018).

Ki-67 is another most reported protein which is responsible for cellular proliferation as well as playing an essential role in pathogenesis of BC. Numerous studies have reported that an up-surged concentration of this factor can act as predictive element in the monitoring of individuals suffering from BC (Lippman et al., 2018). Besides these factors, progesterone associated receptors are also employed BC TUM subtyping. The hormone which is steroidogenic in nature i.e., estradiol particularly Er-Alpha is crucial in the initiation as well as development of BC (Zografos et al., 2016; Bui et al., 2022).

MicroRNAs and exosomes

MicroRNAs (miRNAs) are categorized as an essential factor in the regulation of certain target genes at the post-transcriptional position. They are reported as essential elements in biological processes including differentiation as

well as development (Dykes & Emanueli, 2017). Recent studies have revealed that dysregulation in miRNAs possesses the ability to effectively modulate the initiation as well as development of cancer related ailments. In the framework of BC, miRNAs have garnered substantial interest owing to their essential role in particular expression profile correlated with TUM proliferation as well as treatment outcomes (Fridrichova & Zmetakova, 2019).

The STs of BC particularly intrinsic STs necessitate certain treatment options as well as the expression of miRNAs that specifically varies with different STs. Nevertheless, evaluation of the expression of miRNA has displayed a remarkable promise as a tremendous approach for the diagnosis as well as monitoring of BC. Furthermore, miRNAs particularly miRNA have been reported as potent diagnostic factor for BC (Heneghan et al., 2010). For instance, miR-1260 has exhibited altered expression in the blood specimen of BC individuals, displaying a correlation with clinical results. Numerous other miRNAs incorporating miR-34c have been used in certain stages of BC that influence different targets linked with TUM-triggering factors (Imani et al., 2018).

The miRNA family factors, particularly miR-200, have been recognized for their function in mitigating the clonal expansion of BC as well as the prevention of TUM formation originating from cancer stem cells. In addition to this, miRNAs incorporating miR-106B-25 group contribute to MTSTs via targeting certain pathways involved in epithelial-mesenchymal transition (EMT) (Shimono et al., 2015). Besides, exosomes are nano-vesicles that are biological in nature and possess the ability to carry protein with them as well as have garnered tremendous attention as a diagnostic and therapeutic element for individuals suffering from BC. Moreover, exosomal miRNAs (EmiRNAs) particularly miR021 are present in high intensity in BC as well as plasma concentrations of these EmiRNAs display diagnostic substantial potential. EmiR-10b has been reported as a crucial factor that possesses the ability to induce MTSTs in BC cells, emphasizing the function of EmiRNAs in disorder development. Furthermore, Del-1 is the most highly reported extracellular protein matrix that has been recognized as a potent cancer-specific factor. Edel-1 concentrations were remarkably surged in individuals with initial-stage BC, signifying its characteristics as a diagnostic factor (Liu et al., 2021).

THERAPEUTIC APPROACHES

Cytotoxic drugs

One of the leading strategies for improving patient survival involves the development of innovative cytotoxic (CTC) compounds (Table 1). Taxanes and anthracyclines are reported as the primary treatments for early and locally advanced BC (Di Costanzo et al., 2019). However, resistance often limits their effectiveness, contributing to approximately ninety percent of treatment disappointments in MBC (MBC) patients (Fehm et al., 2007; Gote et al., 2021). TTs, such as MCNL antibodies against human HER-2, show promising results, particularly in patients receiving chemotherapy treatment. Nevertheless, their efficacy is confined to specific patient groups, necessitating the exploration of new CTC agents with broader applicability (Gogia et al., 2014; Eble & Niland, 2019).

Several compounds exhibit promising results in MBC treatment, including epothilones, a novel category of antineoplastic drugs originating from the myxobacterium Sorangium cellulosum (Jaiswal & Sedger, 2019). Epothilones induce TUM cell death by elevating microtubule stability and bundling during mitosis, similar to taxanes, yet they appear less affected by drug resistance mechanisms. Ixabepilone, a derivative of the semi-synthetic vinorelbine, gained FDA approval for treating MTC or locally advanced BC after anthracycline and taxane failure (VanderLaan et al., 2017; Villegas et al., 2023).

Vinflunine is another reported derivative of vinorelbine, which binds to tubulin, inhibiting microtubule assembly and demonstrating antiangiogenic and anti-MTC activity. It is a weak substrate of drug efflux pump protein P-glycoprotein (P-gp), making it less prone to inducing resistance. Clinical trials evaluating vinflunine in combination with other agents i.e., capecitabine and TZB, for the management of MBC are ongoing (Bennouna et al., 2008).

Nab-paclitaxel (PXL), a polyethoxylated castor oil-free nanoparticle colloidal suspension of PXL, offers advantages over conventional formulations, including shorter infusion times and enhanced drug delivery with a better safety profile. In a phase III trial, nab-PXL demonstrated greater response, longer time to progression (TTP) and a favorable safety profile compared to standard PXL. These advantages were further confirmed in a recent phase II trial combining nab-PXL with gemcitabine in previously untreated MBC patients (Bennouna et al., 2008) In addition to this, pemetrexed is reported as folate-based antimetabolite first approved for the management of malignant mesothelioma in MBC (Harrison & Scott, 2003).

Table 1. Most significant therapeutic innovations with CTC drugs

Agent	TUMs tested in MBC	Development in MBC
Vinflunine	Breast, gastrointestinal, genitourinary, lung	II
Folate antimetabolites Pemetrexed	Breast, CNS, gastrointestinal, head and neck, hematological, lung	I/II
Trabectedin	Breast, sarcoma	III

Marine-derived anti-cancer compounds

The aquatic environment acts as a tremendous reservoir of natural products (NP) that exert potential therapeutic benefits. Marine organisms exhibit the property to generate potent chemical agents, providing a suitable way for the innovation of novel CTC elements (Gupta et al., 2013). Out of these therapeutic agents trabectedin (TDN) has been reported as one of the potent anti-TUM candidates. This therapeutic agent

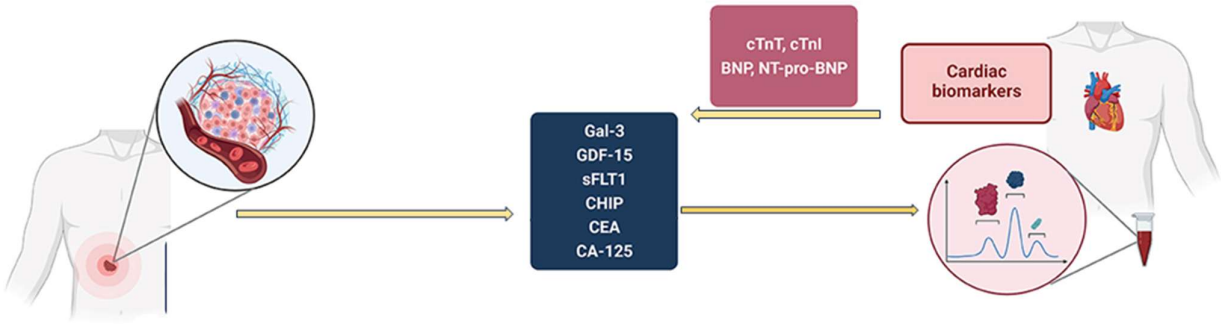

Fig 3. Intercommunication between cardiac and cancer biomarkers

possesses the ability to bind with the guanine base of DNA and affect numerous TFs for CP (Bortolini et al., 2021). Analysis of TDN in MBC with 27 individuals who were previously administrated with anthracyclines reported a 29% treatment response and with similar proportion of TUM amelioration. The examined toxicity was curable, primarily constrained to noncumulative transaminitis (D'Incalci & Zambelli, 2016).

Another notable marine-derived CTC compound is eribulin mesylate which is a synthetic mirror image of the marine sponge halichondrin B. In a recent phase II trial involving 103 heavily pretreated MBC women, eribulin mesylate demonstrated an effective response rate of 12% and a clinical benefit rate of 17%. These results underscore its favorable anti-TUM activity with manageable toxicity, providing insights into its potential as a therapeutic option for MBC (McIntyre et al., 2014).

Anti-HER-2

HER-2, also reported as ErbB2 or the neu oncogene is a transmembrane tyrosine kinase (TK) receptor that belongs to the epidermal EGFR family. While the HER-2 receptor is commonly found in normal tissues, it is overexpressed in 18–20% of BCs, potentially higher in MTC disease (Montemurro et al., 2013). HER-2 protein overexpression is linked to augmented CP, progressive MTSTs, accelerated AGs and reduced apoptosis, resulting in a poorer clinical outcome. TZB, a MCNL IgG1 class humanized murine antibody, binds particularly to the EC portion of the HER-2 receptor, revolutionizing the treatment of HER-2-positive MBC. It has proven effective in both adjuvant and MTC settings, as first, second, or third-line treatment, either as MT or in combination (Montemurro et al., 2013).

Furthermore, TZB possesses the ability to regulate survival even after progression of the disease. The pivotal phase III trial demonstrated the substantial impact of TZB in MBC, revealing significant TTP, higher impartial response rates and longer survival when combined with chemotherapy compared to chemotherapy alone. Subsequent studies exploring TZB in combination with other CTC agents, such as vinorelbine, gemcitabine, capecitabine, liposomal doxorubicin and platinum, have yielded interesting results without significant added toxicity (Han et al., 2019). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines currently recommend TZB in co-administration with different chemotherapeutic elements as first-line treatment for HER-2-positive MBC. Additionally, ongoing studies explore the combination of TZB with endocrine therapy and other TTs, such as pertuzumab (PZB) (Brufsky, 2010) Furthermore, Table 2 provides some innovative therapeutic methods with targeted drugs.

Table 2. Novel therapeutic approaches with targeted drugs

Agent	Specific target	Main TUM tested	Development in MBC
Erlotinib	HER-1 TK	Breast, CNS, gastrointestinal, genitourinary, head and neck, lung	II
BSI-201	PARP1	Breast, glioblastoma	I/II
Mapatumumab	DR4	Breast, liver	I/II
Pazopanib	PDGFR, all VEGFR and c-KIT	Breast, gastrointestinal, genitourinary, head and neck, lung	I/II
Neratinib	HER-1 and HER-2	Breast	III
Olaparib	PARP1	Breast, gastrointestinal, ovarian	I/II

TZB-DM1, an antibody drug, selectively delivers DM1 to HER-2-positive TUM cells, showing efficacy even in patients resistant to TZB (Bhat et al., 2022). Despite these advantages, around 2% of patients receiving TZB may develop cardiac dysfunction, with increased incidence in certain patient populations (Montemurro et al., 2013). Acquired and de novo resistance to TZB pose significant clinical challenges, with mechanisms including loss of function of the TUM suppressor PTEN gene and decreased interaction between TZB and HER-2. Additionally, TZB's inability to cross the blood-brain barrier allows the progression of brain MTSTs in some patients with extended survival due to TZB treatment (Hunter et al., 2020).

PZB is a humanized MCNL antibody designed to bind with HER-2, thereby inhibiting the heterodimerization of HER-2 with other members of the HER family (Nami et al., 2018). Preclinical studies conducted in BC cell lines have revealed a significant synergy between TZB and PZB, prompting their

combined use in clinical trials. Preliminary data from a phase II trial investigating the combination of TZB and PZB in heavily pretreated women with advanced HER-2-positive MBC, whose disease had progressed during TZB therapy, showed an impartial response rate in six of 33 evaluable patients (Miller et al., 2016; Dagogo-Jack & Shaw, 2018).

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