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REVIEW

Breast cancer in the era of precision medicine

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Abstract

Breast cancer is a heterogeneous disorder with different molecular subtypes and biological characteristics for which there are diverse therapeutic approaches and clinical outcomes specific to any molecular subtype. It is a global health concern due to a lack of efficient therapy regimens that might be used for all disease subtypes. Therefore, treatment customization for each patient depending on molecular characteristics should be considered. Precision medicine for breast cancer is an approach to diagnosis, treatment, and prevention of the disease that takes into consideration the patient's genetic makeup. Precision medicine provides the promise of highly individualized treatment, in which each individual breast cancer patient receives the most appropriate diagnostics and targeted therapies based on the genetic profile of cancer. The knowledge about the molecular features and development of breast cancer treatment approaches has increased, which led to the development of new targeted therapeutics. Tumor genomic profiling is the standard of care for breast cancer that could contribute to taking steps to better management of malignancies. It holds great promise for accurate prognostication, prediction of response to common systemic therapies, and individualized monitoring of the disease. The emergence of targeted treatment has significantly enhanced the survival of patients with breast cancer and contributed to reducing the economic costs of the health system. In this review, we summarized the therapeutic approaches associated with the molecular classification of breast cancer to help the best treatment selection specific to the target patient.

Keywords Breast cancer · Targeted treatment · Molecular profiling · Molecular subtype · Precision Medicine

Introduction

Breast cancer is a heterogeneous complex disease (in terms of etiology and pathological characteristics) with different molecular subtypes and distinct biological features which lead to differences in response patterns to the various treatments and also in the clinical outcomes [1].

A high proportion of breast cancer cases is associated with pregnancy-associated factors, hormonal therapy, lifestyle factors (e.g., alcohol, cigarette use, and obesity) [2–4] and about 10% of all cases of breast cancer are related to the hereditary gene mutations (e.g., *BRCA 1/2*), age, and family risks [5, 6]. So that, if one first-degree relative has had breast cancer, the probability of contracting the disease is around two times higher, and possibly five times higher if the relative had breast cancer as a young [7].

Breast cancer is the most common cancer and the second leading cause of death among women globally [8]. Despite advances in the survival rates, breast cancer remains the fourth most frequent cause of cancer death (627,000 deaths among women in 2018) [9]. The growing incidence of breast cancer represents its effect on society worldwide, and the need for urgency in preventive and treatment measures.

There is a clear need to enhance the knowledge of new both prognostic and predictive markers that is critical to assisting clinicians in diagnosis, risk stratification, disease subtyping, prediction of response to treatment, and monitoring to facilitate personalized management of breast cancer patients in both primary and metastatic settings [10].

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Therefore, more knowledge regarding the molecular pathways provide ways to the development of new targeted therapeutics [1].

Breast cancer therapy involves a multidisciplinary approach comprising surgery, radiotherapy, neoadjuvant and adjuvant therapy. Although controversy has emerged in recent years regarding the treatment of the breast cancer, it remains important to detect and treat breast cancer before it has spread. In the era of personalized medicine, there has been significant progress regarding the molecular analysis of breast cancer subtypes.

This article provides an overview of treatment options for breast cancer patients based on molecular classification and pathways to know the best therapeutic approaches.

Genetic of breast cancer

Breast cancer heterogeneity makes a desirable and challenging stream to diagnose and treatment. The genetic mechanism behind breast cancer development is a complicated one. Multiple signaling cascades with different genes have been implicated in the pathogenesis of breast cancer [11]. It is estimated that about 10–30% of cases are associated with hereditary factors [12]. Several genes are associated with breast cancer and here we review high-, moderate-, and low-penetrance breast-cancer-susceptibility alleles. [13]

High penetrance genes

Some familial breast cancer clustering occurs as part of certain familial breast cancer syndromes, in which the disease is caused by single alleles providing a high risk.

BRCA1, located on chromosome 17, was first identified in 1990 in families with suggestive pedigrees using linkage analysis and associated with breast cancer especially triple-negative breast cancer (TNBC) [14].

BRCA1 mainly controls DNA repair through interaction with cell cycle regulators, tumor suppressors, and DNA repair proteins [15]. BRCA1 protein contains the BRCA1 C-terminal domain and the ring structure which are responsible for the inhibition tumorgenesis especially breast and ovarian cancer [16]. BRCA1 C-terminal domain interacts with phosphoproteins which are important for the tumor suppressor activity of BRCA1 at the DNA damage sites. Therefore, mutations at these domains are responsible for the disruption in double-stranded DNA damage and subsequently breast cancer development.

The function of the zinc finger domain in BRCA protein is not definitively established. Missense mutations in the *BRCA1* ring domain (e.g., C61G) disrupt the *BRCA1:BARD1* interaction, and mutations in the *BARD1* gene, also have been detected in the breast, ovarian, and uterine cancers. The *BARD1* interacts with an RNA polyadenylation factor (Cst-50) and inhibits its activity the *BARD1* regulates the RNA processing during transcription and DNA repair.

Mutation in the *BRCA1* gene is often accompanied by a *TP53* mutation and causes a rise in the risk of breast cancer [17]. Moreover, *BRCA1* deficiency could be associated with the epigenetic silencing by promoter hyper-methylation, which leads to downregulation of the *BRCA1* gene [15].

The *BRCA2* gene with a 10.3 kb open reading frame is larger than *BRCA1*. It is located on chromosome 13q12-13 and encoded a 384 kDa nuclear protein. The *BRCA2* offers instructions for coding a protein that acts as a tumor suppressor. The BRCA2 protein is a transcription factor with a DNA binding domain in the N-terminous and a protected helix domain in the C-terminal region. Furthermore, two nuclear localization signals (NLS) are detected in the C-terminal region of the BRCA2. BRCA2 protein has important cellular functions including transcriptional regulation, embryonic development, and repair of DNA damage [18]. The BRCA2 protein mainly functions in homologous recombination for repairing DNA damage by directing the RAD51 protein to the sites of double-strand breaks [15]. The *BRCA2* gene is associated with six different germline mutations in familial cancer which disrupts the transcription unit reading frame. Currently, more than 1,800 mutations in the *BRCA2* have been identified that are classified as insertion, frame change, deletion, and nonsense mutations, leading to premature protein [15]. Any changes or mutations in the *BRCA2* can increase the risk of breast, ovarian, and prostate cancer development [19]. It should be noted that *BRCA2*-related tumors are mostly sporadic, and only 15% of familial breast cancers are related to the mutations and rearrangements or deletions in the *BRCA2* gene [20].

TP53 is a tumor suppressor gene mutated in various cancers including breast cancer [21]. The P53 is a protein that is involved directly in some conditions including cell growth, DNA repair, and apoptosis. The P53 protein has an active role in genome stability through involvement in the DNA repair activity directly or indirectly [22]. Activation of p53 protein occurs in response to cellular stresses. The *TP53* is associated with more than 50% of cancers [15] that is mutated in approximately 80% of triple-negative tumors and 30–35% of other types of breast cancer. Due to the high prevalence, *TP53* and its mutated state is both a potential biomarker and therapeutic target for patients with breast cancer, especially in the triple-negative subtype [23]. Changes in the *TP53* gene lead to an altered expression of various genes that are directly or indirectly controlled by the p53 transcription factor. Different mutations in *TP53* gene have been reported especially in exon 4 and intron 3

which are frequently mutated in triple–negative breast cancer patients [24]. The missense mutation is the most common one which often are seen in higher stages of cancers or aggressive forms [15].

Phosphatase and tensin homolog deleted on chromosome ten (PTEN) was the first phosphatase enzyme identified as a tumor suppressor gene and shows diverse functions such as cell cycle regulation, apoptosis, and metastasis [25]. *PTEN* dephosphorylates the focal adhesion kinase which leads to inhibition of the cell migration, spreading and focal adhesion. Moreover, *PTEN* has a role in the 1-phosphatidylinositol 3-kinase pathway modulating that is consequently involved in cell proliferation and survival [26]. Cowden syndrome (CS) is the result of the germline mutations in the *PTEN* gene, which is characterized by a high risk of breast cancer [25].

Serine/Threonine Kinase 11 (STK11) gene-encoded as a Serine/threonine kinase and identified as a tumor suppressor gene. Mutations in *STK11* can cause Peutz–Jeghers syndrome (PJS) [27]. The STK11 protein, as a master kinase, plays many roles in diverse cellular processes such as cell cycle arrest, *p53*-mediated apoptosis, cell polarity, and energy metabolism. The risk of breast cancer in PJS patients is 8% at the age of 40 but 45% by the age of 70. Also, *STK11* gene mutations were found in patients with breast cancer. Furthermore, downregulation of *STK11* can lead to papillary breast carcinoma [27].

Moderate penetrance genes

Uncommon variants minor allele frequency (MAF) with moderate effects on risk are another set of genetic variants linked to breast cancer risk. Checkpoint Kinase 2 (CHEK2) protein truncating variant, *PALB2*, *BRIP1*, and Ataxia-Telangiectasia Mutated (ATM) are among them. These genes are all involved in DNA repair pathways in some way.

By phosphorylating p53 and BRCA1, CHEK2 encodes a protein that regulates the repair of DNA double-strand breaks. PALB2 is a protein that promotes BRCA2 location and stability, which aids BRCA2-mediated DNA repair.

BRIP1 is a helicase that interacts with BRCA1 and helps to modulate checkpoints.

ATM gene are not common and hold moderate risk of breast cancer [28] [13]. *ATM* was mapped to chromosome 11q by genetic linkage analysis and belongs to a protein family referred to as the phosphoinositide 3-kinase (PI3K)-related protein kinases (PIKK). It is involved in the phosphorylation of multiple proteins including p53, BRCA1 and BRCA2 [29]. *ATM* monomers dissociate in response to ds-DNA breaks, and participated in many processes such as recognition of damaged DNA, recruitment of repair proteins, signaling to cell cycle checkpoints, transcriptional regulation, and finally activation of apoptosis [30]. Mutations in *the ATM* gene were common in ER-positive and/or PgR-positive breast cancer [31].

Other possible breast cancer genes have been proposed, such as *MRE11*, which encodes a component of the MRE11-RAD50-NBS1 complex, which is important for tumor suppression and genomic integrity.

Due to the small risk increases and low frequency of this class of genetic variations, their contribution to familial relative risk is predicted to be less than 3%. Since few genes have been studied in this way, it is likely that additional susceptibility variants of this class exist.

Low penetrance genes

A polygenic model incorporating a mixture of many individual variants with weak relationships with risk, the so-called low-penetrance polymorphisms, is likely to explain the majority of the unexplained portion of familial relative risk [13].

GWAS in breast cancer so far have led to the discovery of genetic markers that are so common and hold a low risk and located in 12 susceptibility loci including *FGFR2, TOX3, MAP3K1, c.MYC, LSP1, NEK10, COX11, CASP8, TNP1, NOTCH2, RAD51L, MRPS30, ESR1* [13].

TP53 (4%), *PIK3CA* (3.8%), *TTN* (2.73%), *MUC4* (2.21%), *MUC16* (1.69%), *CDH1* (1.67%), *GATA3* (1.58%), *MUC2* (1.28%), *KMT2C* (1.14%), and *MAP3K1* (1.02%) are the top 10 mutant genes found by the (TCGA-https://portal.gdc.cancer.gov/). There were also 156,432 somatic mutations found, each with its own nature, consequences, number of affected individuals, and impact on survival.

Only three genes (*TP53*, *PIK3CA*, and *GATA3*) have somatic mutations at levels greater than 10% across all breast cancer subtypes. More than 1600 probable driver mutations in 93 breast cancer genes have been discovered based on TCGA data.

Somatic mutations in only three genes (*TP53*, *PIK3CA*, and *GATA3*) occurred at levels of more than 10% across all breast cancer subtypes. In total, based on TCGA data, more than 1600 likely driver mutations in 93 breast cancer genes were identified [32]. However, there were numerous subtype-associated and novel gene mutations, including the enrichment of specific mutations in *GATA3*, *PIK3CA*, and *MAP3K1* with the Luminal A subtype.

This raises the question of whether we should move our clinical focus away from subgroups and toward genomics [32].

Molecular profiling assays

Individuals with a personal or family history of hereditary cancer should consider for genetic testing, particularly if the findings affect risk management and care. It is now routine practice to order phenotypically-directed multi-gene panel tests to assess the pathogenic changes in multiple relevant genes simultaneously, as opposed to single-gene testing [33]. Hence there are several different studies in this field that one of which is considered genetic assays that are included in both molecular and pathology assays. Generally, genomic assays are classified into different tests containing Oncotype

Table 1 Molecular Profiling Assays

Tests	Method (Genes Number)	Number of Genes Assay	FDA Approved	Output Score	Prognostic, Predictive	Recommendations
Oncotype DX	qRT-PCR (16 genes)	21-gene	No	Risk score and category. High risk RS ≥ 31 Intermediate RS (18–31) Low risk RS < 18	Yes for both	NCCN ASCO ESMO St. Gallen, AJCC NICE EGTM
MammaPrint	DNA micro-arrays (70 genes)	70-gene	Yes	Risk category High risk Low risk	Only Prognostic	NCCN ASCO ESMO St. Gallen,
BluePrint	RNA micro-arrays (80 genes)	(80 genes)	No	Risk score and category with MammaPrint < 14% (low-risk) ≥ 14% (high-risk)	-	-
Prosigna (PAM50)	Microarray and quantitative RT-PCR (50 genes)	50-gene	Yes	Intrinsic subtype, risk of recurrence score High risk RS 41–100 Low risk RS(0–40)	Yes for both	NCCN ASCO ESMO St. Gallen EGTM
EndoPredict	qRT-PCR (8 genes)	12-gene	No	Risk score and category (ranged from 0 to 7) High risk EPclin-score ≥ 3.3 Low risk EPclin-score < 3.3	Only Prognostic	ASCO ESMO St.Gallen EGTM
Breast Cancer Index	qRT-PCR (7 genes)	7-gene	No	Risk score and category (ranged from 0 to 10) High risk RS > 5 Low risk RS < 5	Yes for both	ASCO St. Gallen EGTM
Genomic Grade Index	DNAmicroarrays (97genes) or qRT-PCR (4 genes)	97-gene	No	Risk category High risk Low risk	-	-
Immunohistochemistry	Immunohistochemistry (Assessment of ER, PR, HER2, and Ki67 expression)	-	No	Risk score and category High risk Low risk	-	-
OncPx	-	14 genes	No	Risk score and category High risk Moderate risk Low risk	Only Prognostic	-

ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; EGTM, European Group on Tumor Markers; AJCC, American Joint Committee on Cancer; NICE, National Institute for Health and Care Excellence

DX, MammaPrint, PAM50, etc, (Table 1). Although there are significant differences among genetic tests, these assays are all prognostic biomarkers and can estimate recurrence risk and each of the assays can potentially report discordant results for the same individual patient [34].

Oncotype DX was the first genomic biomarker test introduced for breast cancer treatment in 2004. It was fulfilled as a trial basis in 2007 and after that, in 2011, it was greatly accessible [35]. It is important to mention that Oncotype DX is a multiplex gene assay and has developed according to three segregate studies. So that first it was identified 250 candidate genes as the result of 447 tumor paradigms from patients [36]. On the other hand, the most significant usages of these data were the limitation of these genes to 21-genes and then they were derived into two categories. The first group is containing 16 genes that were related to cancer. Moreover, this set is divided into 5 subgroups including invasion genes (*MMPP11*, *CTSL2*), HER2 genes (*GRB2*, *HER2*), estrogen genes (*ER*, *PGR*, *BCL2*, *SCUBE2*), and other cancer-related genes (*GSTM1*, *CD68*, *BAG1*), proliferation genes (*Ki67*, *STK15*; Survivin, *CCNB1*, *MYBL2*). The second group is covered 5 genes related to reference genes including *ACTB*, *GAPDH*, *RPLPO*, *GUS*, and *TFRC* [37]. The Oncotype DX genomic assay is based on real-time PCR with the purpose of evaluating the probability of breast cancer recurrence in patients with hormone-receptor-positive such as estrogen receptor (ER), being negative in HER2 and the lymph-node, invasive breast cancer and patients who get tamoxifen less than 5 years. According to the recurrence score, patients have been classified as low-, intermediate-, or high-risk group. This algorithm computes the function, correlated expression, or both for each cancer-related gene. Increased risk of recurrence is dependent on an increased expression of a certain cancer-related gene. To note, the low-risk group has been described as a recurrence score of < 18, while the high risk has been defined as a score of ≥ 31 and intermediate-risk is between 18 and 31 [38]. On the other hand, the Trial Assigning Individualized Options for Treatment (TAILORx) has been designed for prospective randomized trials for patients with node-negative and ER + breast cancer. This trial illustrates whether patients would benefit from adjuvant endocrine therapy alone and shows that women with RS < 11 were specified to hormonal therapy alone. Patients with recurrence score of 11 to 25 were randomly selected to received endocrine therapy alone or chemotherapy plus endocrine therapy and women with an RS > 25 were defined to chemotherapy plus hormonal therapy [39].

MammaPrint is the other breast cancer genomic test that describes an expression of 70-genes profile and it has been approved by the Food and Drug Adminstration (FDA) [40]. It has been known as a prognostic marker regardless of clinical and pathologic factors like tumor size and ER/HER2 status. The biological function of the 70 genes contains hallmarks of cancer that are involved in tumor development and apoptosis evasion genes [41]. In this assay, patients are divided into two groups including low and high risk based on overall expression levels. In low-risk breast cancers, expression patterns of 70 genes could discriminate the non-metastasizing and in high-risk groups, the risk of metastasis in this group has been considered which obviously required systemic therapy. In addition, factors such as tumor size, age, nodal status, and other pathological and clinical factors are considered in the high-risk groups [42]. Generally, MammaPrint can more accurately forecast discordant patients. Finally, it is worth mentioning that American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and St Gallen'sdoes recommend the use of MammaPrint 70-gene assay [35].

BluePrint is a genomic assay which is not still approved by the FDA. This assay is a molecular sub typing profile test that measures the expression of the mRNA levels of 80 genes. These genes classify tumors to 3 separate molecular subtypes which include Luminal-type, Basal-type, and Her2-type [43]. Megering the 70- and 80-gene signatures stratify patients to four subgroups that including luminal subtype A/MammaPrint Low Risk; luminal subtype B/MammaPrint High Risk; HER2-type and Basal-type. Combining these two assay together assist to better prognostic estimation and the selection of treatment. Luminal A is describe as having a MammaPrint expression < 14% (low-risk) and luminal B is interpret as having a MammaPrint ≥ 14% (high-risk) [44, 45].

PAM50 is the predictor analysis of microarray 50 that has been described as a 58-genes assay to recognize the intrinsic subtypes of breast cancer containing luminal A luminal B, HER2-enriched, and basal-like [46].

It is an independent predictor of clinicopathologic change in breast cancer which is approved by FDA in 2013 (34). PAM50 test gives extra data about the biology of tumors and quantitative information for proliferation, luminal gene expression, *ESR1*, *PGR*, and *ERBB2* [36]. PAM50 assay is used to predict the risk of recurrence (RoR) scores. In breast cancer, these (RoR) scores are categorized as low (0–40) or high (41–100) risk [47].

EndoPredict is a prognostic multigene assay based on RT-PCR that assays the expression level of 12 genes which have been divided into three genes entities. The first is including eight cancer-related genes, the second and third entities are containing three RNA reference genes and one DNA reference gene. It categorized tumors recurrence into low and high risk [48]. EndoPredict assay computes the endopredict (EP) risk score a thorough risk score by using incorporate

clinical parameters including tumor size and the number of involved lymph nodal (EPclin). An EPclin-score higher than 3.3287 differentiates between high-risk and low-risk patients. Generally, these data are used for treatment decisions of CT and an 6-hormonal therapy [47]. EndoPredict test has emerged in the guidelines of ESMO, St Gallen's, ASCO, and EGTM [49] .

Breast cancer Index is one of the most important biomarker tests that is a mixture of two profiles including the expression ratio of the antiapoptotic homeobox B13-to-interleukin 17B receptor (H: I ratio) and the molecular grade index (MGI) representing five proliferation genes. The scores lower than five are classified in low-risk groups and malignancies whit scores > 5.1 correspond to high-risk groups [50]. Generally, breast cancer Index test is a prognostic and predictive biomarker because it assesses how the possibility of a woman benefiting from taking endocrine therapy [51].

The Genomic Grade Index (GGI) is a significant characterization for precision breast cancer treatment. It is the level of expression of 97 genes that can be an assessment tool for histological tumor grade determination [50]. The GGI assay has been developed by smaller six-genes version that uses RT-PCR technology on FFPE tissue. GGI can categorize histologically intermediate grade (grade II) into high or low molecular grades so it can predict different responses to similar tumors [52].

Immunohistochemistry (ICH4) is used as prognostic and predictive methods to assess the risk of metastasis in breast cancer. The most prevalent immunohistochemical markers in breast cancer includes estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 and Ki-67. The levels of each marker used to diagnose subgroups of patients. It can be an effective technique that calculated recurrence risk by an algorithm [50].

BreastOncPx is a signature test of 14 genes that provides prognostic data associated with patients with lymph node-negative, ER + breast cancer patients. BreastOncPx test is used to recognize risk of distant metastasis. The recurrence scores of metastasis is according to 10 years post-diagnosis and it classify into (low, moderate, high) risk [53].

Molecular classification

Breast cancer can be classified into molecular subgroups based on histology, cellular etiology, mutations, metastatic dissemination, tumor growth, therapeutic response, and clinical prognosis [54]. There are 12 categories and three main categories for this disease based on histological and molecular characteristics, respectively. Although there are many agreements between these two classification schemes, there have been some disagreements over the data [55]. Gene expression profiling studies classified breast cancers into three intrinsic subtypes by hierarchical clustering, namely hormone-receptor positive breast cancer, HER2-positive breast cancer, and TNBC that each subtype is associated with a unique panel of mutated genes (Table 2) [56].

Table 2 Breast cancer molecular classification

Molecular Subtypes		Biomarkers	Frequency (%)	Tumor Grade	Therapies	Prognosis	Hormonal Expression	Aggressive
Luminal A		ER (+) PR (+) HER2 (-) Ki67 (low)	40–50	Grade I	Endocrine Therapy	Good	High	Low
Luminal B	**HER2-**	ER (+) PR (+) HER2 (-) Ki67 (high)	20–30	Grade II	Endocrine Therapy Chemotherapy Target Therapy	Intermediate	High	Low
	HER2+	ER (+) PR (-/+) HER2+ Ki67 (low/high)	20–30	Grade II	Endocrine Therapy Chemotherapy Target Therapy	Intermediate	High/ Intermediate	Low
HER2+		ER (-) PR (-) HER2 (+) Ki67 (high)	15–20	Grade III	Target Therapy Chemotherapy	Poor	Low	High
TNBC		ER (-) PR (-) HER2 (-) Ki67 (high)	10–20	Grade III	Chemotherapy PARP Inhibitors	Poor	Low	High

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer

Hormone-receptor positive breast cancer

Hormone-receptor-positive breast cancer is a kind of breast cancer that expresses estrogen receptors (ER) and, or progesterone receptors (PR). Tumors with estrogen receptors are called "ER-positive" and progesterone receptors are called "PR-positive". Hormone-receptor-positive breast cancer can happen at any age, but it is more common in post-menopausal. The estrogen-receptor subtype is classified as luminal A and luminal B type [56].

Luminal A breast cancer is the most common subtype. About 50% of all breast cancers indicate the high expression of HR-related genes (ER+/PR + with a low proliferation index), low expression of HER2 genes, and proliferation-related genes such as Ki-67 protein [56].

Luminal A has a better prognosis than the luminal B subgroup also has a better response to endocrine therapy such as anti-estrogen or aromatase inhibitors. The most common mutations in luminal A include *PIK3CA* (45%), *MAP3K1*, *GATA3*, *TP53*, *CDH1*, and *MAP2K4*. Hormone therapy and chemotherapy are the appropriate treatment for the luminal A subtype. Histologically, tumors in this group are low grade and are often non-invasive [57, 58].

Luminal B is less common than luminal A (about 20% of all breast cancers) and has a relatively worse prognosis. Luminal B is divided into two groups, the first group has a higher degree of Nottingham (ER+/PR + with a high proliferation index), HER2-overexpressing (HER2 + disease), and higher expression levels of proliferation-related genes but the difference between the second group and the first group is that in this group sometimes progesterone receptors are negative plus the main difference between them is that HER2 is positive in the second one. As a result, expression of hormones in this group is sometimes less than the others. Also, the expression of proliferation-related genes such as Ki-67 protein is sometimes high and sometimes low. Luminal B cancers have completely heterogeneous genetic mutations that often occur in TP53 and PIK3CA genes. Luminal B tumors are more aggressive than Luminal A [58].

HER2-positive breast cancer

HER2-positive breast cancer is another type of hormone receptor breast cancer that compose about 20% of breast cancers and has a poor prognosis. This group is related to the HER2 gene expression. So there is plenty of the HER2 protein in tumor cells that leads to an increase in growth signaling molecules, contribute to tumor growth rapidly, and the faster progression of breast cancer. Of course, HER2 mutation can also cause other cancers, such as ovarian, gastric and uterine. HER2-positive breast cancer can be either hormone-receptor-positive or hormone-receptor-negative. So cancers with no or low levels of the HER2 protein and, or few copies of the HER2 gene are called HER2 negative breast cancer [59]. Unlike luminal subtypes, HER2-positive breast cancers have a high frequency of the *TP53* and *PI3K* mutation (72% and 39%, respectively) and have increased expression, proliferation-related genes such as Ki-67 protein. HER2-positive breast cancer is a very invasive type of cancer with a very high risk of recurrence. Recurrence can occur at any time but usually occur within five years after treatment. Today, the probability of recurrence is very low compared to the past due to the development of targeted therapies [60].

Triple-negative breast cancer (TNBC)

TNBC is a heterogeneous tumor that accounts for 15 to 20% of all breast cancers that its prevalence varies among different ethnicities and is usually negative (triple-negative) for ER, PR, and HER2 expression. TNBC is estimated to affect 170,000 women worldwide per year, out of a total of one million breast cancer diagnoses. Some of the well-known characteristics of TN tumors include distinct metastatic patterns, poor prognosis, and aggressive biological behavior [61].

TNBC seems to be more common among younger women (usually premenopausal), particularly younger black women [62].

Although the *BRCA1/BRCA2* gene mutation is associated with a high lifetime incidence of all breast cancers, the highest incidence of *BRCA1/BRCA2* is found within the TNBC subgroup. It's thought that about 20% of TNBC patients had a *BRCA1/BRCA2* germline mutation. As a result, professionals recommend that all people with TNBC, especially those younger than 50 years, should be tested for BRCA1/BRCA2 gene mutations [62].

TNBC has a distinct clinical phenotype due to its molecular characteristics. It is distinguished by distant metastases (visceral and brain metastases), the lack of bone metastases, and early recurrent (usually within three years). TNBC is associated with aggressive clinical behavior that grows faster and spread to surrounding tissues, is less treatable, and has a lower prognosis [63].

Treatment approaches

There are several standard therapies including CDK4 and CDK6 inhibitors, PI3K inhibitors, poly (ADP-ribose) polymerase (PARPis), and anti-programmed death-ligand 1 (anti-PD-L1) immunotherapy for metastatic breast cancer based on the tumor classification and molecular profile. The treatment strategy is determined by breast cancer's biology

and behavior. Different factors such as molecular subtypes and stage of breast tumor, genetic markers, patient characteristics, and inherited gene mutations largely influence treatment options and recommendations [64].

Management of hormone receptor- positive breast cancer

The estrogen receptor (ER)-positive subtype responds well to endocrine therapy due to the high expression of hormones. Some patients show sensitivity and resistance to endocrine therapy so, treatment begins with chemotherapy [65]. In recent years, targeted therapy has come to the aid of conventional treatments such as endocrine therapy and chemotherapy consequently, it has increased the rate of treatment. In targeted therapy, unlike traditional therapies, a specific part of the cell is targeted, thus reducing the possibility of damage to healthy cells and improving survival outcomes [66].

As summarized in Fig. 1, in women who are diagnosed with estrogen-receptor-positive breast cancer with undetermined or unknown endocrine sensitivity or resistance, chemotherapy is started as a first-line option with an optimal regimen that includes a taxane-based regimen with or without anthracycline. The use of anthracycline has often been controversial, but seems necessary for high-risk patients [67].

In the next step, some medicines such as PARP inhibitors, eribulin, vinorelbine, and capecitabine are recommended

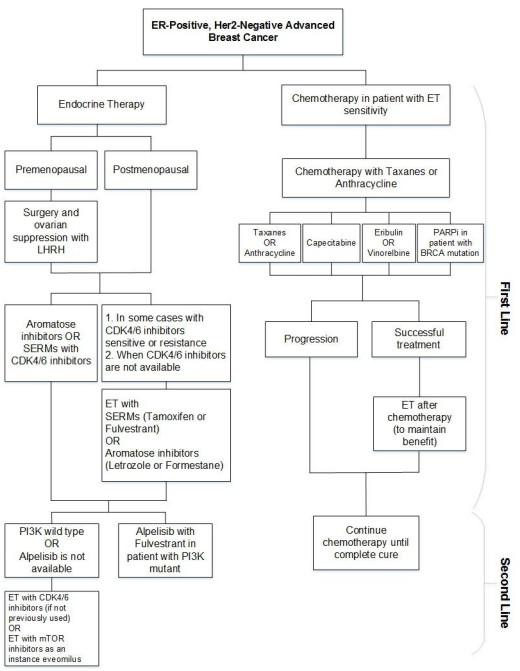

Fig. 1 Treatment algorithm for ER-positive and HER2-negative metastatic breast cancer

[68]. Metabolism of capecitabine is related to *DPYD*. For patients with DPYD poor metabolizers with an activity score of 0, the CPIC Dosing Guideline recommends capecitabine as an alternative medicine. If an alternative medication is not considered a viable therapeutic choice poor metabolizers with an activity score of 0.5, capecitabine should be administered at a significantly reduced dose with early therapeutic drug monitoring. Patients with an activity score of 1 or 1.5 who are intermediate metabolizers should have their doses cut in half. Patients with the genotypes 2846 A > T and 2846 A > T can need a dose reduction of up to 50% [69].

ER-positive patients, often harboring a mutation in *BRCA1* or *BRCA2*. BRCA genes (*BRCA1* and *BRCA2*) also help repair DNA. Still, a mutation in one of these genes can prevent this from happening plus PARP proteins typically help repair damaged DNA inside cells, PARP inhibitors such as olaparib or talazoparib work by blocking PARP proteins which can improve survival in patient with *BRCA1* or *BRCA2* mutation, PARP inhibitors are a kind of targeted therapy [70].

In the second-line treatment, chemotherapy with capecitabine, eribulin, vinorelbine, anthracycline (if not used previously), or a taxane (if not used previously) is continued for a period to achieve definitive result [71].

In patients who do not have endocrine sensitivity and have metastatic breast cancer, endocrine therapy is a preferred option. Women are separated into two groups in this situation; the first group includes women who are premenopausal, treatment start with ovarian ablation or suppression with luteinizing hormone-releasing hormone (LHRH) analogs, which stops the ovaries from making estrogen; The second group includes women who are post-menopausal and did not need ovarian suppression or ablation, so at this stage endocrine therapy starts for both groups [72].

CDK4/6 inhibitors, and endocrine therapy, are helpful to treat patients with ER-positive, HER2 negative metastatic breast cancer. CDK4/6 inhibitors (as a targeted therapy) in combination with endocrine therapy leads to a higher response rate compared to endocrine therapy alone. CDK4/6 inhibitors such as palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio) (In September 2017, abemaciclib was approved by the FDA) block cellular proteins called cyclin-dependent kinases (CDKs), especially CDK4 and CDK6 that block these proteins in hormone receptor-positive cancer cells that help prevent cell division [73]. CDK4/6 inhibitors can be combined with an aromatase inhibitor (preferably in endocrine-sensitive disease). The use of aromatase inhibitor (AI) began out in the early 2000s for post-menopausal women. AI blocks the motion of peripheral aromatase, stopping the conversion of androgens to estrogen. Letrozole and anastrozole are non-steroidal reversible AIs, while exemestane is a steroidal irreversible

which recommends with fulvestrant or probably tamoxifen (in endocrine-resistant disease) in de-novo or recurrent metastatic breast cancer, second-line step, or more, and premenopausal and post-menopausal women. Tamoxifen and fulvestrant belong to selective estrogen receptor modulator medicine (SERMs) that binds competitively to estrogen receptors and might have agonistic impact relying upon the tissue of action. Nowadays, Tamoxifen and raloxifene are two of the most widely used SERMs. SERMs may be utilized in each pre-and post-menopausal woman [73]. It is reported that tamoxifen metabolism could be altered in women with CYP2D6 variants. The comprehensive metabolizer phenotype allele CYP2D6*2A has been linked to increased tamoxifen efficacy, while CYP2D6*4 has been linked to lower tamoxifen efficacy [74].

The CPIC Dosing Guideline for tamoxifen recommends alternative hormonal therapies such as aromatase inhibitor for post-menopausal women or aromatase inhibitors with ovarian function suppression in post-menopausal women for CYP2D6 metabolism is contraindicated if aromatase inhibitor is not used. If the utilization of an aromatase inhibitor is contraindicated, it should be noted that a higher but FDA-approved dose of tamoxifen should be used for the intermediate metabolites of *CYP2D6* and the *CYP2D6* allelic compounds resulting in AS 1[74].

For the women with hormone receptor-positive, HER2-negative breast cancer who have mutated PIK3CA gene, Alpelisib (Piqray) can be used in combination with fulvestrant to treat post-menopausal. Alpelisib (Piqray) is a targeted drug known as a PI3K inhibitor that blocks a PI3K protein (phosphatidylinositol-3-kinase) in cancer cells that can stop them from growing abnormal activation of the PI3K pathway could result in artificial cell proliferation [75].

If patients have *PIK3CA* wild-type, treatment continues with different ET plus CDK4/6 inhibitor if not previously used, or different ET plus everolimus, or different AI, fulvestrant, or tamoxifen. Everolimus (Afinitor) is an mTOR inhibitor. mTOR is a protein in cells that usually helps them grow and divide. Everolimus may also stop tumors in post-menopausal women from forming new blood vessels, which can help limit their growth. It is used with the exemestane as an aromatase inhibitor (Aromasin) for women whose cancer has grown while being treated with letrozole or everolimus and significantly improved progression-free survival more than twice in ER-positive patients, HER2-negative endocrine metastatic cancer HER2-negative endocrine metastatic cancer [76, 77].

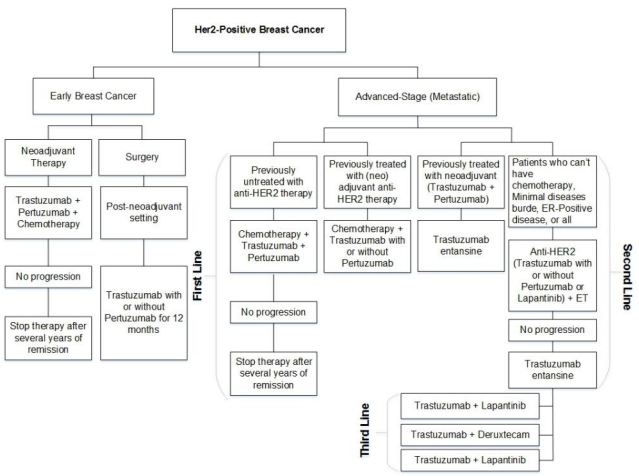

Fig. 2 Treatment algorithm for HER2-positive breast cancer

Management of HER-2-positive advanced breast cancer

In the 1980s, human epidermal growth factor receptor 2-positive (HER2+) breast cancer was recognized as one of the attacking subtypes. HER2 is a member of the HER family of tyrosine kinases that is overexpressed in breast cancer [78]. It contributes in the regulation of cell proliferation, survival, and other processes which are important for carcinogenesis. Currently, the amplified HER2 gene is used as a biomarker to identify breast cancer patients and some HER2-targeted agents, such as trastuzumab (or herceptin), lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) are used to treat these patients [79]. HER2-positive breast cancer is associated with worse survival outcomes as compared to other kinds of breast cancer [80]. Untreated HER-2-positive advanced breast cancer is an aggressive disease, associated with poor prognosis and short survival but HER-2-directed therapy prolongs both the disease progression and survival. Before development of targeted therapies, surgery and chemotherapy were the main treatment for HER2-positive breast cancer [81].

Since the last 30 years until now, several anti-HER2 agents have been developed which improved the therapeutic outcomes in both early and advanced HER2-positive breast cancer [80]. Chemotherapy and trastuzumab have been presented to be the main therapeutic option of HER2-positive [82].

ASCO has recommended the combination of pertuzumab, trastuzumab and taxane but the NCCN has preferred the combination of pertuzumab, trastuzumab, and docetaxel or pertuzumab, trastuzumab, and paclitaxel as the first line regimens for breast cancer treatment [83].

As Fig. 2 shows, trastuzumab was the first anti-HER2 monoclonal antibody and interferes with the HER2 signaling pathway [82]. The overall survival was improved in women with HER2-positive advanced breast cancer when trastuzumab was added to chemotherapy. Also, the positive

results is observed in the use of trastuzumab as an adjuvant treatment in women with early-stage disease [80].

Pertuzumab is also a kind of recombinant humanized anti-HER2 IgG1 monoclonal antibody (targeted antibody) which was designed to be bound to the HER2 extracellular domain (ERBB2) and inhibits its dimerization [82]. Pertuzumab is always used in combination with trastuzumab and chemotherapy to treat some HER2-positive breast cancer subjects and leads to reducing the risk of breast cancer recurrence by about 20% [84, 85].

Both in vitro and in vivo pre-clinical models showed that trastuzumab and pertuzumab combination have synergistically inhibitory effects on the cancer cells' growth [82]. In a phase III trial, the combination of pertuzumab, trastuzumab, and docetaxel prolonged the median overall survival by 15.7 months as compared with placebo, trastuzumab, and docetaxel treatment. Also, data from one study demonstrated that pertuzumab improves invasive HER2-positive breast cancer disease when added to adjuvant trastuzumab plus chemotherapy [82].

The matter of whether to stop HER2-directed therapy in the presence of a continuous radiologic full response to therapy is an important one, and further research is required to determine which patients should safely stop taking trastuzumab [86].

Trastuzumab emtansine (T-DM1) is a targeted therapy used that is typically administered in the second-line metastatic setting. Trastuzumab emtansine is a trastuzumab antibody linked to the DM1 (tubulin-binding agent) through a stable thioether linker. T-DM1 is effective in women with HER2-positive advanced breast cancer who previously treated with trastuzumab and in those with HER2-positive early-stage breast cancer [87].

Also, common options in the third-phase metastatic setting and beyond, are including the combination of trastuzumab plus chemotherapy, lapatinib plus capecitabine, lapatinib plus trastuzumab, trastuzumab plus capecitabine, and endocrine therapy plus HER2-directed therapy [88, 89].

Trastuzumab in combination with chemotherapy dramatically has improved both disease-free survivals and have become the standard of care for those with HER2-positive breast cancer both in the early and advanced stage [80].

Lapatinib is typically used as a tyrosine kinase inhibitor and interlinks reversibly and finally inhibits both HER1 and HER2. Lapatinib is specially approved for patients with HER2-positive advanced-stage breast cancer and showed more toxicity and a remarkable improvement when composed with trastuzumab or chemotherapy [90].

Capecitabine is utilized in first- and second-line metastatic breast cancer. In the metastatic setting, the effectiveness of the combination of capecitabine and lapatinib improved in time to progression so they were utilized as a later-line therapy [90].

The FDA-approved drug label for lapatinib states that *HLA-DQA1**02:01 and *HLA-DRB1**07:01 alleles influence hepatotoxicity in people who have taken lapatinib. trastuzumab deruxtecan (DS-8201a), neratinib, and tucatinib are newly emerged drugs approved by FDA and margetuximab is currently under consideration by the FDA [87].

Also, trastuzumab deruxtecan is using as a novel antibody-drug conjugate created through the conjugation of an anti-HER2 antibody to the topoisomerase I inhibitor DXd (an exatecan derivative), and a self-immolating, enzymatically cleavable peptide linker [82].

The neratinib (inhibitor of HER1, HER2, and HER4) can be given to women with HER2-positive breast cancer who have completed treatment with trastuzumab and may lower the chance of recurrence of breast cancer in certain women [87].

Tucatinib is a kinase inhibitor that is used in tandem with trastuzumab and capecitabine to treat adult patients with advanced unresectable or metastatic HER2-positive breast cancer, and those with brain metastases, who have had one or more previous anti-HER2-based metastatic regimens [91].

The results of the one clinical trial showed that paclitaxel is effective as docetaxel and also it is less toxic. It is suggested that the disease was progressed in patients who were treated with (neo) adjuvant trastuzumab and thus they should receive T-DM1 but in patients who did not previously treated with T-DM1, paclitaxel can be used [87].

Combinations of immunotherapy, CDK4/CDK6 antagonists, novel antibody-drug conjugates, other TKIs, and novel HER2-targeted antibodies are among the other regimens being tested [87].

Management of triple negative breast cancer (TNBC)

Surgery, radiation therapy, chemotherapy, and a variety of targeted therapies are all used to treat TN tumors. As a result of the progress of genomic techniques, novel diagnostic and prognostic biomarkers, such as miRNAs and long non-coding RNAs, have been found, providing insights into using them as therapeutic targets [61].

Although TNBC is associated with a poor prognosis, recent new effective treatment strategies have improved its outcomes.

Chemotherapy has been the cornerstone in the metastatic TNBC treatment for a long time. However, this approach has recently changed with the integration of PARPis for patients with *BRCA* mutations and also with the positive results of the combination of chemotherapy and immunotherapy in patients with programmed death-ligand 1 (PD-L1)-positive

tumors (PD-L1 expression on tumor-infiltrating immune cells ≥ 1%) (Fig. 3).

PD-L1 is clinically used as biomarker in response to checkpoint inhibition in advanced malignancies. It plays an important role in regulating the immune system, preventing T cell overactivation, and increasing regulatory T-cell differentiation [92].

For the women with TNBC who have a *BRCA* mutation, both platinum-based chemotherapy (carboplatin/cisplatin) and PARPis at disease progression are recommended as a first-line treatment option. Platinum-based regimens have shown to be effective in patients with *BRCA1/BRCA2* mutant TNBC and other homologous recombination defects. Platins are less expensive, but they come with the drawbacks of intravenous administration and the risk of side effects like neuropathy, nausea, ototoxicity, and hematological toxicities. PARPis have the benefit of being taken orally, but the higher costs and severity of hematological toxicities must be considered [93].

The proteins encoded by *BRCA* contribute to repair DNA double-strand breaks as part of the homologous recombination pathway [94]. As a result, cells with a *BRCA* mutation have a faulty DNA repair mechanism. Platins as the alkylating agents destroy cancerous cells by interfering with the DNA and causing numerous single-strand breaks, thereby inducing apoptosis and preventing cell division.

The formation of Platinum (Pt)-DNA adducts, which contribute to cell-cycle arrest and apoptosis, is the primary anti-tumor mechanism until platinum is within the cell. High mobility group box protein 1 (HMGB1*)* plays a role in the identification of Pt-DNA adducts by cells, and thus signals a cellular response to these adducts.

Mismatch repair genes, such as *mutS homolog 6 (MSH6)* and *mutL homolog 1 (MLH1)*, reduce the susceptibility of cells to platinum drugs. Furthermore, the genes *X-Ray Repair Cross Complementing 1 (XRCC1)*, *excision repair cross-complementation group 1 (ERCC1)*, *ERCC2*, and *xeroderma pigmentosum group A (XPA)* are involved in nucleotide excision repair, and identified mutations in these genes influence the patient's reaction to platinum-based drugs. These genes work by identifying single-strand breaks and deleting proteins from the DNA helix, making easier access to restorative enzymes. Tolerance to platinum-based drugs has been demonstrated in *POLH* and *POLB* genetic variations, and thus represents a significant determinant of the cellular response to platinum drugs. Furthermore, multiple genes, such as myeloperoxidase *(MPO)*, superoxide dismutase type 1 (SOD1), *GSTM1*, *NAD(P)H Quinone Dehydrogenase 1 (NQO1)*, *Glutathione S-Transferase Pi 1 (GSTP1)*, and *metallothioneins (MT)* are involved in reducing the intracellular concentration of platinum compounds and thus play a key role in cellular resistance to these drugs.

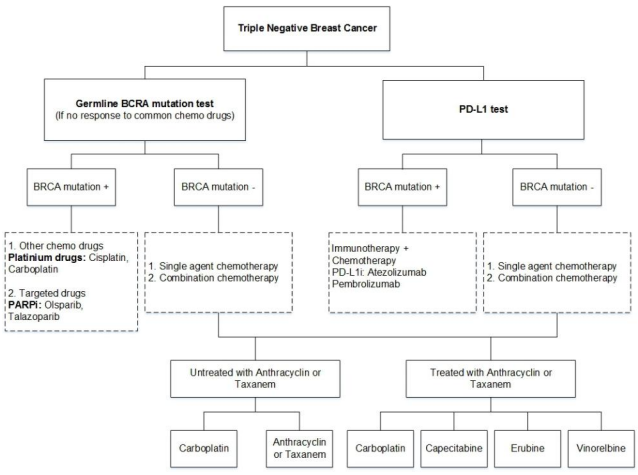

Fig. 3 Treatment algorithm for triple-negative breast cancer (TNBC)

The FDA has approved four PARPi including olaparib (2014; Lynparza, AstraZeneca) [95], rucaparib (2016; Rubraca, Clovis Oncology, Inc.) [96], niraparib (2017; Zejula, Tesaro, Inc.), talazoparib (2018; Talzenna, Pfizer), and a second-generation PARPi currently in development [97] for BRCA-deficient tumors such as advanced breast cancer treatment with deleterious *BRCA* mutations [98]. The clinical data available indicate that these PARPi can significantly improve PFS [99].

Olaparib is only recommended for patients with "deleterious or suspected deleterious" germline variants [100], while new clinical trials have recruited patients with germline or somatic deleterious variants, or tumors with BRCAness phenotype, regardless of whether or not a *BRCA* variant exists [101]. While PARPi are seen to increase progression-free survival, cancer cells can eventually develop resistance and making long-term use of PARPi difficult [98].

There are several emerging therapies and repurposed drugs targeting tumor-driving signaling pathways in TNBC, including epidermal growth factor (EGFR/HER1) antibodies, PI3K/AKT/mTOR, and angiogenesis inhibitors, androgen receptor (AR) antagonists,and estrogen receptor beta (ER) agonists [102]. These drugs are currently still under clinical investigation with limited or mixed results, and therefore they are not a part of standard of care (SOC) therapy. Epidermal growth factor receptor inhibitors (EGFRi), fibroblast growth factor receptor 2 (FGFR2), vascular endothelial growth factor inhibitor (VEGFi), and mammalian target of rapamycin inhibitors (mTORi) are among the other targeted agents being developed for the treatment of TNBC [103].

In the case of PD-L1 expression (is encoded by the *CD274* gene), first-line treatment with atezolizumab (a PD-L1 blocking antibody) or pembrolizumab incombination with nabpaclitaxel (chemotherapty) should be considered [93].

The FDA-approved drug label is recommended the use of Atezolizumab (TECENTRIQ) in patients with EGFR or anaplastic lymphoma kinase (ALK) genomic tumor aberrations and disease progression on other FDA-approved therapy, and patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma [91].

Patients with no EGFR or ALK genomic tumor aberrations, as well as those with EGFR and ALK genomic tumor aberrations that have progressed on FDA-approved therapies, will use pembrolizumab as a first-line therapy. Pembrolizumab is also approved for the treatment of unresectable or metastatic cancers with elevated levels of microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), as well as tumors with a high mutational burden (TMB-H) [91]. The FDA-approved drug label for pembrolizumab (KEYTRUDA) mentions *BRAF* V600 mutations [91].

Single agent chemotherapy with taxanes (paclitaxel or docetaxel) is the first-line treatment option for patients with *BRCA*-wild-type and without PD-L1 expression (PD-L1-negative tumours).

For patients with high grade, combination chemotherapy such as anthracyclines plus cyclophosphamide or platins with taxanes is recommended as a valid option treatment. Anthracyclines are an alternative for patients who underwent taxanes after progression to first-line chemotherapy, and conversely [104].

For patients who advanced to taxanes and anthracyclines or those for whom the drugs are prohibited, fluorouracil/capecitabine, eribulin, gemcitabine, cisplatin/carboplatin, vinorelbine, and ixabepilone are substitutes [105].

TNBC treatment is still changing, but patients should be advised to participate in ongoing studies testing novel targeted drugs, immunotherapy, and predictive biomarkers in order to enhance metastatic TNBC treatment results. New study will indicate the novel treatment approaches (immunotherapy, and predictive biomarkers) with the aim of improving the care of patients with metastatic TNBC in the future.

Conclusions

The mortality of breast cancer has decreased over the last years due to the improvement of prognostic and predictive data assisting in clinical decision-making. The treatment landscape for breast cancer is slowly developing toward the objective to optimize the treatment of breast cancer patients in the forthcoming years by the development of new targeted agents and predictive biomarkers with promising anticipations.

The use of genomic assays according to the latest guidelines has many added benefits to our management of patients that include individualized treatment, progression of patients' dependency, and an increased rate of cancer detection. Collectively, these developments underscore the contemporary reality that molecular testing is now part of the clinical management for the majority of patients with breast cancer. The combination of the conventional and new therapeutic approaches ensures the improvement of clinical outcomes for our patients.

With the introduction of the concept that breast cancer is a systemic disease and the validation of a huge number of clinical data in the age of evidence-based medicine, breast cancer patients with different immunohistochemical types have obtained fruitful results in selecting appropriate treatment modalities, such as chemotherapy, endocrine therapy, or targeted therapy. Precision medicine adds to the meaning of evidence-based medicine because of its more personalized and refined disease management.

Cancer treatment was one of the first medical specialties to use precision medicine. A better understanding of genomic landscapes could pave the way for multitargeted approaches. Improved algorithms for incorporating the new diagnostics methods into medical decisions are critical for translating genomics data into valuable clinical utility. Finally, the precision medicine strategy will be very useful in maximizing the application of current drugs.

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Declarations

Conflict of interest The authors do not have any financial or non-financial conflict of interest.

Informed consent All the authors declare their consent for publication.

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