Precision Medicine in Breast Cancer Treatment: Past, Present, and Future

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Cancer is the second leading cause of death worldwide, and breast cancer is the second leading cause of cancer death in women worldwide. Breast cancer is a heterogeneous disease based on its distinct histopathological subtypes. In recent decades, its prognosis and treatment modalities have greatly benefited from the introduction of precision medicine. This review highlights the emergence of precision medicine which targets the genes that drive breast cancer development and progression. This paper also details how precision medicine has transformed the treatment landscape of breast cancer. The paper concludes by exploring the newest therapy in precision medicine for breast cancer and the possible challenges it encounters.

Introduction

Cancer is a complex disease, characterized by the uncontrolled cell division, and it is the second leading cause of death worldwide behind heart disease[1]. Standard cancer treatments include surgery, chemotherapy, and radiation therapy; however, these treatments are less effective if the cancer has reached the late stages or has metastasized[2]. Furthermore, chemotherapy also comes with several toxicities such as fatigue and nausea due to indiscriminate killing of healthy cells as well as cancer cells[2].

In recent decades, there has been a shift towards a new era of cancer treatment called precision medicine. Precision medicine is a newer practice that takes into account a patient's genetics, lifestyle, and the environment he or she lives in. No two patients have the same type of cancer, even if they have the same histopathological subtype of cancer[1]. Since more molecular factors are being considered, not just disease types, doctors can better devise personalized treatment plans that tailor to a patient's cancer condition. Precision medicine has seen a lot of success in breast cancer treatments. In the past 35 years, the mortality rate of breast cancer has dropped from 33.14 deaths in 100,000 to 18.72 deaths in 100,000 in the US[3]. This review discusses the journey of precision medicine in breast cancer, and how new targeted therapies have impacted the treatment outcomes of breast cancer patients.

Precision Medicine Treatments in Breast Cancer

Based on the molecular profile, there are three main subtypes of breast cancer: estrogen receptor positive (ER+) breast cancer, human epidermal growth factor receptor 2 positive (HER2+) breast cancer, and triple negative breast cancer (TNBC)[4,5,6].

Highly Mutated Genes in Breast Cancer

Breast cancer is a heterogeneous disease. Between 10 and 30 percent of breast cancer cases are inherited[4]. The two main cancer susceptibility genes for breast cancer are breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). BRCA1, first discovered in 1990, is located on chromosome 17[4]. It is mainly responsible for DNA repair through interaction with cell cycle regulators[4] . The C-terminal domain of BRCA1 protein is responsible for suppressing tumor growth, especially in breast cancer [4]. BRCA2, located on chromosome 13, is larger than BRCA1[4]. There are over 1800 mutations that have been identified in BRCA2 gene[8]. It codes the BRCA2 protein, which is responsible for transcriptional regulation, embryonic development, and repairing of damaged DNA[4].

On the other hand, tumor protein p53 gene (TP53) is typically mutated somatically in breast cancer as well as phosphatase and tensin homolog deleted on chromosome ten (PTEN), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) genes[4,9]. TP53 is mutated in roughly 84% of patients with TNBC and 75% of HER2+ patients (Table 1)[4,9]. TP53 gene is responsible for coding tumor suppressor protein p53 (p53), which is involved in cell mitosis, DNA repair, and cell apoptosis[4]. PTEN, which is another tumor suppressor gene, is a negative regulator of the phosphatidylinositol-3 kinase (PI3K) pathway and acts to regulate gene transcription, translation, cell cycle progression, and induction of cell death[4]. PIK3CA is an oncogene that regulates signaling pathways involved in cell proliferation, adhesion, survival and motility[4]. Different types of breast cancer have different variations in mutation/deletion rates of PTEN and PIK3CA (Table 1). People with any of these germline or somatic mutations are two to three times more likely to get breast cancer in their lifetime compared to the general

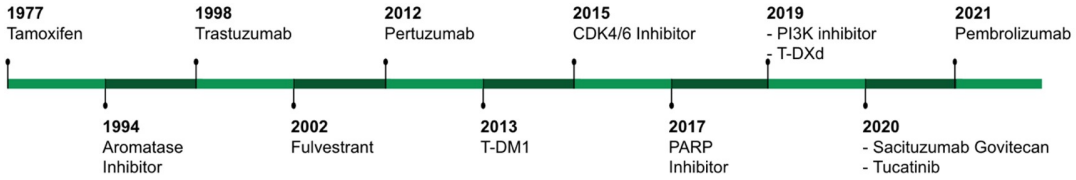

Figure 1. Timeline of precision medicine drugs approved by the FDA for breast cancer treatment[7].
Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; PARP: poly-ADP ribose polymerase; T-DM1: Trastuzumab Emtansine; T-DXd: Trastuzumab Deruxtecan

population[10].

Estrogen-receptor Positive (ER+) Breast Cancer

Overview

Estrogen-receptor positive (ER+) breast cancer is highly dependent on estrogen receptor activity for tumor cell growth and proliferation. It has two molecular subtypes, luminal A and luminal B[5]. Luminal A is the most common breast cancer subtype, accounting for 40-50% of all breast cancer cases (Table 1), and it has a good prognosis. The immunohistochemical profile of luminal A breast cancer is ER+ (>1%), high expression of progesterone receptor (>20%), and low expression of HER2 (<10%)[4,9]. The most mutated gene in luminal A breast cancer is PIK3CA with 49% (Table 1) of patients having the mutation, and other genes that are often mutated include MAPSK1, GATA3, TP53, CDH1, and MAP2K4[4,9]. Luminal A tumors are low grade, typically non-invasive tumors that respond well to endocrine therapy (ET) like anti-estrogen or aromatase inhibitors[5,6]. The five-year relative survival percentage for luminal A breast cancer across all stages is 95.1%[11].

Compared to luminal A, luminal B breast cancer has worse prognosis (higher likelihood of relapse) and is less common, accounting for around 20-30% of breast cancer cases (Table 1)[5,6] . It typically has mutations in TP53 and PIK3CA genes, and its tumors are more aggressive than luminal A[4,9]. Luminal B is split into two groups, and the main difference is that one has HER2 over-expression and the other one does not. Generally, treatment for luminal B breast cancer is endocrine therapy along with chemotherapy (Table 1)[5,6].

Precision Medicine Treatments for ER+ breast cancer

The association between estrogen and breast cancer was first established in the late 19th century[12]. George Beaton discovered that surgically removing the ovaries in patients with advanced breast cancer can improve disease outcome in a subset of breast cancer patients[12]. Subsequently it was discovered that estrogen, which is mainly produced in the ovary, is crucial for the growth of ER+ breast cancer tumors[12]. Targeting ER receptors present in some breast cancer cells is the beginning of precision medicine in breast cancer treatment.

Patients with early ER+ breast cancer can be treated with surgery first, followed by endocrine therapy (ET). ER+ breast cancer has a tendency of recurrence, so patients are recommended to receive ET up to five years after the tumor has been removed[10]. Premenopausal women are recommended to receive ovarian suppression treatment with luteinizing hormone-releasing analogs, which stops the ovaries from producing estrogen, before starting ET[4]. On the other hand, postmenopausal women skip the ovarian suppression and start ET directly[4].

Tamoxifen and aromatase inhibitors are the most common type of drug used to treat ER+ breast cancer[13]. Tamoxifen is a selective estrogen receptor modulator (SERM), a group of synthetic molecules that bind to estrogen receptors in the body, acting like estrogen agonists or antagonists, preventing the growth of breast cancer cells (Table 2)[13]. Tamoxifen was the first SERM drug approved in 1977 by the U.S Food and Drug Administration (FDA) for treatment of metastatic breast cancer (Figure 1). During the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, 2644 patients with ER+, node-negative disease were split into two groups: one that received tamoxifen and the one that received placebo after surgery[13,14]. After 10 years of follow-up, the group that received tamoxifen after surgery saw a significant increase in disease-free survival (DFS) compared to placebo (69% vs. 57%, P<0.0001)[13,14]. Additionally, there was a significant survival advantage (80% in tamoxifen group vs 76% in placebo group; p= 0.02)[13,14]. The DFS with tamoxifen was beneficial for women regardless of their age[14]. Furthermore, the Early Breast Cancer Trialists' Collaborative Group reviewed 194 randomized trials and found that five years of adjuvant tamoxifen therapy for patients with ER+ breast cancer saw a 31% reduction in the breast cancer mortality rate compared to 1 or 2 years of tamoxifen therapy[13,15].

Aromatase inhibitors (AI) block the enzyme aromatase, which turns androgen into estrogen (Table 2)[4]. AIs decreases the amount of circulating estrogen to nearly zero in post-menopausal women and reduce growth-stimulatory effects in ER+ breast cancer[4] . There are two types of AIs: steroidal

Table 1: Molecular subtypes of breast cancer with dominant genetic mutations and unique protein features[4,5,6,8]

	Luminal A	Luminal B		HER2	TNBC
		HER2-	HER2+		
Case Frequency	40-50%	20-30%		15-20%	10-20%
Biomarkers	ER+ PR+ HER2-	ER+ PR- HER2-	ER+ PR-/+ HER2+	ER- PR- HER2+	ER- PR- HER2-
P53 mutation rate	12%	32%		75%	84%
PIK3CA mutation rate	49%	32%		42%	7%
PTEN mutation/loss rate	13%	24%		19%	35%
RB1 Pathway	High expression of RB1	n/a		n/a	Low expression of RB1 RB1 mut/loss
Prognosis	Good	Intermediate		Poor	Poor
Treatment	Endocrine therapy	Endocrine therapy and chemotherapy		HER2 targeted therapy	Chemotherapy PARP inhibitors

Abbreviations: ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; PIK3CA: phosphatidylinositol -4,5-bisphosphate 3-kinase catalytic subunit alpha; PR: Progesterone Receptor; PTEN: phosphatase and tensin homolog deleted on chromosome 10; P53: Tumor Protein p53; RB1: retinoblastoma; TNBC, Triple Negative Breast Cancer; n/a: not applicable

which are irreversible inhibitors, such as exemestane; and nonsteroidal which are reversible inhibitors such as anastrozole and letrozole[4]. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, 9366 postmenopausal women with localized breast cancer were given tamoxifen or anastrozole. The trial found that patients given anastrozole had prolonged DFS (81.6% vs. 79%, p=0.01) and time to recurrence (87.2% vs. 84%, p=0.0005). As for letrozole, a Phase III clinical trial conducted by The Breast International Group (BIG) found that five year disease-free survival is slightly better in letrozole group compared to the tamoxifen group (84% vs 81.4%)[16]. All these clinical trials found that venous thromboembolic events, endometrial cancer, and hot flashes were lower in patients treated with AIs, but the number of bone fractures were higher in AIs treated groups[13]. Among different AIs, the clinical trials found there was no significant difference in efficacy and safety[13].

Selective ER down-regulator (SERD) binds competitively to ER receptors with a higher affinity than SERMS, permanently degrading the estrogen receptor (Table 2)[13]. In 2002, fulvestrant became first and only SERD approved in the US (Figure 1)[17]. Fulvestrant can be used for breast cancer patients that have disease progression following anti- estrogen therapy. In two phase III clinical trials (one in the USA and one in Europe), fulvestrant was compared to anastrozole[17]. In the USA trial, there was no increase in response rate, and only a 0.3 month increase in median time to progression (TTP)[17]. In the European trial, there was a 5% increase in response rate, and a two month increase in TTP[17].

For patients with ER+ advanced breast cancer, ribociclib, a type of cyclin dependent kinase (CDK) 4/6 inhibitor, along with an AI or fulverstrant have become the standard of care (Figure 1)[18]. It was discovered that retinoblastoma (Rb) is phosphorylated by CDK4/6. This event is important for cells to transition from G1 to S phase of the cell cycle. Some ER+ breast cancer cells were found to up-regulate this pathway, causing the cells to grow more rapidly[18]. In a phase III, randomized, double blind trial (MONALEESA-2 trial), postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer were split into two groups: one group received ribociclib and letrozole while the other group received placebo and letrozole. In the ribociclib group 181 of 334 patients (54.2%) died, while in the placebo group, 219 of 334 patients (65.6%) died during the trial. The median overall survival in the ribociclib group was 63.9 months, while the placebo group was just 51.4 months (P=0.008)[19].

HER2+ breast cancer

Overview

HER2+ breast cancer accounts for around 20% (Table 1) of breast cancer cases and has poor prognosis[4]. These patients have a higher quantity of HER2 protein expression on tumor cell surfaces, leading to an increase in growth signaling pathway, causing rapid tumor growth and a more aggressive type of breast cancer. Patients with HER2+ breast cancer have a high likelihood of mutations in both TP53 and PIK3CA genes, with 75% of patients having a mutation in TP53 and 42% of patients having a mutation in PIK3CA (Table 1)[4,9]. HER2+ breast cancer has poor prognosis compared to luminal A. It is very invasive, with a high risk of recurrence, typically happening within five years after treatment[4]. The five-year relative survival percentage for hormone receptor (HR) negative and HER2 positive across all stages is 85.7%[11].

Precision Medicine Treatments for HER2+ Breast Cancer

HER2+ breast cancer patients have greatly benefited from HER2 targeted therapy. Accurate determination of HER2 status is crucial for the optimized treatment for these breast cancer patients. The two main types of HER2 testing are immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH)[21]. IHC tests measure protein expression of HER2 on the cell membrane in the cancer cells, resulting in a score of 0, 1+, 2+, or 3+[21]. A score of 0 or 1+ means negative HER2 protein expression. A score of 2+ requires another test to be run for confirmation. A score of 3+ means positive HER2 protein expression. FISH test examines the HER2 gene amplification, based on the results of the HER2/CEP17

Table 2: ER+ breast cancer precision medicine treatment options and their clinical outcomes

	Drug Type	Drug Name	Clinical Trial Results Summary
Target Therapies for Early ER+ Breast Cancer	Selective Estrogen Receptor Modulator	Tamoxifen	**Trial Name: NSABP B-14**[13, 14] - After ten years, there was a significant increase in DFS (69% vs 57%, p<0.0001) for patients who received tamoxifen compared to placebo
	Aromatase Inhibitors	Anastrozole	**Trial Name: ATAC**[13] - Patients who received anastrozole saw prolonged DFS (p=0.01) and time to recurrence (p=0.005) compared to patients treated with tamoxifen
		Letrozole	**Trial Name: Breast International Group (BIG 1-98)**[13, 16] - The five-year DFS is slightly better in letrozole group compared to the tamoxifen group (84% vs 81.4%)
	Selective Estrogen Receptor Degrader	Fulvestrant	**Company: AstraZeneca**[17] - In the US trial, there was no increase in response rate, and a 0.3 month increase TTP in the patients who received fulvestrant compared to anastrozole group - In the European trial, there was a 5% increase in response rate, and a 2 month increase TTP in the patients who received fulvestrant compared to anastrozole group
Targeted Therapies for Advanced ER+ Breast Cancer	CD4/6 Inhibitor	Ribociclib	**Trial Name: MONALEESA-2**[19] - Ribociclib with letrozole improved mortality rate by 11.4% vs letrozole alone - Ribociclib with letrozole improved median overall survival by 12.5 months vs letrozole alone (p=0.008)
	PI3K Inhibitor	Alpelisib	**Trial Name: SOLAR-1**[20] - Alpelisib with fulvestrant improved PFS by 5.3 (P<0.001) months vs. patient received with fulvestrant alone - Patients must have PI3KCA mutations to benefit

Abbreviations: CD4/6, Cyclin-dependent kinase 4 and 6; DFS, Disease Free Survival; ER, Estrogen Receptor; mTOR, Mammalian Target of Rapamycin; PFS: Progression Free Survival; PI3K, Phosphatidylinositol 3-kinase; TTP: Median Time to Progression; DFS: disease free survival

ratio[21]. Thus, patients with IHC score of 3+ or IHC score of 2+ with FISH ratio of greater than 2.0 will be treated with HER2 targeted therapy. Patients with early stage HER2+ breast cancer are recommended to receive either neoadjuvant or adjuvant trastuzumab and pertuzumab in combination with taxane-based chemotherapy (Table 3)[22]. Neoadjuvant therapies are those delivered before surgery to shrink the size of a patient's tumor, and adjuvant therapies are those that kill cancerous cells remaining after surgery.

Trastuzumab is a targeted therapy that binds to the extracellular domain of HER2 receptors, inducing internalization and degradation of the HER2 receptor using a type of ubiquitin E3 ligase called c-CBL (Figure 1 and Table 3)[22]. In a phase III, randomized trial conducted by the International Herceptin Study Group, trastuzumab in combination with chemotherapy was compared to chemotherapy alone. The trial found that patients who received trastuzumab in combination with chemotherapy had a significantly longer time to disease progression (7.6 vs 4.6 months, P=0.0001, greater overall response rate (49% vs 32%, p=0.0002), longer median response duration (9.3 vs 5.9 months, p=0.0001), and an improved median survival from 20.3 to 25.4 months ($P < 0.025$)[23].

Despite trastuzumab in combination with chemotherapy increased median survival and response rate, cardiotoxicity remains the top toxicity of concern. To manage this side effect, the type of chemotherapy taken in combination with trastuzumab must be considered carefully. For example, trastuzumab with anthracycline and cyclophosphamide has a higher risk of cardiotoxicity than trastuzumab with paclitaxel. Furthermore, early detection and therapeutic management are important, as cardiotoxicity is typically reversable[7].

Pertuzumab is another monoclonal antibody therapy that is always used in combination with trastuzumab, and it has led to a decreased risk in breast cancer recurrence (Table 3)[4]. In some patients, the use of trastuzumab can lead to HER3 up-regulation, causing cancer to persist; therefore, trastuzumab and pertuzumab used in combination can prevent this up-regulation[24]. In June 2012, the FDA approved pertuzumab in combination with trastuzumab and or in combination with docetaxel for patients with HER2+ metastatic breast cancer, based on the results from the CLEOPATRA trial (Figure 1 and Table 3). In the CLEOPATRA trial, patients who received the pertuzumab combination (pertuzumab, trastuzumab and docetaxel) had a median overall survival that was 15.7 months longer than the placebo combination (placebo, trastuzumab, and docetaxel) patients (56.5 months vs 39.6 months, P<0.001). Furthermore, patients in the pertuzumab combination group had an increased median progression-free survival (PFS) by 6.3 months and extended median duration response by 7.7 months[25].

Antibody-drug conjugates (ADC) have also changed the way HER2+ breast cancer is being treated (Table 3). The monoclonal antibody specific to HER2 is coupled with cytotoxic agents to efficiently kill HER2+ breast cancer cells, and ADCs are typically used as mono agents[26].

Trastuzumab emtansine (T-DM1) was the first ADC to receive FDA approval in 2013 based on the results of the EMILIA clinical trial (Figure 1 and Table 3)[27]. T-DM1 is trastuzumab linked to the cytotoxic agent DM1, which inhibits microtubule formation, an important component in cell cytoskeleton. In the EMILIA trial, T-DM1 was tested in patients with HER2+ advanced breast cancer who were previously treated with trastuzumab and a taxane[27]. The trial found that patients who received T-DM1 had an overall survival of 30.9 months, 5.8 months longer than patients who received lapatinib plus capecitabine (30.9 vs. 25.1 months, P<0.001), and the median PFS was 3.2 months longer for patients who received T-DM1 (9.6 vs 6.4 months)[26]. Six years later, T-DM1 approval was expanded to include early stage HER2+ breast cancer based on KATHERINE trial. In the KATHERINE trial, T-DM1 was tested in patients with HER2+ early breast cancer with residual invasive disease at surgery after neoadjuvant therapy with trastuzumab and a taxane. The trial found a 10% increase in invasive disease-free survival for patients who received T-DM1 (87.8% vs 77.8%, P<0.001). Distance recurrence occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group, a drop of 5.4%[28].

The second ADC to receive FDA approval in 2019 was trastuzumab deruxtecan (T-DXd) based on the data from multiple clinical trials including the DESTINY-BREAST04 phase III[29] (Figure 1 and Table 3). In the DESTINY-BREAST04 phase III trial, T-DXd was tested in patients with HER2 low metastatic breast cancer who had previously been treated with chemotherapy. The trial showed that the median PFS was 4.8 months longer (9.9 vs 5.1 months, P<0.001) for patients who received T-DXd and the overall survival was 6.6 months longer (23.4 vs. 16.8 months, P<0.003) compared to patients who received physician's choice of chemotherapy[29].

In the DESTINY-Breast03 trial, results showed T-DXd was more beneficial to patients with HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane than T-DM1. Among 524 patients in the trial at 12 months, 75.8% of patients who received T-DXd had no disease progression, while only 34.1% of patients who received T-DM1 had no disease progression (P<0.001). The survival rate after 12 months was 8.2% higher (94.1% vs 85.9%) in patients who received T-DXd[30].

Triple Negative Breast Cancer (TNBC)

Overview

TNBC accounts for 10-20% of breast cancer cases and is negative for ER and HER2 expression (Table 1)[4]. TNBC tumors have poor prognosis with aggressive biological behaviors and

Table 3: HER2+ breast cancer precision medicine treatment options and their clinical outcomes

	Type of Drug	Drug Name	Clinical Trial Results
First Line of Treatment	Monoclonal antibody	Trastuzumab	**Study Group: International Herceptin Study Group**[23] • Trastuzumab with chemotherapy increased median survival by 5.1 months vs chemotherapy alone (P<0.025)
		Pertuzumab	**Trial Name: CLEOPATRA**[25] • Pertuzumab in combination with trastuzumab and docetaxel increased median overall survival by 15.7 months (P<0.001) and median PFS by 6.3 months compared to trastuzumab with docetaxel
Second Line of Treatment	Antibody-drug conjugates	T-DM1	**Trial Name: EMILIA**[27] • Overall survival was 5.8 months longer (P<0.001) and PFS was 3.2 longer in patients who received T-DM1 vs patients received lapatinib plus capecitabine **Trial Name: KATHERINE**[28] • 10% increase in invasive DFS (P<0.001) and a 5.8% increase from distant recurrence for patients treated with T-DM1 vs patients treated with trastuzumab
		T-DXd	**Trial Name: DESTINY-BREAST04**[29] • PFS was 4.8 months (p<0.001) longer and overall survival was 6.6 (P<0.002) months longer in patients who received T-DXd vs patients who received chemotherapy
Newest Therapy	Tyrosine kinase inhibitors	Tucatinib	**Trial Name: HER2CLIMB**[31] • After 1-year, PFS in the tucatinib combination group is 33.1% vs. 12.3% placebo combination group (p<0.001) and the median duration of PFS was 2.2 months longer • After 2-year, the estimated overall survival rate was 18.3% higher in tucatinib combination group (p=0.005)

Abbreviation: PFS, Progression Free Survival; T-DM1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan

distinct metastatic patterns[31]. Twenty percent of TNBC patients have germline mutations in the BRCA1 or BRCA2 genes[31]. Since the cancer cells in patients with TNBC do not express hormone receptors or HER2 receptors, precision medicine treatment for TNBC is very limited. The five-year relative survival rate for TNBC across all stages is 78%[11]. Currently, the main treatment options for TNBC are still surgery and chemotherapy[31].

Precision Medicine Treatments for Triple-Negative Breast Cancer

Besides surgery and chemotherapy, there are also targeted therapies that are being studied like immunotherapy and PARP inhibitors for TNBC (Table 4)[32]. Immunotherapy, which helps stimulate the immune system to fight cancer cells, is a targeted therapy that is being used in TNBC patients. In March of 2019, the FDA gave atezolizumab in combination with an albumin-bound paclitaxel accelerated approval (Table 4)[20]. The treatment was approved for patients with unresectable locally advanced or metastatic TNBC with sufficient expression of programmed death-ligand 1 (PD-L1). Atezolizumab is a monoclonal antibody treatment that targets PD-L1, helping the immune system recognize cancer cells. The initial trial of atezolizumab and nab-paclitaxel group showed prolonged progression-free survival compared to placebo and nab-paclitaxel group (7.4 vs 4.8 months); however, the final overall survival analysis did not prove it benefited the intention-to-treat population, and the FDA and pharmaceutical company withdrew the US accelerated approval[33].

In July of 2021, the FDA approved pembrolizumab (Figure 1 and Table 4), an immune checkpoint inhibitor, in combination with chemotherapy as a neoadjuvant treatment, and continued as a single adjuvant treatment after surgery for patients with high-risk, early-stage, TNBC based on the KEYNOTE-522 trial. The KEYNOTE-522 trial was a randomized (2:1), multi-center, double-blind, placebo-controlled trial conducted in 1174 patients who had been newly diagnosed with previously untreated high-risk early-stage TNBC. The two main outcomes measured were pathological complete response (pCR) rate and event free survival (EFS). The pCR rate in patients who received pembrolizumab in combination with chemotherapy was 63% compared to 56% for patients who only received chemotherapy, and the percentage of patients who experienced EFS event was 16% and 24% respectively (p=0.00031)[34].

PARP (poly-ADP ribose polymerase) inhibitors were the first targeted therapies to receive FDA approval for TNBC[35, 33]. The cancer cells with BRCA1/2 mutations rely on PARP proteins to repair DNA; therefore, PARP inhibitors can induce apoptosis in cancer cells[36]. Currently the only two PARP inhibitors approved are olaparib and talazoparib, and the major side effects of PARP inhibitors are anemia, neutropenia, and thrombocytopenia[35, 33]. Before patients receive either PARP inhibitor treatments, they must be tested for BRCA mutations. BRACAnalysis CDx is a companion diagnostic test that uses polymerase chain reaction (PCR) to test for BRCA mutations. The results of the PCR test can be classified as follows: positive for a deleterious mutation, suspected deleterious, no mutation detected. The categories of genetic variant (favor polymorphism) and genetic variant of uncertain significance indicate that patient most likely does not have BRCA mutation[37].

Olaparib was the first PARP inhibitor approved for patients with triple negative breast cancer with germline BRCA-mutations (Figure 1 and Table 4). In a randomized trial with a 1:1 ratio, 1836 patients, previously received local treatment and neoadjuvant and adjuvant chemotherapy, were split into two groups, one group received oral olaparib and the other received placebo[38]. After 3 years, the percentage of patients alive and free of invasive disease in the olaparib group was 85.9%, while in the placebo group it was 77.1% ($p<0.001$). The distant disease-free survival in the olaparib group was 87.5% and 80.4% in the placebo group ($p<0.001$), and there were fewer deaths reported in the olaparib group with 59, compared to the placebo group with 86 deaths[38]. When olaparib was first approved by the FDA in January of 2018, and it was only approved for patients with germline BRCA-mutated, HER2-negative metastatic breast cancer who have already received either adjuvant, neoadjuvant, or metastatic chemotherapy. More recently in 2022, it has also been approved for patients with BRCA-mutated, HER2-negative high-risk early breast cancer, who were already treated with either adjuvant or neoadjuvant chemotherapy[35]. The second PARP inhibitor to receive FDA approval is talazoparib in October of 2018[33]. It was approved for patients with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer[39]. Patients who received talazoparib had a median PFS of 8.6 months, while it was only 5.6 months for physician's choice group ($p<0.001$)[39]. PARP inhibitors are a promising new type of therapy for TNBC patients with BRCA mutation. Other PARP inhibitors being tested for TNBC include rucaparib, veliparib, and niraparib, however, none of them have been approved by the FDA for TNBC[39] . PARP inhibitor resistance can develop if there is a restoration of homology repair (HR) in HR-deficient tumors[30]. Genetic reversion mutations such as insertion/deletion can restore the open reading frame of BRCA protein, leading to expression of functional protein.

Utility of Multigene Signature Genomic Tests in Breast Cancer Treatment

Multigene signature genomic tests are an extremely important part of precision medicine in breast cancer treatment because they help doctors make informed decisions. It can predict the risk of recurrence, and how well a patient may benefit

Table 4: Triple negative breast cancer precision medicine treatment options and their clinical outcomes

First Line of Treatment	Chemotherapy Surgery		
	Type of Drug	**Drug Name**	**Clinical Trial Results**
Second Line of Treatment	Immunotherapy	Atezolizumab	**Trial Name: IMpassion130**[20] - Initial trials showed prolonged PFS - Final results did not show benefit for intention-to-treat population
		Pembrolizumab	**Trial Name: KEYNOTE-522**[34] - pCR was 13% higher in patients who received pembrolizumab in combination with chemotherapy vs chemotherapy alone ($p<0.001$)
Targeted Therapy for patients with BRCA1/2 Mutations	PARP inhibitors	Olaparib	**Trial Name: OlympiA**[38] - 8.8% more patients were alive and free of invasive disease in the olaparib group vs placebo ($P<0.001$) -7.1% more patients in the olaparib group has distant DFS vs placebp ($P<0.001$) - The olaparib group had 27 fewer deaths than the placebo group
		Talazoparib	**Trial Name: EMBRACA**[39] - Talazoparib increased median PFS by 3 months ($p<0.001$)
Newest Therapy	Antibody Drug Conjugate	Sacituzumab Govitecan	**Trial Name: ASCENT**[34] - Median PFS was 3.9 months longer and median overall survival was 5.4 months ($p<0.001$) longer in the group that received sacituzumab govitecan compared to chemotherapy alone

Abbreviations: DFS, Disease Free Survival; pCR, Pathological Complete Response; PFS, Progression Free Survival

from extended endocrine therapy or whether chemotherapy is needed in conjunction[40]. There are many different types of multigene signature tests used in breast cancer prognosis including: Oncotype DX, PAM50, and MammaPrint (Table 5)[4]. In 2004, Oncotype DX was the first genomic biomarker test introduced for ER+ breast cancer (Table 5)[40]. It is based on 21 genes: 16 related to cancer and 5 reference genes. It uses real-time polymerase chain reaction (RT-PCR) to evaluate the risk of recurrence, and whether chemotherapy is needed along with hormone therapy to treat the patients with ER+ breast cancer after the patient has had surgery. The patients are classified into three groups (low, intermediate, or high risk) based on the recurrence score[40]. Patients with low and intermediate risk scores need only hormone therapy, while the patients with high-risk scores need both hormone therapy and chemotherapy.

PAM50 is very similar to Oncotype DX, as it also measures relapse risk in patients with ER+ breast cancer (Table 5). However, PAM50 consists of 58 genes: 50 related to molecular subtype and 8 control genes. Based on results, patients are classified into two groups: high risk of recurrence and low risk of recurrence[4]. MammaPrint received FDA approval in 2007 and is based on the expression of 70-gene that are related to tumor development and apoptosis (Table 5)[41]. It classifies patients, regardless of HR or HER2 status, into two groups, low risk and high risk of metastasis. Aside from genetics, MammaPrint also considers the patient's tumor size, age, nodal status, and other pathological and clinical factors that can be considered high risk[42]. Additionally, the American Society of Clinical Oncology, National Comprehensive Cancer Network, European Society for Medical Oncology, and St Gallen all recommend using MammaPrint genomic testing for early breast cancer patients regardless ER status[42] .

Newest Therapies

Newest Therapy for ER+ Advanced Breast Cancer

The effectiveness of ET hinges on the breast cancer cells' dependence on ER for proliferation and differentiation; therefore, loss of ER is a cause of ET resistance. There is also growing evidence that abnormal activation of PI3K-Akt-mTOR (PAM) pathway plays a role in acquired resistance to ET in ER+ breast cancer. The PAM pathway is important for cell growth, survival, and proliferation[43]. Therefore, researchers are turning to PI3K inhibitors and mTOR inhibitors to help treat patients with advanced ER+ breast cancer[43] Alpelisib is an α-specific class I PI3K inhibitor that inhibits the downstream PI3K targets and inhibits the growth of PI3KCA mutant breast cancer cell lines (Figure 1 and Table 2)[44]. Currently, alpelisib approved by the FDA for patients with ER+, HER2-negative breast cancer with PI3KCA-mutated breast cancer[7]. In a phase III, randomized, double blind trial, patients with ER+ and HER2 negative advanced breast cancer were given alpelisib in combination with fulvestrant, or placebo and fulvestrant. After a median follow-up of 20 months, patients with PI3KCA mutations who were given alpelisib with fulvestrant had a disease-free progression of 11 months compared to just 5.7 months for patients who were given placebo with fulvestrant ($p<0.001$)[44].

Newest Therapy for HER2+ Metastatic Breast Cancer

Trastuzumab based therapy has transformed the lives of HER2+ early and advanced breast cancer patients. However, for HER2+ metastatic breast cancer patients with brain metastases, treatment options have become limited. Tyrosine kinase inhibitors (TKI) along with trastuzumab are offering hope to those patients[42]. The newest TKI is tucatinib (Figure 1 and Table 3). It is for patients with HER2+ metastatic breast cancer who had already received trastuzumab, pertuzumab, and T-DM1, and who had or did not have brain metastases. In the HER2CLIMB trial, patients were then split into two groups, one group received tucatinib in combination with trastuzumab and capecitabine, and the other only received placebo in combination with trastuzumab and capecitabine. After one year, the PFS in the Tucatinib-combination group was 33.1% while in the placebo-combination group it was 12.3% ($P<0.001$), and the median duration of PFS was 7.8 months in the tucatinib-combination group, compared to 5.6 months in the placebo-combination group.

After two years the estimated overall survival in the tucatinib-combination group was 44.9% while in the placebo-combination group it was 26.6% ($P=0.005$). The median duration of overall survival was 21.9 months in the tucatinib-combination group and 17.4 months in the placebo- combination group, and the risk of death was 34% lower in the tucatinib-combination group than in the placebo-combination group ($P=0.005$). Finally, among patients with brain metastases the 24.9% of patients had PFS at in the tucatinib-combination group after one year, while in the placebo-combination group it was 0% ($P<0.001$)[45].

Newest Therapy for Metastatic TNBC

Unlike ER+ and HER2+ breast cancer, TNBC has a few useful biomarkers identified, making it harder to treat. The most successful targeted therapies involve PARP inhibitors for germline BRCA mutations. The recent immune checkpoint inhibitor is more successful in patients with high expression of PD-L1. Some new biomarkers under investigation include trophoblast cell-surface antigen 2 (Trop-2), LIV-1, and mucin 1-attached sialoglycotope CA6, which are cell surface proteins that are overexpressed on TNBC cells[46].

One of the more successful biomarkers is Trop-2, which researchers have developed a new ADC as a possible treatment

Table 5: Breast cancer genomic testing methods[4,42]

	Objective	Patient Group	Number of Genes	Results
Oncotype DX	Evaluate the risk of recurrence and whether chemotherapy is needed along with hormone therapy	ER+ breast cancer patients	21 genes (16 related to cancer and 5 reference genes)	- Low risk of recurrence - Intermediate risk of recurrence - High risk of recurrence
PAM50 (Prosigna)	Risk of recurrence in patients with ER+ breast cancer	ER+ breast cancer patients	58 genes (50 related to molecular subtype and 8 control genes)	- Low risk of recurrence - High risk of recurrence
MammaPrint	Risk of metastasis	All early breast cancer patients	70 genes	- Low risk of metastasis - High risk of metastasis

for TNBC[47]. In 2020, sacituzumab govitecan received FDA approval for patients with triple negative metastatic breast cancer who already received two prior therapies based on the results from the ASCENT trial (Figure 1 and Table 4)[47,48]. The ASCENT trial was a randomized trial, and it compared sacituzumab govitecan to chemotherapy. The trial found that patients who received sacituzumab Govitecan had median progression-free survival of 5.6 months, 3.9 months longer than patients who received chemotherapy, and the median overall survival was 5.4 months longer for patients who received sacituzumab govitecan ($p < 0.001$)[48].

Challenges and Possible Solutions

Although precision medicine in breast cancer has saved lives, limitations of precision medicine include cost, accessibility, and standardization. Precision medicine therapies and their associated genomic testing are expensive, likely costing the patients and their families hundreds of thousands of dollars. Furthermore, developing new and effective medicines is also an expensive endeavor for pharmaceutical companies. To address the issue of cost, the pharmaceutical industry needs to work closely together with the healthcare industry, insurance companies, and the government to make sure precision medicine is affordable to all patients[36].

Accessibility is another concern. Clinical trials typically focus on a highly selective group of patients, often excluding elderly people, people from different ethnic backgrounds, and people from different socio-economic groups. This could lead to the adoptions of misleading biomarkers. Furthermore patients from low and middle-income countries might not have access to the newest treatments, exacerbating this disparity. There are many initiatives and programs around the world that are trying to reduce healthcare inequalities, and improve prevention, detection, and treatment for cancer. One of these programs is the Europe's Beating Cancer plan which is aiming to provide more access to precision medicine for patients who face healthcare inequalities[7].

The lack of standardization in molecular testing and treatment approaches is another challenge that precision medicine faces. There are many different molecular testing approaches which can lead to confusion among healthcare providers and inconsistent results. A survey of 1281 US oncologist found that only around 38% were very confident in using Next-generation sequencing (NGS), and a survey done across 19 European countries found that around 39% of clinician were concerned with interpretation and reliability of NGS results[7]. To address issues with genomic testing, new technology needs to be developed to improve the accuracy and sensitivity of molecular testing. Currently the Clinical and Laboratory Standards Institute is working towards standardizing molecular testing[49].

Finally, real-world evidence (RWE) is also important in precision medicine to identify gaps in treatment; however, there are many technical and logistical barriers like comparing cross-study data as well as data storage and collection. To address these issues, guidelines for standardizing data sharing and protection will help improve RWE in the field of precision medicine[7].

Conclusion

Precision medicine has changed the landscape of breast cancer treatments. Instead of chemotherapy being the first line and the only option for patients, now treatment plans are based on the genetic makeup of a patient's cancer. As a result, precision medicine has improved the survival rate of breast cancer, allowing patients to live longer. In the last 35 years the mortality rate of breast cancer in the US has dropped from 33% in 1985 to 19% in 2020. Furthermore, the 5-year survival rate of breast cancer has increased from 75.2% in 1979 to 92.8% in 2015[2].

Despite these improvements, precision medicine needs

to be made accessible to everyone. Funding needs to go to communities where there are healthcare disparities to ensure that all patients have equal access to the genomic testing, treatment centers, and treatment options. Education for healthcare providers and patients around precision medicine is also important, so that healthcare providers can make better informed decisions about treatment, and patients can understand the potential benefits of precision medicine. Most importantly, there needs to be more research done to discover new therapies that will treat patients who do not benefit from the current available options. Currently, hundreds of clinical trials are testing new therapies that can possibly save lives, and precision medicine will continue to lead the way in breast cancer treatment.

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