Evaluating the Therapeutic Impact of Targeted Therapy in Advanced Breast Cancers including TNBC

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Abstract

Triple-negative breast cancer (TNBC) represents one of the most aggressive and clinically challenging subtypes of breast cancer, characterized by a poor prognosis and high rates of recurrence. Although chemotherapy is the main treatment option with TNBC, the effectiveness of chemotherapy for TNBC is still limited. In addition, TNBC has its unique composition of lacking three common receptors in breast cancer such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2), which makes TNBC hard to treat due to lack of specific therapeutic targets. Despite its molecular heterogeneity, advances in whole-genome sequencing studies have enabled the identification of distinct molecular subtypes within TNBC, offering new insights into the tumor's underlying biology. Recent studies also have identified specific genetic alterations and aberrant signaling pathways to explore novel targeted therapeutic strategies.

These efforts have led to development of several targeted therapeutic agents including, Poly (ADP-ribose) polymerase inhibitors (PARPi), Androgen Receptor (AR) antagonists, Cyclin-Dependent Kinase (CDK) 4/6 inhibitors, Phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway inhibitors, Epidermal Growth Factor Receptor (EGFR) signaling pathway inhibitors, and immune checkpoint inhibitors targeting Programmed Death Receptor (PD-1) or Program-cell Death-Ligand 1 (PD-L1). In this study, we summarize multiple targeted therapies in patients with advanced breast cancer, mostly focusing on TNBC, with an emphasis on the mechanism of action of each drug class and their clinical efficacy such as overall survival, progression-free survival, or objective response rates.

Introduction

Breast cancer is the most common cancer and is the second leading cause of cancer-related death among women in the United States[1]. It is a disease in which cells grow and divide without any control, causing them to lump together in the breast tissue. The majority of the cases begin in the lobules or ducts. Other cases may develop in the nipple area, or inner quadrant. Symptoms can include but not limited to a lump in the breast, changes in shape, dimples in the skin, discharge from the nipple, an inverted nipple, or a red, rash-like patch of skin. Invasive breast cancer accounts for approximately one-third of all new female cancers each year. In 2024, about 310,720 new invasive breast cancer cases are expected to be diagnosed in women in the United States, with an estimated 42,250 women dying from the disease[1]. Between 1990 and 2021, the global burden of breast cancer had a drastic growth with disparities demonstrated across socio-demographic index (SDI) regions. Despite high SDI regions showing improvements in mortality and disability-adjusted life years, lower SDI regions suffered from the burdens[2].

Breast cancer can be classified into four molecular types based on the presence of hormone receptors and human epidermal growth factor receptor (HER2)[3]. Hormone receptors are categorized into two types: estrogen receptor (ER) and progesterone receptor (PR). The most common breast cancer is Luminal A, which is ER positive, PR positive, and HER2 negative. This type accounts for 70% of all breast cancer cases. It grows slowly, is less aggressive, and responds to hormonal therapy. Additionally, it has low Ki-67, a protein related to associated with cell division[4]. Another type is known as Luminal B, which is ER positive, PR positive, or negative depending on cases, and HER2 negative. This type accounts for about 9% of all breast cancer cases. It is a higher grade than Luminal A and usually associated with poorer prognosis. The way to differentiate it from Luminal A is usually the Ki-67 levels, which in case of Luminal B are high[4]. HER2-enriched, which is ER negative, PR negative, and HER2 positive, is the least likely breast cancer subtype, accounting for 4% of all diagnoses. It used to have the worst prognosis, however, with the development of targeted therapies for HER2+ cancer such as tyrosine kinase inhibitors and immunotherapy, the outcomes have been significantly improved, especially with the lack of recurrence in the cancer[5]. The last type is known as triple-negative or basal type breast cancer, which is ER negative, PR negative, and HER2 negative. It accounts for around 10% of all breast cancer cases. It is generally a more aggressive type of tumor and has a higher risk of growth and return, making it more dangerous[6]. Unlike the other subtypes, triple-negative breast cancer (TNBC) commonly occurs in young women and is associated with increased mortality[7]. About 45% of patients with TNBC have distant metastases in the brain or elsewhere, and median survival is only about 13.3 months[8].

Breast cancer is classified not only by molecular differences but also by the stage of the disease. There are five stages of breast cancer, ranging from Stage 0 to Stage IV. The stage is determined using Tumor size, Number of cancer infected lymph nodes, and Metastasis (TMN) system[9]. Stage 0 to III are distinguished by the size of the tumor and the number of infected lymph nodes. At Stage IV, metastasis occurs, meaning the cancer has spread to other parts of the body. For early

staged breast cancer, breast-conservation surgery and radiotherapy or mastectomy alone are viable options. Up until stage III, the surgeries that follow are mainly breast conservation surgery or mastectomy. The adjuvant systemic therapy is administered depending on the status of lymph nodes, and the presence of hormone receptors and HER2. Stage III is when neoadjuvant chemotherapy occurs before surgery. The main purpose of the treatment of metastatic breast cancer is to extend survival and maintain quality of life. The main treatment options are radiation therapy, hormonal therapy, or chemotherapy[10].

There are several methods of surgery and treatment for breast cancer. Most common surgery types are lumpectomy, mastectomy, breast reconstruction, and sentinel lymph node biopsy. They all deal with various parts of the breast and how it is affected later in the future. After surgery, hormonal therapy or radiotherapy is applied to the patient. Not surprisingly, the standard therapy for TNBC is adjuvant and neoadjuvant chemotherapy due to lack of the targeted therapies. Conventional chemotherapy has shown some effectiveness in patients with TNBC. However, the toxicity of chemotherapy is harmful for patients. Therefore, finding effective targets for TNBC remains a challenging issue that needs to be addressed. Continuous efforts have led to development of several treatment options targeting Poly-ADP Ribose Polymerase (PARP), Androgen Receptor (AR), CDK4/6, PI3K/AKT/mTOR signaling pathway, Epidermal Growth Factor Receptor (EGFR), Programmed Death Receptor (PD-1), Program-cell Death-Ligand 1 (PD-L1), etc. This study provides an overview of each drug class, describing its primary mechanism of action and clinically beneficial outcomes such as overall survival (OS), progression-free survival (PFS), objective response rate (ORR) in patients with advanced breast cancers, mostly focusing on TNBC.

Poly (ADP-ribose) polymerase (PARP) inhibitors

PARP enzymes primarily serve to transfer ADP-ribose groups to the glutamate, aspartate, and carboxy-terminal lysine residues of proteins[11]. They also convert NAD+ into polymers of ADP-ribose, playing an important role in PARP-mediated cell death[12]. Currently, there are 17 known members in the PARP family[13]. PARP family is classified into three groups: PARP 1-5 have a conserved glutamate residue, PARP 6-8, 10-12, and 14-16 are putative mono-(ADP-ribose) polymerases. PARP 9 and 13 do not have a PARP signature motif that binds NAD+ nor do they have Glu988, implying inactivity[14]. PARP3 is known to selectively suppress the growth, survival, and tumorigenicity of breast cancer gene1 (BRCA1)-deficient TNBC cells. Since PARP3 and BRCA1 are synthetic lethal, targeting the catalytic activity of PARP3 would be a promising therapeutic strategy for BRCA1-associated cancers[15]. PARP inhibitors have been effective treatments in clinical trials for sporadic TNBC and BRCA-mutated cancers[16]. PARP enzymes, particularly PARP1 and PARP2, are known to be crucial against DNA repair. They detect single-strand breaks (SSBs) and facilitate repair through the base excision repair (BER) pathway. When DNA damage is detected by PARP1, the enzymes attach to the damaged DNA, which allows the NAD+ to bind themselves to the active site. This action catalyzes the addition of ADP-ribose polymers to itself and other nuclear proteins. This process is also known as PARylation[17]. PARP

inhibitors (PARPi) attach to the catalytic domain of PARP enzymes. It prevents them from repairing SSBs. The binding also traps PARP on the DNA, creating a more complex and toxic form of DNA damage known as PARP-DNA trapping mechanisms. The PARPi disrupt any DNA repair pathways by targeting tumors with germline BRCA1/2 mutations via these methods of synthetic lethality. Double-strand breaks (DSBs) require homologous recombination (HR) as a critical source for repair. TNBC cells lack HR repairing mechanisms and cannot effectively repair these DSBs, resulting in a cell death[18].

Olaparib

The efficacy of the oral PARP inhibitor, Olaparib, was demonstrated in patients with HER2-negative metastatic breast cancer carrying a germline BRCA mutation[19]. In the OlympiAD trial (NCT02000622), Olaparib monotherapy extended progression-free survival (PFS) by 2.8 months longer than the standard chemotherapy. Interestingly, the median overall survival (OS) was not different between the Olaparib and chemotherapy groups including capecitabine, vinorelbine, or eribulin. However, a subgroup analysis revealed that patients who had not received prior chemotherapy for metastatic breast cancer and were treated with Olaparib experienced a 7.9 month longer median OS than those who received standard chemotherapy. Olaparib was reported to be ineffective in patients with late stage, metastatic TNBC who had wild type BRCA1/2. However, the PETREMAC trial (NCT02624973) showed that Olaparib monotherapy led to a high response rate in TNBC patients with HR deficiency who had not previously received chemotherapy such as platinum[20]. This may be because acquired resistance to the DNA crosslinking agents is linked to secondary mutations that restore HR function, which can promote tumor cells to become resistant to PARP inhibitors. The OlympiA trial (NCT02032823) confirmed the efficacy of Olaparib in patients with high-risk, HER2-negative early breast cancer carrying germline BRCA1/2 mutations[21]. In this study, patients received either oral Olaparib or a placebo for one year after the completion of adjuvant or neoadjuvant chemotherapy and local treatment. The results showed a significantly higher 3-year invasive disease-free survival rate in the Olaparib group (85.9%) compared to the placebo group (77.1%). A similar benefit was observed in 3-year distant disease-free survival, with rates of 87.5% in the Olaparib group versus 80.4% in the placebo group. The recent clinical trial, DORA (NCT03167619) investigated the efficacy of Olaparib, with or without PD-L1 inhibitor durvalumab, as chemotherapy-free maintenance approach in advanced TNBC patients who were sensitive to platinum-based chemotherapy[22]. The results indicated that Olaparib, with or without durvalumab, significantly enhanced PFS compared to the historical control, irrespective of BRCA mutation or PD-L1 status.

Talazoparib

Talazoparib is reported to provide a significant benefit over the standard chemotherapy in patients with advanced metastatic breast cancer carrying germline BRCA1/2 mutations (EMBRACA, NCT01945775)[23]. The PFS was notably longer in the talazoparib group than in the standard single-agent therapy group, which included capecitabine, eribulin, gemcitabine or vinorelbine (8.6

months vs 5.6 months). Additionally, the efficacy of Talazoparib as a single agent in germline BRCA1/2 mutated advanced breast cancer patients who had prior platinum therapy was investigated in the ABRAZO (NCT02034916) trial[24]. Findings suggested that a longer platinum-free interval was associated with greater efficacy as patients with a platinum-free interval of more than six months achieved an objective response rate (ORR) of 47%, whereas those with an interval of less than eight weeks showed no response (0% ORR). Another clinical trial (NCT04039230) investigated the clinical efficacy of the combination therapy of Talazoparib and an antibody-drug conjugate (ADC), sacituzumab govitecan, in patients with metastatic TNBC[25]. The study found that sequential dosing resulted in a median progression-free survival (PFS) of 7.6 months without dose-limiting toxicities, whereas concurrent dosing led to a shorter PFS of 2.3 months and increased toxicities.

Niraparib

TOPACIO trial (NCT02657889) evaluated the efficacy of a combination therapy using Niraparib and the anti-programmed death receptor-1 inhibitor, pembrolizumab, in metastatic TNBC patients[26]. Results showed that this combination treatment exhibited clinical activity in patients regardless of BRCA mutation or PD-L1 status, as the treatment achieved an objective response rate (ORR) of 21% and a disease control rate of 49%. Notably, the response rate was more substantial in patients whose tumors were BRCA mutated or PD-L1 positive. Another clinical trial, BRAVO (NCT01905592) was designed to investigate the efficacy of Niraparib in patients of HER2-negative advanced breast cancer carrying a germline BRCA mutation[27]. The median PFS in the Niraparib group was 4.1 months, that is longer than 3.1 months in those receiving standard chemotherapy.

Veliparib

Veliparib was combined with an alkylating agent temozolomide to assess the efficacy in metastatic breast cancer patients with or without germline BRCA1/2 mutations (NCT01009788)[28]. The study found that the patients with BRCA1/2 mutations had a significantly higher ORR and longer median PFS compared to those without BRCA mutations. Similarly, improved outcomes were observed in patients who had not previously received platinum chemotherapy compared to those who had platinum chemotherapy. Notably, in platinum-naïve patients with BRCA-associated metastatic breast cancer, the combination treatment demonstrated clinical activity, achieving a higher ORR of 32% and a median PFS of 6.2 months. Another study, S1416 (NCT02595905), was conducted to evaluate the efficacy of platinum chemotherapy, cisplatin, combined with or without Veliparib in metastatic TNBC patients[29]. This study included three predefined groups such as germline BRCA1/2-mutated, BRCA-like, and non-BRCA-like. The addition of Veliparib to cisplatin significantly improved PFS in BRCA-like metastatic TNBC patients who have wildtype BRCA, increasing the median PFS from 4.2 months in the cisplatin plus placebo group to 5.9 months in the cisplatin plus veliparib group. The BrighTNess study (NCT02032277) assessed the efficacy of Veliparib, with or without carboplatin, to standard neoadjuvant chemotherapy in TNBC patients[30].

Results indicated that the combination of paclitaxel, carboplatin, and Veliparib led to a higher pathological complete response rate (53%) compared to paclitaxel alone (31%). However, the addition of Veliparib had less impact as a pathological complete response was 58% in the paclitaxel and carboplatin group without Veliparib.

Androgen Receptor (AR) antagonists

AR is a steroid nuclear receptor that is frequently expressed in breast cancer and has been considered an attractive therapeutic agent, even though androgen signaling in breast cancer remains incompletely understood[31]. AR functions differently on ER status. In ER positive disease, AR seems to oppose ER action by displacing ER from estrogen response elements and recruiting ER to androgen response elements to inhibit activation of ER-responsive oncogenes. AR expression has also been linked to prognostic outcomes as AR positive tumors are associated with better overall survival while AR negative tumors tend to be larger, higher-grade, and more linkely to involve lymph nodes[32, 33]. In ER negative disease, AR may bind differently to activate AR responsive oncogenes as well as recruit typically ER responsive oncogenes to facilitate tumor progression[31].

Bicalutamide

Bicalutamide was used as an antiandrogen therapy to assess its efficacy in patients with AR positive TNBC in TBCRC011 clinical trial (NCT00468715)[34]. The median PFS was 12 weeks, which is comparable to outcomes seen with single-agent or combination chemotherapy in TNBC patients. In another trial (NCT02605486), Bicalutamide was combined with the CDK4/6 inhibitor Palbociclib to evaluate whether the combination would enhance efficacy in patients with androgen dependent metastatic TNBC[35]. This combination resulted in a PFS of 6 months with no reported toxicity.

Enzalutamide

The MDV3100-11 study was designed to evaluate the efficacy of Enzalutamide in patients with locally advanced or metastatic AR positive TNBC (NCT01889238)[36]. The findings suggested that Enzalutamide exhibited clinical activity, with a median PFS of 2.9 months in the intent-to-treat population and 3.3 months in the evaluable group. Likewise, median OS was 12.7 months in the intent-to-treat population and 17.6 months in the evaluable group. In addition, the efficacy of Enzalutamide in combination with Trastuzumab was evaluated in patients with HER2 positive and AR positive metastatic breast cancer who had received prior treatment (NCT02091960). The median progression-free survival was 3.4 months[37].

GTx-024/Enobosarm

The efficacy of Enobosarm (GTx-024) combined with an immune check point inhibitor, pembrolizumab, was evaluated in patients with AR-positive TNBC who had received more than

two prior treatments (NCT02971761)[38]. The results demonstrated modest efficacy with a response rate (RR) of 12% and a clinical benefit rate (CBR) of 25% at 16 weeks, with one patient achieving a complete response. PFS was 2.6 months, and OS was 25.5 months. The modest response rate is comparable with the single-agent pembrolizumab RR of 12% in KEYNOTE-12 trial[39] and 5% in KEYNOTE-86 trial[40]. The combination therapy was well tolerated with only a few grade 3 adverse events reported, including diarrhea[38]. In the G200802 study (NCT02463032), Enobosarm was evaluated for its efficacy in patients with AR-positive, ER-positive, HER2-negative locally advanced or metastatic breast cancer that had progressed following prior endocrine therapy[41]. Patients were randomized to receive either 9 mg or 18 mg of oral Enobosarm daily. At 24 weeks, the clinical benefit rate (CBR) was 32% in the 9 mg group and 29% in the 18 mg groups among the evaluable population. The median PFS was 5.6 months for the 9 mg group and 4.2 months for the 18 mg group. Most treatment-related adverse events were mild to moderate (grade 1 or 2), and there was no additional benefit at higher dosage group.

CDK4/6 Inhibitors

Cell cycle checkpoints regulate mitotic cell cycle progression through the four phases-G1, S, G2, and M-by controlling transition timing. These transitions are regulated by cyclin-dependent kinase (CDK) family with associated cyclins. Specifically, CDK4/6 pairs and cyclin D1 form a complex that is phosphorylated by CDK-activating kinase upon entering the nucleus. This activated complex phosphorylates the retinoblastoma protein (Rb). Once phosphorylated, pRb binds to the E2F transcription factors that subsequently trigger DNA replication and promote cellular transition into S phase[42]. Loss of control over this pathway often occurs in cancer cells, resulting in aberrant cell proliferation. In TNBC, Rb dysfuction had been identified in about 30% of cases, while about 51% of TNBC patients were found to be Rb positive[43]. Preclinical studies have shown that a CDK4/6 inhibitor, palbociclib can inhibit the growth of TNBC cells, and significantly reduce tumor size in LAR type xenograft tumor models. Therefore, CDK4/6 inhibitors suppress tumor growth by blocking cyclin D-CDK4/6-meidated Rb phosphorylation, leading to cell cycle arrest in the G1 phase[42].

Palbociclib

In 2015, Palbociclib was evaluated for its efficacy in patients with metastatic TNBC who were Rb-positive and had received prior treatment (NCT01037790)[44]. Median PFS was 3.7 months overall, with a significantly longer PFS in HR-positive patients compared to HR-negative patients, 4.5 vs 1.5 months, respectively. Among HR-positive patients, those who had received more than two prior hormonal therapies had a median PFS of 5 months, versus 2 months in those who had received fewer than two. However, no difference in PFS was observed between patients who had received fewer than two prior chemotherapy regimens and those who had received more than two. In another clinical trial (NCT01320592), the efficacy of Palbociclib in combination with a chemotherapeutic agent, Paclitaxel, was evaluated in patients with Rb-positive advanced

metastatic breast cancer[45]. The combination therapy demonstrated a clinical benefit rate of 55% without evidence of additive toxicity.

Abemaciclib

In the MONARCH 2 trial (NCT02107703), the combination of Abemaciclib and fulvestrant was assessed for their efficacy versus fulvestrant alone in patients with HR-positive, HER2-negative advanced or metastatic breast cancer that had progressed after endocrine therapy[46]. The study demonstrated a significant improvement in median PFS, with 16.4 months in the Abemaciclib along with fulvestrant group compared to 9.3 months with fulvestrant alone. Among patients with measurable disease, the ORR was 48.1% for the combination therapy versus 21.3% for fulvestrant alone. Both treatment regimens exhibited manageable safety profiles. In MONARCH 3 trial (NCT02246621), the efficacy of Abemaciclib combined with a nonsteroidal aromatase inhibitor, anastrozole or letrozole, was evaluated in patients with HR-positive, HER2-negative advanced breast cancer[47]. The combination Abemaciclib group significantly improved median PFS, reaching 28.18 months compared to 14.76 months in the placebo plus aromatase inhibitor group. The ORR was 61.0% in the Abemaciclib group versus 45.5% with the placebo group. The treatment had an acceptable safety profile, with the most common grade ≥ 3 adverse events being neutropenia (23.9%), diarrhea (9.5%), and leukopenia (8.6%). Abemaciclib monotherapy was investigated for its efficacy in patients with Rb-positive metastatic TNBC who had received prior treatment (NCT03130439)[48]. The results showed that Abemaciclib did not offer durable clinical benefit. Although the median PFS was 1.94 months and the median OS was 8.44 months, the study did not meet its primary endpoint. The ORR was 0% and clinical benefit rate was 14.8% after a median follow-up of 28.5 months.

Ribociclib

In the MONALEESA-2 trial (NCT01958021), the efficacy of Ribociclib in combination with letrozole was evaluated in patients with advanced HR-positive, HER2-negative breast cancer[49]. After a median follow-up of 6.6 years, the Ribociclib with letrozole group demonstrated a significant overall survival benefit with a median OS of 63.9 months compared to 51.4 months in the placebo with letrozole group. Additionally, no new safety signals were identified. Next, Ribociclib in combination with either tamoxifen or letrozole was assessed for efficacy in patients with HR-positive, HER2-negative advanced breast cancer through MONALEESA-7 trial (NCT02278120)[50]. The study demonstrated a significantly longer median PFS in the ribociclib group at 23.8 months, compared to 13 months in the placebo group. The treatment was generally tolerated with a manageable safety profile. Ribociclib is currently being evaluated in combination with bicalutamide in AR-positive TNBC (NCT03090165) in an ongoing Phase I trial[51]. While efficacy data are not yet available, preliminary findings suggest that the combination of Ribociclib and bicalutamide is tolerated with no unexpected toxicities reported.

PI3K/AKT/mTOR signaling pathway inhibitors

Phosphoinositide 3-kinase (PI3K) is a kinase that is recruited to the plasma membrane and activated to phosphorylate PIP2 to produce PIP3[52]. PIP3 recruits and binds AKT and 3-phosphoinositide-dependent protein kinase-1 (PDK1). Subsequently, AKT that is phosphorylated and activated by PDK1 promotes cell growth and survival by activating other downstream kinases, including the mammalian target of rapamycin (mTOR) complex. In addition, PI3K/AKT/mTOR signaling pathway was abnormally altered in about 70% of breast cancer that includes 25% of primary TNBC and potentially more frequently in metastatic TNBC[53]. Moreover, elevated expression of PI3K and mTOR proteins has been linked to poor prognosis in TNBC[54]. These findings support the PI3K/AKT/mTOR pathway as a promising molecular target for treating TNBC.

Alpelisib

The SOLAR-1 study (NCT02437318) investigated the efficacy of Alpelisib in combination with fulvestrant in patients with PIK3CA-mutated, HR-positive, and HER2-negative advanced breast cancer who had previously received endocrine therapy[55]. In this study, patients with PIK3CA mutations achieved a median PFS of 11 months, compared to 5.7 months in the placebo-fulvestrant group. Another clinical trial (NCT2379247) evaluated Alpelisib combined with nab-paclitaxel in patients with HER2-negative metastatic breast cancer including those with TNBC, who had received prior treatments[56]. The combination showed comparable efficacy in HR-positive and TNBC cohorts, with objective response rate of 58% and 60%, respectively. Notably, patients with PIK3CA mutations demonstrated a longer PFS of 11.9 months, versus 7.5 months in the non-mutated group.

Gedatolisib

Gedatolisib, in combination with anti-tumor agents such as cisplatin, was evaluated for efficacy in patients with metastatic or locally recurrent/advanced TNBC (NCT01920061)[57]. As a result, the combination of Gedatolisib with cisplatin led to an overall response rate (ORR) of 40% in first-line treatment and 33.3% in second/third-line treatment setting. The ORR observed in the first-line setting is comparable to that reported for cisplatin and carboplatin in the TBCRC0096 trial (32.6%). Notably, the ORR in the second/third-line setting was higher than that in TBCRC0096 trial (18.6%). Additionally, the median PFS was 4.8 months and 8.5 months in first-line treatment and second/third-line treatment, respectively. In another clinical trial (NCT03243331), Gedatolisib was tested in combination with cofetuzumab pelidotin, an antibody-drug conjugate targeting the Wnt pathway receptor PTK7, in patients with metastatic TNBC who had received at least one prior chemotherapy[58]. Across three dose cohorts, the combination yielded an overall response rate (ORR) of 16.7% and a clinical benefit rate (CBR) at 18 weeks of 27.8%. With a median follow-up of 7.9 months, the median PFS was 2 months, and the median OS was 9.4 months.

Everolimus

Everolimus was used in combination with the chemotherapeutic agent, eribulin, in patients with metastatic TNBC who had received prior chemotherapy (NCT02120469)[59]. The regimen resulted in a median PFS of 2.6 months, and a median OS of 8.3 months. Another study (NCT01127763) evaluated the combination of Everolimus and the platinum agent, carboplatin, in patients with metastatic TNBC[60]. This combination demonstrated a clinical benefit rate (CBR) of 36% with a median PFS of 3 months and OS of 16.6 months.

Buparlisib

Buparlisib was evaluated for its efficacy in patients with metastatic TNBC in a clinical trial (NCT01790932)[61]. This monotherapy resulted in a clinical benefit rate of 12% and no confirmed partial or complete responses were observed. The median PFS was 1.8 months and the median OS was 11.2 months.

Epidermal growth factor receptor (EGFR) signaling pathway inhibitors

EGFR is a transmembrane receptor tyrosine kinase and is activated by binding to ligands. Upon activation, EGFR triggers a cascade of downstream signaling pathways, including PI3K/AKT and RAS/RAF/MEK/ERK pathways, which promote cell proliferation, survival, angiogenesis, and metastasis[62]. In addition, EGFR is more frequently overexpressed in TNBC compared to other breast cancer subtypes, and the overexpression is linked to shorter survival[63].

Erlotinib

The clinical trial (NCT00834678) was designed to evaluate the efficacy of Erlotinib in combination with a chemotherapeutic agent, bendamustine, in patients with metastatic TNBC who received prior chemotherapy[64]. While the combination therapy resulted in a median PFS of 3.7 months and a median OS of 10.8 months, it was associated with excessive toxicity. Notably, 91% of participants developed grade 3/4 lymphopenia, and 36% of patients experienced grade 3 or higher opportunistic infections that is likely related to the lymphopenia. As a result, the trial was terminated after phase I, and the phase II study was not initiated. Another phase I study (NCT01650506) investigated the efficacy of Erlotinib combined with metformin in patients with metastatic TNBC who received at least one prior treatment[65]. Although the combination was well tolerated with no grade 4 adverse events reported, the study did not demonstrate any objective response. The best observed response was stable disease in 25% of patients with a median PFS was 60 days.

Immune Checkpoint inhibitors

Immune checkpoints are regulatory pathways that become active when proteins on the surface of immune cells, particularly T cells, interact with partner proteins on other cells such as tumor cells. These proteins are called immune checkpoint proteins[66]. When checkpoint proteins bind to their partner proteins, they transmit an “off” signal to T cells, which suppresses immune activity and

can allow tumor cells to evade immune surveillance. Immune checkpoint inhibitors (ICIs) are cancer immunotherapies designed to block these interactions. By preventing the binding of checkpoint proteins with their ligands, ICIs inhibit the suppressive signaling, thereby restoring T cell activity and enabling the immune system to target and eliminate cancer cells. Among the extensively studied checkpoint pathways are the programmed death receptor (PD-1) and its ligand PD-L1. PD-L1, commonly expressed on tumor cells, binds to PD-1 receptors on tumor infiltrating lymphocytes, impairing T cell function and cytokine release, which facilitates immune escape from cancer cells. Compared with other types of BC, TNBC exhibits a higher tumor mutation burden, increased immune cell infiltration in the tumor environment, and elevated PD-L1 expression, and the findings were supported by RNA sequencing data from the cancer genome atlas (TCGA)[67]. These features make TNBC the most immunogenic breast cancer subtype and a strong candidate for immunotherapy. The immunomodulatory (IM) subtype of TNBC accounts for about 24% of TNBC cases and shows increased sensitivity to ICIs. Currently approved ICIs such as PD-1 and PD-L1 inhibitors include pembrolizumab, atezolizumb, and nivolumab, which are widely used in clinical practice for treating cancers including TNBC.

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor, and was evaluated for its efficacy in patients with PD-L1 positive metastatic TNBC who had previously received treatment in KEYNOTE-012 study (NCT01848834)[39]. In this study, Pembrolizumab monotherapy demonstrated an overall response rate of 18.5%. The median PFS was 1.9 months, and the median OS was 11.2 months. The KEYNOTE-086 (NCT02447003) further explored Pembrolizumab monotherapy in patients with metastatic TNBC, enrolling two distinct cohorts based on treatment history and PD-L1 status. Cohort A group included previously treated patients regardless of PD-L1 expression. In this group, an overall response rate (ORR) was 5.7% among PD-L1 positive patients and 4.7% among PD-L1 negative patients[40]. Cohort B group included PD-L1 positive patients who had no prior systemic treatment, representing the use of Pembrolizumab as first-line therapy. In this cohort, Pembrolizumab demonstrated a higher clinical benefit, with an ORR of 21.4%, a median PFS of 2.1 months, and a median OS of 18 months[68]. In the KEYNOTE-355 study (NCT02819518), the efficacy of Pembrolizumab with chemotherapy was evaluated in patients with previously untreated, advanced TNBC whose tumors expressed PD-L1[69]. PD-L1 expression was assessed using the combined positive score (CPS), which is calculated by dividing the number of PD-L1-staining tumor cells, lymphocytes, and macrophages by the total number of viable tumor cells, multiplied by 100. Patients were categorized into subgroups based on CPS: those with a CPS of 10 or higher (CPS-10 subgroup) and those with a CPS of 1 or higher (CPS-1 subgroup). Notably, in the CPS-10 subgroup, overall survival was significantly longer in the Pembrolizumab plus chemotherapy group compared to chemotherapy alone, with a median OS of 23 months versus 16.1 months, respectively. In the CPS-1 subgroup, the median OS was 17.6 months for the combination therapy and 16 months for chemotherapy alone. The KEYOTE-119 study (NCT02555657) assessed Pembrolizumab monotherapy versus chemotherapy in second-line treatment of patients with

metastatic TNBC with prior chemotherapy exposure and PD-L1 positive tumors[70]. In the CPS-10 subgroup, the median OS was 12.7 months with Pembrolizumab versus 11.6 months with chemotherapy. In the CPS-1 subgroup, the median OS was 10.7 months in the Pembrolizumab arm and 10.2 months in the chemotherapy arm. The results indicate a modest overall survival benefit with pembrolizumab in the second-line setting of PD-L1 positive mTNBC patients.

Atezolizumab

Atezolizumab is a PD-L1 inhibitor, and its combination with paclitaxel was evaluated as a first-line therapy in patients with advanced TNBC who were either treatment-naive or had completed neoadjuvant or adjuvant chemotherapy more than 12 months prior in IMpassion 130 study (NCT03125902)[71]. The study found that adding Atezolizumab to paclitaxel did not significantly improve PFS in PD-L1 positive subgroup, with a median PFS of 6.0 months compared to 5.7 months for paclitaxel alone. Similarly, the median OS was 22.1 months for the combination therapy versus 28.3 months for paclitaxel alone in PD-L1 positive subgroup. Results in the intent-to-treat (ITT) population were consistent with the findings in the PD-L1 positive subgroup, indicating that the addition of Atezolizumab to paclitaxel did not provide a meaningful benefit in terms of PFS or OS compared to paclitaxel alone. In a separate study (NCT03206203), Atezolizumab was combined with carboplatin and evaluated in patients with metastatic TNBC, regardless of PD-L1 status[72]. This trial demonstrated a clinically meaningful benefit from the combination therapy. Median PFS increased to 4.1 months compared to 2.2 months with carboplatin alone, the objective response rate (ORR) from 8.0% to 30.4%, and median OS improved from 8.6 months to 12.6 months. Notably, PD-L1 positive tumors did not show benefit from the addition of Atezolizumab. Interestingly, patients with obesity or those with on-treatment blood glucose levels above 125 mg/dL experienced better PFS with the combination therapy.

Nivolumab

Nivolumab is a PD-1 inhibitor, and was evaluated in combination with carboplatin in patients with metastatic TNBC who had received 0-1 prior lines of chemotherapy (NCT03414684)[73]. In this study, the addition of Nivolumab did not significantly improve the clinical outcomes in the overall population. The median PFS was 4.2 months with the combination versus 5.5 months with carboplatin alone. The objective response rate (ORR) was 25% with Nivolumab plus carboplatin, compared to 23% with carboplatin alone. The median OS was 17.5 months versus 10.7 months, respectively, at a median follow-up of 23.5 months. However, in the PD-L1 positive subgroup, patients experienced a notable benefit from the addition of Nivolumab. In this group, the median PFS increased from 4.7 months with carboplatin alone to 8.3 months with the combination. Similarly, the median OS improved from 9.6 months to 17.5 months. The findings suggest that Nivolumab combination may provide a clinical benefit in PD-L1 positive mTNBC patients. In another study (NCT03316586), Nivolumab was combined with carbozantinib, a VEGFR2/MET inhibitor, to assess its efficacy in patients with metastatic TNBC who had received up to three prior treatments[74]. Unfortunately, the trial showed limited clinical activity. The objective response rate

(ORR) was 6% and the clinical benefit rate was 17%. The median PFS was 3.6 months. As a result, this study did not meet the pre-specified criteria to advance to the second stage.

Summary

Breast cancer remains a major global health concern and a leading cause of cancer-related mortality among women. Among various subtypes of breast cancer, TNBC presents a particularly urgent clinical challenge due to its aggressive progression, lack of hormone receptor expression, and limited therapeutic options. This review evaluated several targeted therapies for advanced breast cancer, with a primary focus on identifying treatment options with improved clinical outcomes. The therapeutic classes analyzed included PARP inhibitors, AR antagonists, CDK 4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors, EGFR inhibitors, and immune checkpoint inhibitors. Current evidence indicates that PARP inhibitors and immune checkpoint inhibitors exhibit the most favorable efficacy profiles in the management of TNBC. Clinical trials have shown that these agents are associated with superior outcomes in progression free survival (PFS), overall response rate (ORR), disease control rate (DCR), pathological complete response (PCR), and overall survival (OS) compared to other targeted therapies. These findings underscore the potential of PARP inhibitors and immune checkpoint inhibitors as key therapeutic strategies in the treatment landscape of advanced and triple-negative breast cancer.

Table 1. Summary of Clinical Trials of Targeted Therapies in Advanced Breast Cancer including TNBC.

Drug Class / Drug	Clinical Trial	Molecular Status	Therapeutic Benefits	Refs
PARP Inhibitors **Olaparib**	OlympiAD (NCT02000622)	• HER2-negative mBC • gBRCAm • Less than 2 lines of prior chemotherapy for mBC	• Olaparib monotherapy extended PFS by 2.8 months longer than the standard chemotherapy. • Olaparib monotherapy extended OS by 7.9 months longer in patients without prior chemotherapy than those who received standard chemotherapy.	[19]
	PETREMAC (NCT02624973)	• mTNBC • Wild-type BRCA and HR deficiency	• Olaparib monotherapy led to a high response rate in patients without prior chemotherapy such as platinum.	[20]
	OlympiA (NCT02032823)	• High-risk, HER2-negative early BC • gBRCA1/2m • Had local treatment and neoadjuvant or adjuvant chemotherapy	• Olaparib monotherapy led to higher 3-yr invasive disease-free survival rate (85.9%) compared to the placebo group (77.1%). • The monotherapy group exhibited 3-yr distant disease-free survival rate (87.5%) compared to the placebo group (80.4%).	[21]
	DORA (NCT03167619)	• Advanced TNBC • Sensitive to platinum chemotherapy	• Olaparib, with or without durvalumab, monotherapy enhanced PFS compared to the control, irrespective of BRCA mutation or PD-L1 status.	[22]
Talazoparib	EMBRACA (NCT01945775)	• gBRCA1/2m • HER2-negative advanced mBC	• Talazoparib monotherapy group extended PFS by 3 months longer than standard therapy group with capecitabine, eribulin, gemcitabine, or vinorelbine.	[23]
	ABRAZO (NCT02034916)	• gBRCAm • Advanced BC • Prior platinum therapy	• In the talazoparib monotherapy group, patients with a platinum-free interval of more than six months had an ORR of 47%. Those with an internal of less than eight weeks had an ORR of 0%.	[24]
	NCT04039230	• mTNBC	• Talazoparib and sacituzumab govitecan combination therapy led to a median PFS of 7.6 months without dose-limiting toxicities in sequential dosing and 2.3 months with increased toxicities in concurrent dosing.	[25]
Niraparib	TOPACIO (NCT02657889)	• mTNBC	• Niraparib and pembrolizumab combination therapy had an ORR of 21% and DCR of 49%.	[26]
	BRAVO (NCT01905592)	• gBRCAm, HER2-negative advanced BC • Less than 2 prior chemotherapy	• The niraparib monotherapy arm had a median PFS of 4.1 months compared to the standard chemotherapy with a median PFS of 3.1 months.	[27]
Veliparib	NCT01009788	• mBC (with and without gBRCA1/2m)	• Veliparib and temozolomide combination therapy, among BRCA1/2 carriers, had an ORR of 32% with platinum-naïve patients vs 9% among platinum-exposed patients.	[28]
	S1416 (NCT02595905)	• Metastatic or recurrent TNBC • gBRCA 1/2m, BRCA-like, non-BRCA like	• In the BRCA-like group, a median PFS of 5.9 months in cisplatin and veliparib group and 4.2 months in placebo with cisplatin.	[29]

	BrighTNess (NCT02032277)	• TNBC	• The paclitaxel, carboplatin, and veliparib combination therapy led to a pCR of 53% compared to the 31% in the paclitaxel alone and 58% in paclitaxel-carboplatin group.	[30]
AR antagonists **Bicalutamide**	TBCRC011 (NCT00468715)	• ER/PgR-negative, AR-positive advanced BC	• In the bitcalutamide monotherapy group, 6-month CBR was 19%. • This monotherapy group led to a median PFS of 12 weeks.	[34]
	NCT02605486	• AR-positive mTNBC	• Bicalutamide and palbociclib combination therapy resulted in a PFS of 6 months without reported toxicity.	[35]
Enzalutamide	MDV3100-11 (NCT01889238)	• AR-positive locally advanced or metastatic TNBC	• The enzalutamide monotherapy led to a median PFS of 2.9 months in ITT group vs 3.3 months in evaluable group, and a median OS of 12.7 months in ITT group vs 17.6 months in evaluable group.	[36]
	NCT02091960	• Advanced HER2-positive, AR-positive BC • Had prior treatment	• The enzalutamide-trastuzumab combination therapy had a median PFS of 3.4 months.	[37]
GTx-024 / Enobosarm	NCT02971761	• AR-positive mTNBC • More than 2 prior treatments	• The enobosarm-pembrolizumab combination therapy had the RR of 12% and CBR of 25% at 16 weeks.	[38]
	G200802 (NCT02463032)	• ER-positive, HER2-negative, locally advanced or mBC • Prior endocrine therapy	• The enobosarm monotherapy led to a CBR of 32% in 9 mg group and 29% in 18 mg group at 24 weeks. • This monotherapy had a median PFS of 5.6 months in 9 mg group and 4.2 months in 18 mg group.	[41]
CDK4/6 Inhibitors **Palbociclib**	NCT01037790	• Rb-positive mTNBC • Had prior treatment	• Palbociclib led to a median PFS of 4.5 months in HR-positive patients and 1.5 months in HR-negative patients. • In HR-positive patients, those received more than 2 prior hormonal therapies had a PFS of 5 months vs 2 months in those with fewer than two therapies.	[44]
	NCT01320592	• Rb-positive advanced mBC	• Palbociclib-paclitaxel combination therapy led to a CBR of 55%.	[45]
Abemaciclib	MONARCH 2 (NCT02107703)	• HR-positive, HER2-negative advanced or mBC • Progressed while endocrine therapy	• Abemaciclib-fulvestrant combination therapy led to a median PFS of 16.4 months compared to 9.3 months with fulvestrant alone. • Abemaciclib-fulvestrant combination therapy had an ORR of 48.1% and fulvestrant monotherapy had an ORR of 21.3%.	[46]
	MONARCH 3 (NCT02246621)	• HR-positive, HER2-negative advanced BC • No prior systemic therapy in advanced disease setting	• Abemaciclib monotherapy led to a median PFS of 28.18 months compared to the PFS of 14.76 months with placebo-aromatase inhibitor. • ORR was 61.0% in abemaciclib group vs 50% in placebo group.	[47]
	NCT03130439	• Rb-positive mTNBC • Had prior treatment	• Abemaciclib monotherapy did not meet the primary endpoint. • This monotherapy resulted in a median PFS of 1.94 months and a median OS of 8.44 months.	[48]

Ribociclib	MONALEESA-2 (NCT01958021)	• HR-positive, HER2-negative recurrent/metastatic BC	• Ribociclib-letrozole combination led to a median OS of 63.9 months compared to 51.4 months with placebo-letrozole combination after a median follow-up of 6.6 years.	[49]
	MONALEESA-7 (NCT02278120)	• HR-positive, HER2-negative advanced mBC	• Ribociclib-tamoxifen or ribociclib-letrozole combination therapies had a median PFS of 23.8 months and placebo monotherapy had 13 months.	[50]
	NCT03090165	• AR-positive TNBC	• Efficacy data not yet available.	[51]
PI3K/AKT/mTOR Inhibitors **Alpelisib**	SOLAR-1 (NCT02437318)	• PIK3CA-mutated, HR-positive, and HER2-negative advanced BC • Had prior endocrine therapy	• Alpelisib-fulvestrant combination led to a median PFS was 11 months compared to 5.7 months with placebo-fulvestrant combination.	[55]
	NCT2379247	• HER2-negative mBC • Prior chemotherapies	• Alpalisib with nab-paclitaxel led to an ORR of 58% in HR-positive group and 60% in TNBC group. • This combination therapy had a median PFS of 11.9 months in patients with PIK3CA mutation vs 7.5 months in patients without the mutation.	[56]
Gedatolisib	NCT01920061	• Locally recurrent/advanced or mTNBC	• Gedatolisib with cisplatin led to an ORR of 40% in first-line treatment and 33.3% in second/third-line setting. • In this combination therapy, the median PFS was 4.8 months in first-line treatment and 8.5 months in second/third-line treatment.	[57]
	NCT03243331	• mTNBC • Had more than one prior chemotherapy	• Gedatolisib-cofetuzumab pelidotin combination led to an ORR of 16.7%, CBR of 27.8% at 18 weeks. • This combination led to a median PFS of 2 months and a median OS of 9.4 months at a median follow-up of 7.9 months.	[58]
Everolimus	NCT02120469	• mTNBC • Had up to four lines of prior chemotherapies	• Everolimus-eribulin combination therapy led to a median PFS of 2.6 months and a median OS of 8.3 months.	[59]
	NCT01127763	• mTNBC	• Everolimus-carboplatin combination therapy had a CBR of 36% with a median PFS of 3 months and OS of 16.6 months.	[60]
Buparlisib	NCT01790932	• mTNBC	• Buparlisib monotherapy led to a CBR of 12% and no confirmed partial or completed responses with a median PFS of 1.8 months and OS of 11.2 months.	[61]
EGFR Inhibitors **Erlotinib**	NCT00834678	• mTNBC • Had prior chemotherapy	• Erlotinib-bendamustine combination led to a median PFS of 3.7 months and median OS of 10.8 months with excessive toxicity. • In this combination therapy, grade 3/4 lymphopenia developed in 91% of participants.	[64]
	NCT01650506	• mTNBC • Had more than one prior treatment for metastatic disease	• Erlotinib-metformin combination did not demonstrate any objective response. Its best observed response was stable disease in 25% of patients with a median PFS of 60 days.	[65]
	KEYNOTE-012 (NCT01848834)	• PD-L1-positive mTNBC • Prior treatment	• Pembrolizumab monotherapy led to an ORR of 18.5% with a median PFS of 1.9 months and a median OS of 11.2 months.	[39]

Immune Checkpoint Inhibitors **Pembrolizumab**	KEYNOTE-086 (NCT02447003)	• mTNBC • Cohort A: prior treatment regardless of PD-L1 expression • Cohort B: PD-L1 positive and treatment-naïve	• In cohort A, Pembrolizumab monotherapy led to an ORR of 5.7% in PD-L1-positive populations and 4.7% in PD-L1 negative patients. • In cohort B, this monotherapy led to an ORR of 21.4% with a median PFS of 2.1 months and a median OS of 18 months.	[40] [68]
	KEYNOTE-355 (NCT02819518)	• PD-L1 positive, locally recurrent inoperable or metastatic TNBC • Previously untreated	• In patients with high PD-L1 expression, a median OS was 23 months with pembrolizumab-chemotherapy vs 16.1 months with chemotherapy alone. • In patients with low PD-L1 expression, a median OS was 17.6 months with the combination vs 16 months with chemotherapy alone.	[69]
	KEYNOTE-119 (NCT02555657)	• PD-L1 positive mTNBC • Had more than one prior systemic treatments • Progression on their most recent therapy	• In patients with high PD-L1 expression, a median OS was 12.7 months with Pembrolizumab vs 11.6 months with chemotherapy. • In patients with low PD-L1 expression, a median OS was 10.7 months with Pembrolizumab vs 10.2 months for chemotherapy.	[70]
Atezolizumab	IMpassion130 (NCT03125902)	• Advanced TNBC • No prior systemic therapy or had (neo)adjuvant chemotherapy more than 12 months prior to this trial	• In PD-L1 positive patients, a median PFS was 6 months with atezolizumab-paclitaxel combination vs 5.7 months with paclitaxel alone. • In PD-L1 positive patients, a median OS was 22.1 months with the combination vs 28.3 months with paclitaxel alone.	[71]
	NCT03206203	• mTNBC	• The atezolizumab-carboplatin combination led to a median PFS of 4.1 months, a median OS of 12.6 months, and an ORR of 30.4% compared to PFS of 2.2 months, OS of 8.6 months, and an ORR of 8% with carboplatin alone.	[72]
Nivolumab	NCT03414684	• Unresectable locally advanced or mTNBC • Had 0-1 prior lines of chemotherapy in metastatic setting	• The nivolumab-carboplatin combination led to a median PFS of 4.2 months vs 5.5 months with carboplatin alone. • ORR was 25% with this combination vs 23.3% with carboplatin alone. • In PD-L1 positive group, this combination led to a median PFS of 8.3 months and a median OS of 17.5 months with this combination vs PFS of 4.7 months and OS of 9.6 months with carboplatin alone.	[73]
	NCT03316586	• mBC with ER and PR less than 10% and HER2-negative • Received 0-3 prior lines of chemotherapy in advanced setting	• The Nivolumab-carbozantinib combination led to an ORR of 6%, CBR of 17%, and a median PFS of 3.6 months. • This study did not meet the pre-specified criteria to advance to next stage.	[74]

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