Immunotherapy in Triple-Negative Breast Cancer (TNBC): Immune Checkpoint Inhibition

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Abstract: Triple-negative breast cancer (TNBC), the subtype of breast cancer marked by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2), is known for its lack of systematic therapies and poor prognosis. The mainstream method of treating TNBC is cytotoxic chemotherapy, which is proven to be effective in both adjuvant and neoadjuvant settings. Nevertheless, as chemotherapy appears to generate nondurable responses and cells start to grow resistant to certain chemotherapy drugs, immunotherapy seems to be a new way out for TNBC patients. Treatments of immunotherapy involve cancer vaccines and immune checkpoint blockade. The latter is the focus of this article. Immune checkpoint blockade, especially when combined with other therapies, is shown to be promising, improving the patients' progression-free survival and overall survival.

Yet as an emerging set of therapies, the efficacy and safety of the combination of drugs are still to be determined. Numerous clinical trials are designed and implemented to test the effectiveness and safety of both single-agent immune checkpoint inhibitors and their conjugation with other therapies including chemotherapies, radiotherapies, and cryotherapies. In this article, the design and results of recent clinical studies involving immune checkpoint inhibitor drugs are summarized. The drugs include programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab, programmed death ligand 1 (PD-L1) inhibitors atezolizumab, avelumab, and durvalumab, and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors ipilimumab and tremelimumab

1. Introduction

Breast cancer is the most prevalent cancer diagnosed in women in the United States (excluding skin cancers) and the second greatest cause of cancer death in women, following lung cancer [1]. More than 1.3 billion cases of breast cancer are diagnosed globally [2]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the lack of hormone receptors and human epidermal growth receptors (HER2). Early age at breast cancer diagnosis, young age at menarche, high parity, absence of breastfeeding, high body mass index, and African American ethnicity are all risk factors for TNBC [3].

Treating TNBC has always been a challenge since there are no systematic therapies recommended for TNBC. Chemotherapy is the most common standard treatment [2]. However, as tumors grow increasingly resistant to chemotherapy drugs [4], immunotherapy was introduced as a promising treatment. Common immunotherapies include cancer vaccines and immune checkpoint blockade. Numerous researches and clinical trials have been done to prove the efficacy of these treatments.

Cancer vaccines promote the body to produce tumor-specific antigens, hence enables a truly precise therapy. Cancer vaccines are categorized into monovalent or polyvalent vaccines, the difference being that polyvalent vaccines provide more tumor-associated antigens than monovalent vaccines. There are about 10 trials ongoing testing vaccines targeting breast cancer. For example, NCT02018458 is a trial that aimed to test the efficacy of the HER2 pulsed dendritic cell vaccine in preventing the recurrence of invasive breast cancer. Each patient received six HER2 pulsed dendritic

cell vaccines weekly and then three booster vaccines once every three months. The study is currently active and has an estimated date of completion in December 2021 [5]. Cancer vaccines could play a role in preventing repulse in TNBC despite that most cancer vaccines show modest outcomes [6].

In treating TNBC, immune checkpoint inhibitors, including programmed cell death protein 1 (PD-1) inhibitors, programmed death ligand 1 (PD-L1) inhibitors, and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, are used to target immune checkpoints PD-1, PD-L1, and CTLA-4, which are regulators of the immune system. Chemotherapy, radiotherapy, and cryotherapy are sometimes combined with immune checkpoint inhibitors (ICIs). Results are shown positive in preclinical mice models when combining local radiotherapy with immune checkpoint blockade [7, 8]. For example, a single-arm, phase II clinical trial (NCT02730130) tested the safety and efficacy of the combination of radiotherapy and pembrolizumab, a PD-1 inhibitor. The combination was well tolerated by the patients and showed modest but promising clinical activities [9].

Although carrying high expectations, as a newly emerged therapy, immunotherapy is not thoroughly studied. The efficiency and safety of vaccines and some immunotherapy drugs remain unclear. Efforts putting into treating TNBC by immunotherapy, especially therapies involving ICIs, are examined and summarized in this review article. Following the general introduction of breast cancers are summaries of the recent studies conducted investigating the antibody drugs pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, ipilimumab, and tremelimumab.

2. Subtypes of Breast Cancer

2.1 Luminal Breast Cancer

Luminal breast cancer cells are estrogen receptor (ER) positive and/or progesterone receptor (PR) positive. Luminal breast cancer can be further classified into subtypes like luminal A and luminal B, the difference being that luminal A does not have HER2 while HER2 receptor in luminal B can be both present or absent, and luminal A patients have low Ki67 (an antigen related to the division of the cell; the higher Ki67 level is, the faster the division of the cancer cell is) level while luminal B patients have higher Ki67 level. Moreover, luminal B is usually diagnosed at an early age and has higher grades and a worse prognosis than luminal a [10].

Common therapy applied treating luminal breast cancers are endocrine therapy. Blocking estrogen, which promotes cancer cell growing and dividing, from binding to the ERs on the surface of cancer cells inhibit the breast cancer from further developing. For example, the ER antagonist tamoxifen, when applied in an adjuvant therapy, could reduce mortality of the patients in throughout the first fifteen years [11].

2.2 $HER2^+$ Breast Cancer

HER2-amplified breast cancer has HER2 receptors but lacks ER and PR. The tumor is caused by the overexpression of HER2. 5% to 15% of breast cancers are HER2-positive. The malignancy of HER-amplified breast cancers is normally high, and patients have a relatively poor prognosis [10].

Targeted therapy is usually applied to cases of HER2-amplified breast cancer. Proven by CLEOPATRA, by using an anti-HER2 dimerization inhibitor called pertuzumab along with trastuzumab and chemotherapy, the overall survival of the patients increased by 6.1 months [12]. Second-line treatment of HER2-amplified breast cancer includes lapatinib, a tyrosine kinase inhibitor (TKI), plus chemotherapy [13]. However, the toxicity of this second-line treatment is proved by trials to be higher than some other TKIs like neratinib [14]. Further clinical trials are needed to put neratinib into standardized treatments. Other target therapies include the combinative use of trastuzumab etamine and brentuximab vedotin, which also has lower toxicity than lapatinib plus chemotherapy [15]. Though not fully proved, the tyrosine kinases inhibitors used to treat HER2-amplified breast cancer, for instance, lapatinib and afatinib, are able to cross the blood-brain barrier and cause metastasis to the brain [16]. This remains a problem unsolved.

2.3 Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC) refers to the subtype of breast cancer that lacks ER, PR, and over-expressed HER2+. TNBCs are of 15%-20% prevalence among all BC patients. TNBC tumors are usually proliferated and their histologic grades are high [10]. The chance for TNBC to metastasize to viscera is higher than that of other subtypes of breast cancer. Nevertheless, the possibility for them to metastasize to bones is relatively low [17-19].

The missing of ER, PR, and HER2 receptors make endocrine therapies impossible for TNBC patients. The most widely-used systematic treatment is chemotherapy. However, there are agreements that no current treatments are effective to TNBC [10].

It is worth noticing that, in many cases, triple-negative breast cancers also belong to another subtype of breast cancer called basal-like breast cancer, which is characterized by low levels of expressed ER, low overexpression of HER2, but high expression of genes normally present in basal cells of human breast [20]. Because basal-like breast cancer is not analyzed under supervised conditions, the term is not recognized internationally [20, 21]. However, data shows that triple-negative breast cancer and basal-like breast cancer are not the same, despite that they share great similarities in phenotypes [10, 20].

3. Immune Checkpoint Inhibitors (ICIs) Targeting TNBC

Immune checkpoints regulate the activity of the immune system, functioning by sending either inhibitory or excitatory signals to prevent the immune system from randomly harming other cells. This property is harnessed by some cancer cells to evade the attacks from the immune system. PD-1, PD-L1, and CTLA-4 are most commonly targeted in clinical trials. Figure 1 shows the mechanisms and drugs targeting the immune checkpoints. .

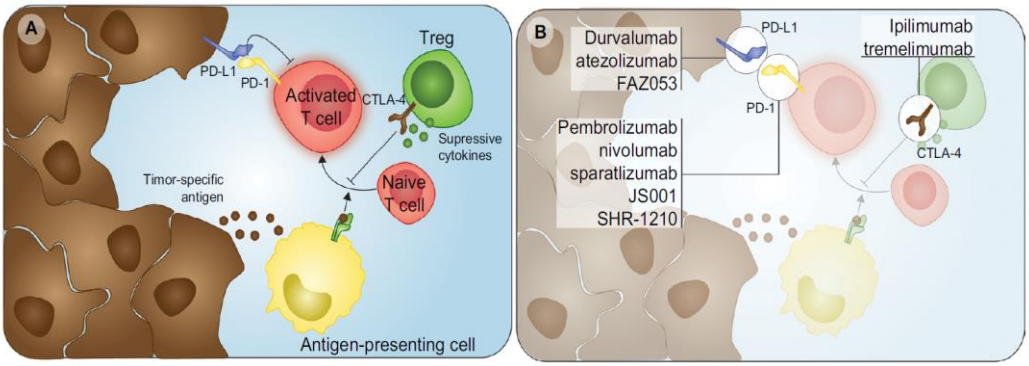

Figure 1. Mechanisms and drugs targeting the immune checkpoints [5].

Figure 1A. In the intracellular environment, the antigen-presenting cell presents tumor-specific antigens, which are recognized by native T cells and regulatory T cells (T reg). CTLA-4, the receptor present on T reg, sends inhibitory signals to immune cells to suppress immune activities. Native T cells are activated when stimulated by tumor-specific antigens. PD-1 on the surface of T cells could lead to cancer cell apoptosis. Yet the T cells could be inactivated when PD-1 combines with PD-L1 on the surface of cancer cells.

Figure 1B. The figure shows therapies targeting the three immune checkpoints. The trials testing pembrolizumab, nivolumab, atezolizumab, durvalumab, ipilimumab, and tremelimumab are examined later in the article.

3.1 PD-1 Inhibitors

PD-1 is a receptor located on the surface of T cells. When PD-1 binds to PD-L1 presented on the surface of some of the tumor cells, an inhibitory signal is sent to the T cell and inactivates it, impeding the immune reactions and enabling tumor cells to further replicate. PD-1 inhibitors are hence developed as an approach of immunotherapy to compete with PD-L1, binding to the PD-1 receptors and thus preventing PD-L1 from binding to the same site. With the inhibitory signal absent, cytotoxic

T cells can carry on the killing process. Pembrolizumab, which directly binds to the PD-1 receptor, and Nivolumab are two antibodies approved by the FDA to be used on some solid cancers including TNBC.

3.1.1 Pembrolizumab.

A phase II clinical trial (NCT02971761) was originally aimed for testing the safety of the combination of pembrolizumab and enobosarm, an androgen receptor modulator, on treating androgen receptor (AR) positive TNBC. Eligible participants were required to have AR+ metastatic TNBC (mTNBC) and no undiagnosed brain metastasis. The trial was conducted at a length of 16 weeks, on 16 female patients whose median age is 64. The patients were treated with 20 mg of pembrolizumab once per 3 weeks intravenously, and 18 mg of enobosarm orally, daily. The primary endpoints were safety and overall response rate (ORR); secondary endpoints were progression-free survival (PFS), overall survival (OS), correlative endpoints, and toxicity. The safety was assessed. Grade 4 adverse events (AE) were not observed, and grade 3 AEs appeared in 3 patients, including one musculoskeletal pain, one dry skin, and one diarrhea. 1 of the 16 (6%) patients achieved complete response (CR), and 1 (6%) achieved partial response (PR). 2 of the remaining 14 (13%) patients had stable disease (SD), and the rest 12 (75%) had progressive disease. The overall response rate was 2 out of 16 (13%). PFS was 2.6 months, and OS was 25.5 months. The combination of pembrolizumab and enobosarm was well tolerated, and the results were encouraging. However, unfortunately, the research was cut short due to the insufficient supply of enobosarm, which made the efficacy of the AR-targeted therapies appeared to be modest. A more effective combination of therapies was expected to be tested [22].

Chemotherapy and pembrolizumab are sometimes conjugated to treat mTNBC. In trial ENHANCE 1 (NCT02513472), a phase Ib/II study, pembrolizumab was used along with eribulin, a chemotherapy drug. All patients eligible were aged over 18, had mTNBC, had life expectancy over 3 months, had bone marrow, kidneys, and liver functioning well, had gone through two or less prior systematic treatments, and had received no therapy targeting the PD-1 pathway in the last 6 months. The study evaluated the safety and tolerability of patients to pembrolizumab and eribulin. The primary endpoint was the ORR, and secondary endpoints were PFS, OS, the duration of the response, and clinical benefit rate. A total number of 167 eligible patients participated in the trial from September 2015, to July 2019 (the data was then cut off). For every 21-day-cycle, the 7 patients who participated in the phase Ib trial received 1.4 mg/m2 eribulin on day 1 and day 8, and 200 mg pembrolizumab on day 1. Both drugs were delivered intravenously. In the phase II test, patients were separated into two groups based on the number of prior treatments received: no prior treatment for stratum 1 (66; 40%) and 1-2 prior treatments for stratum 2 (101; 60%). Since no patients experience dose-limiting toxicity, the same dose would continuously be applied for the phase II test. The top 3 common AEs include fatigue (66%), nausea (57%), and peripheral sensory neuropathy (41%). Neutropenia was the only grade 3 AE experienced by over 10% of patients (26.3%). 2 patients experienced life-threatening treatment-related disease, including 1 case of pyrexia and 1 case of neutropenia. The treatment combining eribulin and pembrolizumab for the total 167 patients had a median of ORR of 23.4%, including 8 (4.8%) patients achieving CR and 31 (18.6%) patients achieving PR. Patients with no prior treatments (stratum 1) had a higher ORR than patients with 1 or 2 prior treatments (stratum 2). The median PFS was 4.1 months, and was similar for both stratums; the median OS was 16.1 months, and the OS was higher for stratum 1 (17.4 months) than for stratum 2 (15.5 months). The efficacy was affected by the presence of PD-L1 on tumors. Patients who had PD-L1+ tumors had higher median ORR, median PFS, and median OS compared to those who had PD-L1- tumors. Overall speaking, the therapy combining eribulin and pembrolizumab was well tolerated by the patients. Eribulin plus pembrolizumab has a promising future in treating mTNBC [23].

3.1.2 Nivolumab.

NCT03316586 is a single-armed phase II study conducted to test the efficacy of the therapy combing nivolumab with cabozantinib, a small-molecule inhibitor of VEGFR2, a tyrosine-protein

kinase and a cell surface receptor, and MET, another receptor tyrosine kinase [24]. Eligible patients were required to have mTNBC tumors that are measurable per RECIST 1.1. The participants are allowed to have up to 3 chemotherapy lines, but any who were treated with MET inhibitor or other immune checkpoint inhibitors are excluded from this trial. The primary endpoint is ORR, and the secondary endpoints include the clinical benefit rate (CBR), the proportion of patients with responses or stable diseases at a specific week, PFS, and the frequency of adverse events. From December 2017, to January 2019, 18 patients with a median age of 58 years participated in the first phase of the trial. In every 28-day cycle, they were treated with 480 mg nivolumab on day 1 and 40 mg of cabozantinib every day. The AEs with the highest frequencies were increased AST (50%), increased ALT, anorexia, fatigue, hypothyroidism, and Palmar-plantar erythrodysesthesia. The latter 5 AEs all happened at the rate of 39%. The doses of nivolumab and cabozantinib were decreased in the majority of participants due to safety issues. Only 1 in the 18 patients achieved partial response (ORR was 6%); 14 (78%) patients have stable disease. The CBR was 95%, and the median of the PFS was 3.6 months. Failed to meet the pre-set criteria, the study was then closed [25].

Another trial studying the effect of nivolumab on TNBC was a randomized three-arm study OXEL (NCT03487666), in which nivolumab was applied alone or along with the chemotherapy drug capecitabine. Patients enrolled in this trial had been treated with adequate neoadjuvant chemotherapies but still had residual TNBC. The primary endpoint was to evaluate the effects on the immune system when applying nivolumab alone, applying capecitabine alone, or combining the two. Other endpoints include assessing the toxicity, distant recurring free survival (DRFS), and OS. Participants randomly distributed into three arms intravenously received 360 mg of nivolumab once per three weeks, or 1250 mg/m2 capecitabine twice per day from day 1 to day 14, or both nivolumab 360 mg per three weeks and 1250 mg/m2 capecitabine twice per day from day 1 to day 14. The study, which began in 2018, is ongoing. No results are published yet [26].

The study of the use of nivolumab in treating TNBC is limited. Based on the current results, therapies including nivolumab are not as promising as those including pembrolizumab. Further therapies involving pembrolizumab and nivolumab are being developed.

3.2 PD-L1 Inhibitors

PD-L1 antibodies perform well when treating malignant cancers [27]. As mentioned above, PD-L1 is the protein normally present on the surface of tumor cells, which when recognized by PD-1 can send inhibiting signals to impede downstream immune responses. PD-L1s in TNBC are seen more frequently on tumor-infiltrating immune cells than on tumor cells [28, 29]. PD-L1 inhibitors, whose mechanism similar to that of PD-1 inhibitors, prevent the interaction between PD-1 and its ligand. PD-L1 inhibitors atezolizumab, and durvalumab, which are approved by the FDA for therapies of other solid tumors, are involved in treatments for TNBC.

Table 1. The summary of drugs and the trials mentioned in this article.

Target	Antibody	Trade Name	Initial Approval Time	Clinical Trial	Other Drugs Used	Current State
PD-1	Pembrolizumab	Keytruda	9/5/2014	NCT02971761	Enobosarm	Active, not recruiting
				NCT02513472	Eribulin	Completed
	Nivolumab	Opdivo	6/22/2015	NCT03316586	Cabozantinib	Completed
				NCT03487666	Capecitabin	Active, not recruiting
PD-L1	Atezolizumab	Tecentriq	5/18/2016	NCT02425891	Placebo, nab-paclitaxel	Active, not recruiting
				NCT03125902	Placebo, nab-paclitaxel	Active, not recruiting
	Avelumab	Bavencio	5/23/2017	NCT01772004	N/A	Completed
	Durvalumab	Imfinzi	5/1/2017	NCT02489448	N/A	Active, not recruiting
				NCT02299999	AZD2014, AZD4547, AZD5363, AZD8931, Selumetinib, Vandetanib, Bicalutamide, Olaparib, Anthracyclines, Taxanes, cyclophosphamide,A DNA intercalators, Methotrexate, vinca alkaloids, Platinum based chemotherapies, Bevacizumab, Mitomycin C, Eribulin, MEDI4736	Active, not recruiting
CTLA-4	Ipilimumab	Yervoy	3/25/2011	NCT03546686	Nivolumab	Recruiting
	Tremelimumab	N/A	4/15/2015	NCT02527434	MEDI4736	Active, not recruiting

3.2.1 Atezolizumab.

IMpassion130 (NCT02425891) is a double-blind phase III trial comparing the efficacy of the combination of placebo and nab-paclitaxel (nP; a chemotherapy drug combining paclitaxel with a protein called albumin [30]) and the combination of atezolizumab and nab-paclitaxel. Patients were considered eligible if they were aged over 18, had unresectable, locally advanced, or metastatic TNBC that were measurable per RECIST 1.1, and had received no chemotherapies before. The primary endpoints were PFS and OS. Secondary endpoints were objective response rate, response duration, and time to deterioration. From April 2015, to April 2020, a total number of 902 patients were enrolled in this study. 451 patients were randomly assigned to the atezolizumab plus nP (A + nP) arm, and the other 451 were assigned placebo plus nP (P + nP) arm. In every 28-day cycle, each patient was treated with 100 mg/m2 nP on day 1, 8, and 15, and 840 mg atezolizumab or placebo on day 1 and 15. Safety was evaluated in this trial. The most common AEs for both arms include alopecia (57.2% for arm A + nP and 57.4% for arm P + nP), fatigue (47.0% for arm A + nP and 45.1% for arm P + nP), and nausea (46.7% for arm A + nP and 38.4% for arm P + nP). Grade 3 or 4 AEs were obtained by 50.7% of patients receiving A + nP and 42.6% of patients receiving P + nP. The PFS was significantly improved for the A + nP group, and especially for patients who have PD-L1 positive tumors. The final OS had a mean of 18.8 months, which should not be considered significant. Nevertheless, the combination of atezolizumab and nP was proven to be safe and deserved further attention [31].

However, there are pieces of evidence provided by trial IMpassion131 (NCT03125902), a double-blind, randomized phase III study, proving that atezolizumab plus paclitaxel (PAC) is not effective in improving PFS and OS compared with placebo plus PAC, conflicting with IMpassion130's results. Eligible patients, who had received no prior systematic treatments or had received adjuvant chemotherapy in over 12 months, were assigned to two arms, which were then treated both with 90 mg/m2 of PAC and with 840 mg atezolizumab or placebo, respectively. PFS was the primary endpoint; OS and ORR were the second endpoints. The primary outcome showed the median of the PFS of arm atezolizumab plus PAC to be 5.68 months, which was very close to the median of PFS of the arm placebo plus PAC (5.55 months). The reasons causing this difference are still undetermined. The results of the secondary study have not been obtained yet. The study is currently ongoing and is estimated to be completed on December 2, 2021 [32, 33].

3.2.2 Avelumab.

The JAVELIN (NCT01772004) is a phase I trial aiming to assess the activity of avelumab, an anti-PD-L1 antibody, in patients with metastatic breast cancer (MBC). Patients were eligible if they were aged over 18, had an estimated life expectancy of over 3 months, and have MBC that progressed after standard chemotherapy. The primary outcomes were dose-limiting toxicity and the best overall response rate. From November 2013 to February 2015, the 168 patients enrolled, in which 58 (34.5%) are TNBC patients, received 10 mg/kg of avelumab intravenously every two weeks. Safety was evaluated. 115 (68.5%) patients had treatment-related AEs, and the most common AE was fatigue (19.0%). The objective response rate in TNBC patients was 5.2%. Although clinical activity was modest, avelumab was well tolerated by most patients [34].

3.2.3 Durvalumab.

Not only could nab-paclitaxel combine with atezolizumab to form therapies, but also could it be used concurrently with dose-dense doxorubicin/cyclophosphamide (ddAC), another chemotherapy drug, and durvalumab, a human immunoglobulin antibody that binds to PD-L1 and inhibits its interaction with PD-1 and CD80 [35]. A phase I/II trial (NCT02489448) tested the efficacy and safety of the combination of ddAC and durvalumab. The primary end-point is the pathologic complete response (pCR), the lack of all signs of cancer in tissue samples removed during surgery after the treatment [36]. Eligible patients were required to have stage I to III TNBC and were qualified for systematic chemotherapy. 59 participants with a median age of 50 enrolled in the trial, in which 7 joined the phase I study and 52 joined the phase II study. The dose of 3 and 10 mg/kg was tested in

phase I, and no toxicities were observed. In phase II, each patient received 10 mg/kg durvalumab along with chemotherapy, which include 12 treatments of weekly nab-paclitaxel followed by 4 treatments of ddAC every two weeks. Durvalumab was not continued in 19 patients due to disease progression or AEs. The top 3 common AEs were fatigue (85%), nausea (73%), and alopecia (66%). 18 (31%) patients experienced grade 3 or 4 AEs. All immune-related AEs were seen in previous studies, and no new safety issues were brought up. The pCR rate was 44%. It should be noted that pCR rate of participants with PD-L1 positive tumors was 55%, and pCR rate for PD-L1 negative patients was 32%. Patients with pCR have higher tumor-infiltrating lymphocytes (TIL) counts, although TIL count, on its own, could not be used to determine whether the patient benefited from the immune checkpoint treatment or not. The study is currently ongoing, and the estimated completion time is December 2021 [37, 38].

Another trial, the substudy 2 of trial SAFIR02-BREAST IMMUNO (NCT02299999), compared the efficacy of durvalumab alone with that of maintenance chemotherapy. Eligible patients have stable or responding diseases after 6-8 rounds of chemotherapy, and have no targetable features that could be recognized by Molecular Tumor Board, and hence could not develop personalized therapies. PFS was the primary endpoint; OS, ORR, and safety were the secondary endpoints. 199 patients were randomized at a 2:1 ratio into two arms, one arm taking durvalumab and the other arm taking maintenance chemotherapy. Of the 191 patients involved in this trial, 82 (43%) had TNBC. Durvalumab was taken 10 mg/kg every two weeks. The chemotherapy drug most commonly applied to TNBC patients in the maintenance arm was bevacizumab alone or in combination. This ongoing study has an estimated primary completion date of December 2021, and an estimated study completion date of December 2022. Results so far showed that durvalumab improved the OS of TNBC patients, and the efficacy of single-agent durvalumab in maintenance therapy targeting TNBC could be further evaluated using the rationale provided in this study [39, 40].

3.3 CTLA-4 Inhibitors

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or CD152, is the first co-receptors to be found, the first immune checkpoint receptor to be clinically targeted, and the first ICI to gain FDA approval to be used on humans [41]. CD28 is a T cell co-stimulatory protein, activating T cells when binding to its ligands CD80 or CD86. However, CTLA-4, which is present on regulatory T cells, has a higher affinity for CD80 and CD86 [42], and hence outcompetes CD28. Upon blocking the stimulatory signal, CTLA-4 sends inhibitory signals to the cell. CTLA-4 blockades prevent CTLA-4 from interacting with its ligands, and hence rescues T cell hypo responsiveness. Common CTLA-4 inhibitors include ipilimumab and tremelimumab.

3.3.1 Ipilimumab.

Patients who undergo cryoablation is under high risk of inflammation, which could lead to immune responses that may cause cancer recurrence. NCT03546686, a randomized phase II study, compares the disease-specific impact of the combination of peri-operative ipilimumab plus nivolumab plus cryoablation and standard care. The primary endpoint is event-free survival. Eligible patients are women aged over 18, have residual TNBC, and had experienced neoadjuvant chemotherapy. Approximately 160 patients will be randomized into two arms: the control arm, which receive standard care, and the intervention arm, which receive the peri-operative ipilimumab plus nivolumab plus cryoablation. The patients in intervention arm will be intravenously injected 1 mg/kg ipilimumab and 240 mg nivolumab 1 to 5 days before the cryoablation, and 3 doses of 240 mg nivolumab once per two weeks after the cryoablation. The trial is currently recruiting, and is estimated to be completed by June 2024 [43].

3.3.2 Tremelimumab.

NCT02527434 is a phase II, open-label, multi-center trial. Of all 64 eligible patients involved, 12 had TNBC and were assigned to the TNBC cohort, in which they received tremelimumab monotherapy. The primary endpoint was the objective response rate, and secondary endpoints were

PFS, OS, and duration of response. Patients in TNBC cohort were administered 750 mg tremelimumab intravenously every 4 weeks for 7 cycles, and then every 12 weeks for 2 cycles. If disease progression was observed, the patients could either re-receive tremelimumab monotherapy or receive durvalumab plus tremelimumab combination therapy. 4 (33.33%) patients experienced serious AEs including vomiting, pain, pyrexia, hyponatraemia, dizziness, mental status changes, dyspnoea, dyspnoea exertional, and respiratory failure. 11 out of the 12 TNBC patients failed to complete the study, including 2 lost to follow-up, 6 deaths, and 3 withdrawals by subject [44].

4. Conclusion

Although TNBC remains the subtype of breast cancer that has the worst prognosis, immunotherapy is shown to offer promising treatments to the cancer. The therapies using solely a single immune checkpoint inhibitor gained modest outcomes. The efficacy could be improved when immune checkpoint inhibitors are combined with other therapies such as chemotherapy or radiotherapy. Immunotherapy is making personalized treatments as well as full prevention of TNBC possible. Future studies should focus on testing new combinations of drugs in order to improve efficacy as well as safety. Studies should be targeting TNBC of all stages to determine the stage of disease progression in which the immune checkpoint blockade could generate the most encouraging outcomes. The immunotherapy era is coming.

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