Review Article

Narrative review on efficacy and safety of anti-angiogenesis in combination with immunotherapy in the treatment of breast cancer

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Background and Objective: Breast cancer was the second frequently diagnosed cancer in 2022 among all cancers. Besides classical chemotherapy and radiation, immunotherapy and targeted therapy are both identical treatment options for patients with advanced breast cancer. Immunotherapy is a therapeutic approach to control and eliminate tumors by restarting and maintaining the tumor-immunity cycle and restoring the body's normal anti-tumor immune response. Immunotherapy alone or in combination with other therapies has been shown to be clinically beneficial in a variety of solid tumors with a manageable safety profile. However, immunotherapy alone cannot fully satisfy the therapeutic needs for patients with breast cancer. Therefore, there is an urgent need for immunotherapy to be combined with other therapeutic approaches to increase treatment efficacy.

Methods: We systematically searched PubMed database for relevant studies published over the past 5 years. Articles were screened for eligibility and key data extracted.

Key Content and Findings: We assess the current breast cancer treatment landscape, summarizing efficacy and safety of recent immunotherapy, chemotherapy combined with immunotherapy, immunotherapy combined with anti-angiogenic therapy. In the treatment of breast cancer, aiming to promote further research and applications of this novel treatment regimen in patients with breast cancer. Since anti-angiogenic therapy can reprogramme the tumor immune microenvironment, immunotherapy in combination with anti-angiogenic therapy might have a synergistic effect, igniting a new hope for immunotherapy for breast cancer patients. The review's conclusions offer insightful information on the state of breast cancer treatment today. In the end, improving clinical practice and pertinent research for immunotherapy combination therapy will contribute to bettering patient outcomes, raising quality of life, and creating more potent treatments.

Conclusions: This review emphasizes the potential of immunotherapy combinations, especially with anti-angiogenic therapeutic regimens, as a viable strategy for the treatment of breast cancer through a thorough study of the literature. To improve treatment approaches, lessen side effects for patients, and find trustworthy biomarkers to forecast response to immunotherapy combo medicines, further research is necessary.

Keywords: Breast cancer; immunotherapy; anti-angiogenesis; chemotherapy; combination therapy

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Introduction

Background

Annually, over 2.3 million new breast cancer cases are diagnosed, accounting for roughly 11.7% of all global cases. This makes it the fifth most prominent cause of cancer fatalities, with 685,000 deaths annually. It is estimated that by 2040, the number of new breast cancer cases will be around 3 million, and the number of deaths from the illness will have risen by more than half (1, 2). Molecularly, breast cancer can be categorized as luminal subtype, human epidermal growth factor receptor 2 (HER2)-overexpressing type and triple-negative breast cancer (TNBC). The expression of progesterone and estrogen receptors, independent of HER2 status, is known as luminal type. If all of the three receptors are negatively expressed, it is defined as TNBC, an aggressive subtype with the worst prognosis (3-6). As the investigations on cytokines like tumor necrosis factor (TNF), interferon-α (IFN-α), and interleukin-2 (IL-2) go deeper. Checkpoint inhibitors gained attention as a cancer therapeutic tool soon after. In the year 2010, the FDA firstly approved Ipilimumab for metastatic melanoma treatment, which specifically targets checkpoints as an immunotherapy drug in cancer treatment (7). These inhibitors are vital in cancer management because they target the programmed cell death protein-1/programmed death ligand 1 (PD-1/PD-L1) pathway. It has been proposed that combining checkpoint inhibitors with chemotherapy may offer a survival advantage in treating patients with TNBC. However, there are still many patients who gain little benefit from combination therapy or developed resistance to immunotherapy. This might be attributed to endogenous and exogenous mechanisms of the tumor or even host-related mechanism, which prevent immunotherapeutic drugs from working and reduce their efficacy or even make them ineffective. Patients often display suppressed anti-cancer immunity due to the suppression of their immune cells' function, as well as the promotion of suppressor cells. The recent researches on the resistance to anticancer immunity are based on the examination of intrinsic cancer cell factors, immune cells, and other mechanisms (8-10). Normally, the vascular system is in homeostasis. However, if it becomes abnormal, it can lead to a range of negative consequences, including hypoxia, acid accumulation, physical barrier damage or metabolic reprogramming (11). Tumor angiogenesis, a process involving multiple molecules and cells, can be aided by vascular abnormalities, allowing tumors to elude the immune system. Vascular endothelial growth factor (VEGF) obstructs the differentiation and development of lymphoid progenitor cells. Similarly, tumor-associated macrophages (TAM) can be recruited to the tumor microenvironment (TME). There is growing evidence of tumor angiogenesis suggesting that non-coding RNAs have a critical role. Interaction between molecules and cells leads to vascular abnormalities (12).

Rationale and knowledge gap

Abnormal angiogenesis in tumors can lead to the creation of a hypoxic or acidic environment. Since anti-angiogenic therapy can influence the tumor immune microenvironment, immunotherapy in combination with anti-angiogenic therapy might have a synergistic effect, igniting a new hope for immunotherapy for breast cancer patients.

Objective

Our objective is to investigate the growing number of studies support the potential of combining tumor anti-angiogenesis with immunotherapy as a therapeutic strategy for improving patient outcomes (13). However, there are several challenges. The interactions between these approaches are extremely complex, and have not yet been fully elucidated. At present, there are very few reports on this topic in breast cancer patients, and here we have summarized the latest advances in anti-angiogenesis combined with immunotherapy with or without chemotherapy, aiming to deeply understand its mechanisms and promote its clinical applications. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-21/rc).

Methods

We conducted a narrative review using PubMed database, with the latest update performed in February 2024. We also screened the reference lists of retrieved articles and proceedings from relevant cancer meetings held in the past 5 years to find additional sources.

For inclusion, we focused on clinical trials that studied breast cancer patients receiving neoadjuvant/adjuvant treatment with immunotherapy in combination with anti-angiogenic therapy. We also considered trials that reported separate results for molecularly defined subgroups in breast cancer subtypes other than TNBC (*Table 1*).

Table 1 The search strategy summary

Items	Specification
Date of search	01-Feb-2024
Databases and other sources searched	PubMed
Search terms used	"Early-stage triple negative breast cancer" OR "early-stage TNBC" OR "eTNBC" [MeSH]
	"Triple negative breast cancer" OR "TNBC" [MeSH]
	"Advanced triple negative breast cancer" OR "advanced TNBC" OR "aTNBC" [MeSH]
	"Advanced breast cancer" OR "aBC"
	"breast cancer" OR "BC" [MeSH]
	"Immunotherapy" OR "Immune checkpoint inhibitors" OR "Pembrolizumab" OR "Atezolizumab" OR "Durvalumab" [MeSH]
	"Neoadjuvant" [MeSH]
	"Adjuvant" [MeSH]
	"PD-L1" [MeSH]
	"Monotherapy" [MeSH]
	"Combination therapy" [MeSH]
	"Advanced triple-negative breast cancer" [MeSH]
Timeframe	2015–2024
Inclusion and exclusion criteria	Inclusion criteria: research articles, reviews and clinical trials in English about themes such as breast cancer, immunotherapy and anti-angiogenesis
	Exclusion criteria: some papers which we considered with low reliability
Selection process	The included literature was selected by author X.D., reviewed by both authors
Any additional considerations, if applicable	The search was supplemented by scanning reference lists of relevant articles, reviewing relevant guidelines and cancer meetings

Immunotherapy of breast cancer

Considerable research has focused on T-cell characterization, but other immune cells such as B-cells, natural killer (NK)-cells and macrophages also contribute to tumor progression and the response to immunotherapy. The primary approach in immunotherapy is inhibiting the PD-1/PD-L1 axis, which is most extensively researched. Monoclonal antibodies that target PD-1 include cemiplimab, pembrolizumab, nivolumab, camrelizumab, and toripalimab. Those targeting PD-L1 comprise avelumab, atezolizumab, and durvalumab. Recent clinical trials have shown that inhibitors of PD-1 and/or PD-L1 can be applied in a wide variety of tumors, and significantly prolong the survival of patients with advanced tumors, indicating promising prospects for implementation (14-31).

Pembrolizumab has been proposed to have strong anti-tumor effects in PD-L1 positive metastatic TNBC (mTNBC). KEYNOTE-012 study (32) showed the disease control rate (DCR) was 25.9% [95% confidence interval (CI): 11.6–46.3%], median progression-free survival (mPFS) was 1.9 months (95% CI: 1.7–5.5). The KEYNOTE-086 study (33) further revealed a DCR of 23.8%, with median PFS and overall survival (OS) at 2.1 and 18.0 months, respectively. However, the phase 3 KEYNOTE-119 study (34) did not demonstrate positive results in the pembrolizumab monotherapy arm versus the chemotherapy arm.

For the first time, atezolizumab was reported in mTNBC, displaying a slim clinical benefit and safety profile (mPFS: 1.4 months). The study demonstrated a difference in objective response rate (ORR) for atezolizumab as a first-line agent compared to a second-line agent (24% *vs.* 6%). And the median OS was 8.9 months (35).

Avelumab is different from other PD-L1 antibodies

as it possesses a unique strong antibody-dependent cell-mediated cytotoxicity (ADCC) activity. Antibodies of the PD-1/PD-L1 variety have been known to circumvent the ADCC-induced destruction of the immune cells. The PD-1/PD-L1 pathway can be utilized to prevent cancer cells from the immune escape of cancer cells and activate T cells to annihilate them, in addition to the antibody. It can also mediate the action of NK cells on cancer cells through ADCC action to form a killing effect (36-38) and mediate the lysis of tumors (39,40) in mice model. The Food and Drug Administration (FDA), due to the positive outcomes of the JAVELIN Bladder 100 phase III clinical trial, hastened the authorization of avelumab for locally advanced or metastatic uroepithelial cancer (41-43). In a phase 1 trial (JAVELIN Solid Tumor; NCT01772004), The ORR for the total population was 3.0% with one was completely remission and four were only partially remission. Of the 5 patients, 3 were confirmed TNBC and 2 were $HER2^-$ estrogen receptor/progesterone receptor positive (ER/PR^+) breast cancer (ORR: 5.2% *vs.* 2.8%) (44).

Additionally, the phase II BELLINI study (45) reported by European Society of Medical Oncology (ESMO) in 2022 was the first to investigate the feasibility of treating TNBC with dual immune checkpoint inhibitors (ICIs) (nivolumab and ipilimumab) in the neoadjuvant phase of treatment without chemotherapy. Results showed that, after four cycles of treatment, imaging assessment revealed a partial remission rate of 27.0%, with approximately 24% of patients showing circulating tumor DNA clearance. New ideas for neoadjuvant treatment of breast cancer, without chemotherapy, are presented through dual immune checkpoint inhibitor regimens.

Immunotherapy combined with chemotherapy for breast cancer

Though chemotherapy remains the standard systemic treatment for the majority of patients, tumors can quickly become resistant to drugs. Moreover, single-agent immunotherapy is unsatisfactory for high tumor burden mTNBC, so immunotherapy needs to be combined with drugs with multiple mechanisms of action to improve efficacy.

The KEYNOTE-355 and IMpassion130 trials have now shown the effectiveness of ICIs in conjunction with chemotherapy as a first-line treatment for advanced TNBC. Data from the KEYNOTE-355 trial (5) suggested that patients with a high combined positive score (or rich in PD-L1) had a more pronounced benefit from immunotherapy [mPFS 9.7 *vs.* 5.6 months; hazard ratio: 0.65, 95% confidence interval (CI): 0.49–0.86; P=0.001]. Also, in the phase III IMpassion130 study (6), revealed a remarkable enhancement in PFS benefit (7.2 *vs.* 5.5 months). Atezolizumab in combination with the chemotherapeutic agent was the first immunotherapy to be approved for breast cancer, as demonstrated by clinical trial data.

The GP28328 (NCT01633970) study (46) showed that patients who received atezolizumab in combination with albumin-paclitaxel as first-line treatment for advanced TNBC achieved higher efficacy rate. Clinical data from both first-line and two or more lines of treatment showed good anti-tumor activity in terms of ORR (53.8% *vs.* 30.0%), mPFS (8.6 *vs.* 5.1 months), and mOS (24.2 *vs.* 12.4 months). In recent years, several phase II and III studies, such as Neopact and ALICE (47-49), have demonstrated that the combination of PD-1 and/or PD-L1 inhibitors with chemotherapy can significantly improve the long-term prognosis of TNBC patients.

According to the previous phase 1 trial (50), toripalimab was used to treat advanced TNBC with multi-line resistance and still managed to provide safe anti-tumor activity. The TORCHLIGHT study, led by Chinese researcher Professor Zefei Jiang, is the first phase 3 immunotherapy combined with chemotherapy study in patients with advanced TNBC in China (51). The results showed that combining chemotherapy with toripalimab significantly prolonged mPFS by 2 months in the PD-L1-positive group (8.4 *vs.* 5.6 months), while the intention-to-treat group also showed a significant improvement in mPFS (8.4 *vs.* 6.9 months). Furthermore, mOS was found to be 32.8 months in the D-L1-positive group. This clinical study suggests that immunotherapy in combination with chemotherapy can extend survival despite multiple lines of systemic therapy.

One meta-analysis (52) published in 2023 also demonstrated mOS and mPFS of 16.526 and 5.814 months respectively in mTBNC patients treated with atezolizumab alone or in combination with chemotherapy. Subgroup analysis further revealed that PD-L1 positive patients had better OS, PFS, and ORR than patients with PD-L1 negative patients. Additionally, a TBCRC-043 phase II trial revealed the clinical benefit of the combination of carboplatin and atezolizumab (53).

A groundbreaking research paper demonstrated that the dual treatment of KN046, a PD-L1/cytotoxic T-lymphocyte antigen-4 (CTLA-4) bispecific antibody, and nab-paclitaxel,

showed a significant advantage in PFS and OS benefit (mPFS: 7.33 months, mOS: 30.92 months). This regimen is designed to be highly effective with low toxicity, thus it is promising to be a first-line treatment for advanced TNBC (54). Clinical benefit was demonstrated regardless of PD-L1 status and was well tolerated (55).

In the field of neoadjuvant treatment, there were also some studies focusing combined checkpoint inhibitor in combination with chemotherapies. The KEYNOTE-173 trial (56) was that the neoadjuvant chemotherapy (NACT) in combination with pembrolizumab regimen in the treatment of high-risk, early-stage TNBC demonstrated anti-tumor activity with manageable toxicity [pathologic complete response (pCR): 60%]. The KEYNOTE-522 clinical trial (4), which was conducted based on the KEYNOTE-173 trial, affirmed that the clinical benefit of neoadjuvant therapy with pembrolizumab (pCR 64.8% *vs.* 51.2%). Meanwhile, continued use of pembrolizumab in the adjuvant phase resulted in an increased event-free survival (EFS) benefit (36-month EFS rate: 84.5% *vs.* 76.8%; P<0.001). In contrast, for patients with early-stage TNBC, primary results from the previous IMpassion 031 trial (57) showed that neoadjuvant treatment with atezolizumab plus paclitaxel albumin and anthracycline-based chemotherapy significantly improved the pCR (57.6% *vs.* 41.1%). The final results published in 2023 ESMO, gained benefits in terms of EFS, disease-free survival (DFS) and OS (58). However, in the NeoTRIP study (59) which is designed for neoadjuvant treatment for TNBC, there was no significant benefit from immunotherapy compared to chemotherapy (pCR: 43.5% *vs.* 40.8%, P=0.66). The trial's lack of a sequential chemotherapy regimen may have been a factor in the regimen's unfavorable results, thus emphasizing the necessity of a sequential regimen design. The GeparNUEVO trial used durvalumab plus chemotherapy as neoadjuvant therapy for TNBC and observed an increase in pCR, improvement in invasive disease-free survival (iDFS) and distant disease-free survival (DDFS), and a favorable trend in OS (60). The most recent findings from KEYNOTE-756 were reported at the 14th European Breast Cancer Conference (EBCC-14). This multi-center trial, which enrolled 1,278 individuals with $ER^+/HER2^-$ invasive ductal carcinoma, was the first to investigate and evaluate the long-term prognostic effects of immunotherapy on those with this type of breast cancer. The trial highlighted the addition of pembrolizumab to both NACT and subsequent adjuvant chemotherapy, with a statistically significant difference in the pembrolizumab arm compared to the control arm, with pCR rates reaching 24.3% in the pembrolizumab arm compared to 15.8% in the control arm, which highlighted the significance of the addition of pembrolizumab to both neoadjuvant and subsequent adjuvant chemotherapy. This trial suggests that increasing the pCR rate through the neoadjuvant phase, and we are waiting the survival result of continuing to add immunotherapy during the adjuvant phase in patients with HR^+ and $HER2^-$ tumors (61). At 2023 ESMO and San Antonio Breast Cancer Symposium (SABCS), the Checkmate 7FL study (62,63) revealed that nivolumab combined with NACT and adjuvant endocrine therapy had a significant effect on the pCR rate in high-risk $ER^+/HER2^-$ breast cancer patients, increasing it by 10.7% and correlating with the intensity of PD-L1 expression.

Mechanism of combining immunotherapy and anti-angiogenic drugs in breast cancer

As a new targeted therapy strategy, anti-angiogenesis can improve the efficiency of delivery of chemotherapeutic drugs delivered to tumor tissues and enhance the therapeutic effect by inhibiting tumor angiogenesis (64). There exists a delicate control mechanism to maintain the equilibrium of angiogenesis in normal, healthy individuals, a meticulous control mechanism is in place. This control involves the regulation of VEGFs, vasopressors, and other molecules. However, in tumors, this balance shifts to pro-angiogenesis. Studies have demonstrated that malignant tumors are accompanied by elevated angiogenesis levels, and that angiogenic elements such as VEGF, Ang-2, fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) are involved in the process. The glycolytic process occurring within endothelial cells plays a crucial role in orchestrating various cellular activities. This intricate mechanism not only facilitates the migration of T cells but also catalyzes the robust spread of stem cells. Leading to the stimulation of vascular branching and maturation is the initiation of signaling pathways, including recombinant delta like protein 4 (DLL4) and platelet-derived growth factor (PDGF) (65-68).

Abnormalities in the vascular system led to changes in the TME. In breast cancer, a hypoxic state is often observed (69) which is due to aberrant angiogenesis that induces aggregation of immunosuppressive cells and secretion of immunosuppressive cytokines. Ultimately, PD-1 expression in T cells is upregulated (70). According to our previous and other teams' studies, VEGFR2 inhibitors could increase the

efficacy of anti-PD-1/PD-L1 antibodies via reprograming tumor immune microenvironment in multiple-tumor-bearing mice (71-73). The efficacy of immunotherapy mice models of melanoma, breast, and pancreatic cancer can be increased by antiangiogenic drugs that target tumor blood vessels. This is accomplished by bio-specifically targeting vascular endothelial growth factor A (VEGFA) and angiopoietin-2 (ANGPT2), or by inhibiting the vascular endothelial growth factor receptor (VEGFR) (72,73). Zhou's team showcased that fine-tuning the TME is attainable through the strategic use of a low dosage of apatinib, a VEGFR2-tyrosine kinase inhibitor (TKI). This purposeful adjustment leads to a notable improvement in the anti-tumor efficacy, as evidenced in syngeneic mouse models of lung cancer when combined with PD-1/PD-L1 blockade (74). Similarly, our study has found both full-dose and low-dose VEGFR2 inhibitors increased PD-L1 expression in cells such as tumors, endothelial cells and immune cells. The co-administration of a low dosage of anti-angiogenesis with anti-PD-1 resulted in an enhancement of macrophages, $CD8^+$ T cells and B cells. Moreover, the drug's low doses have significantly stimulated tumor-infiltrating immune cells. It causes them to secrete osteopontin (OPN) and TGF-ß, thus upregulating PD-1 on immune cells (71). In addition, another preclinical study showed that anlotinib combined with PD-1 antibody has contributed to the normalization of tumor vasculature, remodeling the tumor immune microenvironment, and inducing neuroblastoma regression (72).

Clinical evidence to combine anti-angiogenesis with immunotherapy in solid tumors

Most anti-angiogenic medications aim at the VEGF signaling system (74-78). Several investigations exploring the combination of PD-1 inhibitors with other therapies for various malignancies, such as hepatocellular carcinoma, endometrial cancer, gastrointestinal cancer, and renal cell carcinoma, are underway. The use of a combination of anti-angiogenic therapy and immunotherapy is of great significance, some of which have received FDA approval for clinical application against hepatocellular carcinoma, ovarian carcinoma and advanced renal cell carcinoma.

The combination of immunotherapy and anti-vascular targeted drugs has started to challenge many types of cancers in the first-line or second-line, and achieved excellent efficacies, especially in the case of refractory and chemotherapy-resistant tumor (79-88).

Immunotherapy combined with anti-angiogenic therapy in breast cancer

The first clinical study (86) focused on an ICI in combination with a VEGFR inhibitor. The use of bevacizumab is involved in a study (87) specifically focused on HER2-negative metastatic breast cancer patients experiencing disease progression after or during first-line chemotherapy. This research provides novel hints concerning the amalgamation of second-line bevacizumab and eribulin. Another study (NCT03222856) (88) has found that the treatment of pembrolizumab plus eribulin leads to good treatment results among HR-positive, HER2-negative metastatic or recurrent breast cancer patients undergoing multiple lines of therapy. Another single-arm, phase Ib/II study (enhance-1) (89) mainly included 167 patients with mTNBC who have received no more than 3 prior systemic treatments in the presence of metastases. Based on the criteria of inclusion, participants were divided into two groups—one with no systemic therapy in the presence of metastases and the other with one or two systemic treatments, with a chemotherapy-free regimen of eribulin plus pembrolizumab. The primary endpoint showed an ORR of 23.4% (95% CI: 17.2–30.5%). The overall mPFS reached 4.1 months (95% CI: 3.5–4.2). The study revealed that, in comparison to stratum two, the overall mOS was 16.1 months (95% CI: 13.3–18.5) and 15.5 months (95% CI: 12.5–18.7) for stratum two, with a better median OS was achieved in both groups (17.4 months (95% CI: 13.2–21.0) for stratum one versus 15.5 months (95% CI: 12.5–18.7) for stratum two). Furthermore, immunotherapy combined with anti-angiogenic therapy in the post-treatment setting in the subgroup reaped the rewards of this regimen. Pembrolizumab plus eribulin demonstrated an acceptable safety profile, with common toxicities like fatigue, nausea, peripheral sensory neuropathy, alopecia, and constipation. Neutropenia was reported as the only grade ≥3 toxicity in over 10% of patients. And no treatment-related death was reported. A single-arm phase I/II clinical study investigated the clinical evidence of the combination therapy involving cabozantinib and nivolumab in patients with mTNBC (90). Phase II could not be conducted due to an ORR result of 6% (1/18) in phase I. In the second part, genomic analyses were performed. Several markers such as growth factors (IL-5, IL-6), growth factors (VEGF-A), and immune checkpoint molecules (CD27 and CD70) were found to be associated with shorter PFS. Palmar-plantar erythrodysesthesia, back pain and increased aspartate aminotransferase were the

most frequent adverse events (AEs) (17%) and were mainly grade 3–4. Additionally, cabozantinib needed to be required adjustment of the treatment dose or discontinuous due to toxicity (90).

From March 2020 to May 2021, our group enrolled 46 qualified advanced TNBC (aTNBC) patients in a multicenter phase II trial. The trial evaluates anti-PD-1 antibody, apatinib and eribulin in treating pretreated patients, the ORR was 37.0% and the mPFS was 8.1 months (91). Besides, our trial suggested that patients who have received previous immunotherapy can benefit from this combinational regimen. Subgroup analysis also suggested that patients can benefit from this regimen regardless of their PD-L1 levels. Grade 3/4 treatment-related adverse events (TRAEs) mainly occurred in the hematologic and digestive system, manifested as neutropenia (30.4%), thrombocytopenia (19.6%), elevated aspartate aminotransferase (17.4%), elevated alanine transaminase (17.4%), and leukopenia (13.0%). Forty of 46 patients had TRAEs possibly related to immunotherapy, of which seven were suspended the dose of camrelizumab. However, this study also demonstrated a dose reduction and discontinued apatinib due to toxicity. Another multicenter retrospective study (92) has included 128 cases of HER2-negative breast cancer. This study's most noteworthy result was the contrast between the chemotherapy regimen and the combination of apatinib with immunotherapy. Hypertension was the most frequent AE (32.8%) but was mainly grade 1. Most patients presented with AEs did not require adjustment of the treatment dose. The highest PFS once more confirmed the considerable impact of apatinib in combination with immunotherapy. Another study (93) enrolled 90 patients with aTNBC. Patients combined with apatinib group had a promising PFS than camrelizumab alone, and the safety was relatively manageable. In addition, Shao's group reported a meaningful finding in the FUTURE-C-PLUS study. The remarkable ORR of 81.3% for patients with aTNBC was clearly demonstrated by the first-line regimen of camrelizumab in combination with albumin-paclitaxel and famitinib, which was highly efficacious. The most common grade 3 or 4 AEs were neutropenia, anemia, febrile neutropenia and thrombocytopenia (33.3%, 10.4%, 10.4%). Serious TRAEs were demonstrated in 2 patients, with grade 3 septicemia and grade 3 immune-related myocarditis (94).

In 2023 SABCS, a phase II study (95) was reported. Exploring the efficacy of sitravatinib, tislelizumab, either alone or in combination with nab-paclitaxel, in treating locally recurrent or metastatic TNBC, a study was conducted. It was initially divided into two cohorts, with cohort A being the sitravatinib (70 mg) plus tislelizumab regimen and cohort B being the sitravatinib (100 mg) plus tislelizumab regimen. Based on the excellent clinical evidence of cohorts A and B, cohort C, a combination chemotherapy regimen, was added to the study to explore the clinical evidence for the first-line treatment of aTNBC with the tislelizumab plus sitravatinib (70 mg) plus albumin paclitaxel regimen. The 35 patients' effectiveness was evaluated, with a remarkable ORR of 77.1% and a DCR of a remarkable 97.1%.

A recently published study in 2023 that included patients with aTNBC similarly achieved favorable clinical benefits. The study was using PD-L1 inhibitors combined with anti-angiogenic drugs. In the first part, total six patients were treated and all were given 1, 200 mg TQB2450, differing in that three patients were given 10 mg anlotinib and the remaining three patients were given 12 mg anlotinib. In the dose-expansion cohort, anlotinib-related incidence was higher than TQB2450-related (48.4% *vs.* 41.9%). Most events were grade 1 or 2, which presented with elevated alanine aminotransferase, elevated aspartate aminotransferase, hand-foot syndrome, hypertriglyceridemia and hypercholesterolemia. 2.9–17.6% of patients had grade 3 or 4, which presented with prolonged QTc and hypertension. Based on the results from the previous stage, patients in the extension phase were all administered 12 mg erlotinib. The ORR was 26.5% (95% CI: 12.9–44.4%) and the DCR was 73.5% (95% CI: 55.6–87.1%). The PFS rate was 49.9% (95% CI: 31.1–66.1%) at 6 months. Of these 31 patients, 16 achieved stable disease, yet their median survival remained indeterminate (95% CI: 7.1–not reached) (96). The biomarker analyses showed that patients with bTMB-L or MSAF-L had significantly more favourable ORR and PFS compared with those with bTMB-H or MSAF-H (97). The above clinical trials are detailed in *Table 2*.

Conclusions

Combining an antiangiogenic agent and immunotherapy enhance immune cells potential to fight against malignant tumors, which significantly improves the prognosis of patients with breast cancer, and this provides more possibilities for clinical choices. The combination of anti-angiogenesis and immunotherapy has been found to not only increase drug efficacy, but also to have a well-controlled safety profile. Investigations into the potential

Table 2 Summary of clinical trials of ICIs in combination with anti-angiogenesis drug and/or chemotherapies in breast cancer

Characteristics	Study design	Patient population	Treatment regimen	Primary endpoint	ORR	mPFS (months)	OS
NCT03394287	Open label, randomized, parallel, non-comparative, two-arm, phase II	aTNBC (n=40)	Camrelizumab plus apatinib	ORR	43.3% (apatinib intermittent dosing cohort, 13 of 30)	3.7 *vs*. 1.9	mOS 8.1 *vs*. 9.5 months
KELLY (NCT032228560)	Open label, multicenter, single-arm, phase II	HR^+, $HER2^-$ negative, inoperable, locally recurrent or metastatic BC (n=44)	Pembrolizumab plus eribulin	Clinical benefit (CR, PR, SD lasting for more than and equal to 24 weeks)	Not reported	6.0	Not reached
ENHANCE-1	Open label, multicenter, single-arm, phase Ib/II	mTNBC (phase Ib, n=7; phase II, n=160)	Pembrolizumab plus eribulin	ORR	23.40%	4.1	Overall mOS 16.1 months
	Single-arm phase II	mTNBC (n=18)	Cabozantinib plus nivolumab	ORR	9%	3.6	Not reported
NCT04303741	Multicenter phase II	aTNBC (n=46)	Camrelizumab plus apatinib-eribulin	ORR	37.00%	8.1	Not reached
NCT03855358	Phase Ib	aTNBC (n=34)	TQB2450 plus anlotinib	ORR	26.50%	5.6	Not reached
FUTURE-C-Plus (NCT04129996)	Open-label, single-arm, phase II	Advanced, immunomodulatory TNBC (n=48)	Camrelizumab plus nab-paclitaxel plus famitinib	ORR	81.3%	13.6	Not reached

ICIs, immune checkpoint inhibitors; aTNBC, advanced triple-negative breast cancer; BC, breast cancer; ORR, objective response rate; mPFS, median progression-free survival; OS, overall survival; mOS, median overall survival; CR, complete response; PR, partial response; SD, stable disease; mTNBC, metastatic triple-negative breast cancer.

of immunotherapy in conjunction with anti-angiogenesis agents to treat breast cancer are being conducted in abundance (the summary of trials in *Table 3*).

In China, massive breast cancer studies are concentrating on the triad of chemotherapy, immunotherapy and the inhibition of angiogenesis in breast cancer. For instance, the ongoing SPACE study in which immunotherapy plus antiangiogenic therapy and metronomic chemotherapy brought encouraging results, in patients with advanced TNBC. Results have indicated that sindilizumab in combination with anlotinib and metronomic chemotherapy has promising effectiveness and tolerable tolerability (98).

Combined anti-angiogenesis and immunotherapy has been established as a standard in the treatment of hepatocellular carcinoma and non-small cell lung cancer. The combination has also been found to show great benefit for patients with advanced breast cancer, particularly those with TNBC. As trials continue, it is estimated that more alternative combinations of ICIs, anti-angiogenic drugs, and chemotherapeutic agents will be administrated in patients with advanced breast cancer. Despite the benefits of combination therapies, more attention should be paid to the AEs. Drug toxicity management is relatively more complex and unpredictable, with excessive revascularization rather impairing drug and oxygen delivery the delicate balance between normalization and excessive revascularization requires careful selection of antiangiogenic drug doses and dosing regimen requirements. Moreover, it is critical to find biomarkers to expedite the screening of a patient group that stands to gain more. In clinical practice, current biomarkers are still determined by pathologic analysis of excised tissues, and there is a lack of a clinical tool that can predict early and non-invasively. At the same time, it is the first non-invasive imaging model in China to accurately predict the response of

Table 3 Summary of ongoing clinical trials of ICIs in combination with anti-angiogenesis drug and/or chemotherapies in breast cancer

Clinical trial number	Breast cancer type	Patients	Regimen	Status	Estimated completion date
NCT03797326	TNBC	590	Pembrolizumab plus lenvatinib	Active, not recruiting	2023
NCT04722718	TNBC	34	Sintilimab plus anlotinib plus chemotherapy	Unknown	2023
NCT03387085	TNBC	79	Avelumab plus cancer vaccine plus bevacizumab	Active, not recruiting	2023
NCT05227664	TNBC	80	AK117/AK112	Recruiting	2023
NCT04914390	TNBC	32	Anlotinib plus tislelizumab plus AT	Unknown	2023
NCT03170960	TNBC	1,732	Cabozantinib plus atezolizumab	Active, not recruiting	2024
NCT03202316	Inflammatory breast cancer	35	Atezolizumab plus cobimetinib plus eribulin	Active, not recruiting	2024
NCT03280563	$HR^+/HER2^-$ BC	138	Atezolizumab plus bevacizumab	Active, not recruiting	2024
NCT05244993	TNBC	42	AK105 plus anlotinib plus albumin paclitaxel	Not yet recruiting	2024
NCT04577963	TNBC	112	Tislelizumab plus fruquintinib	Recruiting	2024
NCT04877821	TNBC	31	Sintilimab plus anlotinib plus chemotherapy	Recruiting	2025
NCT03475953	TNBC	747	Regorafenib plus avelumab	Recruiting	2025
NCT05556200	TNBC	58	Camrelizumab plus apatinib	Recruiting	2025
NCT04243616	$HR^+/HER2^-$ BC or TNBC	36	Durvalumab plus eribulin	Recruiting	2025
NCT05386524	TNBC	41	Sintilimab plus bevacizumab biosimilar plus pegylated liposomal doxorubicin	Recruiting	2025
NCT04732598	$HR^+/HER2^-$ BC	280	Bevacizumab plus paclitaxel plus atezolizumab	Active, not recruiting	2025
NCT04739670	TNBC	31	Bevacizumab plus carboplatin, gemcitabine and atezolizumab	Recruiting	2025
NCT05286437	$HR^+/HER2^-$ BC	40	Lenvatinib plus pembrolizumab plus letrozole	Recruiting	2026
NCT06125080	TNBC	78	Utidelone plus tirelizumab and bevacizumab	Recruiting	2026
NCT06140576	TNBC	58	Lenvatinib plus sintilimab plus nab-paclitaxel	Active, not recruiting	2026
NCT06110793	$HR^+/HER2^-$ BC	43	Lenvatinib, pembrolizumab, and fulvestrant	Recruiting	2026
NCT04427293	TNBC	12	Lenvatinib plus pembrolizumab	Recruiting	2026

ICIs, immune checkpoint inhibitors; TNBC, triple-negative breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; BC, breast cancer.

advanced breast cancer to immunotherapy (99). The potential for improved ORR and survival outcomes in advanced breast cancer treatment through the combination of immunotherapy and anti-angiogenic therapies warrants further, large, randomized controlled trials to validate these results.

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Footnote

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