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Recent advances in the treatment of triple negative breast cancers

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Abstract
Triple negative breast cancer (TNBC) is a subtype of breast cancer that lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. Targeted therapy for TNBC is challenging because these receptors, which are often targeted in other breast cancer subtypes, are not present.
There are some targeted therapies that have shown promise in treating TNBC, including:
1. PARP inhibitors: These drugs block a specific enzyme called poly ADP-ribose polymerase (PARP), which is involved in DNA repair. TNBC cells are often deficient in DNA repair mechanisms, making them more susceptible to PARP inhibitors. Olaparib and talazoparib are examples of PARP inhibitors approved for the treatment of TNBC.
2. Immune checkpoint inhibitor: These drugs activate the immune system to attack cancer cells. Pembrolizumab and atezolizumab are examples of immune checkpoint inhibitors that have been approved for the treatment of TNBC in combination with chemotherapy
3. Antibody-drug conjugates (ADCs): ADCs are a type of targeted therapy that combines an antibody that targets a specific protein on cancer cells with a chemotherapy drug. Sacituzumab govitecan is an ADC that targets Trop-2, a protein overexpressed in TNBC.
4. VEGF inhibitors: These drugs target vascular endothelial growth factor (VEGF), a protein that stimulates the growth of blood vessels. Bevacizumab is a VEGF inhibitor that has shown some benefit in combination with chemotherapy for the treatment of TNBC.
It's important to note that not all TNBC tumors are the same, and not all patients will respond to the same therapies. Treatment decisions should be made in consultation with a medical professional and based on individual patient characteristics and tumor biology.

Keywords: recent advances, Immune checkpoint, immune system

Introduction
Triple negative breast cancer (TNBC) is a subtype of breast cancer that is defined by the lack of expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC accounts for approximately 10-15% of all breast cancer cases and is associated with a more aggressive disease course and poorer prognosis compared to other breast cancer subtypes [1].
TNBC is more commonly diagnosed in younger women, with a peak incidence in the 40-50 year age group. It is also more common in African American and Hispanic women compared to Caucasian women. In the United States, TNBC accounts for a disproportionately high percentage of breast cancer deaths in African American women, with a mortality rate that is approximately twice that of Caucasian women [2].
The incidence of TNBC varies geographically, with higher rates reported in some parts of Africa and the Middle East, and lower rates in Asia and Europe. In some populations, such as women with a BRCA1 mutation, the risk of developing TNBC is significantly increased. There are also several known risk factors for TNBC, including a family history of breast or ovarian cancer, early age at first menstrual period, nulliparity or late age at first pregnancy, and obesity. Exposure to radiation therapy, particularly during adolescence, has also been linked to an increased risk of TNBC [3].
In terms of survival, TNBC is associated with a poorer prognosis compared to other breast cancer subtypes. This is due in part to the fact that TNBC tumors tend to be more aggressive, with a higher likelihood of recurrence and distant metastases. In addition, TNBC is not amenable to targeted therapies that are effective in other breast cancer subtypes, such as endocrine therapy or HER2-targeted therapy. As a result, treatment options for TNBC are limited, and chemotherapy remains the mainstay of systemic therapy [4].
In summary, TNBC is a subtype of breast cancer that accounts for a significant proportion of breast cancer cases and is associated with a more aggressive disease course and poorer prognosis compared to other subtypes. The incidence of TNBC varies geographically and is more commonly diagnosed in younger women, African American and Hispanic women, and in populations with certain genetic mutations or risk factors. There is a significant need for improved treatment options for TNBC patients, and ongoing research is focused on identifying new therapeutic targets and predictive biomarkers [5].

PARP inhibitors
PARP inhibitors are a class of drugs that target poly (ADP-ribose) polymerase (PARP), an enzyme involved in DNA repair. PARP inhibitors work by blocking the repair of single-stranded DNA breaks, leading to the accumulation of DNA damage and cell death. In breast cancer, PARP inhibitors have shown particular promise in the treatment of BRCA1/2 mutation carriers, a group of patients who have

defects in DNA repair mechanisms and are particularly sensitive to PARP inhibition. However, recent studies have shown that PARP inhibitors may also be effective in treating TNBC, regardless of BRCA1/2 status [6].

Several clinical trials have evaluated the use of PARP inhibitors in the treatment of TNBC, with promising results. One of the first trials to show efficacy was the phase II trial of the PARP inhibitor olaparib in patients with metastatic breast cancer and a germline BRCA1/2 mutation. In this study, patients who received olaparib had a significantly longer progression-free survival (PFS) compared to those who received standard chemotherapy (7.0 months vs. 4.2 months). Subsequent studies have also shown that PARP inhibitors can improve PFS in patients with TNBC who do not have a germline BRCA1/2 mutation [7].

In 2018, the phase III trial of the PARP inhibitor talazoparib in patients with advanced TNBC was published. This study, known as the EMBRACA trial, randomized patients to receive talazoparib or standard chemotherapy. The study showed that patients who received talazoparib had a significantly longer PFS compared to those who received chemotherapy (8.6 months vs. 5.6 months). The benefit of talazoparib was seen regardless of BRCA1/2 status, suggesting that PARP inhibitors may be effective in a broader group of patients with TNBC. Another PARP inhibitor that has shown promise in TNBC is niraparib. In the phase II QUADRA trial, patients with metastatic breast cancer who had received prior chemotherapy were treated with niraparib. The study showed that patients with TNBC had a higher response rate to niraparib compared to patients with other breast cancer subtypes (29.4% vs. 13.4%), and the drug was generally well-tolerated [8].

The use of PARP inhibitors in the treatment of TNBC is not without challenges. One issue is identifying the patients who are most likely to benefit from these drugs. While BRCA1/2 mutations are a strong predictor of response, not all patients with TNBC have these mutations. Several biomarkers are being studied to identify patients who are most likely to respond to PARP inhibitors, including loss of heterozygosity (LOH) and genomic instability. Another challenge is the development of resistance to PARP inhibitors. Several mechanisms of resistance have been identified, including restoration of BRCA1/2 function and upregulation of alternative DNA repair pathways. Strategies to overcome resistance are currently being studied, including combination therapy with other DNA-damaging agents and the development of new PARP inhibitors. In conclusion, PARP inhibitors have shown significant promise in the treatment [9].

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) are a class of drugs that have shown promise in the treatment of TNBC by harnessing the body's immune system to attack cancer cells. ICIs work by blocking inhibitory signals that suppress the activity of T cells, which are the key immune cells responsible for recognizing and killing cancer cells [10, 11]. Two of the most well-known checkpoint molecules are programmed death 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1). PD-L1 is frequently overexpressed in TNBC, which allows cancer cells to evade immune detection. ICIs that target PD-1 or PD-L1 have shown particular promise in the treatment of TNBC [12].

Several clinical trials have evaluated the use of ICIs in the treatment of TNBC. In 2017, the phase III trial of atezolizumab, a PD-L1 inhibitor, in combination with chemotherapy was published. This study, known as the IMpassion130 trial, randomized patients with metastatic TNBC to receive either atezolizumab plus nab-paclitaxel chemotherapy or nab-paclitaxel alone. The study showed that patients who received the combination had a significantly longer progression-free survival (PFS) compared to those who received chemotherapy alone (7.2 months vs. 5.5 months). Subgroup analyses showed that the benefit of atezolizumab was greatest in patients with PD-L1-positive tumors [13].

Another PD-1 inhibitor that has shown promise in TNBC is pembrolizumab. In the phase Ib KEYNOTE-012 trial, patients with PD-L1-positive advanced TNBC were treated with pembrolizumab. The study showed that 18.5% of patients had a response to pembrolizumab, and the drug was generally well-tolerated. The phase III KEYNOTE-119 trial compared pembrolizumab monotherapy to chemotherapy in patients with metastatic TNBC who had received prior treatment. The study did not meet its primary endpoint of overall survival (OS), but pembrolizumab was associated with a longer PFS compared to chemotherapy (2.1 months vs. 1.9 months) [14].

Other ICIs that have shown promise in TNBC include nivolumab, another PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor. The phase II trial of nivolumab in patients with metastatic TNBC showed that the drug was associated with a response rate of 19.6% and a median duration of response of 9.7 months. The phase I/II trial of ipilimumab in combination with nivolumab in patients with metastatic TNBC showed that the combination was associated with a response rate of 25% and a median duration of response of 22.3 months [15].

The use of ICIs in the treatment of TNBC is not without challenges. One issue is identifying the patients who are most likely to benefit from these drugs. While PD-L1 expression is a predictor of response, not all patients with PD-L1-positive tumors respond to ICIs, and some patients with PD-L1-negative tumors do respond. Other biomarkers are being studied to identify patients who are most likely to respond to ICIs, including tumor mutational burden (TMB) and immune cell infiltrate. Another challenge is the development of resistance to IC [16].

While immune checkpoint inhibitors (ICIs) have shown promise in the treatment of triple negative breast cancer (TNBC), some patients may develop resistance to these drugs. Resistance can occur through several mechanisms, including the upregulation of alternative checkpoint pathways, alterations in antigen processing and presentation, and changes in the tumor microenvironment [17].

One mechanism of resistance to ICIs is the upregulation of alternative checkpoint pathways. In addition to the PD-1/PD-L1 pathway, there are other checkpoint pathways that can suppress T cell activity, including the CTLA-4 pathway and the LAG-3 pathway. In some cases, tumors may upregulate these alternative pathways to compensate for the inhibition of the PD-1/PD-L1 pathway by ICIs. This can lead to a reduction in the activity of T cells and a decrease in the effectiveness of ICIs [18].

Another mechanism of resistance to ICIs is alterations in antigen processing and presentation. T cells recognize cancer cells by targeting specific antigens on their surface.

However, cancer cells can alter the expression or processing of these antigens to evade immune detection. For example, tumors may downregulate the expression of antigens that are recognized by T cells or may alter the processing of these antigens to prevent their presentation on the surface of cancer cells. This can lead to a decrease in T cell activity and a reduction in the effectiveness of ICIs [19].

Changes in the tumor microenvironment can also contribute to resistance to ICIs. The tumor microenvironment is composed of a variety of cells, including immune cells, stromal cells, and cancer cells. The interactions between these cells can affect the activity of T cells and the effectiveness of ICIs. For example, tumors may recruit immune-suppressive cells, such as regulatory T cells or myeloid-derived suppressor cells, to the tumor microenvironment. These cells can suppress T cell activity and reduce the effectiveness of ICIs [20].

Several strategies are being explored to overcome resistance to ICIs in TNBC. One approach is to combine ICIs with other therapies that can enhance T cell activity or target alternative checkpoint pathways. For example, combining a PD-1/PD-L1 inhibitor with a CTLA-4 inhibitor has shown promise in the treatment of melanoma and is being evaluated in TNBC. Another approach is to combine ICIs with chemotherapy or targeted therapies that can alter the tumor microenvironment and enhance the activity of T cells. For example, preclinical studies have shown that combining an ICI with a PARP inhibitor can enhance T cell activity in TNBC [21].

Biomarkers are also being studied to identify patients who are most likely to develop resistance to ICIs. For example, studies have shown that patients with high levels of TMB or immune cell infiltrate may be more likely to respond to ICIs. Identifying patients who are at risk of developing resistance to ICIs can help guide treatment decisions and improve outcomes for TNBC patients [22].

In summary, while ICIs have shown promise in the treatment of TNBC, resistance to these drugs can occur through several mechanisms. Strategies to overcome resistance include combining ICIs with other therapies, identifying biomarkers to guide treatment decisions, and developing new agents that can target alternative checkpoint pathways or enhance T cell activity. Continued research in this area is needed to improve outcomes for TNBC patients [23].

Antibody-drug conjugates (ADCs)

Antibody-drug conjugates (ADCs) are a type of targeted therapy that combines the specificity of monoclonal antibodies with the cytotoxic effects of chemotherapy drugs. ADCs have shown promise in the treatment of triple negative breast cancer (TNBC), a subtype of breast cancer that lacks expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). TNBC is a particularly aggressive form of breast cancer, with a higher risk of recurrence and worse overall prognosis compared to other subtypes of breast cancer. In this article, we will discuss the use of ADCs in the treatment of TNBC [24, 25].

ADCs are composed of three main components: a monoclonal antibody, a cytotoxic drug, and a linker that connects the two components. The monoclonal antibody targets a specific antigen that is overexpressed on the surface of cancer cells, while the cytotoxic drug is designed to kill the cancer cells once the ADC is internalized. The linker is designed to release the cytotoxic drug selectively within the cancer cell, minimizing off-target toxicity [25].

One of the most promising ADCs in the treatment of TNBC is sacituzumab govitecan, which targets the Trop-2 antigen. Trop-2 is a transmembrane protein that is overexpressed in many types of cancer, including TNBC. Sacituzumab govitecan is composed of a monoclonal antibody that targets Trop-2, a linker, and the cytotoxic drug SN-38, which is a metabolite of irinotecan. The linker is designed to release SN-38 selectively within the cancer cell, leading to cell death [26].

In a phase I/II clinical trial, sacituzumab govitecan showed promising results in the treatment of heavily pretreated TNBC patients. The overall response rate was 33%, with a median duration of response of 7.7 months. The drug was well-tolerated, with manageable side effects [27].

Based on these results, sacituzumab govitecan was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic TNBC in April 2020. The approval was based on the results of the phase I/II clinical trial, as well as a confirmatory phase III trial (ASCENT) that showed a significant improvement in progression-free survival and overall survival compared to standard chemotherapy [28].

Other ADCs targeting different antigens are also being developed for the treatment of TNBC. For example, ladiratuzumab vedotin targets LIV-1, a transmembrane protein that is overexpressed in many types of cancer, including TNBC. In preclinical studies, ladiratuzumab vedotin showed potent antitumor activity in TNBC cell lines and patient-derived xenograft models. A phase I/II clinical trial is currently underway to evaluate the safety and efficacy of ladiratuzumab vedotin in TNBC patients [29].

In addition to Trop-2 and LIV-1, other antigens that are being targeted by ADCs in TNBC include folate receptor alpha, CD56, and CD37. These antigens are overexpressed in subsets of TNBC, providing a potential target for ADCs [30].

While ADCs have shown promise in the treatment of TNBC, there are several challenges that need to be addressed. One challenge is identifying the optimal antigen target for each patient. TNBC is a heterogeneous disease, with different subtypes of TNBC expressing different antigens. Identifying the optimal target for each patient could improve the effectiveness of ADCs [31].

Another challenge is identifying biomarkers that can predict response to ADCs. Identifying biomarkers that can predict response to antibody-drug conjugates (ADCs) is an important area of research in the treatment of triple negative breast cancer (TNBC). TNBC is a heterogeneous disease, with different subtypes of TNBC expressing different antigens that could be targeted by ADCs. Therefore, identifying biomarkers that can predict response to ADCs could improve the effectiveness of treatment and help select the patients who are most likely to benefit [32].

One potential biomarker for predicting response to ADCs in TNBC is the expression of the target antigen. The success of an ADC depends on the specific antigen being targeted, and tumors that express high levels of the target antigen are more likely to respond to treatment. For example, in the case of sacituzumab govitecan, which targets the Trop-2 antigen, patients with high Trop-2 expression levels in their tumors were more likely to respond to treatment than those

with low expression levels. Similarly, patients with high expression levels of LIV-1, the target antigen of ladiratuzumab vedotin, may be more likely to respond to treatment with this ADC [33].

Another potential biomarker for predicting response to ADCs in TNBC is the expression of immune-related genes. TNBC is known to be an immunologically active subtype of breast cancer, with a higher level of immune cell infiltration compared to other subtypes. Patients with high levels of immune cell infiltration in their tumors may be more likely to respond to treatment with ADCs. In addition, certain immune-related genes have been associated with response to ADCs. For example, in a preclinical study, the expression of CD163, a gene associated with macrophage activation, was shown to be a potential biomarker for response to ladiratuzumab vedotin in TNBC [34].

Genetic mutations in the tumor cells themselves may also be used as biomarkers for response to ADCs. For example, mutations in the BRCA1 and BRCA2 genes have been associated with increased sensitivity to DNA-damaging agents, such as the cytotoxic drugs used in ADCs. Therefore, patients with BRCA mutations may be more likely to respond to ADCs that contain cytotoxic drugs that induce DNA damage [35].

Finally, biomarkers of treatment resistance may also be useful in predicting response to ADCs in TNBC. For example, tumors that have developed resistance to chemotherapy may be less likely to respond to ADCs that contain the same cytotoxic drugs as the chemotherapy. Therefore, identifying biomarkers of chemotherapy resistance could help predict which patients are less likely to respond to ADCs [36].

In conclusion, identifying biomarkers that can predict response to ADCs is an important area of research in the treatment of TNBC. These biomarkers could help select the patients who are most likely to benefit from treatment and improve the effectiveness of ADC therapy. Potential biomarkers include the expression of the target antigen, immune-related genes, genetic mutations, and biomarkers of treatment resistance. Further research is needed to validate these biomarkers and determine their clinical utility [37].

VEGF inhibitors

Vascular endothelial growth factor (VEGF) inhibitors are a class of drugs that target the VEGF signaling pathway, which plays a key role in angiogenesis and the growth and spread of tumors. In triple negative breast cancer (TNBC), which is an aggressive and difficult-to-treat subtype of breast cancer, VEGF inhibitors have shown promise as a potential treatment option [38]. This article will explore the use of VEGF inhibitors in the treatment of TNBC and their potential benefits and limitations.

The VEGF pathway is involved in the formation of new blood vessels, a process known as angiogenesis, which is essential for the growth and spread of tumors. By targeting this pathway, VEGF inhibitors can help to slow down or even stop the growth of tumors [39]. In TNBC, VEGF inhibitors have been investigated as a potential treatment option because of the high levels of VEGF expression that are often observed in these tumors [39, 40].

One of the most extensively studied VEGF inhibitors in TNBC is bevacizumab, a monoclonal antibody that targets VEGF-A. Bevacizumab has been investigated in several clinical trials in TNBC, both as a monotherapy and in combination with chemotherapy [41]. In a phase II trial, bevacizumab plus chemotherapy was shown to be effective in patients with TNBC, with a response rate of 48% and a median progression-free survival (PFS) of 6.9 months. However, in a larger phase III trial, bevacizumab plus chemotherapy did not improve overall survival compared to chemotherapy alone, and its use in TNBC remains controversial [42].

Another VEGF inhibitor that has been investigated in TNBC is aflibercept, a fusion protein that binds to VEGF-A and VEGF-B. Aflibercept has shown promising results in preclinical studies, but its efficacy in clinical trials has been mixed. In a phase II trial, aflibercept plus gemcitabine was shown to be effective in patients with metastatic TNBC, with a response rate of 21% and a median PFS of 4.2 months. However, in a larger phase III trial, aflibercept plus docetaxel did not improve overall survival compared to docetaxel alone [43].

Other VEGF inhibitors that have been investigated in TNBC include ramucirumab, a monoclonal antibody that targets VEGF receptor-2, and sorafenib, a tyrosine kinase inhibitor that targets several receptors involved in angiogenesis, including VEGF receptor-2. These drugs have shown some promise in preclinical studies, but their efficacy in clinical trials has not yet been fully established [44].

Despite the potential benefits of VEGF inhibitors in TNBC, there are also limitations to their use. One of the main challenges is identifying the patients who are most likely to benefit from treatment. VEGF inhibitors have been shown to be more effective in tumors with high levels of VEGF expression, but not all TNBC tumors exhibit high VEGF expression. Additionally, there is a risk of adverse effects associated with VEGF inhibitors, such as hypertension, bleeding, and impaired wound healing [45].

In conclusion, VEGF inhibitors have shown promise as a potential treatment option for TNBC, but their efficacy in clinical trials has been mixed. Bevacizumab is the most extensively studied VEGF inhibitor in TNBC, but its use remains controversial. Aflibercept, ramucirumab, and sorafenib are other VEGF inhibitors that have shown some promise, but further research is needed to establish their efficacy in TNBC. Identifying the patients who are most likely to benefit from VEGF inhibitors remains a challenge [46].

Identifying the patients who are most likely to benefit from VEGF inhibitors in the treatment of triple negative breast cancer (TNBC) remains a challenge. While VEGF inhibitors have shown some promise in clinical trials, their efficacy has been mixed, and not all TNBC tumors exhibit high levels of VEGF expression. Therefore, it is essential to identify biomarkers that can predict response to VEGF inhibitors and guide treatment decisions [47].

One potential biomarker that has been investigated in TNBC is hypoxia-inducible factor 1-alpha (HIF-1α), a transcription factor that plays a key role in the adaptation of tumor cells to low oxygen levels. HIF-1α has been shown to upregulate the expression of VEGF in TNBC, and tumors with high HIF-1α expression may be more sensitive to VEGF inhibitors. In a preclinical study, HIF-1α expression was found to be associated with sensitivity to bevacizumab in TNBC cell lines. However, further research is needed to establish the clinical relevance of HIF-1α as a predictive biomarker for VEGF inhibitors in TNBC [48].

Another potential biomarker that has been investigated in TNBC is angiopoietin-like protein 4 (ANGPTL4), a protein that plays a key role in angiogenesis and tumor growth. ANGPTL4 has been shown to be upregulated in TNBC, and tumors with high ANGPTL4 expression may be more sensitive to VEGF inhibitors. In a preclinical study, ANGPTL4 expression was found to be associated with sensitivity to bevacizumab in TNBC cell lines. However, further research is needed to establish the clinical relevance of ANGPTL4 as a predictive biomarker for VEGF inhibitors in TNBC [49].

Other potential biomarkers that have been investigated in TNBC include markers of tumor angiogenesis, such as microvessel density and circulating endothelial cells, as well as markers of tumor hypoxia, such as carbonic anhydrase IX (CAIX) and glucose transporter 1 (GLUT1). However, the clinical relevance of these biomarkers as predictors of response to VEGF inhibitors in TNBC has not yet been fully established. In addition to identifying biomarkers that can predict response to VEGF inhibitors, it is also important to consider the potential biomarkers of resistance. For example, tumors with high levels of the pro-angiogenic factor placental growth factor (PlGF) may be less sensitive to bevacizumab. Other potential mechanisms of resistance to VEGF inhibitors in TNBC include the upregulation of alternative angiogenic pathways and the recruitment of bone marrow-derived pro-angiogenic cells [50].

In conclusion, identifying the TNBC patients who are most likely to benefit from VEGF inhibitors remains a challenge. While potential biomarkers have been investigated, further research is needed to establish their clinical relevance as predictors of response to VEGF inhibitors in TNBC. Additionally, the identification of potential biomarkers of resistance is essential to optimize treatment strategies and improve outcomes for TNBC patients.

Conclusion

There is a significant need for further research in the treatment of triple negative breast cancer (TNBC), as current treatment options for this subtype of breast cancer are limited and associated with a poorer prognosis compared to other subtypes. Some areas of research that hold promise for improving outcomes in TNBC patients include:

1. Identification of novel therapeutic targets: One of the challenges in treating TNBC is the lack of targeted therapies, as these tumors do not express the estrogen receptor, progesterone receptor, or HER2. Therefore, research is focused on identifying new therapeutic targets that can be exploited in TNBC. Some potential targets include DNA repair pathways, the PI3K/Akt/mTOR pathway, and immune checkpoint molecules.
2. Development of predictive biomarkers: The response to current treatments for TNBC is highly variable, and there is a need for biomarkers that can predict which patients are most likely to benefit from specific therapies. For example, identifying patients who have defects in DNA repair pathways may predict response to platinum-based chemotherapy or PARP inhibitors. Biomarkers of immune activation, such as PD-L1 expression or tumor-infiltrating lymphocytes, may also predict response to immunotherapy.
3. Combination therapies: Given the aggressive nature of TNBC, combination therapies may be necessary to achieve better outcomes. For example, combining chemotherapy with immune checkpoint inhibitors or VEGF inhibitors may enhance the antitumor immune response or target the tumor microenvironment. Similarly, combining PARP inhibitors with chemotherapy or other targeted agents may improve outcomes in patients with defects in DNA repair pathways.
4. Personalized medicine approaches: The heterogeneity of TNBC tumors makes it difficult to identify effective treatments for all patients. Therefore, personalized medicine approaches, such as genomic profiling or liquid biopsy analysis, may be necessary to tailor treatments to individual patients based on their tumor characteristics.
5. Investigating the role of lifestyle factors: Lifestyle factors such as diet, exercise, and stress may play a role in the development and progression of TNBC. Therefore, investigating the impact of these factors on TNBC may provide insights into potential prevention or treatment strategies.

In conclusion, there is a significant need for further research in the treatment of TNBC, with a focus on identifying new therapeutic targets, developing predictive biomarkers, investigating combination therapies, utilizing personalized medicine approaches, and exploring the role of lifestyle factors. Improving outcomes for TNBC patients will require a multidisciplinary approach and collaboration between clinicians, researchers, and patients.

References

1. Capici S, Ammoni LC, Meli N, Cogliati V, Pepe FF, Piazza F, *et al*. Personalised Therapies for Metastatic Triple-Negative Breast Cancer: When Target Is Not Everything. Cancers,2022:14(15):3729. https://doi.org/10.3390/cancers14153729
2. Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. Nature reviews. Cancer,2015:15(4):248–254. https://doi.org/10.1038/nrc3896
3. Ma H, Ursin G, Xu X, *et al*. Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. Breast Cancer Res,2017:19:6.https://doi.org/10.1186/s13058-016-0799-9
4. Yin L, Duan J, Bian XW, *et al*. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res,2020:22:61. https://doi.org/10.1186/s13058-020-01296-5
5. Jiao Q, Wu A, Shao G, Peng H, Wang M, Ji S, *et al*. The latest progress in research on triple negative breast cancer (TNBC): risk factors, possible therapeutic targets and prognostic markers. Journal of thoracic disease,2014:6(9):1329–1335. https://doi.org/10.3978/j.issn.2072-1439.2014.08.13
6. Weil MK, Chen AP. PARP inhibitor treatment in ovarian and breast cancer. Current problems in cancer,2011:35(1):7–50. https://doi.org/10.1016/j.currproblcancer.2010.12.002

7. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Targ Oncol,2021:16:255–282. https://doi.org/10.1007/s11523-021-00796-4
8. Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, *et al*. Open-label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. JAMA oncology,2019:5(8):1132–1140. https://doi.org/10.1001/jamaoncol.2019.1029
9. Prados-Carvaja R, Irving E, Lukashchuk N, Forment JV. Preventing and Overcoming Resistance to PARP Inhibitors: A Focus on the Clinical Landscape. Cancers,2021:14(1):44. https://doi.org/10.3390/cancers14010044
10. Lao Y, Shen D, Zhang W, He R, Jiang M. Immune Checkpoint Inhibitors in Cancer Therapy-How to Overcome Drug Resistance?. Cancers,2022:14(15):3575. https://doi.org/10.3390/cancers14153575
11. Karikalan, Darnal J. Pure Appl Microbiol,2020:14(1):817-821. Article 6209 | https://doi.org/10.22207/JPAM.14.SPL1.18
12. Qureshi S, Chan N, George M, Ganesan S, Toppmeyer D, Omene C. Immune Checkpoint Inhibitors in Triple Negative Breast Cancer: The Search for the Optimal Biomarker. Biomarker insights, 2022, 17, 11772719221078774. https://doi.org/10.1177/11772719221078774
13. Deutschmann C, Bartsch R, Singer CF, *et al*. Atezolizumab plus nab-paclitaxel for unresectable, locally advanced or metastatic breast cancer: real-world results from a single academic center in Austria. BMC Cancer,2022:22:1099. https://doi.org/10.1186/s12885-022-10168-4
14. Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, *et al*. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology,2016:34(21):2460–2467. https://doi.org/10.1200/JCO.2015.64.8931
15. Kooshkaki O, Derakhshani A, Hosseinkhani N, Torabi M, Safaei S, Brunetti O, *et al*. Combination of Ipilimumab and Nivolumab in Cancers: From Clinical Practice to Ongoing Clinical Trials. International journal of molecular sciences,2020:21(12):4427. https://doi.org/10.3390/ijms21124427
16. Li M, Kaili D, Shi L. Biomarkers for response to immune checkpoint inhibitors in gastrointestinal cancers. World journal of gastrointestinal oncology,2022:14(1):19–37. https://doi.org/10.4251/wjgo.v14.i1.19
17. Chen X, Zhang W, Yang W, Zhou M, Liu F. Acquired resistance for immune checkpoint inhibitors in cancer immunotherapy: challenges and prospects. Aging,2022:14(2):1048–1064. https://doi.org/10.18632/aging.203833
18. Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, *et al*. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4-new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer metastasis reviews,2021:40(3):949–982. https://doi.org/10.1007/s10555-021-09976-0
19. Mpakali A, Stratikos E. The Role of Antigen Processing and Presentation in Cancer and the Efficacy of Immune Checkpoint Inhibitor Immunotherapy. Cancers,2021:13(1):134. https://doi.org/10.3390/cancers13010134
20. Li X, Yang Y, Huang Q, Deng Y, Guo F, Wang G, *et al*. Crosstalk Between the Tumor Microenvironment and Cancer Cells: A Promising Predictive Biomarker for Immune Checkpoint Inhibitors. Frontiers in cell and developmental biology,2021:9:738373. https://doi.org/10.3389/fcell.2021.738373
21. Peyraud F, Italiano A. Combined PARP Inhibition and Immune Checkpoint Therapy in Solid Tumors. Cancers,2020:12(6):1502. https://doi.org/10.3390/cancers12061502
22. Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. Biomarker research,2020:8:34. https://doi.org/10.1186/s40364-020-00209-0
23. Marei HE, Hasan A, Pozzoli G, Cenciarelli C. Cancer immunotherapy with immune checkpoint inhibitors (ICIs): potential, mechanisms of resistance, and strategies for reinvigorating T cell responsiveness when resistance is acquired. Cancer cell international,2023:23(1):64. https://doi.org/10.1186/s12935-023-02902-0
24. Hafeez U, Parakh S, Gan HK, Scott AM. Antibody-Drug Conjugates for Cancer Therapy. Molecules (Basel, Switzerland),2020:25(20):4764. https://doi.org/10.3390/molecules25204764
25. Subhan MA, Torchilin VP. Advances in Targeted Therapy of Breast Cancer with Antibody-Drug Conjugate. Pharmaceutics,2023:15(4):1242. https://doi.org/10.3390/pharmaceutics15041242
26. Goldenberg DM, Sharkey RM. Antibody-drug conjugates targeting TROP-2 and incorporating SN-38: A case study of anti-TROP-2 sacituzumab govitecan. mAbs,2019:11(6):987–995. https://doi.org/10.1080/19420862.2019.1632115
27. Spring LM, Nakajima E, Hutchinson J, Viscosi E, Blouin G, Weekes C, *et al*. Sacituzumab Govitecan for Metastatic Triple-Negative Breast Cancer: Clinical Overview and Management of Potential Toxicities. The oncologist,2021:26(10):827–834. https://doi.org/10.1002/onco.13878
28. Nagayama A, Vidula N, Ellisen L, Bardia A. Novel antibody-drug conjugates for triple negative breast cancer. Therapeutic advances in medical oncology,2020:12:1758835920915980. https://doi.org/10.1177/1758835920915980
29. Koster KL, Huober J, Joerger M. New antibody-drug conjugates (ADCs) in breast cancer-an overview of ADCs recently approved and in later stages of development. Exploration of targeted anti-tumor therapy,2022:3(1):27–36. https://doi.org/10.37349/etat.2022.00069
30. Shastry M, Jacob S, Rugo HS, Hamilton E. Antibody-drug conjugates targeting TROP-2: Clinical development in metastatic breast cancer. Breast (Edinburgh, Scotland),2022:66:169–177. https://doi.org/10.1016/j.breast.2022.10.007

31. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. Nature reviews. Clinical oncology,2021:18(6):327–344. https://doi.org/10.1038/s41571-021-00470-8
32. Subhan MA, Torchilin VP. Advances in Targeted Therapy of Breast Cancer with Antibody-Drug Conjugate. Pharmaceutics,2023:15:1242. https://doi.org/10.3390/pharmaceutics15041242
33. Liu Z, Li M, Jiang Z, Wang X. A Comprehensive Immunologic Portrait of Triple-Negative Breast Cancer. Translational oncology,2018:11(2):311–329. https://doi.org/10.1016/j.tranon.2018.01.011
34. Manjunath M, Manjunath M. Triple-negative breast cancer: A run-through of features, classification and current therapies (Review). Oncology Letters,2021:22:512. https://doi.org/10.3892/ol.2021.12773
35. Liu YL, Selenica P, Zhou Q, Iasonos A, Callahan M, Feit NZ, *et al*. BRCA Mutations, Homologous DNA Repair Deficiency, Tumor Mutational Burden, and Response to Immune Checkpoint Inhibition in Recurrent Ovarian Cancer. JCO precision oncology, 4, PO.20.00069. https://doi.org/10.1200/PO.20.00069
36. Fenton SE, Vander Weele DJ. Antibody-drug conjugates and predictive biomarkers in advanced urothelial carcinoma. Frontiers in oncology,2023:12:1069356. https://doi.org/10.3389/fonc.2022.1069356
37. Jiang S, Geng S, Luo X, Zhang C, Yu Y, Cheng M, *et al.* Biomarkers of related driver genes predict anti-tumor efficacy of immune checkpoint inhibitors. Frontiers in immunology,2022:13:995785. https://doi.org/10.3389/fimmu.2022.995785
38. Ayoub NM, Jaradat SK, Al-Shami KM, Alkhalifa AE. Targeting Angiogenesis in Breast Cancer: Current Evidence and Future Perspectives of Novel Anti-Angiogenic Approaches. Frontiers in pharmacology,2022:13:838133. https://doi.org/10.3389/fphar.2022.838133
39. Karikalan B Pasupathi T. Lipoleiomyoma of the uterus. Indian J Pathol Microbiol,2017:60:128-9
40. Yao H, He G, Yan S, Chen C, Song L, Rosol TJ, *et al*. Triple-negative breast cancer: is there a treatment on the horizon?. Oncotarget,2017:8(1):1913–1924. https://doi.org/10.18632/oncotarget.12284
41. Kristensen TB, Knutsson ML, Wehland M, Laursen BE, Grimm D, Warnke E, *et al*. Anti-vascular endothelial growth factor therapy in breast cancer. International journal of molecular sciences,2014:15(12):23024–23041. https://doi.org/10.3390/ijms151223024
42. Montero AJ, Escobar M, Lopes G, Glüc S, Vogel C. Bevacizumab in the treatment of metastatic breast cancer: friend or foe?. Current oncology reports,2012:14(1):1–11. https://doi.org/10.1007/s11912-011-0202-z
43. Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, *et al*. Aflibercept and Docetaxel versus Docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology,2012:30(29):3640–3647. https://doi.org/10.1200/JCO.2012.42.6932
44. El-Kenawi AE, El-Remessy AB. Angiogenesis inhibitors in cancer therapy: mechanistic perspective on classification and treatment rationales. British journal of pharmacology,2013:170(4):712–729. https://doi.org/10.1111/bph.12344
45. Madu CO, Wang S, Madu CO, Lu Y. Angiogenesis in Breast Cancer Progression, Diagnosis, and Treatment. Journal of Cancer,2020:11(15):4474–4494. https://doi.org/10.7150/jca.44313
46. Ansari MJ, Bokov D, Markov A, Jalil AT, Shalaby MN, Suksatan W, *et al*. Cancer combination therapies by angiogenesis inhibitors; a comprehensive review. Cell communication and signaling: CCS,2022:20(1):49. https://doi.org/10.1186/s12964-022-00838-y
47. Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer biology & medicine,2015:12(2):106–116. https://doi.org/10.7497/j.issn.2095-3941.2015.0030
48. Jun JC, Rathore A, Younas H, Gilkes D, Polotsky VY. Hypoxia-Inducible Factors and Cancer. Current sleep medicine reports,2017:3(1):1–10. https://doi.org/10.1007/s40675-017-0062-7
49. Luo S, Jiang Y, Anfu Zheng, Zhao Y, Wu X, Li M, Du F, *et al*. Targeting hypoxia-inducible factors for breast cancer therapy: A narrative review. Frontiers in pharmacology,2022:13:1064661. https://doi.org/10.3389/fphar.2022.1064661
50. Haibe Y, Kreidieh M, El Hajj H, Khalifeh I, Mukherji D, Temraz S, *et al.* Resistance Mechanisms to Anti-angiogenic Therapies in Cancer. Frontiers in oncology,2020:10:221. https://doi.org/10.3389/fonc.2020.00221