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Review Article

Triple-negative breast cancer: unmet needs and emerging targeted and immunotherapeutic approaches

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ABSTRACT

Triple-negative breast cancer (TNBC) is a tough type of breast cancer. It does not have estrogen, progesterone, or HER2 receptors. This makes it hard to treat because common hormone and HER2 therapies do not work, often leading to poor results. To look at new treatments for TNBC, focusing on new molecular targets, antibody-drug conjugates (ADCs), immunotherapy, resistance issues, and future personalized medicine. A detailed review was done, combining information from molecular biology, clinical trials, immuno-oncology, and new technologies like artificial intelligence and liquid biopsy to assess progress in TNBC treatment. TNBC is very diverse at the molecular level, involving pathways like PI3K/AKT, TP53 mutations, and DNA repair problems. New treatments include ADCs like sacituzumab govitecan targeting TROP-2, and immune checkpoint inhibitors targeting PD-1/PD-L1 pathways, which have helped some patients live longer. Combining ADCs and immunotherapy shows better results by causing cancer cells to die in a way that triggers the immune system. However, resistance to treatment is still a big problem due to tumor diversity, loss of antigens, poor drug delivery, and resistance to the drug's effects. Advances in liquid biopsy, ctDNA monitoring, and AI-driven models are helping create real-time, personalized treatment plans. TNBC treatment is moving from standard chemotherapy to more precise approaches using targeted therapies, immunotherapy, and flexible treatment plans. Despite progress, overcoming resistance and improving long-term survival need more research into biomarkers, combination therapies, and personalized medicine.

Keywords: Triple-negative breast cancer, Antibody drug conjugates, Molecular targets, Tumor heterogeneity, Drug resistance, Liquid biopsy

INTRODUCTION

Triple-negative breast cancer (TNBC) is a biologically aggressive and clinically difficult subtype of breast carcinoma, identified by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) expression during immunohistochemical analysis.[1,5] This receptor-negative characteristic sets TNBC apart from other molecular subtypes of breast cancer and plays a crucial role in therapeutic decision-making. Due to the absence of hormonal receptors and HER2 amplification, TNBC does not respond to endocrine therapies like tamoxifen or aromatase inhibitors, nor to HER2-targeted treatments such as trastuzumab. As a result, systemic chemotherapy has traditionally been the primary treatment option.[5,7] The lack of clearly defined molecular targets has led to poorer clinical outcomes and has spurred extensive research into alternative therapeutic approaches. Worldwide, TNBC accounts for about 10-20% of all breast cancer cases, although its prevalence varies based on ethnicity, geographic location, and population genetics.[1,2] Epidemiological studies indicate that TNBC is more commonly diagnosed in younger women, especially those under 40, and is disproportionately found among

individuals with hereditary breast cancer syndromes.[1,2] The link between TNBC and BRCA1 mutations is particularly noteworthy, as BRCA1 dysfunction leads to impaired homologous recombination DNA repair mechanisms, resulting in genomic instability and tumor progression.[1,2] Besides BRCA1 mutations, other genetic susceptibility factors may contribute to the disease's development, highlighting the importance of genetic screening in high-risk populations.[1,2,7] Clinically, TNBC often manifests as high-grade invasive ductal carcinoma, marked by significant nuclear atypia, a high mitotic index, and central tumour necrosis.[1,5] Compared to hormone receptor-positive breast cancers, TNBC tumors typically grow rapidly and are often larger at diagnosis.[1,7] The disease exhibits a unique metastatic pattern, with a higher likelihood of visceral metastases, particularly affecting the lungs, liver, and brain, rather than the bones.[5,7] A key clinical feature of TNBC is its tendency for early recurrence, usually within the first three to five years after initial treatment.[5,7] Dent et al found that TNBC patients have a distinct relapse pattern, with a higher risk of distant recurrence in the early post-treatment period compared to other subtypes.[5] This early relapse pattern significantly affects prognosis and highlights the aggressive biological nature of TNBC.

At the molecular level, TNBC is not a single, uniform entity but rather consists of a range of biologically distinct subtypes.[6] Studies on gene expression have identified several TNBC subgroups, each with unique activation of signalling pathways, such as basal-like, mesenchymal, immunomodulatory, and luminal androgen receptor subtypes.[6] This molecular diversity leads to variations in clinical behaviour and responses to treatment. Commonly observed in TNBC are abnormalities in key signalling pathways like PI3K/AKT/mTOR, TP53 mutations, DNA damage response mechanisms, and immune checkpoint pathways.[2,6,8] The frequent presence of TP53 mutations further enhances genomic instability and tumour progression.[6,8] Recent proteomic studies have discovered distinct protein expression patterns linked to tumour aggressiveness and metastatic potential, which could serve as potential biomarkers for developing targeted therapies.[10] Genomic comparisons between TNBC and non-TNBC subtypes have shown higher mutational burdens and unique mutational profiles in TNBC, underscoring its aggressive molecular nature.[9] These genomic changes contribute to chemotherapy sensitivity in some cases, especially in tumors with homologous recombination deficiency.[2,9] The biological complexity of TNBC has driven research into precision medicine approaches aimed at identifying actionable molecular targets and predictive biomarkers.[6,8] Immunologically, TNBC shows a relatively high level of tumor-infiltrating lymphocytes (TILs) and increased expression of immune checkpoint molecules, indicating an immunogenic tumor microenvironment.[8,11] This feature has justified the inclusion of immune checkpoint inhibitors in treatment plans. The KEYNOTE-355 trial demonstrated that adding pembrolizumab to chemotherapy significantly improved progression-free survival in patients with advanced PD-L1–positive TNBC.[3]These results have established immunotherapy as a crucial component of treatment for selected patients. Additionally, research into immunotherapeutic strategies from a single-cell perspective has highlighted the complex interactions between tumor cells and the immune microenvironment, paving the way for more personalized immunotherapy approaches.[15]

TNBC remains challenging to treat because of the absence of hormone and HER2 targets, with anthracycline-, taxane-, and platinum-based chemotherapy serving as the mainstay of treatment. Although neoadjuvant chemotherapy can achieve high pathological complete response rates, patients without pCR have an increased risk of recurrence; newer approaches including PARP inhibitors, antibody-drug conjugates, artificial intelligence, nanomaterial-based phototherapy, and vaccine-based immunotherapy are being explored to improve outcomes. Despite advances in molecular profiling, immunotherapy, and precision medicine, TNBC continues to be associated with poor survival due to its aggressive behavior and early relapse, highlighting the need for continued research to overcome resistance and reduce recurrence.[1-4,7,8,10,12-14]

REWIRING TNBC BIOLOGY: TARGETS THAT CHANGED THE THERAPEUTIC LANDSCAPE

Trophoblast cell-surface antigen 2 (TROP-2) is a transmembrane glycoprotein that is significantly overexpressed in TNBC and is crucial for tumor progression. According to Kaboli et al, TROP-2 acts as an oncogenic driver by triggering intracellular signaling pathways like PI3K/AKT and MAPK/ERK, which facilitate cell growth, survival, migration, and invasion.[16] The overexpression of TROP-2 is linked to more aggressive tumor behavior, increased metastatic potential, and worse clinical outcomes in TNBC patients. The therapeutic importance of TROP-2 became apparent with the creation of antibody-drug conjugates (ADCs), especially sacituzumab govitecan. This ADC specifically targets TROP-2 on tumor cells, is internalized, and releases SN-38, the active metabolite of irinotecan, leading to DNA damage and apoptosis. This targeted delivery system enhances antitumor effectiveness while reducing systemic toxicity, marking a significant advancement in treating metastatic TNBC.[16]

Programmed death-ligand 1 (PD-L1) is an immune checkpoint protein commonly found in TNBC, playing a crucial role in helping tumors evade the immune system. As noted by Mittendorf et al PD-L1 expression in TNBC is frequently linked to a higher presence of tumor-infiltrating lymphocytes (TILs), indicating an active immune environment within the tumor.[17] TNBC is known for having a higher mutational load compared to other breast cancer types, which enhances its immunogenicity. PD-L1 on tumor or immune cells interacts with PD-1

receptors on activated T-cells, resulting in the inhibition of T-cell growth, cytokine release, and cytotoxic function. This mechanism allows tumor cells to avoid detection by the immune system. Recognizing PD-L1 expression as a predictive biomarker has advanced the clinical application of immune checkpoint inhibitors like Pembrolizumab and Atezolizumab, which counteract the PD-1/PD-L1 pathway to reinstate antitumor immunity. These drugs, especially when used alongside chemotherapy, have shown improved survival rates in patients with PD-L1-positive TNBC.[17,18]

Deficiencies in DNA damage repair systems are a characteristic feature of TNBC, especially issues within the homologous recombination repair (HRR) pathway. A significant number of TNBC tumors show homologous recombination deficiency (HRD), which arises due to mutations or the loss of function in crucial repair genes. Under normal circumstances, when double-strand DNA breaks occur, the HRR pathway, facilitated by BRCA proteins, ensures precise repair. However, in TNBC with HR deficiency, the compromised repair process results in genomic instability, mutation accumulation, and aggressive tumor behavior. This weakness has been therapeutically targeted using the concept of synthetic lethality. Poly (ADP-ribose) polymerase (PARP) inhibitors like olaparib and talazoparib hinder single-strand DNA repair, leading to the buildup of DNA damage and the selective death of HR-deficient cancer cells. This targeted strategy has led to better outcomes for patients with germline BRCA-mutated TNBC.[19]

BRCA1 and BRCA2 are crucial tumor suppressor genes involved in DNA repair through homologous recombination.

ANTIBODY-DRUG CONJUGATES: REDEFINING PRECISION LETHALITY IN TNBC

In TNBC, ADCs are a targeted therapy method that uses the specificity of monoclonal antibodies to deliver extremely powerful cytotoxic medicines straight into tumour cells. A monoclonal antibody that identifies a tumor-associated antigen on the surface of cancer cells, a cytotoxic payload that can kill the cell once internalised, and a chemical linker that maintains these two components together until the ADC is within the tumour cell are the three main components of an ADC.[21,22]

Architecting the ADC: antibody, linker, payload-the lethal triad

ADCs are meticulously crafted medications that combine the potency of chemotherapeutic treatments with the accuracy of antibodies. This method helps the medicine target cancer cells while causing the least amount of harm to healthy tissues by selecting an antibody that can identify and bind precisely to an antigen present mostly on tumour cells. By attaching to certain antigens like TROP2 on the tumour surface then release the drug Inside the tumour cell, ADCs, on the other hand, combine a highly effective cytotoxic medication with a tumor-targeting antibody to introduce a cytotoxic agent to tumour cells selectively. Therapeutic trials have demonstrated that this design dramatically improves progression-free survival, overall survival, and therapeutic benefit rates in patients with aTNBC while decreasing off-target toxicity. Consequently, the development of ADCs has completely changed the management landscape for aTNBC, filling a major gap in this aggressive and difficult-to-treat subtype of breast cancer by providing a more targeted and efficient therapeutic approach where none previouslyexisted.[23]

The antibody

The main factor influencing target specificity and a key factor in the therapeutic efficacy of ADCs is the antibody component of an antibody-drug combination. In order to minimise off-target damage, it is essential to choose a target antigen that has a high and uniform expression on tumour cells and little or no expression on healthy tissues. To enable the ADC to be transported into endosomes and lysosomes, in which the cytotoxic payload can be delivered intracellularly, the target antigen-antibody combination must demonstrate effective internalisation upon binding in conjunction with selective expression. ADC intensity and clinical efficacy are directly impacted by variations in antigen load and internalisation kinetics. Humanisation of monoclonal antibodies has greatly decreased immunogenicity and increased patient tolerability, while Fc region modifications have been used to improve antibody stability, extend circulation half-life, and modify immune effector functions like antibody-dependent cellular cytotoxicity (ADCC). These developments in antibody engineering have further optimised ADC performance. When combined, intelligent target antigen identification and advanced antibody engineering techniques guarantee accurate tumour targeting, efficient intracellular transport, and an enhanced medicinal effectiveness of ADCs.[24]

The linker and its role in antibody drug conjugate

They link a monoclonal antibody to the cytotoxic payload and significantly influence ADC capacity, drug release, and toxicity profile, linkers are an essential structural element of antibody-drug conjugates. To avoid unnecessary payload release, which could result in off-target toxicity and decreased therapeutic efficiency, an ideal linker must be extremely stable in systemic circulation. The linker should facilitate the effective and prompt delivery of the active medication once the ADC has been internalised into the tumour cell. Linkers are widely characterised as either cleavable or non-cleavable according to their release mechanism.[25]

The payload

An antibody-drug conjugate's payload, or cytotoxic component, is a key factor in determining how effective it is against tumours. Since each antibody can only carry a

limited amount of drug molecules to the specific cancer cell, payloads employed in ADCs need be highly effective. After internalisation and release, payloads typically show sub-nanomolar to picomolar cytotoxic activity to guarantee efficient tumour cell death. ADC payloads are generally divided into three categories based on how they work: topoisomerase inhibitors, DNA-destroying agents, and microtubule inhibitors. Among the most often used payloads in clinically approved ADCs are microtubule inhibitors, such as auristatins and maytansinoids, which interfere with tubulin polymerisation and cause cell cycle arrest and apoptosis. and are some of the most often utilised payloads in ADCs that have received clinical approval. Even in non-dividing cells, DNA-damaging substances such as calicheamicins and pyrrolobenzodiazepine (PBD) dimers cause irreversible cytotoxicity by causing double-strand DNA breaks or DNA cross-linking. Deruxtecan and SN-38 derivatives are examples of topoisomerase I inhibitors that disrupt DNA replication by stabilising the topoisomerase-DNA cleavage complex, which causes replication stress and cell death. To optimise the therapeutic index while reducing systemic side effects, the payload selection must strike a compromise between exceptional potency and tolerable toxic effect, stability during circulation, and compliancewithlinkerchemistry.[26]

The synergy between antibody and payload and the determinants of efficacy and toxicity

The exact synergy between the cytotoxic payload and the targeted antibody determines the therapeutic efficacy of ADCs. Once released intracellularly, the payload exhibits strong cytotoxic action, and the antibody guarantees that the payload is delivered selectively to tumour cells that express antigen. The drug-to-antibody ratio (DAR), payload efficacy, and antigen expression levels are important variables affecting this synergy. The amount of cytotoxic medication given per antibody molecule is determined by DAR; larger DAR can boost anticancer activity, but it can also affect pharmacokinetics, decrease antibody stability, and promote off-target toxicity because of premature drug release. Efficacy and safety are balanced in optimal DAR.[27]

Sacituzumab govitecan: first-in-class TROP-2 directed precision therapy

A humanized IgG1 antibody that targets TROP-2, a transmembrane glycoprotein excessively expressed in many epithelial cancers, is joined to SN-38, an active metabolic product of irinotecan with strong topoisomerase I inhibitory activity, via a hydrolysable CL2A linker to form sacituzumab govitecan, also known as Trodelvy, the first-ever TROP-2-directed antibody-drug conjugate (ADC). This design produces an elevated drug-to-antibody ratio (~7.6-8:1) and permits the extracellular diffusion of SN-38 in the tumor microenvironment as well as intracellular release following receptor-mediated internalization, resulting in a bystander killing effect that can affect nearby tumor cells despite TROP-2 expression levels. When compared to traditional irinotecan therapy, the technique increases SN-38 delivery to tumors and decreases systemic toxicity while causing DNA damage and cancer cell apoptosis. In the randomized phase III ASCENT trial, SG significantly prolonged median progression-free survival (PFS) and overall survival (OS) when in comparison with chemotherapy in metastatic triple-negative breast cancer, with results across subgroups independent of TROP-2 expression. Additionally, SG demonstrated statistically significant increases in PFS and OS compared to physician-selected chemotherapy in the TROPiCS-02 phase III study for HR+/HER2-metastatic breast cancer. Neutropenia and diarrhea are frequent high-grade toxicities in studies, although the agent's advantages have resulted in international regulatory approvals in a number of breast cancer scenarios.[27,28]

IMMUNO-ONCOLOGY IN TNBC: AWAKENING A SILENT IMMUNE DESERT, IMMUNO-PHENOTYPING

Immunophenotyping, a transformative method in immunology, has significantly advanced our comprehension of the immune system's complexities. This technique involves identifying and quantifying specific cell populations in a sample by examining the expression of surface antigens or markers. These markers, which are proteins on the cell surface, help differentiate one cell type from another. Researchers utilize flow cytometry or other imaging technologies to analyze and classify cells.[28,29,32]

Checkpoint inhibition: breaking the PD-1/PD-L1 shield

Role of PD-1/PD-L1 pathway in TNBC

PD-1 is a receptor that inhibits immune responses and is found on activated T cells. Its ligands, PD-L1 and PD-L2, are often present on tumor cells and immune cells in the tumor microenvironment of TNBC. The interaction between PD-L1 and PD-1 reduces T-cell growth, cytokine release, and cytotoxic function, allowing tumors to evade the immune system. TNBC is characterized by higher levels of PD-L1 and TILs compared to other breast cancer types, making it a promising candidate for checkpoint blockade therapy.[33]

Pembrolizumab

Pembrolizumab, a PD-1 inhibitor, enhances antitumor immunity by blocking the PD-1/PD-L1 pathway and is FDA-approved for MSI-H tumors. In advanced triple-negative breast cancer with PD-L1 CPS ≥10, pembrolizumab plus chemotherapy significantly improved progression-free survival compared with chemotherapy alone. Trials such as KEYNOTE-173 and I-SPY2 also demonstrated increased pathological complete response rates when pembrolizumab was combined with neoadjuvant chemotherapy.[37]

Atezolizumab

Atezolizumab was the first immunotherapy drug to receive approval for breast cancer, following its expedited approval by the U.S. Food and Drug Administration in 2019. It was sanctioned for use in metastatic PD-L1-positive triple-negative breast cancer when combined with the chemotherapy agent nab-paclitaxel.[38] Atezolizumab is a humanized monoclonal IgG1 antibody targeting PD-L1, approved for treating patients with non-small cell and small cell lung cancer, urothelial cancer, hepatocellular carcinoma, and TNBC. It is important to note that the VENTANA PD-L1 (SP142) test is the sole validated method for evaluating PD-L1 expression when planning atezolizumab treatment.[39]

Checkpoint inhibition has revolutionized the treatment of TNBC by reactivating the body's anti-tumor immune response, especially in PD-L1-positive and immune-inflamed tumors.

Remodeling the tumor microenvironment: TILs, IFN signatures, APC activation

Tumor infiltrating lymphocytes

TILs are currently among the most reliable prognostic biomarkers in TNBC, associated with better clinical outcomes and responses to systemic treatment. The immune system significantly influences cancer progression and prognosis. In the tumor microenvironment (TME) of TNBC, lymphocytes are the most prominent immune cells. T lymphocytes make up about 60% of the immune cells in the TME, with 20% being cytotoxic CD8+ T cells and 40% helper CD4+ T cells (CTL and Th cells), followed by B cells (20%), natural killer (NK) cells (5%), and macrophages (5%), with dendritic cells making up less than 1.[40]

Interferons signatures

Interferons (IFNs) are a group of immune cytokines initially discovered for their capacity to effectively "interfere" with or halt viral and bacterial replication within infected cells, playing a crucial role in immune surveillance to eliminate host infections. Type 1 IFNs, specifically IFN-α and IFN-β, have been thoroughly researched for their ability to inhibit tumor cell growth through proapoptotic and cytotoxic mechanisms. These IFNs trigger the phosphorylation of the IFN-stimulated gene factor 3 (P-ISGF3) transcription factor complex, which includes signal transducer of activated transcription 1 (STAT1), STAT2, and IRF9, leading to the activation of numerous interferon-stimulated genes (ISGs).[41]

Absolute neutrophil count activation

In pathological circumstances, a rise in neutrophil counts is typically considered a sign of acute inflammation. Neutrophils have been linked to the prognosis of cancer, according to growing data. The neutrophil-to-lymphocyte ratio (NLR) is typically elevated in patients with various cancer types, indicating a notable increase in the amount of circulating neutrophils. The NLR is a straightforward and readily accessible marker that represents systemic inflammation and is frequently employed as a prognostic indication in a number of cancer types, including TNBC. In individuals with TNBC, greater NLR values have been linked to a worse prognosis, which includes shorter disease-free survival, overall survival, and an increased chance of recurrence.[42]

Why some respond and some fail: the biomarker puzzle

The most poorly known is TNBC, which is resistant to existing targeted treatments. Due to the limited number of available treatments, it is a major contributor to breast cancer mortality. In addition to suggesting potential targets for innovative treatments, biomarkers may be helpful as prognostic or predictive indicators. It is difficult for clinicians to treat this unique disease because targeted therapy aimed at numerous biomarkers has not demonstrated significant improvements in outcome in TNBC. Research into efficient medications and approaches for the therapy of TNBC should be prioritized. Therefore, biomarkers, molecules, and GEP tests that reliably identify TNBC and can be readily translated to the clinic are required to transform the current understanding of TNBC into oncological management. Epidermal growth factor receptor, vascular endothelial growth factor, c-Myc, C-kit, and basal cytokeratins, poly (ADP-ribose) polymerase-1, p53, tyrosinase kinases, m-TOR, heat and shock proteins, and TOP-2A in TNBC are among the biomarkers.[43] Although several biomarkers in TNBC have prognostic significance, they are unable to accurately forecast therapy response. It is still very difficult to distinguish prognostic indicators from predictive biomarkers.[44]

CONVERGENCE ONCOLOGY (THE SYNERGY OF ADCs AND IMMUNOTHERAPY)

The combination of ADCs along with immunotherapy has shown significant potential as a novel therapeutic approach for triple-negative breast cancer.[45] Antibody drug conjugates are the new generation of targeted cancer therapeutic agents that include monoclonal antibodies along with cytotoxic compounds, which selectively eliminate tumor cells expressing defined surface antigens (IJMS).[46] On the other hand, immunotherapies, especially immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors, function by reactivating the immune system, enabling it to recognize and eliminate malignant cells.[47]

ADCS induced immunogenic cell death- a new trigger for immunotherapy

This combination not only increases the cytotoxic drug activity but also simultaneously boosts the tumor's immunogenic potential.

Triggering immunogenic cell death (ICD) in cancer cells is a key strategy for increasing tumor immunogenicity and thereby enhancing the effectiveness of cancer immunotherapy.[48]

ADCs are designed to exert cytotoxicity through the selective delivery of highly potent payloads; however, accumulating evidence suggests that they also promote ICD, thereby augmenting anti-tumor immune responses. Mechanistically, ADC payloads capable of inducing endoplasmic reticulum stress or inflammatory forms of cell death stimulate the release of damage-associated molecular patterns (DAMPs), including calreticulin translocation, ATP efflux, and HMGBI release, which collectively support dendritic cell activation and antigen presentation.[6] Preclinical investigations further demonstrate that ADC-induced pyroptotic cell death enhances the recruitment and functional activation of cytotoxic T lymphocytes within the tumor microenvironment, indicating that immune modulation represents an important component of ADC therapeutic efficacy beyond direct tumor.[47]

Immunooncology-antibody drug conjugate combinations

Combining antibody conjugates along with immune checkpoint blockade has become an increasingly important area of innovation in triple negative breast cancer treatment.[8]

Despite the demonstrated efficacy of ADC monotherapy such as sacituzumab govitecan, the durability of treatment responses remains limited, indicating the importance of combination-based therapeutic strategies.[49]

ADCs contribute to anti-tumor immunity through induction of immunogenic cell death, modulation of the tumor microenvironment, and enhancement of antigen presentation, providing a strong rationale for this combination with immunotherapy. Early-phase trials are progressively focusing on the therapeutic potential of ADCs combined with ICIs, with particular emphasis on PD-1/PD-L1 target approaches.[45]

Preclinical and early clinical evidence suggests that topoisomerase 1-based ADC payloads promote type 1 interferon signaling, drive dendritic cell activation, and facilitate T-cell recruitment, therapy mimicking the tumor, and immune checkpoint inhibitors.[42]

Future studies are expected to use biomarker-driven enrollment strategies that account for tumor antigen expression, immune microenvironment characteristics, and genomic determinants of treatment sensitivity.[13] Adaptive trial frameworks and basket studies are increasingly employed to assess multiple ADC-immunotherapy combinations efficiently across different triple-negative breast cancer subtypes.[44] Emerging sequencing strategies, including ADC induction followed by immunotherapy maintenance, aim to enhance treatment efficacy while reducing adverse effects.[45]

CRACKING RESISTANCE: THE HIDDEN BARRIERS TO MODERN TNBC THERAPIES

Overview of therapeutic resistance in TNBC

Antineoplastic resistance, commonly referred to as chemotherapy resistance, is the phenomenon in which cancerous cells can endure and proliferate despite anticancer treatments. In certain cases, cancers may develop resistance to multiple drugs simultaneously, a phenomenon known as multidrug resistance. The failure of antineoplastic therapy can generally be attributed to two primary factors: intrinsic genetic traits that confer resistance to cancer cells and acquired resistance that develops after exposure to drugs, which is linked to the concept of variability among cancer cells. Resistant cells typically exhibit characteristics such as modified membrane transport, improved DNA repair mechanisms, defects in apoptotic pathways, changes in target molecules, and alterations in proteins and pathways, including enzymatic inactivation.[50]

Tumor heterogeneity and clonal evolution

Tumor heterogeneity is a key feature of cancer and presents a challenge in oncology. It is the primary reason for drug resistance, which often results in treatment failure. Drug resistance is the leading cause of unsuccessful treatment in cancer patients. Factors that contribute to drug resistance include tumor growth rate, tumor size, tumor heterogeneity, physical barriers, the immune system, the TME, an unendurable genome, and treatment pressures.[51]

Resistance mechanism to antibody-drug conjugates

ADCs necessitate adequate and consistent expression of the target antigen on tumor cells to enable effective binding, uptake, and delivery of the payload. Changes in antigen expression-whether through down-regulation or uneven distribution-lead to decreased ADC absorption and play a role in both intrinsic and acquired resistance. In TNBC, alterations in TROP2 expression have been identified as a clinically significant resistance mechanism against TROP2-targeted ADCs like sacituzumab govitecan.[53]

Target antigen modulation

TROP-2 downregulation

The effectiveness of ADCs in therapy relies heavily on the adequate and stable presence of the target antigen on the surface of tumor cells, allowing for efficient binding of the antibody, its internalization, and the subsequent release of the therapeutic payload within the cells. As a result, modifications in the expression of antigens have been identified as a significant factor in the development of

resistance to ADC therapies. In-depth examinations of the mechanisms behind ADC resistance categorize variations in target antigen expression as a key avenue through which tumors avoid the cytotoxic effects of ADCs.[54]

Antigen heterogeneity

Antigen heterogeneity is a major limitation to the efficacy of ADCs, as variable target antigen expression can lead to uneven drug uptake and reduced payload delivery. In TROP2-targeted ADCs, TROP2-low tumor regions exhibit decreased sensitivity, allowing antigen-low subclones to survive and contribute to disease progression and resistance.

Clinical studies have also shown that baseline TROP2 expression does not consistently predict response to sacituzumab govitecan, highlighting the limitations of single-biopsy biomarker assessment.[3,5,52]

Impaired ADC internalization and trafficking

Before payload release occurs following lysosomal degradation, ADCs must first bind to their target antigen on the cancer cell surface and then be internalized by endocytosis. Thereby, interfering with either endocytosis or lysosomal processing can reduce the efficiency of treatment and enhance resistance.

Endocytosis defects

ADCs primarily enter cells via caveolin-mediated endocytosis. Clathrin-caveolin-independent routes. Clathrin-mediated endocytosis (CME)-the most common route. The effectiveness of trafficking can be influenced by the preferred utilization of distinct routes by different receptors.[56]

Mechanisms and defects

Decreased endocytic uptake: restricts the transport of the payload to intracellular locations. Certain ADC targets, such as HER2, have a natural tendency to internalize poorly, resulting in inefficient uptake of ADCs.[52]

Changes in endocytic machinery or adaptor proteins (like Endophilin A2) diminish effective internalization and reduce the cytotoxic effects of ADCs.[50]

In resistant cells, ADCs may be misrouted to caveolin-positive compartments that do not efficiently deliver the cargo to lysosomes, leading to a decreased release of the payload.[56]

Lysosomal dysfunction

After internalization, ADCs are transported to lysosomes, where acidic pH and proteases cleave the linker and release the cytotoxic payload. Dysfunctional lysosomes reduce payload release and contribute to therapeutic resistance.

Impaired lysosomal acidification

Increased lysosomal pH limits activation of proteases needed for ADC degradation and payload release, reducing efficacy of non-cleavable ADCs.[54]

Reduced proteolytic activity

Lower lysosomal protease function (e.g., cathepsins) impairs antibody and linker breakdown, leading to ADC accumulation and limited cytotoxic drug liberation.[54]

Lysosomal sequestration of payloads

Weak-base or hydrophobic payloads can be trapped in lysosomes, preventing escape to the cytosol and reducing interaction with intracellular targets.[52]

Altered intracellular trafficking leading to prolonged lysosomal residence

ADCs may spend extended time in lysosomes due to trafficking defects, further reducing efficient processing and payload release.[53]

Payload-related resistance

Topoisomerase I inhibitor resistance

Many ADCs used in TNBC, including Trodelvy, deliver SN-38, a topoisomerase I inhibitor. Resistance occurs through the following mechanisms. Downregulation or mutation of topoisomerase I: reduced expression or structural alterations in TOP1 decrease drug-target interaction and cytotoxicity.[53] Drug efflux transporter overexpression: increased expression of ABC transporters (e.g., ABCG2, ABCB1) reduces intracellular accumulation of SN-38.[51]

CONCLUSION

TNBC is recognized as one of the most aggressive and biologically intricate subtypes of breast cancer, characterized by its molecular diversity, immune variability, and early resistance to treatment. The introduction of antibody-drug conjugates like sacituzumab govitecan and immune checkpoint inhibitors such as pembrolizumab has significantly altered the treatment paradigm, shifting from traditional chemotherapy to biologically targeted approaches. Convergence oncology, which combines ADCs with immunotherapy, provides a robust framework to enhance immunogenic cell death, overcome resistance, and improve the durability of response. Progress in liquid biopsy, ctDNA monitoring, and AI-driven precision modeling is facilitating adaptive, real-time therapeutic personalization. In the coming decade, approaches that integrate biomarkers, are guided by multi-omics, and are based on combinations are anticipated to revolutionize TNBC management from reactive treatment to proactive disease interception.

Achieving long-term survival will rely on translating molecular insights into intelligently sequenced, resistance-aware, and patient-specific therapeutic strategies.

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REFERENCES

1. Peters RE, al-Ismail S. Immunophenotyping of normal lymphocytes. Clin Lab Haematol 1994;16(1):21-32.
2. Schmid P, Dent R, O'Shaughnessy J. Pembrolizumab for early triple-negative breast cancer. Reply. N Engl J Med. 2020;382(26):e108.
3. Gouda MA, Subbiah V. Tissue-agnostic cancer therapy approvals. Surg Oncol Clin N Am. 2024;33(2):243-64.
4. Telisnor G, DeRemer DL, Frimpong E, Agyare E, Allen J, Ricks-Santi L, et al. Review of genetic and pharmacogenetic differences in cytotoxic and targeted therapies for pancreatic cancer in African Americans. J Natl Med Assoc .2023;115(2):164-74.
5. Xian P, Zou L, Zhang J, Pan X, Song Y, Nan Y, et al. Precision targeted cancer-associated fibroblast nano-regulator enhanced chemo-immunotherapy for triple-negative breast cancer. Biomaterials. 2026;326:123679.
6. Cetin B, Gumusay O. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(26):e108.
7. Lehmann BD, Abramson VG, Dees EC, Shah PD, Ballinger TJ, Isaacs C, et al. Atezolizumab in combination with carboplatin and survival outcomes in patients with metastatic triple-negative breast cancer: The TBCRC 043 phase 2 randomized clinical trial: The TBCRC 043 phase 2 randomized clinical trial. JAMA Oncol. 2024;10(2):193-201.
8. FDA. Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761034s043lbl.pdf. Accessed on 15 May 2026.
9. Gorenšek R, Kresnik M, Takač I, Rojko T, Sobočan M. Advances in tumour-infiltrating lymphocytes for triple-negative breast cancer management. Breast Cancer (Dove Med Press). 2023;15:773-83.
10. Doherty MR, Jackson MW. The critical, clinical role of interferon-beta in regulating cancer stem cell properties in triple-negative breast cancer. DNA Cell Biol. 2018;37(6):513-6.
11. Zheng C, Xu X, Wu M, Xue L, Zhu J, Xia H, et al. Neutrophils in triple-negative breast cancer: an underestimated player with increasingly recognized importance. Breast Cancer Res. 2023;25(1):88.
12. Yadav BS, Chanana P, Jhamb S. Biomarkers in triple negative breast cancer: A review. World J Clin Oncol. 2015;6(6):252-63.
13. Kelloff GJ, Sigman CC. Cancer biomarkers: selecting the right drug for the right patient. Nat Rev Drug Discov. 2012;11(3):201-14.
14. Matar-Ujvary R, Fecanji K, Sevilimedu V, Montagna G, Gemignani ML. Impact of age on outcomes in women with triple-negative breast cancer treated with neoadjuvant chemotherapy. J Adolesc Young Adult Oncol. 2026:21565333261421530.
15. Yuan Z, Liu Z, Zhou M, Wen H, Li B. Research progress on immunotherapeutics for triple-negative breast cancer from a single-cell perspective. Crit Rev Oncol Hematol. 2026;218:105111.
16. Jabbarzadeh Kaboli P, Shabani S, Sharma S, Partovi Nasr M, Yamaguchi H, Hung M-C. Shedding light on triple-negative breast cancer with Trop2-targeted antibody-drug conjugates. Am J Cancer Res. 2022;12(4):1671-85.
17. Mittendorf EA, Philips AV, Meric-Bernstam F, Qiao N, Wu Y, Harrington S, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014;2(4):361-70.
18. Fan Y, He S. The characteristics of tumor microenvironment in triple negative breast cancer. Cancer Manag Res. 2022;14:1-17.
19. Lee KJ, Mann E, Wright G, Piett CG, Nagel ZD, Gassman NR. Exploiting DNA repair defects in triple negative breast cancer to improve cell killing. Ther Adv Med Oncol. 2020;12:1758835920958354.
20. Ossovskaya V, Wang Y, Budoff A, Xu Q, Lituev A, Potapova O, et al. Exploring molecular pathways of triple-negative breast cancer. Genes Cancer. 2011;2(9):870-9.
21. Nagayama A, Vidula N, Ellisen L, Bardia A. Novel antibody-drug conjugates for triple negative breast cancer. Ther Adv Med Oncol. 2020;12:1758835920915980.
22. Jiang K, Wang S. Advances in antibody-drug conjugates in the treatment of advanced triple-negative breast cancer: a narrative review. Transl Breast Cancer Res. 2025;6(0):9.
23. Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017;16(5):315-37.
24. Peters C, Brown S. Antibody-drug conjugates as novel anti-cancer chemotherapeutics. Biosci Rep. 2015;35(4):e00225.
25. Pettinato MC. Introduction to antibody-drug conjugates. Antibodies (Basel). 2021;10(4):42.
26. Diamantis N, Banerji U. Antibody-drug conjugates--an emerging class of cancer treatment. Br J Cancer. 2016;114(4):362-7.
27. Kang C. Sacituzumab govitecan: A review in unresectable or metastatic HR+/HER2- breast cancer. Target Oncol. 2024;19(2):289-96.
28. López de Sá A, Díaz-Tejeiro C, Poyatos-Racionero E, Nieto-Jiménez C, Paniagua-Herranz L, Sanvicente A, et al. Considerations for the design of antibody drug conjugates (ADCs) for clinical development: lessons learned. J Hematol Oncol. 2023;16(1):118.
29. Rosa K. Sacituzumab govitecan prompts clinical benefit in metastatic TNBC, regardless of Trop-2 expression. CancerNetwork. 2020. Available at:

https://www.cancernetwork.com/view/sacituzumab-govitecan-prompts-clinical-benefit-in-metastatic-tnbc-regardless-of-trop-2-expression. Accessed on 15 May 2026.
30. Clinical Review. Canadian Agency for Drugs and Technologies in Health. 2022. Available at: https://www.cda-amc.ca/. Accessed on 15 May 2026.
31. Pérez-Bermejo M, Caballero-Pascual M, Legidos-García ME, Martínez-Peris M, Casaña-Mohedo J, Llorca-Colomer F, et al. Sacituzumab Govitecan in Triple Negative Breast Cancer: A Systematic Review of Clinical Trials. Cancers (Basel). 2024;16(21):3622.
32. Peters RE, al-Ismail S. Immunophenotyping of normal lymphocytes. Clin Lab Haematol. 1994;16(1):21-32.
33. Schmid P, Dent R, O'Shaughnessy J. Pembrolizumab for early triple-negative breast cancer. Reply. N Engl J Med. 2020;382(26):e108.
34. Gouda MA, Subbiah V. Tissue-agnostic cancer therapy approvals. Surg Oncol Clin N Am. 2024;33(2):243-64.
35. Telisnor G, DeRemer DL, Frimpong E, Agyare E, Allen J, Ricks-Santi L, et al. Review of genetic and pharmacogenetic differences in cytotoxic and targeted therapies for pancreatic cancer in African Americans. J Natl Med Assoc. 2023;115(2):164-74.
36. Xian P, Zou L, Zhang J, Pan X, Song Y, Nan Y, et al. Precision targeted cancer-associated fibroblast nano-regulator enhanced chemo-immunotherapy for triple-negative breast cancer. Biomaterials. 2026;326:123679.
37. Cetin B, Gumusay O. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(26):e108.
38. Lehmann BD, Abramson VG, Dees EC, Shah PD, Ballinger TJ, Isaacs C, et al. Atezolizumab in combination with carboplatin and survival outcomes in patients with metastatic triple-negative breast cancer: The TBCRC 043 phase 2 randomized clinical trial: The TBCRC 043 phase 2 randomized clinical trial. JAMA Oncol. 2024;10(2):193-201.
39. FDA. Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761034s043lbl.pdf. Accessed on 15 May 2026
40. Gorenšek R, Kresnik M, Takač I, Rojko T, Sobočan M. Advances in tumour-infiltrating lymphocytes for triple-negative breast cancer management. Breast Cancer (Dove Med Press). 2023;15:773-83.
41. Doherty MR, Jackson MW. The critical, clinical role of interferon-beta in regulating cancer stem cell properties in triple-negative breast cancer. DNA Cell Biol]. 2018;37(6):513-6.
42. Zheng C, Xu X, Wu M, Xue L, Zhu J, Xia H, et al. Neutrophils in triple-negative breast cancer: an underestimated player with increasingly recognized importance. Breast Cancer Res. 2023;25(1):88.
43. Yadav BS, Chanana P, Jhamb S. Biomarkers in triple negative breast cancer: A review. World J Clin Oncol. 2015;6(6):252-63.
44. Kelloff GJ, Sigman CC. Cancer biomarkers: selecting the right drug for the right patient. Nat Rev Drug Discov. 2012;11(3):201-14.
45. Beck A, Goetsch L, Dumontet C, Corvaïa N. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017;16(5):315-37.
46. Catanzaro E, Beltrán-Visiedo M, Galluzzi L, Krysko DV. Immunogenicity of cell death and cancer immunotherapy with immune checkpoint inhibitors. Cell Mol Immunol. 2025;22(1):24-39.
47. Xu X, Yu T, Wang Z. Combining antibody-drug conjugates with immune checkpoint inhibitors: A new paradigm for breast cancer therapy. Cancer Treatment Rev. 2025;140:103012.
48. Dou L, Fang Y, Yang H, Ai G, Shen N. Immunogenic cell death: A new strategy to enhancing cancer immunotherapy. Hum Vaccin Immunother. 2024;20(1):2437918.
49. Liu Q, Hu Y, Zheng P, Yang Y, Fu Y, Yang Y, et al. Exploiting immunostimulatory mechanisms of immunogenic cell death to develop membrane-encapsulated nanoparticles as a potent tumor vaccine. J Nanobiotechnology. 2023;21(1):326.
50. Wikipedia: The Free Encyclopedia. Antineoplastic resistance. Available at: https://en.wikipedia.org/w/index.php?title=Antineoplastic_resistance&oldid=1314027404. Accessed on 15 May 2026.
51. Zhou Z, Zhou Q. Immunotherapy resistance in triple-negative breast cancer: Molecular mechanisms, tumor microenvironment, and therapeutic implications. Front Oncol. 2025;15:1630464.
52. Abelman RO, Wu B, Spring LM, Ellisen LW, Bardia A. Mechanisms of Resistance to Antibody-Drug Conjugates. Cancers (Basel). 2023;15(4):1278.
53. Khoury R, Saleh K, Khalife N, Saleh M, Chahine C, Ibrahim R, et al. Mechanisms of Resistance to Antibody-Drug Conjugates. Int J Mol Sci. 2023;24(11):9674.
54. Rasche M, Steidel E, Zimmermann M, Bourquin JP, Boztug H, Janotova I, et al. Second Relapse of Pediatric Patients with Acute Myeloid Leukemia: A Report on Current Treatment Strategies and Outcome of the AML-BFM Study Group. Cancers (Basel). 2021;13(4):789.
55. Liang K, Mei S, Gao X, Peng S, Zhan J. Dynamics of Endocytosis and Degradation of Antibody-Drug Conjugate T-DM1 in HER2 Positive Cancer Cells. Drug Des Devel Ther. 2021;15:5135-50.
56. Li S, Zhao X, Fu K, Zhu S, Pan C, Yang C, et al. Resistance to antibody-drug conjugates: A review. Acta Pharm Sin B. 2025;15(2):737-56.

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