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REVIEW

Multi-Omics-Driven Advances in Targeted and Immunologic Therapies for Triple-Negative Breast Cancer

Kimiya Ganjooi, Sophia Strukel, Emma Eddy, Ryan Au and Vikrant Rai*

Department of Translational Research, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA

*Corresponding Author: Vikrant Rai. Email: vrai@westernu.edu

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ABSTRACT: Triple-negative breast cancer (TNBC) is defined by the absence of estrogen, progesterone, and human epidermal growth factor receptor 2 expression and exhibits significant molecular heterogeneity and aggressive clinical behavior. The main treatment remains traditional chemotherapy, despite the modest duration of its effects, which has intensified the search for novel, non-chemotherapeutic drugs. Over the past few years, various molecularly targeted and immune-based treatments targeting TNBC's diverse oncogenic drivers have been uncovered. In immunotherapy, checkpoint blockade and chimeric antigen receptor (CAR)-T cells show growing promise, enabling selective tumor targeting with reduced off-target toxicity. Multi-omics investigations integrating genomic, transcriptomic, proteomic, and metabolomic information have further delineated TNBC subclassification and revealed actionable metabolic vulnerabilities, particularly in lipid metabolism. Such discoveries are now informing rational drug-combination strategies and patient stratification methods. Current trials have established immature, but promising data on PI3K inhibitors. The Lotus (ORR 40% vs. 32% in placebo), IPATunity130 (ORR 39% vs. 35% in placebo), FAIRLINE neoadjuvant (ORR 39% vs. 9%), and PAKT (ORR 34.8% vs. 28.8%) trials evaluated the overall response rate (ORR) of specific P13K inhibitors vs. placebo. By dissecting the intense molecular, spatial, and functional heterogeneity of TNBC, these platforms identify actionable, subtype-specific therapeutic targets and predict patient responses to treatment, overcoming the limitations of current, less-effective therapies.

KEYWORDS: Triple negative breast cancer; immunotherapy; chimeric antigen receptor T-cells; chemotherapy; multi-omics; metabolic reprogramming

1 Introduction

Triple negative breast cancer (TNBC) accounts for 10–15% of breast cancer (BC) incidence and is associated with poor prognosis [1]. This aggressive phenotype of BC is characterized by the loss of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) expression [2]. TNBC disproportionately affects pre-menopausal and Black women, with Black women having the lowest survival rates associated with the disease [1,3]. Increased body mass index and White non-Hispanic ethnicity have also been linked to higher TNBC risk [4]. Beyond its prevalence, TNBC is distinguished by its aggressive tumor biology and limited targeted treatment options.

Histologically, TNBC typically presents as a moderate-to-high grade, highly proliferative, invasive ductal carcinoma [1]. Compared to HER+ BCs, TNBC is known for its large tumor size, lymph node involvement, high tumor grade, higher recurrence rates, and more aggressive disease course [5]. Metastasis

often occurs in visceral organs and soft tissues, with recurrence of TNBC most often occurring in the central nervous system or lungs [6]. Approximately 45% of the patients with TNBC experience distant metastases, frequently in the brain or elsewhere [2]. TNBC often has a relatively poor prognosis, with the overall 5-year survival rate of 91.3%, 65.8%, and 12.0% for localized, regional, and distal disease, respectively [7]. Additionally, metastatic TNBC has an average survival ranging from 8 to 13 months [5].

One of the factors resulting in the poor prognosis associated with TNBC is its substantial heterogeneity, both within its molecular subtypes and within the tumor microenvironment (TME). Gene expression profiling has revealed that TNBC is not a single disease entity but rather encompasses several distinct molecular subtypes. Based on the differential gene analysis, Lehmann classification identifies six major subtypes of TNBC: Basal-like 1 (BL1), Basal-like 2 (BL2), Mesenchymal (M), Mesenchymal Stem Like (MSL), Immunomodulatory (IM), and Luminal Androgen Receptor (LAR) subtypes [8,9]. Subtype characterization was done by specific gene expression patterns and signaling pathways. For example, BL1 and BL2 are enriched in DNA damage response and cell cycle genes, but have decreased immune gene expression, whereas IM is associated with immune gene expression and cytokine signaling [10]. On the other hand, Mesenchymal Subtype (MES) is characterized by stem cell pathways, and LAR shows activation of hormonal receptor pathways [10]. This molecular diversity results in varying responses to standard neoadjuvant chemotherapy and demonstrates one of the challenges in treating TNBC.

Beyond intrinsic tumor properties, the TNBC TME adds further complexity. In addition to the different molecular subtypes of TNBC, this cancer can be further divided into immune cell-rich “hot tumors” and immune cell-low “cold tumors” [11]. Generally, TNBC TME demonstrates both immunosuppressive and immunoreactive properties. Immunosuppressive components include antigens expressed on BC cells and tumor-infiltrating lymphocytes (TILs), including Programmed death-ligand 1 (PD-L1) and programmed death protein-1 (PD-1), respectively. These molecules subsequently inhibit immune TIL activation, allowing the tumor cells to survive through immune escape [11,12]. Forkhead box P3 positive regulatory T-cells ($Foxp3^+$ Tregs) also play an important role in the immunosuppressive nature of the TNBC TME. They are involved in downregulation of anti-inflammatory mediators such as interleukin (IL)-4, IL-5, and IL-10, decreased secretion of cytokines such as interferon gamma (IFN-γ) and IL-17, and activation of the signal transducer and activator of transcription 1 and 3 (STAT1/STAT3) [9,13]. STAT1/3 specifically plays an important role in TNBC cell proliferation, survival, cell cycle progression, migration, invasion, angiogenesis, chemoresistance, and stem cell self-renewal [14]. Additionally, M2 macrophages and myeloid-derived suppressor cells (MDSCs) play an important role in the immunosuppressive network of TNBCs [9]. In contrast, immunoreactive cells such as natural killer (NK) cells are abundant in the early cancer tissue of solid tumors [15]. $CD8^+$ TILs and M1 macrophages also play important roles against tumorigenesis and offer potential routes for immunomodulatory therapy of TNBC [9].

Traditional models of treatment for TNBC are surgery-based and involve postoperative adjuvant chemotherapy to prevent recurrence. However, if malignancy is inoperable at the time of diagnosis, neoadjuvant chemotherapy is used to reduce tumor size and increase the possibility for breast-conserving surgical removal. It is of note that preoperative systemic treatment is not associated with disease-free survival (DFS) or overall survival (OS). However, patients who underwent pathologic complete response following neoadjuvant treatment did have increased survival when compared to patients who showed residual disease [16]. While the development of novel therapies such as HER2-targeting monoclonal antibodies, antibody–drug conjugates (ADC), and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has dramatically improved the survivability of hormone receptor (HR)+ and HER2+ BC, these improvements have not been translated to TNBC due to the lack of ER/PR/HER2 protein expression [9,16]. Current

TNBC treatments being explored include platinum agents, anthracyclines, taxanes, and immune checkpoint inhibitors (ICIs), with a combination of pembrolizumab with anthracycline, taxane, and carboplatin as the current treatment of choice [16]. However, 20–60% of TNBC patients still have residual tumor burden after neoadjuvant chemotherapy, reinforcing the need to better understand the TNBC TME to create more effective treatments [17]. A defining hallmark of TNBC is intrinsic and acquired drug resistance that contributes to relapse, limited length of response, and poor long-term survival. This is due to tumor heterogeneity, pathway redundancy, enrichment of cancer stem-like cells, and adaptive remodeling of the tumor microenvironment, which are key drivers of this resistance [2]. Emerging multi-omic technologies present another potential solution by allowing researchers to further synthesize tissue imaging, cytometry, next-generation sequencing, and spatial omics to more specifically target TNBC TME [17].

Challenges to TNBC treatment go beyond significant tumor heterogeneity and high recurrence rates. Even the diagnosis of TNBC remains difficult, as emerging approaches such as liquid biopsy and next-generation sequencing offer promising avenues but continue to face limitations related to tumor biological complexity, sensitivity, current technical capacity, and high costs [18]. Additionally, single therapeutic modalities have demonstrated limited efficacy, prompting a shift towards combination treatment strategies aimed at enhancing therapeutic response and overcoming resistance [19]. Moreover, many existing regimens are associated with considerable long-term toxicity, limited response, and frequent trial failure to demonstrate long-term survival benefit [20,21]. Despite numerous ongoing clinical trials and advancements in identifying molecular targets and signaling pathways, TNBC still requires further investigation to translate these discoveries into standardized clinical care and meaningfully improve patient outcomes [19,22]. Another significant challenge in TNBC treatments is the lack of standardization in translating precision medicine into routine clinical practice. As new insights into the molecular and microenvironmental biology of TNBC continue to emerge, there remains a critical need for coordinated implementation strategies and effective interdisciplinary collaborations between genetic counselors, pathologists, oncologists, and healthcare administrations alike to optimize TNBC outcomes [19]. In summary, TNBC remains one of the most aggressive and heterogeneous breast cancer subtypes. Its defining lack of ER, PR, and HER2 receptors limits the applicability of conventionally targeted treatments, while its complex molecular and microenvironmental landscape contributes to high recurrence and poor prognosis [7]. This narrative review discusses the underlying pathogenesis of TNBC and explores emerging therapeutic strategies, emphasizing the evolving role of targeted, immunologic, and metabolic approaches in addressing current clinical limitations and overcoming the intrinsic complexity of the disease.

2 Methodology of Review

This narrative review was conducted through a comprehensive literature search of Scopus, Web of Science, and PubMed databases. Peer-reviewed articles published between January 2010 and June 2025 were considered. Search terms included combinations of “triple-negative breast cancer”, “current therapy”, “PARP inhibitors”, “PI3K/AKT/mTOR”, “DNA damage repair pathways”, “CAR-T cells”, “multi-omics”, and “metabolic reprogramming.” Journal articles were included if they discussed molecular mechanisms, preclinical design, and clinical outcomes regarding TNBC treatment, with priority given to phase I–III clinical trials and large sample sizes.

3 Mechanism of Oncogenesis

Oncogenesis encompasses the multistep process through which healthy somatic cells acquire the capacity for uncontrolled proliferation, invasion, and metastasis because of genetic and epigenetic alterations.

The central mechanism underlying this transformation involves dysregulation in proto-oncogenes and tumor-suppressor genes encoded within the genome [23]. Proto-oncogenes encode proteins that promote cell division, growth, and survival through tightly signaling pathways such as Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT). Oncogenic transformation occurs through activation of these proto-oncogenes into oncogenes via point mutations, gene amplification, or chromosomal translocations (Fig. 1) [19,20].

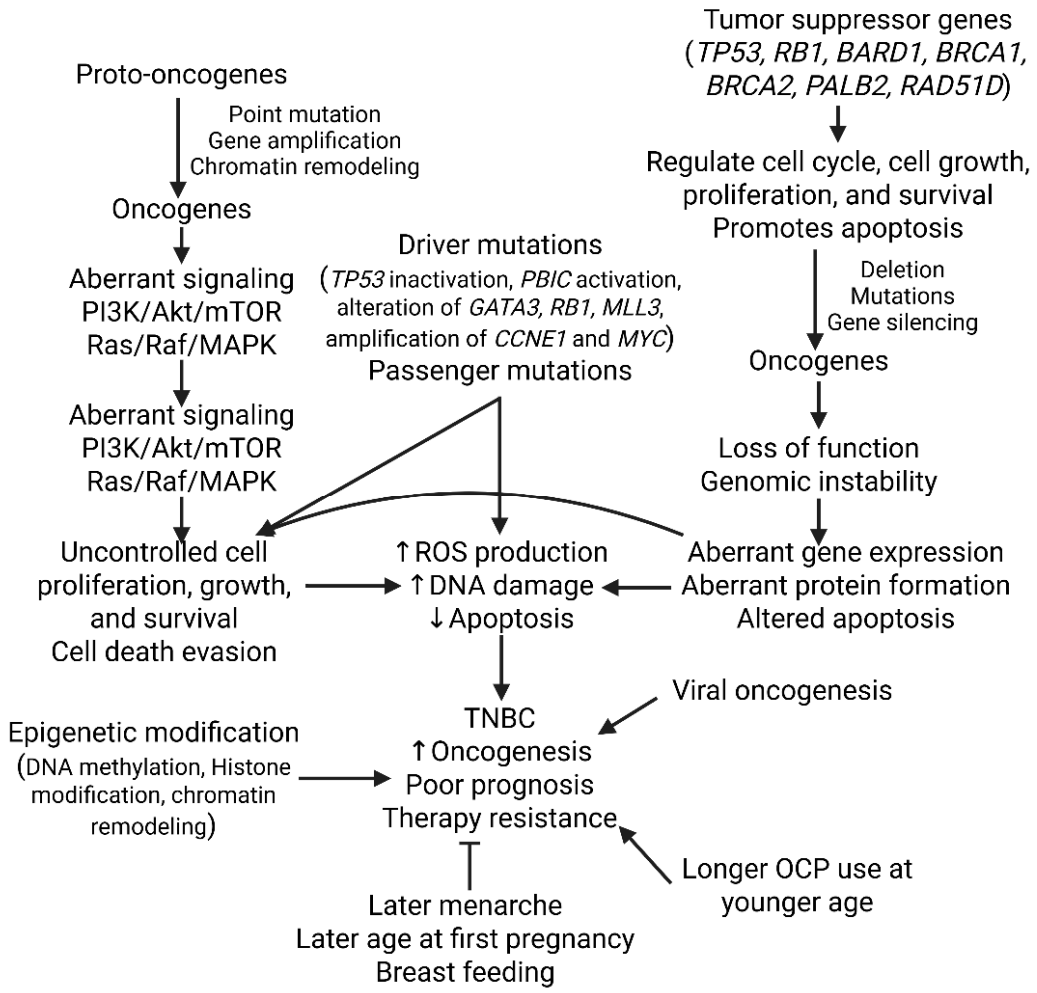

Figure 1: Molecular mechanisms underlying the oncogenesis of triple-negative breast cancer (TNBC). Oncogenesis in TNBC involves complex pathways driving its aggressive nature, lack of targeted therapies, and high metastasis/chemoresistance. Key mechanisms include dysregulated signaling (Wnt, TGF-β, EGFR/Met), altered splicing (NEK2), specific protein interactions (BCL11A-CHD8), and oncogenic drivers (BCL11A, CD24, AURKA, TRIM37, c-Myc) that promote stemness, invasion, and drug resistance, creating new therapeutic targets. Upward arrows (↑) indicate increased activity or expression, whereas downward arrows (↓) indicate decreased activity or expression. Abbreviations: TNBC, triple-negative breast cancer; OCP, oral contraceptive pill. Created in BioRender. Rai, V. (2025) https://BioRender.com/p2xo52v.

Eventually, these changes lead to the constitutive activation of cell growth pathways and thus gain the ability to evade cell death. Researchers have studied the role of genetic alterations in K-Ras, part of the RAS oncogene family, and its association with resistance to therapy. K-Ras regulation through non-coding

RNAs and specific mutations leads to downstream effects of increased ROS production, DNA damage, and apoptosis activation [24] (Fig. 1). Interestingly, cancer cells harboring K-Ras mutations can evade cell death through the formation of apoptotic cell-derived "blebbishields", the apoptotic blebs shedding and forming stable, distinct structures. These blebbisheilds enable the fusion and regeneration of tumorigenic spheres, a process termed the blebbisheild emergency program, representing an adaptive survival mechanism during oncogenic stress [25,26] (Fig. 1). These blebbishields are not simply waste products; they actively signal back to the parent cell, promoting a survival pathway. They contain specific proteins, notably active forms of Rho-associated coiled-coil containing protein kinase (ROCK), which suppresses further apoptosis and promotes the cell's recovery [27].

Conversely, tumor-suppressor genes encode proteins that inhibit cell proliferation and promote apoptosis when genomic integrity is compromised. Inactivation of these genes, such as TP53 and RB1, through mutations, deletions, or genetic silencing, results in loss of function and allows aberrant cells to evade apoptosis. The TP53 gene encodes the p53 protein, which serves as a pivotal transcription factor that coordinates DNA repair processes, surveillance of DNA damage, and regulation of apoptosis progression [28]. Mutations in TP53 are among the most prevalent alterations across all human cancers and are strongly associated with genomic instability, poor prognosis, and resistance to conventional chemotherapy and radiation therapy [26] (Fig. 1). Multigene panel testing identified increased risk of TNBC associated with pathogenic variants in tumor suppressor genes, BARD1, BRCA1, BRCA2, PALB2, and RAD51D [29].

Tumor characteristics reflect the accumulation of driver and passenger mutations that confer selective growth advantages to malignant cells. Advances in next-generation sequencing have allowed longitudinal monitoring of tumor evolution, genetic variability, and clonal expansion throughout the course of a patient's disease. Driver mutations serve as the causative agent that promotes malignant transformation and represent valuable targets for immunotherapy drugs, such as BRAF inhibitors in BRAF mutant melanoma. These mutations arise through both endogenous mechanisms, such as replication errors and oxidative stress, and exogenous carcinogens, including ionizing radiation, ultraviolet light, oncogenic viruses, and environmental toxins [30]. In TNBC, driver mutations are critical genetic alterations that drive tumor growth and progression, while passenger mutations are acquired randomly and do not have a significant impact on cancer's development. Key driver mutations in TNBC include high-frequency alterations in TP53 (inactivation), along with others in genes like phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (activation of PI3K signaling) and GATA-binding protein-3 GATA3 (Fig. 1). Identifying these drivers is crucial for finding potential therapeutic targets. Other genes frequently altered in TNBC include retinoblastoma (*RB1*), mixed-lineage leukemia 3 (*MLL3*), and amplifications of genes like cyclin E1 (*CCNE1*) and *MYC* [31,32] (Fig. 1). Intratumoral heterogeneity, defined as the coexistence of genetically and phenotypically distinct subclones within a single tumor, poses another major challenge to consider when determining the prognosis, etiology, and treatment plan of the cancer discussed. Some cancers, such as colorectal carcinoma, follow a relatively ordered sequence of driver mutations, while others evolve through a more diverse acquisition of driver alterations [33].

Epigenetic modifications further contribute to tumor initiation and progression through heritable yet reversible changes in gene expression without alteration of the DNA sequence itself. These modifications include DNA methylation, histone post-translational modifications, and chromatin remodeling (Fig. 1). Metabolic intermediates often act as substrates or cofactors that determine histone modification and chromatin accessibility. Missense mutations in histones, particularly histone H3, have been implicated in highly penetrant pediatric malignancies, such as diffuse intrinsic pontine glioma and osteosarcoma. Research has also supported the association of global reduction of monoacetylated lysine 16 of histone H4

with early-stage BC. Normally, histone acetylation diminishes the proliferation of MCF-7 BC cells that are stimulated by estrogen [34]. In both tumor cells and components of the TME, DNA methylation facilitates disease progression and immune escape in TNBC. These distinct differentially methylated regions can be used in comprehensive disease assessment and to stratify TNBC patients with different disease outcomes (prognosis) [35]. Epigenetic alterations also regulate extracellular matrix alterations in triple-negative breast cancer [36]. This highlights the intricate interplay between epigenetic regulation and oncogenesis. Moreover, viral oncogenesis has been associated with aberrant epigenetic changes, as viral genomes can develop abnormal DNA methylation patterns that dysregulate host gene expression. The interaction between epigenetic modifications, genetic mutations, and environmental exposures underscores the complexity and heterogeneity of cancer pathogenesis. Understanding these early determinants provides critical insight for designing novel epigenetic-based therapies targeting cancers derived from embryonic or adult stem cells [32].

TNBC exemplifies the complexity of the combination of genomic instability, tumor suppressor gene mutations, germline and somatic BRCA1/2, and aberrant activation of signaling pathways. This combination allows for a highly heterogeneous tumor type that is classically divided into molecular subtypes with distinct genetic profiles of basal-like, mesenchymal, and luminal androgen receptor [31]. Stevens et al. [37] studied the genetic susceptibility of TNBC, in which they revealed the association of three loci specific to TNBC: TERT, c19orf62, and MDM4. The TERT gene catalyzes within telomerase. MDM4 acts as a repressor of TP53 and TP73. Lastly, C19orf62 encodes a protein that is responsible for localizing the BRCA1 complex during DNA repair. Moreover, angiogenesis driven by vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang-1) enables tumor cells to recruit and penetrate vascular networks that supply the tumor cells with oxygen and nutrients, while depleting the surrounding healthy tissue. The resultant hypoxic microenvironment forces a metabolic shift from aerobic respiration to anaerobic respiration, leading to lactate accumulation and acidification of the tumor milieu. This acidity suppresses cytotoxic immune responses by exhausting T cells and natural killer (NK) cells while further promoting angiogenic signaling [38]. Altogether, these features contribute to the highly invasive and treatment-resistant nature of TNBC, underscoring the multifactorial intricacies of oncogenesis. A comprehensive meta-analysis examining the known risk factors associated with TNBC in women discussed the role of longer duration use of oral contraceptives, especially in younger women. Prolonged exogenous hormonal exposure can influence breast epithelial cell proliferation in genetically susceptible individuals. Another risk factor was more breast density due to the increased chance of malignant transformation, as well as making it more difficult to detect [38]. On the other hand, later age at menarche, later age at first birth, and breastfeeding demonstrated protective factors against TNBC [38] (Fig. 1).

4 Current Therapy

TNBC is characterized as an aggressive malignancy with limited therapy options due to complex and heterogeneous molecular profiles. Chemotherapy, most commonly involving taxanes and anthracyclines, remains the cornerstone of treatment; however, recent novel approaches have proven to be effective in specific patient populations. Cytotoxic chemotherapy is commonly administered either in the neoadjuvant or adjuvant setting. Despite its clinical benefits, the well-documented adverse effects of chemotherapy continue to challenge researchers to find a more targeted and effective approach [1,4,6] (Fig. 2). Additionally, intrinsic or acquired chemoresistance is common and represents a major hurdle for successful TNBC treatment [39]. Moreover, cumulative toxicities, such as anthracycline-induced cardiomyopathy and taxane-associated peripheral myopathy, underscore the need for more targeted therapeutic approaches [40].

The absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in TNBC makes it difficult to employ targeted therapies that are effective in receptor-positive breast cancers. Furthermore, the tumor immune microenvironment demonstrates limited responsiveness to anti-tumor immune activity, partly due to the role of tumor-associated macrophages (TAMs) and myeloid-derived suppressive cells (MDSCs), which secrete various immunosuppressive cytokines. These findings have prompted the pursuit of a multidimensional, personalized approach that targets angiogenesis and immune checkpoint inhibitors [1,4,6].

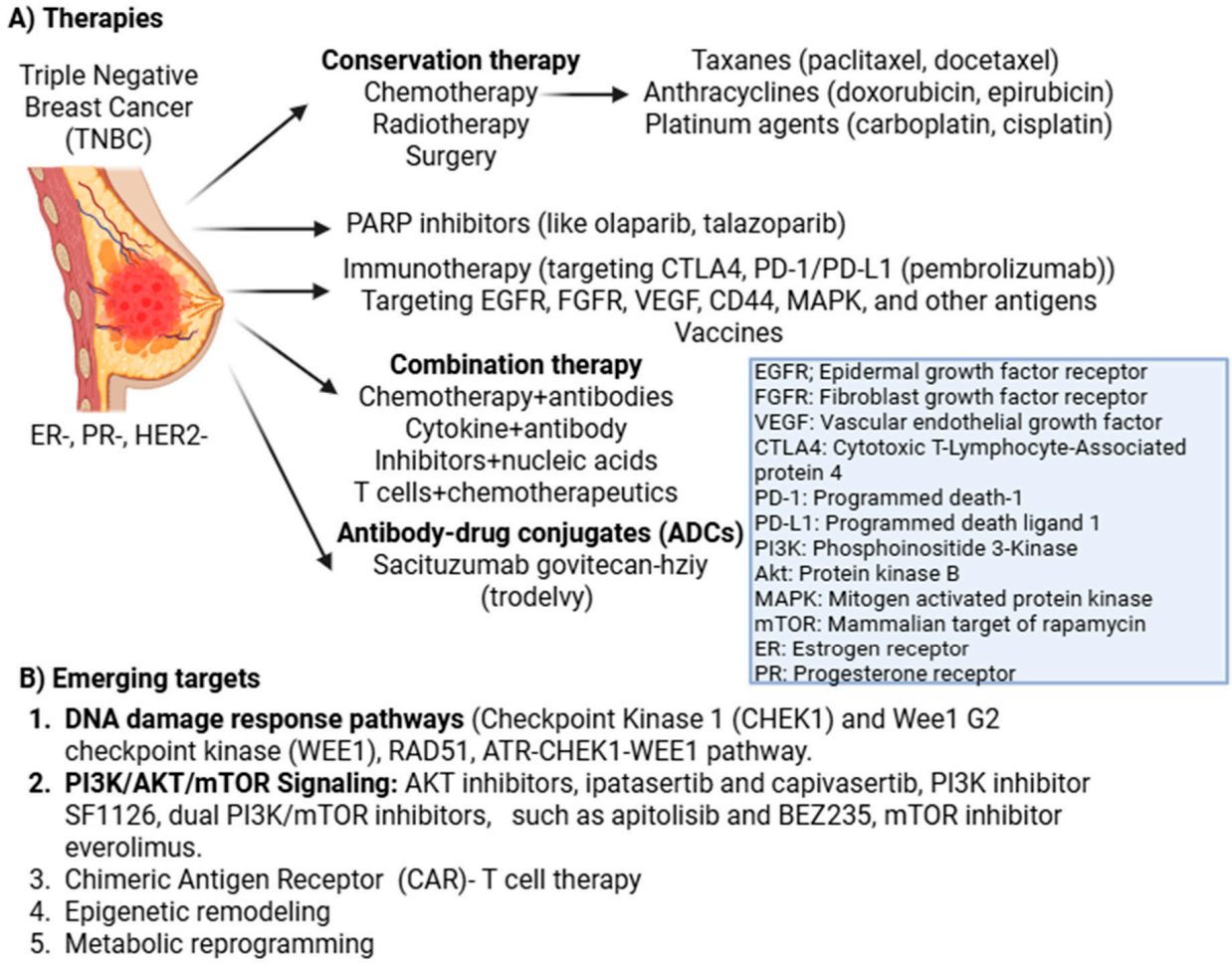

Figure 2: Existing and emerging therapeutics for triple-negative breast cancer (TNBC). (**A**) Current therapeutics for TNBC include conservation therapy (chemotherapy, radiotherapy, and surgery), PARP inhibitors, immunotherapies, combination approaches, and antibody-drug conjugates. (**B**) Emerging therapeutic strategies include DNA damage response pathways, PI3K/AKT/mTOR signaling, CAR-T cell therapy, epigenetic remodeling, and metabolic reprogramming. A combination of chemotherapeutic agents and antibodies, cytokines and antibodies, inhibitors and nucleic acids, and T cells and chemotherapeutic agents targets TNBC with receptors including EGFR, CD44, PD-1, PD-L1, and CTLA-4, to efficiently destroy it as well as to treat metastatic cancer by producing T cells. Created in BioRender. Rai, V. (2026) https://BioRender.com/9eylowf.

FDA-approved therapies for TNBC include taxanes (paclitaxel, docetaxel) and anthracyclines (doxorubicin and epirubicin), and poly (ADP-ribose) polymerase (PARP) inhibitors, which are used in combination with chemotherapy [6]. BRCA1/2 proteins play crucial roles in the homologous repair of

double-stranded DNA breaks, providing essential genomic stability during the S phase. Cells deficient in BRCA1/2 display increased chromosome instability, predisposing them to tumorigenesis [6] (Fig. 2).

Anthracycline-based chemotherapy acts primarily through the inhibition of topoisomerase II. Daunomycin, isolated from *S. peucetius* bacteria and the precursor to doxorubicin (Adriamycin), was FDA-approved for metastatic breast cancer in 1974 [41]. Subsequent trials proved the efficacy of doxorubicin in combination with taxanes. Epirubicin (Ellence), approved for adjuvant treatment of breast cancer, showed a reduced cardiac and hematologic toxicity compared to the earlier anthracyclines, permitting use at higher doses [42]. The liposomal variation of doxorubicin further lowered its cardiotoxicity profile and other adverse effects, and both Doxorubicin and liposomal doxorubicin are recommended for combinatorial chemotherapy regimens [41,42] (Fig. 2).

Poly (ADP-ribose) polymerases (PARPs) are enzymes involved in transcription, replication, recombination, and DNA repair. PARP inhibitors, such as Olaparib (Lynparza) and Talazoparib (Talzenna), have shown promising clinical results in BRCA1/2 deficient tumors due to their reliance on PARP-mediated DNA repair mechanisms (Fig. 2). PARP inhibition prevents single-strand DNA damage repair, resulting in replication fork collapse during S phase. Under normal conditions, BRCA1/2 genes facilitate in recognizing these damages and can divert to homologous recombination, but when deficient in these genes, this is unable to occur, leading to synthetic lethality [6].

Given the reliance of TNBC cells on angiogenesis, anti-VEGF therapy has shown promise in enhancing anti-tumor immune responses, especially when combined with immune checkpoint inhibitors in preclinical mouse studies [43]. Immune checkpoint inhibitors, including pembrolizumab (Keytruda) and atezolizumab (Tecentriq), have recently received FDA approval for patients with PD-L1-positive TNBC. These agents target the PD-LI/PD-1 axis, preventing inhibitory signaling and promoting T-cell activation. Clinical studies have demonstrated improved outcomes in early and metastatic settings when used in combination with chemotherapy [12] (Fig. 2).

Lastly, antibody-drug conjugates (ADCs) represent a rapidly advancing therapeutic class. Sacituzumab govitecan-hziy (trodelvy) has been recently approved in an unresectable locally advanced or metastatic TNBC following at least two prior lines of therapy [44]. Recent phase III trials have expanded sacituzumab govitecan's role to earlier treatment settings, with ASCENT-03 demonstrating significantly improved progression-free survival as first-line therapy and ASCENT-04 showing that sacituzumab plus pembrolizumab outperformed chemotherapy plus pembrolizumab in PD-L1 positive TNBC [44,45]. The ADC consists of 3 components: an anti-trop-2 monoclonal antibody, a cytotoxic payload (SN-38, a topoisomerase I inhibitor), and a linker that enables targeted drug delivery. Clinical trials have demonstrated significant benefit in patients regardless of Trop-2 expression, though efficacy was greater in those with higher Trop-2 expression. Given the frequent overexpression of Trop-2 in TNBC tissues, this therapeutic approach has become an important addition to the TNBC treatment landscape [6] (Fig. 2).

5 Drug Resistance in TNBC

Drug resistance in Triple-Negative Breast Cancer (TNBC) is a major clinical challenge, with up to 70% of cases showing resistance to standard chemotherapy. It is driven by tumor heterogeneity, cancer stem-like cells (BCSCs), and the epithelial-mesenchymal transition (EMT), which promotes metastasis and treatment evasion. Key mechanisms include enhanced DNA repair, drug efflux, and altered signaling pathways [46–50]. BCSCs are a subpopulation of cells resistant to standard chemotherapy that can self-renew and drive tumor recurrence. EMT process where tumor cells gain metastatic, stem-like properties, often driven by the TGF-β pathway, leading to increased drug resistance. TNBC cells often have a high capability to repair

DNA damage caused by chemotherapy (e.g., anthracyclines, platinum compounds). Increased activity of transporters, such as ABC transporters, helps expel therapeutic agents from cancer cells. Hypoxia and immune-suppressive components in the TME contribute to resistance. Finally, increased cell survival mechanism that allows TNBC cells to survive chemotherapy-induced stress [46–50]. Drug resistance arises from the selection of pre-existing, resistant subclones within the tumor or the acquisition of new genomic alterations during treatment. Further, alterations in molecular signaling pathways like PI3K/AKT/mTOR, Wnt/β-catenin, and Notch contribute to therapy resistance [46,49]. Research should focus on targeting BCSCs, EMT-related pathways (e.g., TGF-β), and using combinatorial therapies to enhance drug sensitivity. Additionally, using small-molecule inhibitors to reverse resistance may also help.

6 Targeted Therapies

6.1 DNA-Damage Response (DDR) beyond PARP

DNA damage response (DDR) is a process in which damaged DNA is sensed, resulting in the regulation of the cell cycle and activation of DNA repair processes. This pathway is essential in maintaining genomic stability, and drugs targeting this pathway have been highly investigated in cancer therapies. Interestingly, TNBC has been associated with abnormal genetic alterations in the DDR pathways, such as high-frequency p53 dysfunction and BRCA1/2 mutations [51]. Though PARP inhibitors have been investigated as a potential mechanism for targeting DDR in TNBC, resistance can be developed, prompting further investigation into alternative options. These targets predominantly include protein kinases responsible for DNA damage recognition and signal transduction pertaining to cell cycle regulation, such as Checkpoint Kinase 1 (CHEK1) and Wee1 G2 checkpoint kinase (WEE1). However, they can also involve molecules directly involved in DNA repair, such as RAD51 [52] (Fig. 2).

Currently, one of the most heavily investigated DDR pathways in TNBC is the ATR-CHEK1-WEE1 pathway. TNBC exhibits profound genomic instability, high replication stress, and near-universal loss of p53, which collectively impair the G1 checkpoint and force tumor cells to rely heavily on the ATR–CHEK1–WEE1 axis and RAD51-mediated homologous recombination to maintain viability [53]. DDR inhibitors exploit these dependencies through synthetic lethality and block ATR, CHEK1, WEE1, or RAD51 [53] (Fig. 2). For example, an *in vitro* study by Albiges et al. [54] in which TNBC cell lines were used to analyze the effects of CHEK1, found that depletion of CHEK1 resulted in a marked reduction of cell viability and mitotic catastrophe in TNBC cells. Additionally, a separate study found that the ATR inhibitor, VX-970, acts as an *in vivo* tumor-specific radiosensitizer for TNBC. This offers the opportunity for VX-970 to be used in patients with residual TNBC, post-adjuvant chemotherapy, and as an extra step to mitigate relapse [55]. Teo et al. [56] also showed that the WEE1 inhibitor, adavosertib, enhances TNBC cell death both *in vitro* and *in vivo* when combined with a PARPi. RAD51 also showed efficacy in combination treatments for TNBC when combined with PARPi. Together, these agents led to substantial tumor growth inhibition, without notable toxicity, *in vivo* xenografts and patient-derived tumor xenografts [57]. Ngoi et al. [58] explored hematologic concerns regarding ATR inhibitors by retrospectively comparing the complete blood count of patients pre- and during treatment with oral ATR inhibitor. Results indicated anemia in 47.5% of patients, neutropenia in 31.9%, and thrombocytopenia in 11.4%. Baseline predictors of severe anemia include lower hematocrit (HR 3.76), higher red cell distribution width, and higher ATR inhibitor dose. The study also noted that, in combination with PARP inhibitors, there was a significant increase in eutropenia (HR 4.15) and thrombocytopenia (HR 3.90) risk. Deppas et al. [59] revealed an increased risk of cardiotoxicity with high plasma concentrations of ceralasertib in mice studies. CHEK1, WEE1, and RAD51 inhibitors also demonstrate toxicities; however, limited clinical data and an *in vitro*-to-clinical translation gap emphasize

exploring dosing schedules to mitigate toxicity. Giudice et al. [60] evaluated the CHEK1 inhibitor, prexasertib, and its clinical activity in patients with breast or ovarian cancer. Results demonstrated 30% of patients with tumor shrinkage and progression free survival of 4–6 months on average. Although hematologic toxicities were manageable and pre-clinical data are suggestive of benefits, toxicity limits the aggressive potential to benefit patients clinically. Similar to CHEK1 inhibitors, WEE inhibitor, adavosertib, displays dose-limiting gastrointestinal and hematologic toxicities that have restricted clinical development. In the phase II trial of CCNE1-amplified tumors [61], toxicities were most notable for neutropenia (80.2%), hyperglycemia (5.6%), and stomatitis (5.6%). RAD51 inhibitors remain mainly preclinical without regulatory approval. One study [62] evaluated 15 patients treated for more than 100 days with adverse effects such as grade 1–2 fatigue (20.5%), hyperuricemia (11%), and nausea (11%). This highlights the need for further research on how different DDR inhibitors interact with each other and other cancer treatments.

6.2 PI3K/AKT/mTOR Signaling

Two ATP-competitive AKT inhibitors, ipatasertib and capivasertib, have emerged as leading agents targeting this pathway. Clinical outcomes across trials, however, have shown mixed results, emphasizing the importance of biomarker-driven patient selection [63].

The LOTUS trial [64] demonstrated improvement in progression-free survival (PFS) in patients treated with ipataserib and paclitaxel (6.2 months) compared to placebo (4.9 months), particularly in tumors harboring PIK3CA, AKT1, or PTEN alterations in which median PFS further increased (9 months). The IPATunity trial, a randomized double-blind placebo-controlled phase 3 trial, also evaluated the efficacy of Ipatasertib and paclitaxel (n = 186) vs. placebo and paclitaxel (n = 87) in advanced or metastatic TNBC with no prior chemotherapy exposure. Patients had tumor markers with PIK3CA, AKTI, and PTEN alterations [65,66]. Similarly, the PAKT trial displayed improved outcomes with capivasertib with paclitaxel, displaying a median PFS of 5.9 months compared to 4.2 months with placebo (HR 0.74). OS in the treatment group was 19.1 months, which was statistically significant from the placebo group with 12.6 months (HR 0.61, p = 0.04). As in LOTUS, the benefit was accentuated in biomarker-selected tumors, with a median PFS of 9.3 months compared to 3.7 months in the placebo group (HR 0.30, p = 0.01) [67] (Table 1).

The FAIRLANE neoadjuvant trial demonstrated higher pathologic complete response (pCR) rates with ipatasertib in patients with pathway-activated tumors [68]. Despite these encouraging signals, broad application to unselected TNBC cohorts has yielded less consistent improvements, underscoring the mutation-dependent efficacy of AKT inhibition (Table 1).

Emerging evidence also highlights several synergy avenues to enhance PI3K/AKT/mTOR-targeted therapy [69] (Fig. 2). PI3K inhibitors such as SF1126 demonstrate increased cytotoxicity when combined with agents that suppress upstream signaling, including EGFR inhibitors (e.g., gefitinib) [70]. Dual PI3K/mTOR inhibitors, such as apitolisib and BEZ235, show improved pathway suppression by preventing mTOR-mediated feedback activation that often undermines single-node inhibitors [71]. Additionally, modulation of resistance-associated molecules offers novel combinations; loss of B7-H3, for example, enhances sensitivity to the mTOR inhibitor everolimus, indicating a potential interaction between immune evasion pathways and PI3K signaling [72] (Table 1). These multi-targeted strategies collectively support the concept that effective inhibition of PI3K/AKT/mTOR in TNBC may require combined or layered therapeutic approaches rather than monotherapy (Fig. 2). Table 1 summarizes the outcomes of the various trials discussed above.

Table 1: Comparative summary of the LOTUS, IPATunity130, PAKT, and FAIRLANE trials discussed in Section 6.2.

Trial	Trial Phase	Sample Size (*n*)	Treatment	Overall Response Rate (ORR)	Progression Free Survival (PFS)	Hazard Ratio	Overall Survival (OS)	Hazard Ratio	Biomarker Status
LOTUS Trial	2	62	Ipatasertib + Paclitaxel	~40%	6.2 months (95% CI (3.6–9.1))	0.60 (95% CI 0.37–0.98)	Data is immature at time of analysis	Not reported	PTEN Status IP3K/AKT Pathway Alterations
		62	Placebo + Paclitaxel	32%	4.9 months (95% CI (1.9–7.3))				
IPATunity130	3	168	Ipatasertib + Paclitaxel	39%	7.4 (95% CI (5.6–8.5))	1.02 (95% CI (0.71–1.45)	24.4 months	1.08 (95% CI (0.73–1.58)	PIK3CA AKTI PTEN
		87	Placebo + Paclitaxel	35%	6.1 (95% CI (5.5–9.0))		24.9 months		
PAKT Trial	2	70	Capivasertiv + Paclitaxel	34.8%	5.9 (95% CI (3.8–7.5))	0.74 (95% CI (0.5–1.08))	19.1 months	0.61 (95% CI (0.37–0.99))	PIK3CA AKTI PTEN
		70	Placebo + Paclitaxel	28.8%	4.2 (95% CI (3.5–5.2))		12.6 months		
FAIRLANE Neoadjuvant	2	76	Ipatasertib + Paclitaxel	39%	Not reported	Not reported	Not reported	Not reported	PIK3CA AKTI PTEN
		75	Placebo + Paclitaxel	9%	Not reported		Not reported		

6.3 Surface Antigens and Novel ADC/CAR-T Targets

Surface antigens are vital in enabling targeted therapies for TNBC by providing tumor-specific markers for selective drug delivery or immune cell activation [73]. In TNBC, there are several cell surface antigens that have been identified as therapeutic targets due to their overexpression and tumor specificity, which in turn have been shown to enhance treatment outcomes for Antibody-Drug Conjugate (ADC) treatments and Chimeric Antigen Receptor T cell (CAR-T cell) treatments.

ADCs are a new class of molecules comprised of recombinant monoclonal antibodies that are targeted at a specific cell surface antigen [73]. This can be conjugated to a cytotoxic agent to overcome the limitations of conventional chemotherapy. By expressing the specific cell surface antigen, ADCs are able to directly deliver the chemotoxic agent to the tumor cell, minimizing off-target systemic toxicities [73]. (CAR)-T cells have also emerged as a promising immunotherapeutic strategy to treat TNBC [74]. CAR usually is composed of a single chain variable fragment, which recognizes tumor antigen-specific antibodies [75]. Once attached to the tumor cell, the CAR-T cell amplifies the natural immune response to target and destroy the tumor cell. Several CAR-T cell therapies targeting TNBC are currently in early-phase clinical trials, including MUC1-directed huMNC2-CAR44, which has completed dose escalation without dose-limiting toxicities [76]. Preclinical studies of next-generation approaches such as dual-targeting B7-H3/CSPG4 CAR-T cells and fourth-generation armored CARs have demonstrated enhanced efficacy in patient-derived xenograft models [77].

Both ADC and CART-cell treatments can target trophoblast surface antigen 2 (Trop-2) to target tumor cells. Trop-2 is a cell surface glycoprotein that acts as a transmembrane transducer of intracellular calcium signals [73]. When activated, it stimulates cell growth, proliferation, invasion, and survival, and in tumor cells, it is often overexpressed [73]. Sacituzumab govitecan (SG) is an ADC that consists of a humanized monoclonal antibody hRS7, which targets Trop-2 and is linked to the topoisomerase I inhibitor SN-38 by a hydrolysable linker. Once SG is internalized into the cell, it delivers the SN-38 intracellularly. SG treatment has been shown to improve treatment outcomes in patients with TNBC [73].

Another promising target for ADC and CAR T-cell therapy includes lipolysis-stimulated lipoprotein receptor (LSR) [78]. LSR is expressed in the plasma membrane, cytoplasm, and nucleus of cancer cells that are likely to metastasize and is associated with poor prognosis for TNBC patients. Downregulation of LSR is likely to inhibit cell proliferation and invasion. When used as a target, the anti-LSR mAb showed high surface binding to TNBC cells *in vitro* and selective tumor targeting *in vivo* with minimal off-target effects in normal human and mouse organs [78].

In conclusion, surface antigens such as Trop-2 and LSR are driving the development of ADCs and CAR-T therapies in TNBC, with sacituzumab govitecan the current standard for ADCs. Despite these advances, CAR-T cell therapy in TNBC remains limited by challenges inherent to solid tumors, including antigen heterogeneity and escape, off-target toxicity, impaired T-cell trafficking, and persistence within the immunosuppressive TME. These barriers underscore the need for improved antigen selection, dual-targeting strategies, and combination approaches to enhance safety and efficacy [79]. The ongoing investigation and expansion of this field are expected to further improve treatment outcomes for patients with TNBC.

6.4 Surface Antigens and Novel ADC

Surface antigens are vital in enabling targeted therapies for TNBC by providing tumor-specific markers for selective drug delivery or immune-mediated cytotoxicity [73]. In TNBC, several cell surface antigens have been identified as therapeutic targets due to their overexpression and tumor specificity, which have facilitated the development of antibody–drug conjugates (ADCs).

ADCs are a novel class of therapeutics composed of a monoclonal antibody directed against a tumor-associated surface antigen conjugated to a cytotoxic payload [73]. By selectively binding tumor cells that express the target antigen, ADCs enable targeted intracellular delivery of chemotoxic agents, thereby minimizing systemic off-target toxicity compared with conventional chemotherapy [73].

Trophoblast surface antigen 2 (Trop-2) is a transmembrane glycoprotein that functions as a signal transducer involved in calcium signaling, cell proliferation, invasion, and survival, and is frequently overexpressed in TNBC [73]. Sacituzumab govitecan (SG) is an ADC consisting of a humanized anti–Trop-2 monoclonal antibody (hRS7) conjugated via a hydrolysable linker to SN-38, the active metabolite of irinotecan. Upon internalization, SG delivers SN-38 intracellularly, resulting in targeted cytotoxicity. Clinical trials have demonstrated the significant efficacy of SG in TNBC, leading to its regulatory approval and establishment as a standard ADC therapy in this disease [6,73].

Another emerging ADC target is the lipolysis-stimulated lipoprotein receptor (LSR), which is expressed on the plasma membrane, cytoplasm, and nucleus of aggressive TNBC cells and is associated with poor prognosis [78]. Preclinical studies have shown that anti-LSR monoclonal antibodies exhibit strong surface binding to TNBC cells *in vitro* and selective tumor targeting *in vivo* with minimal off-target toxicity, supporting LSR as a promising ADC target [78].

6.5 Epigenetic Reprogramming

Epigenetic and metabolic reprogramming are central to the treatment strategies for TNBC, which allows for new therapeutic approaches for personalized therapy. Epigenetic modifications include DNA methylation, histone modifications, and microRNA regulation, and play a pivotal role in TNBC pathogenesis [34]. In addition, metabolic reprogramming allows for the identification of key signaling molecules and can allow for the possibility of using dietary interventions to modulate epigenetic markers for individualized treatment [80].

Epigenetic modifications, such as DNA methylation, allow for control of gene expression [81]. The major epigenetic alteration in tumor cells is the hypermethylation of tumor suppressor genes (TSG) and the global hypomethylation of DNA replication proteins. Advances in our understanding of DNA methylation can enhance insight into breast cancer pathogenesis, prognosis, and therapeutic response [27]. If DNA methylation can be controlled, halting the growth and metastasis of TNBC can greatly increase treatment outcomes [81]. Epigenetic targets in TNBC include DNA methylation, histone modifications, and noncoding RNAs. These targets are being investigated for therapeutic strategies like using DNA methyltransferase inhibitors (DNMTis) to reactivate silenced tumor suppressor genes, and histone deacetylase inhibitors (HDACis) to restore normal gene function, and miRNAs to affect tumor growth and metastasis. Targeting these pathways can also enhance the effectiveness of immunotherapy by improving the tumor microenvironment and immune response [21,34,35,82,83].

DNA methyltransferase inhibitors (DNMTis), like Decitabine, have been evaluated in preclinical trials of TNBC and shown to reverse silencing and restore BRCA1 expression and PARPi sensitivity, resulting in enhanced DNA damage and apoptosis in tumor cells [84]. More recent murine studies have also shown that decitabine consistently induced epigenetic reprogramming with no significant adverse effects [85,86]. Similarly, the 2025 human phase II clinical trial by Bear et al. found decitabine was well tolerated in TNBC patients as well, with rare adversities including hypothyroidism, adrenal insufficiency, and Guillain-Barré syndrome [87].

Histone deacetylase inhibitors (HDACis) can reverse abnormal histone acetylation and suppress tumor growth [34]. However, despite the well-established role of HDAC enzymes in key cancer pathways, there

remains difficulty in implementing effective anti-tumoral responses in solid tumors, like TNBC [88]. Clinical trials with single agent HDACis have shown disappointing results in TNBC, with limited efficacy compared to their success in hematologic malignancies [89]. On the other hand, combination strategies pairing HDACis with chemotherapy, immunotherapy, or other targeted agents have demonstrated more promising outcomes, with one phase II trial involving romidepsin, cisplatin, and nivolumab achieving a 44% objective response rate in pretreated metastatic TNBC [90].

EZH2, a histone methyltransferase, is another epigenetic target in TNBC, as its inhibition can reverse gene silencing mediated by H3K27me3. A 2024 preclinical study by Schade et al. [91] found that AKT inhibitors synergized with EZH2 suppressors to induce robust tumor regression in multiple *in vivo* TNBC models. Though preclinical studies highlight the therapeutic potential of targeting EZH2, further pre-clinical validation and early-phase clinical trials are required to assess safety, efficacy, and translatability in human patients.

Dysregulation of miRNAs contributes to TNBC progression by altering key cellular processes, including proliferation, apoptosis, epithelial-mesenchymal transition, invasion, and metastasis [92]. Targeting specific miRNAs, like the miR-200 family, can inhibit tumor cell migration and invasion, while restoration of tumor-suppressor miRNAs such as miR-34a, miR-204, and miR-205 demonstrates significant anti-tumor activity in preclinical TNBC models [93–95]. Some miRNAs are silenced by DNA methylation and can be reactivated by DNMTis [21,34,35,82,83]. However, clinical translation of miRNA therapeutics remains limited by challenges such as poor stability, inefficient cellular uptake, off-target effects, and immunologic reactions [96]. Delivery barriers also represent a significant obstacle, as naked miRNA molecules are quickly degraded and therefore require complex nanocarrier systems, such as lipid nanoparticles or exosome-based platforms, to achieve effective therapeutic effects [97]. Despite promising preclinical trials, no miRNA therapies have progressed beyond phase II trials for TNBC, with early trials such as MRX34 being terminated due to immune-related toxicities, highlighting the need for improved delivery, dose optimization, and rigorous safety assessment before clinical advancement [96,98].

6.6 Metabolic Reprogramming

Metabolic reprogramming has been shown to play a key role in molding tumor development and can impact stromal and immune cell fractions, tumor microenvironment composition, and activation [80]. In patients with TNBC, a better survival rate is associated when metabolic reprogramming targets the intracellular energy production processes. In TNBC, the major glycolytic transporters and enzymes significantly upregulate glycolysis and its downstream pathways [99]. Metabolic reprogramming targets in triple-negative breast cancer (TNBC) include glycolysis and its related pathways, as well as glutaminolysis, fatty acid oxidation (FAO), and the pentose phosphate pathway (PPP) [99,100]. One strategy is to use glycolysis inhibitors like 2-deoxyglucose (2-DG) and the combination of cisplatin-tegafur-lonidamine to interfere with glycolysis and sensitize the tumor cell to other chemotherapeutic agents. Using glycolytic inhibitors has shown promising impacts on preclinical trials; however, more research is needed before it can be proven in a clinical setting [80] (Fig. 3). Other specific targets are enzymes like PKM2 and LDHA in glycolysis, PLA2G4F in lipid metabolism, and factors that drive metabolic changes like Myc and HIF-1α [99,100]. TNBC upregulates glucose transporters and key enzymes in glycolysis, such as hexokinase (HK) and lactate dehydrogenase A (LDHA). Pyruvate kinase muscle isozyme M2 (PKM2) is a key enzyme that can be targeted to redirect glycolytic intermediates towards anabolic pathways (Fig. 3). TNBC is often more sensitive to glutamine depletion, making glutaminolysis a potential target. TNBC relies on FAO to meet bioenergetic needs, and this pathway presents a potential target. The Pentose

Phosphate Pathway (PPP) pathway is upregulated in TNBC to generate NADPH for biosynthesis and to cope with oxidative stress [99,100]. PLA2G4F is specifically expressed in malignant cells and promotes proliferation, migration, and survival by disrupting glucose and lipid metabolism [101]. Dysregulation of the c-Myc transcription factor is thought to play a critical role in driving increased glucose metabolism in TNBC [102]. Hypoxia-inducible factor-1 alpha (HIF-1α) is upregulated in TNBC and promotes a glycolytic phenotype. Research is exploring how to use nutrients and nutraceuticals to perturb these metabolic processes, potentially in combination with other therapies. Molecules like Beclin-1 are involved in autophagy, a process that can be impaired in TNBC, leading to increased glycolysis. Thus, enhancing autophagy is another potential strategy [99,100] (Fig. 3).

Overall, epigenetic modulation and metabolism reprogramming can reprogram TNBC towards less aggressive and more treatable states, enhance immune response, and overcome resistance. These treatment methods can be used as powerful adjuncts with traditional chemotherapeutic treatments or target immune therapies to improve treatment outcomes in patients with TNBC.

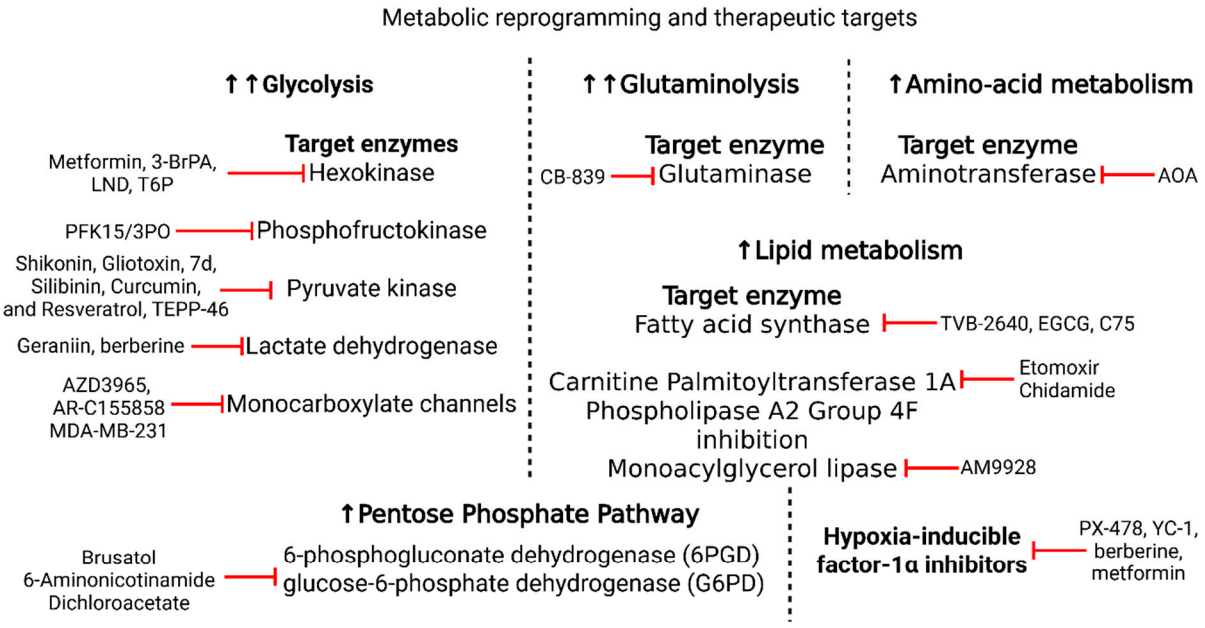

Figure 3: Emerging metabolic targets and molecules in research for triple negative breast cancer. Metabolic targets for Triple-Negative Breast Cancer (TNBC) focus on exploiting its reliance on rapid nutrient consumption and altered metabolic pathways, including high glycolysis, glutaminolysis, and fatty acid oxidation. Key targets include glycolytic enzymes (GLUT, HK, LDH, MCT), glutaminase (GLS1), fatty acid synthesis/oxidation, and the kynurenine pathway to overcome therapeutic resistance and inhibit tumor growth. 3-Bromopyruvic acid (3-BrPA targets HK2), metformin (targets HK1 and HK2), lonidamine (LND targets HK2 and the mitochondrial VDAC1 channel), lovastatin (HK2), trehalose-6-Phosphate (T6P targets HK2), CB-839 (Telaglenastat), aminooxyacetate (AOA), Imidazopyridine-based Thiazole Derivative (7d) [99,103–113]. lactate dehydrogenase A (LDHA), glucose transporters (GLUT), hexokinase (HK), Monocarboxylate Transporter (MCT). Created in BioRender. Rai, V. (2026) https://BioRender.com/5c8cx3p.

6.7 Addressing Heterogeneity

Heterogeneity in TNBC is a major obstacle to treatment responses because the disease is composed of several distinct subtypes—basal-like, mesenchymal, immunomodulatory, and luminal-androgen receptor. Each subtype is driven by a different oncogenic process and possesses different vulnerabilities. Heterogeneity can be addressed by molecular subtyping and biomarker-driven treatment selection, which can enable more personalized and effective therapy. TNBC can be highly heterogeneous at the molecular level, with distinct subtypes. Interpatient and intratumor heterogeneity may be due to genetic abnormalities that eventually drive specific transcriptional factors. van der Noord et al. [114] summarized the heterogeneous genomic landscape in TNBC. The study reported that, along with TP53, mutations or copy number alterations in DNA damage signaling and repair pathways (e.g., BRCA1), growth factor signaling pathways (e.g., PIK3CA, EGFR), cell cycle regulators (e.g., RB1, CDK6, CCND1), or other downstream transcription factors (e.g., MYC) also play a role in TNBC heterogeneity [114]. Understanding the unique tumor markers can allow for more personalized treatment and improved treatment outcomes [115]. In the FUTURE-SUPER phase 2 trial, women between the ages of 18 and 70 years were separated based on molecular subtyping of their TNBC and given treatments based on their specific subtype [116]. This study showed that molecular subtyping allowed for first-line treatments to be tailored to the specific subtype, which drastically improved progression-free survival compared to traditional treatments alone [116]. This improvement was consistent amongst different subtypes, which makes it promising for future treatment methods.

In summary, addressing TNBC heterogeneity through biomolecular subtyping has been shown to enhance personalized treatment protocols and enhance progression-free survival compared to traditional chemotherapeutic treatments alone. The identification of specific vulnerabilities within the molecular makeup of TNBC allows for new targets for treatment combinations. Likely, treatment guidelines will further divide to match the specificity of the subtyping [117]. Further research must be done to analyze additional biomarkers and further refine subtype-based regimens. Additionally, to address the challenges of heterogeneity in clinical trials, incorporating 'omics for enhanced stratification' should be considered. Integrating multi-omics data (genomics, transcriptomics, and proteomics) and leveraging data science and bioinformatics, distinct patient subgroups based on molecular and immune profiles can be identified. Using this approach, tumors can be grouped by gene mutations, pathway activity, and immune landscape, each with different prognoses and therapeutic responses. This will provide precise patient selection for a clinical trial and improved chances of true treatment effects detection and personalized therapies [118].

6.8 Androgen Receptor (AR) Targeted Therapy

An important category of the TNBC tumors is the Luminal Androgen Receptor (LAR) subtype, characterized byhigh Androgen Receptor expression and growth driven by AR signaling despite lacking ER and PR. Gene expression profiling has shown that LAR tumors exhibit significant AR mRNA expression that was 9-fold higher in LAR tumors compared with other subtypes and showed significant luminal gene expression of FOXA1, KRT19, and XBP1 despite ER negativity [8]. Most TNBC tumors are classified as basal-like, but 82% of LAR subtypes were found to be either Luminal A or Luminal B and support a hormone-driven biology distinct from other TNBC subtypes [8]. This unique molecular architecture provides a strong biological rationale for androgen receptor targeted therapeutic strategies in LAR TNBC.

There is robust clinical evidence for the usage of enzalutamide, a second-generation AR antagonist that inhibits AR signaling at multiple levels. A phase II clinical study with Enzalutamide showed that 55% of TNBC patients had AR expression, with ≥10% showing AR expression by IHC [119]. Enzalutamide showed a clinical benefit rate of 33% at 16 weeks and 28% at 24 weeks, with 8% having achieved a complete or partial response.

The data showed that on enzalutamide, there was a median progression free survival (PFS) of 3.3 months and overall survival of 17.6 months, pointing to meaningful clinical activity in AR positive TNBC [2].

Bicalutamide is a first-generation AR antagonist that demonstrates activity in AR positive TNBC. Clinical studies have shown that bicalutamide has a clinical benefit rate of approximately 19% at six months, with a median PFS of 12 weeks. Although the effect is less potent than enzalutamide, it supports AR signaling as a viable therapeutic target for the LAR subtype [2,119].

Importantly, the LAR subtype of TNBC has a high frequency of PIK3CA mutations. LAR cell lines have been shown to have strong sensitivity to AR and PI3K inhibitors, which is similar to ER positive breast cancer. Preclinical studies have shown that LAR TNBC cell lines demonstrate enhanced sensitivity to combined AR and PI3K inhibition, suggesting mechanistic crosstalk between these pathways [2]. As such, dual inhibition of AR and PI3K signaling is currently being explored, with preclinical models supporting this strategy as a promising direction for future combination therapy trials in LAR-TNBC.

6.9 EGFR Targeted Therapies

EGFR is a receptor tyrosine kinase that is overexpressed in approximately 70–78% of basal-like TNBCs, making it a biologically appealing therapeutic target [2]. Inhibition of EGFR has produced meaningful clinical benefits in several malignancies, including colorectal and head and neck cancers, which has led to considerable interest in extending EGFR-targeted strategies to TNBC [115].

Despite this rationale, EGFR-directed monotherapy has yielded disappointing results in TNBC. Agents such as cetuximab, a chimeric anti-EGFR monoclonal antibody that is effective in other EGFR-driven tumors, have demonstrated minimal activity in TNBC populations. This limited efficacy is thought to reflect the complex biology of TNBC, including pathway redundancy, compensatory signaling mechanisms, marked tumor heterogeneity, and the absence of reliable predictive biomarkers [120]. Combination strategies have therefore been explored in an attempt to improve outcomes. In a phase II study of cetuximab plus carboplatin in pretreated TNBC, the objective response rate was 18%, with a clinical benefit rate of 27%, a median progression-free survival of 2 months, and a median overall survival of 12 months, suggesting that benefit was confined to a subset of patients [115].

While conventional EGFR-targeted approaches have not demonstrated consistent clinical benefit in unselected TNBC populations, ADC therapies targeting EGFR have shown encouraging preclinical results. In EGFR-high TNBC models, including MDA-MB-468 cells, an EGFR-targeted ADC achieved an IC_{50} of approximately 0.8 nmol/L, whereas unconjugated cetuximab or control ADCs exhibited minimal cytotoxicity even at concentrations exceeding 10,000 nmol/L. Mechanistic studies further demonstrated efficient internalization of the cetuximab–CDK inhibitor ADC in EGFR-expressing TNBC cells, leading to G1 cell-cycle arrest across monolayer cultures, spheroids, and patient-derived xenograft models [120].

In summary, these findings highlight EGFR as a biologically relevant but therapeutically challenging target in TNBC. Molecular heterogeneity, signaling redundancy, and adaptive compensation limit the effectiveness of EGFR-directed monotherapy and conventional combination regimens. In contrast, ADC-based strategies that leverage EGFR as a delivery target rather than a signaling dependency may offer a more effective path forward for EGFR-targeted therapy in TNBC.

7 Immunotherapy-Based Therapeutics

7.1 PD-1/PD-L1 Signaling and Therapeutic Targeting in TNBC

PD-1 is expressed on activated and exhausted $CD8^+$ T cells and subsets of NK cells. Engagement of PD-1 by PD-L1, which is frequently expressed on TNBC tumor cells and immune cells, suppresses T-cell

receptor signaling and cytokine production, leading to T-cell exhaustion and immune escape despite antigen recognition [121]. PD-L1 expression in TNBC is induced both by IFN-γ signaling within an inflamed tumor microenvironment and by oncogenic pathways such as PI3K/AKT, STAT3, and NF-κB, linking tumor-intrinsic signaling to immune suppression [121].

The efficacy of PD-1/PD-L1 restriction is therefore highly dependent on the TME. Immune-inflamed "hot" TNBCs, characterized by high $CD8^+$ TILs, active IFN-γ signaling, and elevated PD-L1 expression, are more likely to respond to immune checkpoint inhibition. In contrast, immune-cold or immune-excluded TNBCs exhibit low TIL infiltration, suppressive cytokine environment, and stromal barriers that limit T-cell trafficking, resulting in poor responses to monotherapy [11,121].

Clinically, immune checkpoint inhibitors targeting the PD-1/PD-L1 axis include pembrolizumab and nivolumab (anti–PD-1), and atezolizumab, durvalumab, and avelumab (anti PD-L1). Although these agents share a common mechanism of immune reactivation, they differ in immune cell specificity, toxicity profiles, and combinatorial potential [12]. A recent meta-analysis by Zhang et al. [122] evaluating PD-1/PD-L1 inhibitor-based regimens in unresectable locally advanced and metastatic TNBC demonstrated a significant improvement in PFS compared with chemotherapy alone (pooled HR = 0.82, corresponding to an 18% reduction in the risk of progression or death), with benefit enriched in PD-L1 positive tumors [122]. However, pooled analysis did not demonstrate a statistically significant OS benefit, despite numerical improvements in select trials. In the neoadjuvant setting, checkpoint inhibitor-based combinations significantly increased pCR rates, supporting their use in earlier-stage disease [122].

Biomarker analyses indicate that PD-L1 expression enriches for therapeutic benefit but is not an absolute predictor of response, as activity has also been observed in PD-L1 negative tumors, underscoring the limitations of PD-L1 as a standalone biomarker and highlighting the importance of TIL density and immune phenotypes [122]. Resistance to PD-1/PD-L1 blockade is driven by immunosuppressive cytokines and cellular components within the TME, including TGF-β mediated T-cell exclusion, myeloid-derived suppressor cells that inhibit T-cell activation via arginase-1 and reactive oxygen species, and M2-polarized tumor-associated macrophages that secrete IL-10 and TGF-β and express PD-L1 [121]. Additionally, PI3K/AKT pathway activation, often through PTEN loss, promotes PD-L1 upregulation, impairs antigen presentation, and contributes to adaptive immune resistance [121].

Together, these findings support PD-1/PD-L1 blockade as a central immunotherapeutic strategy in TNBC while underscoring the need for combination approaches targeting cytokine signaling, immune-suppressive myeloid populations, and oncogenic pathways to overcome resistance and improve therapeutic durability.

7.2 CAR-T Cell Therapy

Chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising immunotherapeutic strategy for TNBC, leveraging genetically engineered T cells to recognize tumor-specific surface antigens [74]. CAR constructs typically consist of a single-chain variable fragment derived from an antibody that recognizes a tumor-associated antigen, fused to intracellular signaling domains that activate T-cell cytotoxicity upon antigen engagement [75].

Several CAR-T cell therapies targeting TNBC-associated antigens are currently under investigation in early-phase clinical trials. For example, MUC1-directed huMNC2-CAR-T therapy has completed dose-escalation studies without dose-limiting toxicities, demonstrating feasibility and preliminary safety [78]. Preclinical studies of next-generation CAR-T approaches, including dual-targeting B7-H3/CSPG4

CAR-T cells and fourth generation "armored" CAR-T cells, have shown enhanced antitumor efficacy in patient-derived xenograft models [80].

Both ADC and CAR-T strategies can target shared surface antigens such as Trop-2, further highlighting the therapeutic relevance of antigen selection in TNBC. However, CAR-T cell therapy in solid tumors remains limited by challenges including antigen heterogeneity, antigen escape, impaired T-cell trafficking, limited persistence within the immunosuppressive tumor microenvironment, and potential off-target toxicity. These barriers underscore the need for improved antigen selection, combinatorial strategies, and microenvironment-modulating approaches to enhance CAR-T cell efficacy in TNBC [80].

8 Clinical Trials

Clinical trials are conducted to offer cutting-edge therapies while advancing medical knowledge, with a focus on safety and effectiveness compared to current standards, not typically using placebos if standard treatments exist, and involving phases (I–III) to determine safety, effectiveness, and superiority over existing care. Table 2 summarizes the ongoing clinical trials for TNBC. Along with these clinical trials, a study of sacituzumab tirumotecan as monotherapy and in combination with pembrolizumab in participants with TNBC and Sacituzumab Tirumotecan Plus Pembrolizumab versus TPC in TNBC who did not achieve pCR is ongoing at MERCK and the University of California at San Francisco (UCSF) (https://www.merckclinicaltrials.com/oncology/breast/). Another clinical trial at UCSF is evaluating the efficacy of Avelumab with Binimetinib, Sacituzumab Govitecan, or Liposomal Doxorubicin in treating stage IV or unresectable, recurrent TNBC (https://clinicaltrials.ucsf.edu/trial/NCT03971409).

Clinical trials are useful tools to investigate novel and improved treatment; however, there are real world issues. Clinical trials are increasingly expensive, with costs driven by complex protocols, high participant recruitment/retention needs, and strict regulatory compliance. Infrastructure challenges include managing multiple sites, implementing electronic systems (e.g., CTMS, EDC), maintaining specialized equipment (e.g., −80°C storage), and ensuring trained personnel. Key cost components are staff, site monitoring, and data management [123].

Table 2: Ongoing clinical trials for triple-negative breast cancer (TNBC) therapy.

Clinical Trial ID/Phase	Target	Strategy	Patient Population	Outcome/Results
NCT02574455 (ASCENT): Phase III	*Trop-2* (targeted ADC)	Sacituzumab govitecan vs. physician's choice chemotherapy	Metastatic TNBC after ≥2 prior therapies	Improved responses; median PFS and OS benefit over standard chemo (basis of FDA approval).
NCT05374512 (TROPION-Breast02): Phase III	*Trop-2*	Datopotamab deruxtecan (Dato-DxD; "Datroway") vs. chemotherapy	Previously untreated locally recurrent/metastatic TNBC are not candidates for immunotherapy	Significant improvement in OS & PFS vs. chemo; median OS ~23.7 mo vs. ~18.7 mo and median PFS ~10.8 mo vs. ~5.6 mo.
NCT06112379 (TROPION-Breast04): Phase III *ongoing*	*Trop-2 + PD-L1 axis*	Dato-DxD + durvalumab (Imfinzi) neoadjuvant/adjuvant vs. pembrolizumab + chemo (early TNBC)	Stage II-III TNBC (or HR-low, HER2-neg)	Evaluating pCR, iDFS; results pending completion.
NCT05382299/NCT05382286: Phase III *ongoing*	*Trop-2*	Sacituzumab govitecan-hziy ± pembrolizumab vs. standard	Metastatic/advanced TNBC	Designed to assess PFS/OS with combinations vs. standard therapy; results pending.

Table 2: *Cont.*

Clinical Trial ID/Phase	Target	Strategy	Patient Population	Outcome/Results
NCT05633654 (ASCENT-05): Phase III *ongoing*	*Trop-2 + PD-1*	Sacituzumab govitecan + pembrolizumab vs. physician's choice	High-risk early TNBC with residual disease after surgery	Evaluating adjuvant benefit after neoadjuvant therapy; results pending.
NCT06449222: Phase II *ongoing*	*BNT327*	BNT327 with chemo (various agents)	Locally advanced or metastatic TNBC	Safety/efficacy evaluation; estimated completion 2029.
Pembrolizumab + Binimetinib (Mayo listing): Phase I/II *ongoing*	PD-1/MEK	Immunotherapy + MEK inhibitor	Locally advanced/metastatic TNBC	Early phase safety/dose/preliminary efficacy.

Note: Triple negative breast cancer (TNBC), overall survival (OS), progression free survival (PFS), Food and Drug Administration (FDA), programmed cell death protein 1 (PD-1), human epidermal growth factor receptor 2 (HER2), mitogen-activated protein kinase kinase (MEK or MAPKK).

9 Future Directions

Recent advances in triple-negative breast cancer (TNBC) research show a growing shift toward increasingly integrative and precision-based approaches to understanding and treating this highly complex disease. Innovations spanning multi-omic technologies, single-cell and spatial profiling, targeted therapeutics, and artificial intelligence are redefining how tumor biology and the TME are classified. At the same time, developments in liquid biopsy and combination therapies offer new opportunities for dynamic disease monitoring and improved treatment efficacy. While these approaches offer promising directions, they also introduce new challenges related to implementation, cost, and accessibility that remain important considerations moving forward. The following sections discuss the recent advancement in TNBC therapeutics using these strategies.

As technology continues to advance, multi-omics has become an increasingly popular strategy for integrating diverse biological datasets into cancer research. Algorithmic frameworks underlie the basis of multi-omics, enabling the collection and comparison of genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome data. This integrated approach deepens the understanding of the underlying biology in complex diseases such as TNBC [124]. For example, Chappell et al. [125] applied a multi-omics approach to the well-established TNBC lines MCF10A (human breast epithelial), MDA-MB-231 (TNBC-BRCA1wt), and HCC1937 (TNBC-BRCA1 5382insC) to analyze key signaling pathways, gene expression, and epigenetic effects. Their work highlighted significant divergence in pathway activity between BRCA1-mutant and BRCA1-wildtype TNBC cell lines and encouraged future exploration of the systems-level mechanisms underlying this heterogeneity. Additionally, multi-omics analysis may clarify how pathway variability, such as differential PI3K/AKT/mTOR regulation across TNBC subtypes, contributes to treatment resistance and therapeutic response.

Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) also offer hopeful avenues for furthering TNBC therapies. scRNA-seq enables transcriptomic and epigenomic profiling at the individual cellular level, allowing researchers to identify distinct cell subsets within TNBC and map their interactions. Furthermore, ST preserves spatial context, pinpointing where specific genes are expressed within the tumor and revealing how cell populations are arranged and interact within the TME [126]. This approach has been utilized by researchers, such as Hammerl et al. [127], who demonstrated a strong correlation between prognosis and both the presence and spatial positioning of $CD8^+$ T-cells within TNBC tumors.

Other strategies addressing the complex TME of TNBC involve integrating combination therapies. For example, antibody drug conjugates (ADCs) improve specificity while maintaining effective cytotoxicity.

Patients receiving ICIs, PARP inhibitors, and chemotherapy achieve better therapeutic outcomes due to the synergistic mechanisms of the drugs. Moreover, recent developments in nano-formulations may enhance TNBC treatment by improving drug delivery through passive and active targeting. Combining nanocarrier delivery with ADCs or multi-agent regimens could further improve target specificity and toxicity, while minimizing off-target damage [127].

Epigenetic alterations also play an imperative role in shaping the TME and offer another important therapeutic frontier for targeting TNBC heterogeneity. Dysregulations of DNA methylation, histone modifications, and regulatory proteins, such as bromodomain and extra-terminal domain (BET), play a crucial role in TNBC development and treatment resistance [35,128]. Hypermethylation of tumor suppressor gene promoters and imbalances in histone methyltransferases, including Enhancer of zeste homolog 2 (EZH2) and histone deacetylases (HDACs), largely influence tumor cell proliferation, survival, and metastasis. Additionally, epigenetic changes play a role in shaping the TME immune cell composition, cytokine signaling, and immune checkpoint expression, ultimately contributing to immune evasion. Targeting specific inhibitors such as EZH2 and HDAC inhibitors in combination with immunotherapy offers the potential to overcome immune evasion and enhance therapeutic outcomes in TNBC [35]. Additional work has utilized gas chromatography-mass spectrometry-based metabolomics to explore the relationship of metabolic alterations within TNBC subtypes. Through this, researchers hope to explain the metabolic pathways affected by treatment with combining Pigment Epithelium-Derived Factor (PEDF) with Doxorubicin (Dox), to understand the molecular mechanisms driving the synergy or antagonism between these therapies [129]. Studies like this not only evaluate the efficacy of TNBC treatments in cancer eradication but also investigate the specific mechanisms underlying how and why they work, providing a foundation for future therapies.

Liquid biopsy approaches, including circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), offer a promising future strategy for non-invasive monitoring of tumor heterogeneity and treatment response. For example, a 2024 study by Chen et al. [130] demonstrated that persistent ctDNA positivity during mid-neoadjuvant chemotherapy was significantly associated with worse overall survival (OS) and recurrence-free survival (RFS), whereas baseline ctDNA and CTC positivity alone did not show a significant association with these outcomes. However, the authors noted important limitations, including limited scale, heterogeneity within systemic treatment regimens, and reduced generalizability [130]. Additionally, the clinical implementation of ctDNA-based monitoring remains constrained by technical and logistical challenges, including dependence on strict sample handling, lack of assay standardization, variability in analytical sensitivity, and low tumor DNA shedding in early-stage TNBC. As a result, ctDNA levels may fall below detection thresholds despite the presence of residual disease, limiting its ability to reliably influence treatment decisions [131].

Artificial intelligence (AI) modeling also offers an exciting avenue for developing novel TNBC therapies. Machine learning enables the utilization of predictive models based on other successful cancer therapies. For example, a recent study conducted by Garrone et al. [132] collected data from successful immunotherapy trials in melanoma to inform and serve as the foundation for developing new TNBC therapies. AI-guided discovery of genes has also contributed to identifying new therapeutic targets. For example, Ling et al. [133] reported on the AI-driven discovery of YH395A, a novel TGFBR1 inhibitor, which was found to have potent anti-tumor activity against TNBC. However, despite these advances, AI approaches face challenges, including the need for extremely large biological datasets and the computational complexity of building models capable of extracting and integrating such high-volume information [132]. Clinical implementation of AI, scRNA-seq, and spatial transcriptomes faces significant barriers including high costs, need for large, standardized datasets, computational complexity, technical variability, and lack of standardized analytic

protocols [134]. This highlights the need for code sharing between AI models to validate models and ensure the translatability required for large-scale implementation. Moreover, AI faces significant challenges roots in data representativeness, algorithmic fairness and methodological heterogeneity [135]. Disparities relating to race, gender, and socio-economic status influence disease risk and recurrence among individuals, but many datasets are used to train and evaluate AI models that remain fundamentally biased. For example, a 2024 analysis of cancer genomics databases (n = 28,136,410 patients) found that 89.14% of tumor samples were collected from White patients, with only 7% Asian, 0.55% African American and 0.21% Hispanic representation, significantly deviating from global ethnic proportions and emphasizing the persistent underrepresentation of ethnic minority populations [136]. Limitations relating to cost-effectiveness were also demonstrated in a 2026 assessment that found that in 98% of simulations, AI was not cost-effective and yielded only modest reductions in breast cancer mortality [137].

Policy and clinical implications for triple-negative breast cancer (TNBC) management highlight a tension between the clinical, transformative success of immunotherapy and significant, systemic disparities in access and affordability. Key findings indicate that while advanced therapies like pembrolizumab show improved outcomes, their high costs, combined with structural, socio-economic, and geographical barriers, perpetuate inequity, particularly for Black women and in low- and middle-income countries (LMICs) [138,139]. While ICIs have shown efficacy, many novel therapies, such as sacituzumab govitecan, are often deemed less cost-effective due to high prices, with some estimates exceeding $600,000–$1,000,000 per Quality-Adjusted Life Year (QALY) in certain analyses. First-line treatments combining ICIs with chemotherapy, such as pembrolizumab, are standard for PD-L1-positive disease, yet they increase costs significantly compared to chemotherapy alone, creating a high barrier for adoption in resource-limited systems. To maximize cost-effectiveness, some analysts suggest that moving immunotherapies into early-stage (neoadjuvant/adjuvant) settings is more cost-effective than using them only in late-stage metastatic disease [140–142]. Black women in the United States face a disproportionate burden of TNBC, characterized by higher incidence, more aggressive biology, and higher mortality rates compared to white women. Even after accounting for insurance type and comorbidities, Black women are less likely to receive timely surgery and chemotherapy, contributing to a 40% higher death rate from breast cancer. Data shows Black patients with TNBC are less likely to receive immunotherapy than white patients. Structural racism, lower median household income in communities, and limited access to specialized, high-quality cancer centers are major drivers of these disparities. There is an urgent need to increase representation of Black women in clinical trials, improve access to biomarker testing (e.g., PD-L1), and support community-based, Black-led initiatives that address social determinants of health [142–144].

Collectively, these approaches reflect both the progress that has been made and the challenges that remain in improving outcomes for patients with TNBC. While multi-omics integration, spatial and single-cell technologies, and AI-driven discovery hold promise for improving patient stratification and identifying novel targets, barriers related to cost, data standardization, and clinical implementation remain substantial. Persistent disparities in access to care and underrepresentation in research highlight the critical need for more inclusive and equitable frameworks. Addressing these disparities will be critical to fully realize the potential of novel technologies and translate scientific progress into meaningful clinical benefit for all patients with TNBC.

10 Conclusion

Although conventional cytotoxic chemotherapy has proven promising results in TNBC, novel strategies allow for minimizing the adverse systemic effects and achieving personalized care. Recent developments in

multi-omics have refined TNBC subclassification, revealing unique molecular and metabolic vulnerabilities, especially in lipid metabolism. Emerging therapeutic strategies now focus on DNA damage pathways beyond PARP, PI3K/AKT/mTOR blockade, and novel immunotherapies such as checkpoint inhibitors and CAR T-cells. Integrating genomic, transcriptomic, proteomic, and metabolomic data enables rational drug combination designs and patient stratification, moving toward individualized treatment and improved clinical outcomes. AI-guided drug discovery further highlights the potential for precise, individualized therapeutics. Prospective trials will test omics-guided combos for safety and efficacy. Cross-disciplinary collaboration will accelerate translation of these strategies into routine care. Advances in multi-omics technologies have refined TNBC subclassification, illuminating novel therapeutic targets across signaling, immune, and metabolic pathways. While several targeted therapies have already achieved FDA approval, such as pembrolizumab (2021), sacituzumab govitecan (2020) and PARP inhibitors, the clinical translation of multi-omics guided precision strategies is expected to mature in the upcoming years as ongoing phase III trials validate subtype-based treatment approaches [116,145]. Ongoing integration of molecular profiling, immunotherapy, and precision drug development offers a promising avenue for improving survival and personalizing care in TNBC.

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Abbreviations

2-DG	2-Deoxyglucose
ADC	Antibody–Drug Conjugate
ADCs	Antibody–Drug Conjugates
AKT	Protein Kinase B (PKB)
AR	Androgen Receptor
ATR	Ataxia Telangiectasia and Rad3-related protein
BC	Breast Cancer
BET	Bromodomain and Extra-Terminal domain
BL1	Basal-like 1 subtype
BL2	Basal-like 2 subtype
BRCA1/2	Breast Cancer Gene 1/Gene 2
CAR-T	Chimeric Antigen Receptor T-cell
CBR	Clinical Benefit Rate
$CD8^+$ TILs	CD8-positive Tumor-Infiltrating Lymphocytes
CDK4/6	Cyclin-Dependent Kinase 4/6
CHEK1 (CHK1)	Checkpoint Kinase 1
DFS	Disease-Free Survival
DNA	Deoxyribonucleic Acid

DDR	DNA Damage Response
Dato-DxD	Datopotamab deruxtecan
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
EZH2	Enhancer of Zeste Homolog 2
HDAC	Histone Deacetylase
HER2	Human Epidermal Growth Factor Receptor 2
HR+	Hormone-Receptor Positive
ICIs	Immune Checkpoint Inhibitors
iDFS	Invasive disease-free survival
IFN-γ	Interferon Gamma
IL-4/5/10/17	Interleukins 4, 5, 10, 17
IM (subtype)	Immunomodulatory subtype
LSR	Lipolysis-Stimulated Lipoprotein Receptor
LAR	Luminal Androgen Receptor subtype
MAPK	Mitogen-Activated Protein Kinase
MEK	MAPK/ERK kinase
M (MES)	Mesenchymal subtype
MDSCs	Myeloid-Derived Suppressor Cells
M1	Classically activated macrophages
M2	Alternatively activated macrophages
MSC	Mesenchymal Stromal-Cell subtype
mTOR	Mammalian Target of Rapamycin
NK cells	Natural Killer cells
OS	Overall survival
PCR	Pathologic Complete response
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
Trop-2	Trophoblast surface antigen 2

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