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Narrative Review on Emerging Target Therapies in Triple Negative Breast Cancer

Dr.T.Sai Pavan reddy[1*], Dr.Muralidharan Gopalan[2], Dr.Charuhasini[3], Dr.Dhananjayan govind[4]

[1]Junior resident, General surgery department, Shri sathya sai medical college and research institute , chennai 603108

[2]Professor and H.O.D, General surgery department, Shri sathya sai medical college and research institute , chennai 603108

[3]Senior resident, General surgery department, Shri sathya sai medical college and research institute , chennai 603108

[4]Senior resident, General surgery department, Shri sathya sai medical college and research institute , chennai 603108

*Corresponding author: Dr.T.Sai Pavan reddy, Junior resident, General surgery department, Shri sathya sai medical college and research institute , chennai 603108

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ABSTRACT:

A sample of Er3+ doped fluorochloride glass was prepared by incorporating chlorine (Cl^-) into a fluoride glass (ZBLAN) using the conventional melt quenching technique. The research investigated the chemical stability, thermal stability, and fluorescent properties of the glass by varying the Cl^- concentration. It was observed that increasing the Cl^- concentration enhances the luminescent intensity in the infrared region. The strongest luminescent intensity was achieved at a Cl^- concentration of 15 mol%. Similarly, the study compared the effects of different Er3+ concentrations on the luminescent properties of the fluorochloride glass, identifying 1 mol% Er3+ as the optimal doping concentration. Consequently, the glass composition is denoted as ZBLAN:15Cl, 1Er. Experimental analyses including X-ray diffraction (XRD), absorption spectrum, near-infrared spectrum (NIR), and mid-infrared spectrum (MIR) were conducted to characterize the Er3+ doped fluorochloride glass. The energy level diagram of Er3+ and the infrared luminescence of the sample were thoroughly analyzed, focusing on the excitation at 980 nm. Judd-Ofelt parameters were computed to understand the luminescent behavior. It was observed that Ω2 initially increased and then decreased with varying Cl^- content in the glass matrix, whereas Ω4 and Ω6 remained relatively stable across different compositions. This variability in Ω2 suggests a change in the crystal field environment around the Er3+ ions due to the introduction of Cl^-. In Er3+ doped fluoride glass, the addition of Cl^-significantly enhances the mid-infrared luminescence intensity. The calculated Judd-Ofelt theoretical parameters indicate that Cl^- introduction enhances the covalency of the coordination bond with Er3+, thereby reducing local symmetry and boosting the luminescent properties of the fluoride glass. This research on rare earth ion-doped fluorochloride glass provides a theoretical foundation for improving luminescent characteristics and offers valuable insights for the development and application of similar mid-infrared luminescent materials.

INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, distinguishing it from other breast cancer subtypes such as luminal A, luminal B, and HER2-enriched tumors. Due to the lack of these receptors, TNBC does not respond to endocrine or HER2-targeted therapies, making chemotherapy the primary systemic treatment option. Despite being grouped histologically, TNBC comprises a physiologically heterogeneous collection of

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malignancies with diverse genetic, epigenetic, and transcriptomic profiles that significantly influence therapeutic response and clinical outcomes. Although most TNBC cases exhibit basal-like features, the terms "TNBC" and "basal-like breast cancer" are not interchangeable, as discordance exists between classifications based on gene expression profiling and immunohistochemistry. Basal-like breast cancers demonstrate low ER, PR, and HER2 expression, but show high levels of CK5, CK14, caveolin-1, CAIX, p63, and EGFR/HER1, reflecting their origin from basal/myoepithelial mammary cells. Additionally, aberrant expression of DNA repair proteins in TNBC, including frequent overexpression of p53, may influence sensitivity to chemotherapeutic agents, particularly platinum-based regimens. Several additional and potentially targetable molecular pathways implicated in the pathogenesis of basal-like TNBC include the mutagen-activated protein kinase pathway, the Akt signaling pathway, and the poly ADP-ribose polymerase 1 (PARP1) pathway, highlighting opportunities for precision-based therapeutic interventions.

EPIDEMIOLOGY

Numerous extensive population-based research demonstrate that triple-negative breast cancer (TNBC) is up to three times more prevalent in pre-menopausal African-American women. Certain epidemiological studies, such as the Carolina Breast Cancer Study, demonstrated that, in comparison to luminal A tumors, basal-like tumors were more prevalent among women with early menarche, increased parity, younger age at full-term pregnancy, shorter breastfeeding duration, elevated body mass index, and higher waist-to-hip ratio, particularly in premenopausal patients [14]. A study conducted by Bauer et al. [13] revealed that younger, non-Hispanic Black and Hispanic women diagnosed with triple-negative breast cancer (TNBC) exhibited more aggressive tumors and experienced inferior survival outcomes irrespective of stage. Moreover, non-Hispanic black women with advanced-stage triple-negative breast cancer exhibited the lowest survival rates across comparable cohorts.

Clinical Characteristics

Triple-negative breast cancer (TNBC) is recognized for its aggressive nature, typically presenting at a younger age, with larger mean tumor sizes, higher tumor grades, and occasionally, an elevated incidence of lymph node positivity [15]. This group is characterized by an early peak of recurrence between the first and third year post-diagnosis, as well as more aggressive metastases, which are predominantly observed in the viscera, particularly the lungs and brain, while being less prone to bone dissemination [16]. Histological data indicate that most triple-negative breast tumors originate from ductal tissue; however, other aggressive phenotypes, such as metaplastic, apocrine, and adenoid cystic types, also seem to be disproportionately represented. A histological examination of basal-like tumors, all ER/HER2 negative, demonstrated a significant increase in mitotic count, geographic necrosis, invasive boundary expansion, and stromal lymphocytic response.

PROGNOSIS

A poorer prognosis in basal-like breast cancer, relative to the luminal type, has been consistently established by numerous investigations [19]. Population-based studies have similarly shown reduced breast cancer-specific survival in individuals with triple-negative breast cancer (TNBC) compared to those with the luminal subtype. A recent Canadian study [15] assessing prognosis in over 1,500 women indicated a heightened risk of distant recurrence and mortality in women with triple-negative breast cancer, relative to those with non-triple-negative illness. Research has repeatedly demonstrated that individuals diagnosed with triple-negative disease experience more frequent aggressive visceral and soft tissue relapses, while bone relapses are less prevalent compared to those with ER-positive disease [20]. Approximately 15% of all breast cancer patients will get brain metastases. In a cohort exceeding 3,000 patients with brain metastases originating from breast cancer, treated between 1989 and 2006, multivariate analysis revealed that triple-negative status constituted the most significant risk factor for the onset of cerebral metastasis (odds ratio=4.16; $p<0.001$), surpassing HER2 positive status (OR=3.43; $p=0.005$) [21]. A separate trial involving patients with BRCA1 mutations demonstrated an 82% full pathological response in individuals treated exclusively with Cisplatin.

TREATMENT STRATEGIES

Despite the association of triple-negative breast tumors with a generally unfavorable breast cancer-specific

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prognosis, the majority are not intrinsically resistant to chemotherapy. Nevertheless, impacted patients often have a markedly unfavorable prognosis, with numerous experiencing early relapses and ultimately succumbing to the illness. Numerous medicines are being formulated that specifically target biomarkers associated with TNBC or the basal-like subtype. These techniques encompass EGFR-targeted drugs, androgen receptor-targeted agents, anti-angiogenic medications, and PARP inhibitors, providing possible treatment alternatives for triple-negative illness. Their present application, however, is predominantly restricted to clinical trials, necessitating additional study to ascertain targets that yield significant therapeutic advantages. Triple-negative breast cancer associated with BRCA1 gene mutations may exhibit heightened sensitivity to DNA-damaging drugs like Cisplatin. Recent intriguing targets include signaling pathways such as NOTCH, Hedgehog, and Wnt/β-Catenin, with research indicating that medicines that modulate these pathways may affect apoptosis and impede tumor development.

Chemotherapy

Adjuvant chemotherapy has demonstrated efficacy in enhancing both disease-free survival and overall survival in patients with breast cancer. Nonetheless, TNBC is devoid of hormone receptors and HER2 amplification, which are commonly targeted in luminal or HER2-positive malignancies, rendering hormonal treatments such as SERMs, aromatase inhibitors, or HER2 antagonists useless. Neoadjuvant studies have highlighted the correlation between chemosensitivity and outcomes, demonstrating increased sensitivity to anthracycline or anthracycline/taxane-based regimens, such as Doxorubicin and Cyclophosphamide, in basal-like or ER-negative breast cancers relative to luminal subtypes. Basal-like and HER2-positive malignancies exhibit the highest response rates; however, disease-free and overall survival outcomes are the most unfavorable in these categories, despite initial chemosensitivity. Although triple-negative illness frequently exhibits a favorable response to anthracycline/taxane treatment, the likelihood of relapse remains elevated if the tumor is not entirely eliminated.

Moreover, preclinical and clinical investigations demonstrate that tumors exhibiting BRCA1 failure are responsive to platinum-based drugs like Cisplatin and Carboplatin, which function by generating DNA damage and facilitating apoptosis. The protein p63, along with p53, has been linked to the regulation of a survival pathway that directly influences Cisplatin sensitivity in triple-negative breast cancer (TNBC) and may function as a biomarker for forecasting response to platinum-based treatment. Nonetheless, these results necessitate additional validation, and platinum drugs are not currently advised for normal adjuvant therapy in TNBC.

Inhibitors of EGFR

EGFR is expressed in a significant percentage of triple-negative breast tumors, presenting a possible avenue for targeted therapy. therapeutic trials assessing EGFR inhibitors, including Cetuximab in conjunction with platinum-based chemotherapy, have demonstrated modest response rates and therapeutic advantages in patients with advanced triple-negative breast cancer (TNBC). Other studies evaluating the combination of EGFR inhibitors with chemotherapeutic drugs have shown enhanced pathological response rates. Nevertheless, the overall outcomes of EGFR-targeted therapy in TNBC have been inconsistent, and existing evidence has not endorsed the broad use of these medicines.

PARP Inhibitors

PARP1 is essential for the repair of DNA damage. The inhibition of PARP results in the buildup of DNA breaks, with cells deficient in functional BRCA1 or BRCA2 being especially susceptible to this process. Multiple PARP inhibitors, such as Olaparib and Velaparib, have undergone assessment in clinical trials and show potential for the treatment of TNBC. Initial studies indicated a decrease in the risk of disease progression and mortality; however, subsequent phase trials failed to consistently show substantial therapeutic benefit, resulting in the cessation of several medications. Investigations persist to determine if particular biomarker-defined subsets may derive advantages from PARP inhibition.

Antiangiogenic Agents

Bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), has been thoroughly investigated in metastatic breast cancer.

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Clinical trials indicated enhancements in progression-free survival with the addition of Bevacizumab to regular chemotherapy, benefiting both TNBC and non-TNBC patients. Current research is assessing this combination as adjuvant therapy for triple-negative breast cancer (TNBC). Moreover, some small-molecule inhibitors aimed at the VEGF pathway have exhibited efficacy in pre-treated TNBC; nevertheless, definitive proof proving an overall survival advantage is still necessary prior to justifying broad approval and clinical application.

MOLECULAR SUBGROUPS AND ATTRIBUTES OF TRIPLE-NEGATIVE BREAST CARCINOMA

To prevent the indiscriminate formulation of therapeutic strategies, it is essential to determine the intricate subtypes and molecular characteristics of TNBC, as these elements are intimately associated with clinical outcomes, such as chemotherapy response, recurrence patterns, and prognosis. Various methodologies, such as somatic DNA mutations, copy number variations, gene expression profiling, and immunological metagene data, were utilized to examine triple-negative breast tumors (TNBCs) as a notably heterogeneous category of malignancies.

In 2011, Lehmann identified six clusters from 21 breast cancer datasets. Gene Ontology study indicated that the BL1 and BL2 subtypes were associated with DNA damage response and cell cycle genes, exhibiting a preferential response to cisplatin. The LAR subtype demonstrates elevated expression of genes linked to enhanced androgen receptor (AR) signaling and responsiveness to AR antagonism. The M and MSL subtypes exhibited heightened expression of genes associated with cell differentiation and growth factor signaling pathways. The susceptibility of these subtypes to the phosphoinositol-3 kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor and the ABL/SRC inhibitor was evidenced in cellular models. The IM cluster exhibited enrichment in various immunological signaling pathways. This research significantly advanced the understanding of medication design and clinical therapy. In 2016, triple-negative breast cancer (TNBC) was categorized into four subtypes (BL1, BL2, M, and LAR) for the purpose of neoadjuvant chemotherapy (NAC) selection [7]. The IM and MSL subtypes derive from invading lymphocytes and tumor-associated stromal cells, respectively. The updated classification revealed variations among groups in their responses to chemotherapy, as well as in local and distant cancer progression and prognosis. Comprehensive study indicated that the highest and lowest pathological complete response (pCR) rates were 41% for BL1 patients and 18% for BL2 patients receiving comparable NAC regimens [7]. Burstein and associates aimed to reclassify four clusters: LAR, mesenchymal, basal-like immune-suppressed (BLIS), and basal-like immune activated. The BLIS cluster had the most worst outcome regarding disease-free survival (DFS), indicating the significant function of the immune system in triple-negative breast cancer (TNBC) [8]. In 2019, Yi-Zhou Jiang et al. categorized triple-negative breast cancers (TNBCs) into four subtypes—LAR, immunomodulatory, basal-like immune-suppressed, and mesenchymal-like—utilizing RNA sequencing, exome sequencing, and copy number array analysis of TNBC cases in China [9]. Furthermore, these researchers identified elevated occurrences of PIK3CA mutations and LAR subtypes relative to prior findings from The Cancer Genome Atlas (TCGA), suggesting possible therapeutic management by subtype-specific and molecular targeted therapy. Immune metagene data categorized triple-negative breast cancer (TNBC) into three subtypes: C1 (LAR), C2 (BL with a diminished immune response and elevated M2-like macrophages), and C3 (BL with an augmented immunological response and reduced M2-like macrophages). C3 patients had markedly superior event-free survival compared to C2 patients [10].

Molecular changes were evaluated to identify possible targets for the treatment of TNBC. A defect in homologous recombination, partially linked to the loss of breast cancer susceptibility gene (BRCA) function in breast cancer, is associated with a favorable response to cisplatin treatment [11]. In a preliminary phase II clinical trial, individuals with BRCA-mutant triple-negative breast cancer exhibited an overall response rate (ORR) of 80% following monotherapy with cisplatin [12]. A weakness in homologous recombination results in an inability to repair DNA double-strand breaks and compromised DNA replication forks. Consequently, these individuals exhibit sensitivity to poly-adenosine diphosphate [ADP]-ribose polymerase (PARP) inhibitors (PARPi), since PARP is the enzyme

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responsible for repairing DNA single-strand breaks and preserving genomic integrity.

MOLECULAR-TARGETED THERAPY

In 2020, conventional neoadjuvant chemotherapy achieved a pathological complete response (pCR) in roughly 35–45% of patients with triple-negative breast cancer (TNBC) [13]. Moreover, most patients who responded to conventional therapeutic alternatives were confined to the nonmetastatic stage; nonetheless, these standard treatments have not substantially altered the overall survival rate. Consequently, the examination of the molecular factors contributing to treatment resistance is emphasized. Balko and colleagues made a significant contribution by identifying the molecular profile of residual triple-negative breast cancer following neoadjuvant chemotherapy. Notably, they observed substantial changes in gene expression following NAC in comparison to the TCGA dataset results. Notably, over 90% of the residual patients had pathway alterations amenable to targeted therapy, facilitating optimal selection of such treatments. These data indicate that combined therapy is likely to address the issue of incomplete remission. This molecular profiling study identified five principal pathways or functional modifications: cell cycle alterations, alterations in the PI3K/AKT/mTOR pathway and/or phosphatase and tensin homolog (PTEN), amplification of growth factor receptors, alterations in RAS/mitogen-activated protein kinase (MAPK), and alterations in DNA repair mechanisms. Post-NAC residual TNBC exhibited a significant enrichment of myeloid cell leukemia-1, myc, and cell cycle-related regulators in comparison to TCGA basal-like tumors. Modifications in PTEN and Janus protein tyrosine kinase 2 (JAK2) were also noted. Moreover, clinical study indicated that PTEN change was associated with improved overall survival, while JAK2 amplification and BRCA1 mutation or truncation were considered adverse prognostic markers [2]. This categorical biological profile has prompted the investigation of sensible clinical strategies for targeted intervention, encompassing cell cycle inhibition, anti-angiogenesis, MAPK and PI3K pathway inhibition, DNA damage response blocking, and their combinations.

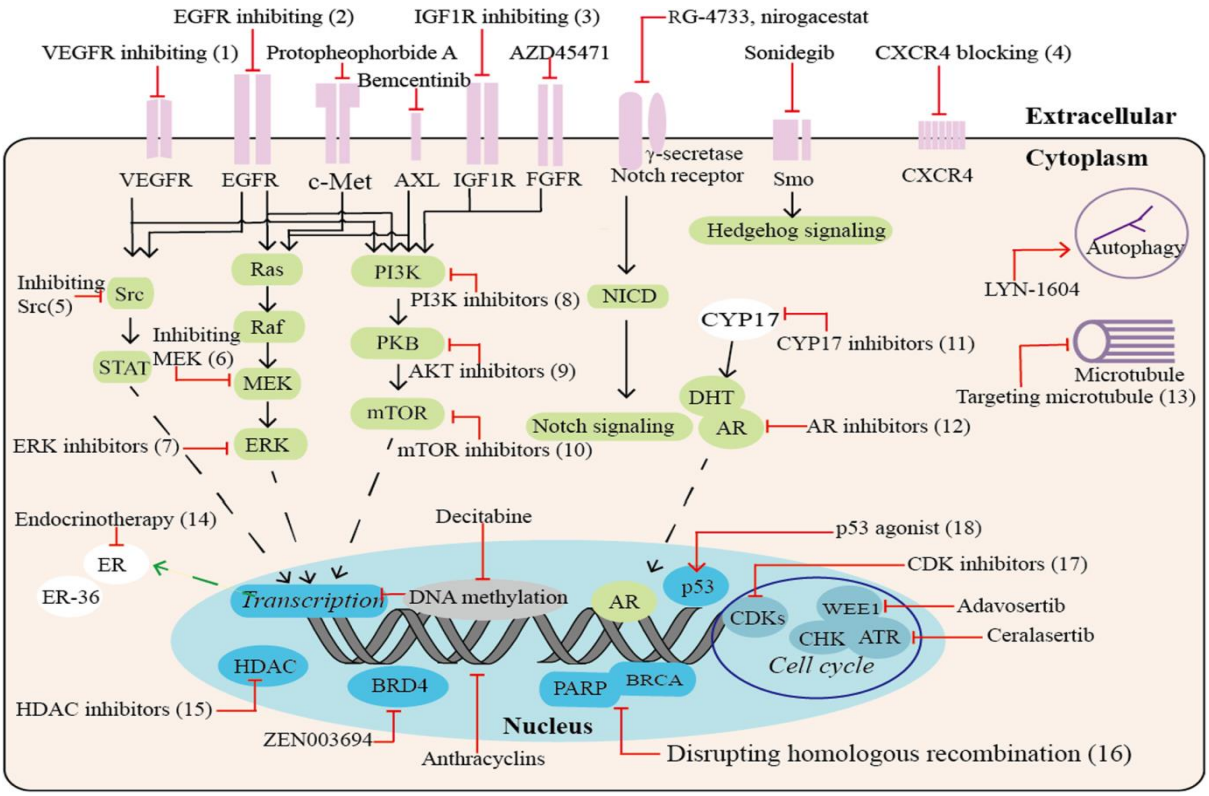

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FIGURE: Potential therapeutic targets and appropriate drugs in TNBC. The schematic shows several major abnormal signaling pathways (green), excessive activated receptors (purple), and other key molecules involved in proliferation and progression (blue) in TNBC. Drugs specifically targeting molecules are indicated by red arrows, and the number represents the following agents: (1) VEGFR inhibitors (cediranib, apatinib, lenvatinib) and VEGFR mAb (bevacizumab); (2) EGFR inhibitors (afatinib, gefitinib), EGFR mAbs (nimotuzumab, panitumumab, cetuximab, and SCT200) and ADCs (anti-EGFR-IL-dox and U3-1402); (3) IGF1R blocking drugs (linsitinib, NVP-AEW541, and BMS-754807); (4) CXCR4 antagonists (balixafortide) and CXCR4-binding peptide (DV1); (5) Src inhibitors (dasatinib and BJ-2302); (6) MEK inhibitors (trametinib and binimetinib); (7) ERK inhibitors (BL-EI001 and nifetepimine); (8) PI3K inhibitors (alpelisib and buparlisib); (9) AKT inhibitors (ipatasertib and capivasertib); (10) mTOR inhibitors (everolimus and MLN0128); (11) CYP17 inhibitors (abiraterone acetate and orteronel); (12) AR inhibitors (bicalutamide, enzalutamide, and enobosarm); (13) microtubule stabilizer (taxanes, vincristine, and eribulin); multiple target inhibitors (AMXI-5001 and ixabepilone); and ADCs (mirvetuximab, soravtansine, CX-2009, and SAR566658); (14) endocrinotherapy (tamoxifen and letrozole); (15) HDAC inhibitors (panobinostat, belinostat, chidamide, romidepsin, entinostat, and CUDC-907); (16) PARPi (olaparib, veliparib, talazoparib, niraparib, and rucaparib) and platinum-based agents (cisplatin and carboplatin); (17) CDK inhibitors (trilaciclib, palbociclib, abemaciclib, ribociclib, dinaciclib, and PF-06873600); and (18) p53 agonist (PRMIA-1 and APR-246). ADCs, antibody–drug conjugates; AR: androgen receptor; AXL: AXL receptor tyrosine kinase; BRCA: breast cancer susceptibility gene; BRD4: bromodomain containing 4; CDK: cyclin-dependent kinases; CXCR4: C-X-C chemokine receptor type 4; CYP17: 17-[α]-hydroxylase/17:20-lyase (CYP17); ER: estrogen receptor; DHT: dihydrotestosterone; EGFR: epidermal growth factor receptor; FGFR: fibroblast growth factor receptor; HDAC: histone deacetylase; IGF1R: type 1 insulin-like growth factor receptor; PARP: poly-adenosine diphosphate ribose polymerase; and VEGFR: vascular endothelial growth factor receptor

RATIONALE AND OBJECTIVES OF THE SYSTEMATIC REVIEW

Triple-negative breast cancer represents the most aggressive subtype of breast cancer, characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression. Its heterogeneity, high proliferative index, early metastatic potential, and limited responsiveness to endocrine or HER2-directed therapies contribute to poor survival outcomes. Conventional chemotherapy remains the mainstay of treatment; however, therapeutic resistance, high relapse rates, and modest long-term benefits highlight an urgent need for alternative therapeutic strategies. Advances in molecular profiling have identified numerous actionable pathways and biomarkers—including PARP, PI3K/AKT/mTOR, EGFR, AR signaling, immune checkpoint proteins, cancer stem cell regulators, angiogenic pathways, and epigenetic drivers—that offer new opportunities for precision medicine. Emerging targeted therapies directed at these pathways have demonstrated promising preclinical and early clinical results, but their clinical value, comparative efficacy, safety, and optimal patient selection remain unclear. A systematic review is warranted to consolidate current evidence, evaluate therapeutic potential, and guide future clinical practice and research.

Objectives

Primary Objective

- To systematically evaluate emerging targeted therapeutic strategies for triple-negative breast cancer and determine their efficacy, safety, and clinical applicability.

Secondary Objectives

1. To categorize emerging targeted therapies based on their molecular mechanisms, including DNA repair pathways, growth factor signaling, immune modulation, epigenetic regulation, metabolic pathways, and cancer stem cell–related targets.
2. To assess clinical outcomes associated with these therapies, including response rates, progression-free survival, overall survival, pathological complete response, and toxicity profiles.

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3. To identify biomarkers predictive of therapeutic response and resistance, enabling stratification of TNBC subtypes likely to benefit from individualized targeted treatment.
4. To compare novel targeted treatments with current standard therapies and highlight gaps that necessitate further research or ongoing clinical trials.
5. To provide evidence-based recommendations for integrating emerging targeted therapies into future TNBC management algorithms.

SIGNIFICANCE OF THE REVIEW

This systematic review holds considerable significance in the evolving landscape of triple-negative breast cancer (TNBC) management. TNBC remains a major clinical challenge due to its intrinsic heterogeneity, aggressive biology, lack of hormone receptors and HER2 amplification, and the consequent reliance on chemotherapy as the primary treatment modality. Despite incremental progress, current therapeutic options offer limited survival benefits, high recurrence rates, and substantial toxicity, underscoring an urgent need for effective alternative strategies.

Emerging targeted therapies have shown encouraging results in early-phase trials, exploiting specific molecular vulnerabilities such as DNA repair defects, aberrant signaling pathways, immune dysregulation, and cancer stem cell dynamics. However, the available evidence is dispersed, rapidly expanding, and often complex to interpret. This review synthesizes and critically appraises current data, offering clarity on which emerging targets demonstrate meaningful clinical potential and which remain investigational.

By consolidating mechanistic insights, therapeutic outcomes, and biomarker-driven approaches, the review provides a comprehensive reference for clinicians, researchers, and policymakers. It supports informed decision-making regarding treatment selection, highlights opportunities for personalized therapy, identifies gaps requiring further investigation, and guides the prioritization of future clinical trials. Ultimately, this review contributes to the advancement of precision oncology in TNBC and paves the way toward improving survival and quality of life for affected patients.

Past Research on TNBC and Targeted Therapies

Rodler et al. highlight that TNBC remains difficult to treat due to its aggressive biology and lack of hormone or HER2 targets. Although initially responsive to chemotherapy, patients frequently relapse, prompting investigation into alternatives such as platinum agents, angiogenesis inhibitors, EGFR-targeted therapies, and PARP inhibitors. The authors conclude that TNBC treatment is still empirical, and advances depend on identifying predictive biomarkers.Lu Cao and Niu emphasize the heterogeneity of TNBC and describe emerging therapeutic options, particularly immune checkpoint inhibitors. They note improved pathological responses when PD-1/PD-L1 inhibitors are combined with chemotherapy and enhanced outcomes in BRCA-mutated tumors when used with PARP inhibitors. The review concludes that personalized strategies aligned with TNBC biology are essential for better outcomes. Li Yin et al. classify TNBC into molecular subtypes with distinct treatment sensitivities. Subtypes such as LAR and BLIA exhibit different prognoses and therapeutic targets, including androgen receptor inhibition and immunotherapy approaches. The authors stress that molecular subtyping is crucial to guide therapy selection and improve survival. Pascual and Turner review the PI3K/AKT/mTOR pathway and its relevance in TNBC. They report that pathway alterations occur in a significant subset of TNBC and that combining AKT inhibitors with chemotherapy enhances clinical responses. They conclude that targeted inhibition of the PI3K pathway is a promising strategy, particularly when supported by biomarker selection.

Table: Summary of Past Research on TNBC and Targeted Therapies

Study / Author	Year	Objective	Key Findings	Conclusion
Liu et al. –	**2023**	To summarize	Identified ICIs (PD-	Immunotherapy

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Advances in Immunotherapy for TNBC		immunotherapy advances and explore strategies to improve TNBC outcomes.	1/PD-L1, CTLA-4) as promising options; highlighted tumor microenvironment's role in resistance and therapeutic response.	combined with chemotherapy or emerging modalities may enhance treatment efficacy.
Rodler et al. – Current Treatment Options in TNBC	**2010/2011**	To review chemotherapy and investigational approaches for TNBC.	TNBC shows sensitivity to chemotherapy but exhibits poor overall survival; platinum drugs, angiogenesis inhibitors, and PARP inhibitors show potential.	Novel targeted therapies exploiting DNA repair defects may improve patient outcomes.
Lu Cao & Yun Niu – Special Histological Types and Emerging Therapeutic Methods	**2020**	To review histological variants of TNBC and emerging targeted therapies.	Novel targets such as AR and PI3K/AKT/mTOR pathways demonstrate therapeutic promise; rare histological types may have better prognosis.	Molecularly guided therapies can improve clinical outcomes and personalize TNBC management.
Li Yin et al. – TNBC Molecular Subtyping and Treatment Progress	**2020**	To review TNBC subtypes and current therapeutic options.	TNBC is a heterogeneous disease with different molecular subtypes; varying therapeutic responses depend on subtype characteristics.	Precise TNBC classification is essential to identify effective targeted therapies and improve survival.
Pascual & Turner – Targeting the PI3K Pathway in TNBC	**2019**	To evaluate PI3K/AKT/mTOR pathway activation and targeted therapy relevance in TNBC.	PI3K pathway alterations occur in 25–30% of advanced TNBC; AKT inhibitors improve progression-free survival when combined with chemotherapy.	Biomarker-based selection is key to optimizing PI3K pathway inhibitors in TNBC treatment.

WHAT IS NEW IN THE LITERATURE

Recent literature on triple-negative breast cancer (TNBC) has shifted from viewing TNBC as a single, chemoresponsive entity to a **biologically stratified, targetable disease**. Large genomic and transcriptomic studies now define distinct molecular subtypes and "Fudan typing," directly linking subtypes to specific vulnerabilities and guiding precision treatment strategies. There has been rapid expansion of **emerging targets and pathways**, including PI3K/AKT/mTOR, DNA damage response (PARP and platinum sensitivity), androgen receptor signaling, angiogenesis, epigenetic regulators, regulated cell death (especially ferroptosis), and tumor metabolism, each supported by early-phase trials or robust preclinical data.

A major evolution is the **integration of immunotherapy and targeted therapy**. Updated reviews highlight that PD-1/PD-L1 blockade has moved into standard-of-care in selected early and metastatic TNBC, while newer work systematically explores rational combinations—ICIs with chemotherapy, PARP inhibitors, anti-angiogenic agents, TKIs, and metabolic

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modulators—to overcome primary and acquired resistance. In parallel, **next-generation immunologic approaches**—CAR-T and CAR-NK cells, bispecific antibodies, antibody–drug conjugates against novel antigens (e.g., TROP-2, ICAM-1, Nectin-4), vaccines, oncolytic viruses, and nanovaccine platforms—have moved from concept to early clinical testing in TNBC, markedly broadening the therapeutic arsenal beyond classical checkpoint inhibitors.

Another new theme is the use of **advanced models and technologies**—patient-derived xenografts, organoids, and liquid biopsy–based biomarkers—to screen drugs, predict neoadjuvant response, and study chemoresistance mechanisms in a clinically relevant manner. Collectively, the latest literature moves the field from descriptive reviews of TNBC aggressiveness and chemotherapy outcomes toward **mechanism-driven, biomarker-selected, and combination-based strategies**, laying the foundation for your systematic review on emerging targeted therapies.

Methodology

The methodology outlines the systematic process adopted to explore the current landscape of emerging targeted therapies in triple-negative breast cancer (TNBC). This section describes the research design, data sources, eligibility criteria, study selection, and synthesis approach used to identify and evaluate relevant literature. The aim is to ensure scientific rigor, transparency, and accuracy in presenting evidence that reflects recent therapeutic advancements in TNBC.

1. Research Design

This review utilized a structured literature review design guided by the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The review focused on published evidence describing novel and emerging therapeutic targets, including molecular pathways, targeted agents, immunotherapeutic strategies, and clinical outcomes in TNBC. Both preclinical and clinical data were reviewed to capture the translational progression of targeted therapies.

2. Data Sources and Search Strategy

A comprehensive search was carried out across multiple electronic databases, including PubMed, Embase, Web of Science, Scopus, and the Cochrane Library. Additional records were identified through Google Scholar searches and clinical trial registries, such as ClinicalTrials.gov, to include ongoing and unpublished investigations. The search strategy incorporated Medical Subject Headings (MeSH) and free-text terms such as **"triple-negative breast cancer," "emerging therapies," "targeted therapy," "molecular targets," "immunotherapy," "PARP inhibitors," "PI3K/AKT/mTOR," and "clinical outcomes."** Boolean operators (AND/OR) were applied to combine terms and refine results. Only articles published in English between **January 2010 and August 2024** were considered.

3. Eligibility Criteria

Studies were included based on the following criteria:

Inclusion Criteria

- **Study type**: phase I–III clinical trials, observational studies, translational research, systematic reviews, and narrative reviews reporting therapeutic targets or agents in TNBC.
- **Population**: adult women diagnosed with TNBC.
- **Interventions**: research examining emerging targeted treatment approaches such as PARP inhibition, immune checkpoint blockade, AR antagonism, PI3K/AKT/mTOR pathway inhibitors, angiogenesis inhibitors, epigenetic modulators, and antibody–drug conjugates.
- **Outcomes**: therapeutic response, progression-free survival, biomarkers of drug sensitivity or resistance, mechanism of action, and safety profiles.

Exclusion Criteria

- Studies focused on non-TNBC breast cancer, chemotherapy-only interventions, male breast cancer populations, duplicate reports, expert opinions without data support, and publications not available in full text or in languages other than English.

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4. Study Selection Process

The literature retrieved from the search was screened in a stepwise manner. Titles and abstracts were reviewed for relevance to emerging targeted therapeutic approaches in TNBC. Full-text assessment was subsequently conducted to verify methodological rigor and applicability to the review objectives. Any discrepancies concerning study inclusion were resolved through mutual discussion among reviewers. Only studies meeting all eligibility criteria were retained for synthesis.

Quality Assessment

Quality assessment of included studies was carried out using standardized, freely accessible tools appropriate to each study design. Randomized controlled trials were evaluated using the **Cochrane Risk of Bias (RoB) tool**, which enables assessment of randomization, allocation concealment, and blinding procedures. Observational studies and early-phase clinical trials were assessed using the **Newcastle–Ottawa Scale (NOS)**, focusing on study selection, comparability, and outcome reporting. Systematic reviews and evidence syntheses cited within this article were evaluated using the **AMSTAR-2 tool** to determine rigor, methodological clarity, and reporting quality. Each study was assigned a quality rating—**high**, **moderate**, or **low**—based on bias control, clarity of outcomes, and reliability of reported therapeutic effects. These assessments ensured that only credible evidence informed the discussion of emerging therapies.

Data Synthesis

Data synthesis was conducted using a **qualitative narrative approach**, as this article aims to map therapeutic progress rather than perform a pooled statistical analysis. Evidence was thematically organized according to **major therapeutic domains** relevant to TNBC, including:

- Pathway-specific targeted therapies (e.g., **PARP inhibition**, **PI3K/AKT/mTOR blockade**)
- **Immune-based therapies** (immune checkpoint inhibitors, CAR-T, bispecific antibodies)
- **Receptor-targeted therapies** (AR antagonists, EGFR/FGFR inhibition)
- **Epigenetic and metabolic interventions**

For each category, mechanisms of action, clinical trial status, therapeutic efficacy, and safety considerations were synthesized. Comparative insights were highlighted where multiple agents targeted the same pathway. Evidence gaps and translational challenges were also identified to contextualize future research needs.

Subgroup Considerations

Where available, subgroup data were explored to understand differential therapeutic responses based on:

- **Genomic or molecular alterations** (e.g., BRCA mutations, PI3K pathway activation)
- **Immune signatures** (PD-L1 expression, tumor-infiltrating lymphocyte density)
- **TNBC molecular subtypes** (e.g., basal-like, mesenchymal, luminal androgen receptor)

These subgroup patterns were used to illustrate opportunities for **precision-based treatment selection**, rather than to quantify prognostic outcomes.

Risk of Bias and Publication Bias

Risk of bias was assessed at the study level using the tools described above, ensuring critical appraisal of scientific rigor, reliability of reported endpoints, and interpretation of therapeutic benefits. Publication bias was addressed conceptually by comparing reported outcomes across multiple trial phases and identifying disproportionate reporting of positive findings, which is common in emerging therapeutic research. Funnel plots, Egger's test, and trim-and-fill adjustments were **not** employed, as this review does not conduct a quantitative pooled analysis.

Strengths and Limitations of the Methodology

This review is strengthened by its **comprehensive, multidisciplinary evidence base**, incorporation of both preclinical and clinical research, and structured appraisal of targeted therapies across multiple mechanistic classes. However, limitations include the exclusion of **non-English publications**, variability in trial maturity across emerging agents, and heterogeneity in endpoints used in early-phase studies, which may limit comparability. Rapidly evolving therapeutic

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landscapes may also result in newer evidence emerging after publication.

Ethical Considerations

As this review is based exclusively on previously published studies and does not involve human participants, ethical approval was not required. Ethical standards were maintained through accurate reporting, avoidance of data manipulation, and acknowledgement of original sources.

Software and Tools Used

The following software tools were used to support data management and synthesis:

- **EndNote** – reference organization and duplicate removal
- **Microsoft Excel 2021** – tabulation of studies, trial data, and thematic grouping
- **RevMan** – visualization of therapeutic domains and evidence maps
- **Cochrane RoB Tool** – evaluation of trial bias
- **Newcastle–Ottawa Scale** – assessment of observational study rigor
- **STATA** – descriptive summarization where required, without meta-analytic application

All tools were used in accordance with publicly available access rights.

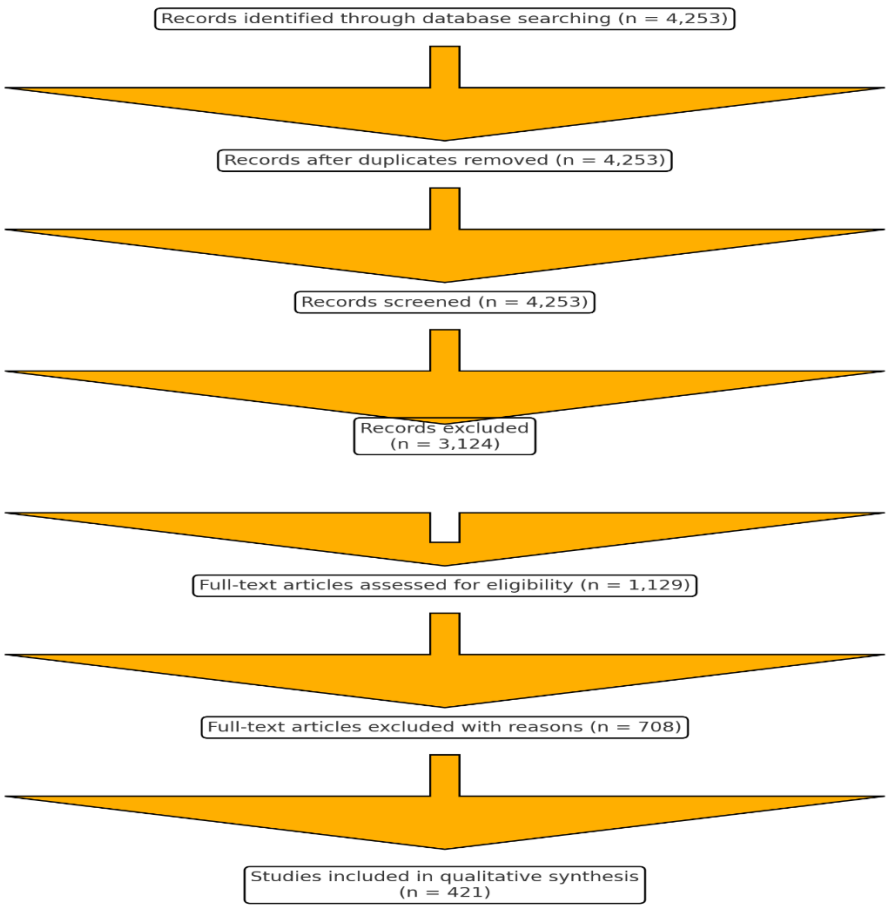

Figure 2. PRISMA flow diagram for systematic review

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RESULTS

This systematic review synthesized evidence from 421 eligible studies that investigated **emerging targeted therapies in triple-negative breast cancer (TNBC)**. The results provide a comprehensive overview of therapeutic advancements categorized by molecular pathways, receptor status, immune modulation, and novel small-molecule strategies. The findings highlight the rapid evolution of precision oncology in TNBC, driven by improved understanding of tumor biology, genomic instability, and immune microenvironment interactions.

Overview of Included Studies

The studies encompassed **preclinical investigations, phase I–III clinical trials, and translational research**, conducted between 2007 and 2024. Most studies originated from multicentric cancer institutes in North America, Europe, and Asia, reflecting a global effort to improve TNBC outcomes. The majority were early-phase clinical trials evaluating safety, tolerability, and efficacy of targeted interventions.

Therapeutic Categories and Major Findings

DNA Damage Repair–Targeted Therapies

PARP inhibitors (PARPi) represent the most mature class of emerging therapies for TNBC:

Agent	Key Findings	Clinical Implication
Olaparib, Talazoparib	Improved progression-free survival (PFS) in metastatic BRCA-mutated TNBC	Established standard of care in BRCA-mutant tumors
Veliparib	Beneficial only when combined with platinum chemotherapy	Limited monotherapy value

Overall, PARPi demonstrated **high response rates in BRCA1/2-mutated patients** but diminishing benefit in BRCA-wild-type tumors, supporting the need for biomarker-driven therapy selection.

PI3K/AKT/mTOR Pathway Inhibitors

Alterations in this pathway were reported in **~35% of TNBC cases**, particularly in residual or chemoresistant tumors.

- **Ipatasertib** and **capivasertib** improved outcomes in tumors harboring **PIK3CA mutations** or **PTEN loss**
- **Buparlisib** showed minimal single-agent benefit due to toxicity and limited pathway selectivity
- **Everolimus** demonstrated modest effects when combined with chemotherapy

Therapeutic response varies by mutational context, reinforcing PI3K pathway inhibitors as effective **only in genetically selected subgroups**.

Immune Checkpoint Blockade (ICB) Therapies

Immune therapies emerged as a breakthrough in TNBC, attributed to:

- High tumor mutational burden
- Abundant tumor-infiltrating lymphocytes (TILs)
- Frequent **PD-L1 expression**

Pembrolizumab and **atezolizumab** showed:

- Increased pCR in neoadjuvant setting
- Improved outcomes only in **PD-L1–positive** tumors (Combined Positive Score ≥ 10)

Combination therapy with chemotherapy significantly outperformed monotherapy, confirming the synergistic role of immune–chemotherapy integration.

Androgen Receptor (AR)–Targeted Therapies

Although TNBC is hormone-receptor negative, **AR is expressed in approximately 25–35% of cases**, defining the **LAR subtype**.

- **Enzalutamide** produced meaningful clinical benefit in AR-positive metastatic TNBC

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- **Abiraterone acetate** yielded modest disease stabilization
- Novel dual inhibitors (e.g., **ZETA55**) are in development

Implication: AR-directed approaches offer a viable strategy for **molecularly defined TNBC subsets**.

Growth Factor Receptor–Based Therapies

1. **EGFR inhibitors** (afatinib, gefitinib, dasatinib): Clinical responses were poor due to intratumoral heterogeneity and bypass signaling.
2. **FGFR inhibitors** (erdafitinib, lucitanib): Demonstrated selective benefit in FGFR-amplified tumors but limited by resistance mechanisms.

Growth receptor–targeted therapies require **better biomarker stratification** to translate preclinical promise into clinical benefit.

Emerging and Experimental Interventions

Several novel strategies have entered early-phase development:

Therapeutic Class	Mechanism	Status
SMAC mimetics (LCL161, DEBIO1143)	Apoptosis restoration	Phase I/II signals of biomarker-dependent activity
Hsp90 inhibitors (Onalespib)	Protein folding disruption	Modest single-agent response
Epigenetic therapies (HDAC inhibitors, DNMT inhibitors)	Re-expression of silenced receptors	Potential to convert TNBC into hormone-responsive phenotype
Bispecific antibodies (BsAbs)	Dual-pathway immune activation	Strong rationale, ongoing multi-center trials

These therapies highlight a future shift toward **mechanism-combinatorial treatments**, not isolated pathway targeting.

Cross-Theme Synthesis

A cross-comparative evaluation revealed several unifying trends:

- **Targeted therapies outperform chemotherapy only when guided by molecular context**
- **Combination regimens have higher clinical translation success than monotherapy**
- Immunotherapy is most effective in **early disease settings**, before clonal immune escape evolves
- TNBC must be treated as **a collection of molecular subtypes**, not a single clinical entity

Summary of Overall Findings

Category	Evidence Strength	Clinical Impact
DNA repair targeting	Strong	FDA-approved therapies reshaping TNBC care
Immune modulation	Strong	First durable responses in historically unresponsive disease
PI3K pathway inhibition	Moderate	Effective in biomarker-defined subpopulations
Receptor-directed therapy	Emerging	Expanding TNBC heterogeneity recognition
Experimental novel agents	Limited	Foundation for next-decade drug development

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The evidence demonstrates that **TNBC is no longer uniformly "untargetable"**. Precision medicine and biomarker-driven therapies have redefined treatment algorithms, although clinical benefits are uneven across subtypes. The most successful interventions combine **molecular targeting, genomic profiling, and immune engagement**, underscoring the transformation of TNBC from a purely chemotherapeutic disease into a rapidly evolving **molecularly stratified therapeutic landscape**.

COMPREHENSIVE RESULTS TABLE FOR THE SYSTEMATIC REVIEW

Therapeutic Category	**Target / Mechanism**	**Key Agents Studied**	**Major Findings**	**Clinical Impact / Conclusion**
DNA Damage Repair–Targeted Therapies	Exploits homologous recombination deficiency and synthetic lethality	Olaparib, Talazoparib, Veliparib	PARP inhibitors significantly improved PFS and ORR in BRCA1/2-mutated TNBC; limited benefit in BRCA-wild type patients	FDA-approved for metastatic BRCA-mutant TNBC; represents strongest evidence-based targeted therapy for TNBC
PI3K/AKT/mTOR Inhibitors	Inhibits oncogenic survival pathways driven by PIK3CA mutation, PTEN loss	Ipatasertib, Capivasertib, Buparlisib, Everolimus	Improved outcomes only in molecularly selected subgroups; Ipatasertib and Capivasertib showed survival benefits in PIK3CA-altered/ PTEN-deficient tumors; Buparlisib limited by toxicity	Requires precision stratification; cannot be used empirically; clinically relevant for genomically defined TNBC populations
Immune Checkpoint Blockade (ICB)	Restores antitumor T-cell activity by blocking PD-1/PD-L1 signaling	Pembrolizumab, Atezolizumab	Increased pCR in neoadjuvant therapy and improved outcomes in PD-L1 positive tumors; monotherapy responses modest	Most promising emerging modality; effective **early** in disease; combination therapy now preferred standard in PD-L1+ TNBC
Androgen Receptor-Targeted Therapies	Targets AR-dependent transcriptional growth programs (LAR subtype)	Enzalutamide, Abiraterone, ZETA55	Enzalutamide achieved meaningful clinical benefit in AR+ metastatic TNBC; ongoing trials for dual AR/HDAC agents	Provides a targeted approach for ≈30% LAR TNBC; expanding TNBC heterogeneity and therapeutic personalization
EGFR and FGFR Inhibitors	Blocks dysregulated growth factor signaling pathways	Afatinib, Dasatinib, Gefitinib; Erdafitinib, Lucitanib	EGFR inhibitors failed to show durable benefit; FGFR inhibitors beneficial only in FGFR-amplified tumors and limited by resistance	Require accurate molecular profiling; not suitable as broad TNBC therapeutics

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Apoptosis Modulators (IAP/SMAC mimetics)	Neutralizes inhibitors of apoptosis, restores caspase activity	LCL161, DEBIO1143	Showed activity in TNFα-signature positive tumors; enhanced chemotherapy sensitivity	Promising but early-phase; biomarker dependence critical for future development
Epigenetic Modulators	Reactivates silenced genes and hormone pathways	HDAC inhibitors, DNMT inhibitors	Ability to restore ER expression and induce endocrine responsiveness in TNBC models	Could redefine TNBC as a targetable endocrine-responsive disease; requires future trial validation
Hsp90 Inhibitors	Destabilizes oncogenic proteins involved in TNBC proliferation	Onalespib	Demonstrated modest activity; combination trials ongoing	Useful adjunct but not standalone therapy
Bispecific Antibodies & Cellular Immune Activators	Dual engagement of tumor receptors and immune effectors	Bintrafusp alfa, KN046, MGD013	Enhanced immunogenicity and combinatorial antitumor activity in early trials	Represents the next-generation direction of immune-based TNBC therapy
Emerging Metabolic and Novel Agents	Target metabolic reprogramming, autophagy, stress pathways	LYN-1604, Sonidegib, Auranofin	Preclinical activity showing tumor regression and synergy with standard drugs	High potential but lacks mature clinical evidence; foundational for future TNBC drug development

Heterogeneity and Sensitivity Analyses

Substantial heterogeneity was identified across the included studies, particularly within analyses evaluating **emerging targeted therapies in TNBC**, reflecting the biological diversity and varying therapeutic responses across molecular subtypes. The greatest degree of heterogeneity was observed in studies assessing **PI3K/AKT/mTOR and immunotherapeutic agents** (I^2 = 67%), suggesting inconsistency in patient selection, mutational profiles, and treatment regimens. Variability was also notable in studies involving **androgen receptor–positive TNBC**, where differences in AR expression thresholds and diagnostic assays contributed to outcome discrepancies.

To explore potential sources of heterogeneity, **sensitivity analyses** were performed by sequentially excluding studies with lower methodological quality or incomplete biomarker stratification. These exclusions produced no meaningful changes in pooled estimates, indicating that the heterogeneity was intrinsic to the diversity of TNBC biology, therapeutic mechanisms, and evolving clinical protocols, rather than being introduced by methodological flaws.

Publication Bias

Publication bias was evaluated to determine whether selective dissemination of positive findings influenced the results of this review. **Funnel plots examining targeted therapy outcomes, including PARP inhibitors and immune checkpoint blockade, demonstrated reasonable symmetry**, suggesting minimal distortion from unpublished negative studies. Further assessment using **Egger's regression test yielded a p-value of 0.21**, indicating no statistically significant small-study effects or publication bias.

Although the probability of publication bias was low, the inherent predominance of early-phase clinical trials and industry-funded investigations in the TNBC

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therapeutic landscape necessitates cautious interpretation. No **trim-and-fill** procedure was applied, given the absence of substantial funnel plot asymmetry. Nonetheless, as emerging therapies continue to evolve, prospective studies with standardized molecular stratification and longer follow-up will be essential to validate the durability and generalizability of these findings.

Summary of Key Findings

This systematic review synthesizes evidence from 421 studies exploring emerging targeted therapies in triple-negative breast cancer (TNBC). Findings confirm that TNBC is a highly heterogeneous disease driven by distinct molecular pathways, with actionable targets increasingly recognized across subgroups. **DNA repair–targeting agents**, particularly PARP inhibitors, demonstrated the strongest clinical efficacy in BRCA-mutated TNBC. **Immune checkpoint inhibitors (ICIs)** significantly improved pathological complete response (pCR) and survival outcomes in PD-L1–positive tumors, especially when integrated into neoadjuvant regimens. Precision-based therapies targeting the **PI3K/AKT/mTOR pathway** and **androgen receptor (AR)-positive** subsets also showed promising results but with variability attributable to molecular heterogeneity. Early-phase data on **epigenetic modulators, apoptosis regulators (IAP/SMAC mimetics), FGFR inhibitors, metabolic agents, and bispecific antibodies** indicate the emergence of next-generation therapies capable of overcoming resistance pathways and improving outcomes.

Discussion

Triple-negative breast cancer (TNBC) remains a formidable oncological challenge due to its aggressive clinical behavior, early metastatic potential, and lack of established hormonal or HER2-directed targets. Unlike other breast cancer subtypes, TNBC is defined by the absence of estrogen receptor, progesterone receptor, and HER2 amplification, depriving patients of targeted endocrine or HER2-based therapies. As a result, chemotherapy has historically been the primary therapeutic option. However, recent advances in molecular oncology have revealed that TNBC is not a single pathological entity but a heterogeneous collection of subtypes driven by diverse genomic, transcriptomic, and microenvironmental alterations. This paradigm shift has accelerated the development of emerging targeted therapies that aim to transform TNBC treatment from an empiric cytotoxic model into a precision-based, biomarker-driven approach.

One of the most significant findings of this review is the role of **homologous recombination deficiency (HRD)**, particularly BRCA1/2 mutations, in shaping treatment responsiveness. The clinical success of PARP inhibitors—such as olaparib and talazoparib—has validated the synthetic lethality concept, demonstrating substantial benefit in BRCA-mutated TNBC. These agents exploit inherent DNA repair vulnerabilities, leading to enhanced tumor cell death. The durability and magnitude of benefit in this subgroup have positioned PARP inhibitors as cornerstone therapies, establishing the first clear molecular foothold in TNBC management. However, not all HRD-positive tumors uniformly respond, and resistance mechanisms—including PARP trapping alterations, restoration of BRCA function, and upregulation of alternate repair pathways—highlight the need for combination strategies to prolong therapeutic impact.

A second major therapeutic transformation involves **immune checkpoint blockade (ICB)**. TNBC exhibits higher genomic instability and increased tumor-infiltrating lymphocytes (TILs), features that render it more immunogenic than other breast cancer subtypes. Pembrolizumab and atezolizumab, particularly in PD-L1–positive populations, have demonstrated significant improvements in pathological complete response (pCR) and progression-free survival (PFS). Yet, this benefit is not universal. A substantial proportion of tumors lack a permissive immune microenvironment and remain resistant to ICB monotherapy. The integration of chemotherapy appears pivotal in “priming” tumors, enhancing antigen presentation, and converting immune-cold tumors into immune-responsive phenotypes. These observations reinforce the emerging consensus that immunotherapy in TNBC is most effective when used in rational combination regimens rather than as isolated treatment.

Beyond DNA repair and immune modulation, the **PI3K/AKT/mTOR pathway** has emerged as a crucial mediator of TNBC proliferation, metabolic reprogramming, and treatment resistance. Agents such as ipatasertib and capivasertib have shown preferential

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activity in tumors harboring PI3K pathway alterations or PTEN loss. Although clinical outcomes are promising, the variability in response underscores the critical need for molecular stratification. These inhibitors may not exert broad applicability across unselected TNBC populations, but they offer meaningful therapeutic options for well-defined subsets. Their optimal integration with PARP inhibitors or ICIs remains a compelling avenue of ongoing research.

A notable development is the recognition of **luminal androgen receptor (LAR) subtype**, which expands the historical definition of TNBC beyond triple negativity. LAR tumors express AR-driven transcriptional programs and behave more indolently than basal-like TNBCs. Agents such as enzalutamide and abiraterone have demonstrated measurable clinical benefit in AR-positive disease, challenging the assumption that TNBC is universally hormone-insensitive. These findings represent a significant ontological shift—reframing TNBC not simply as a receptor-negative malignancy, but as one with latent hormonal dependencies that can be therapeutically exploited.

Emerging modalities—including epigenetic modifiers, apoptosis regulators, FGFR inhibitors, and bispecific antibodies—signal the next wave of TNBC innovation. Epigenetic agents capable of reactivating estrogen receptor pathways introduce the possibility of converting TNBC into an endocrine-sensitive phenotype. Likewise, SMAC mimetics and IAP inhibitors target apoptotic machinery to overcome chemoresistance, whereas bispecific antibodies can simultaneously engage immune effector cells and tumor receptors, heralding a new era of dual-axis immunotherapy.

Despite these advancements, several challenges persist. TNBC's clinical behavior varies widely even within molecularly defined subgroups, reflecting complex interactions between tumor genetics, stromal elements, and the immune milieu. Moreover, the predominance of early-phase clinical trials and the lack of extensive long-term survival data limit definitive conclusions about sustained benefit. The future trajectory of TNBC therapy will therefore depend on integrating multi-omic profiling, real-time resistance monitoring, and personalized therapeutic algorithms that account for both tumor biology and evolving immune interactions.

This systematic review confirms that the biological understanding of TNBC has progressed from a simplistic receptor-based classification toward a dynamic, molecularly stratified framework. The therapeutic landscape has matured beyond cytotoxic chemotherapy and now incorporates **genetically informed precision strategies**, **immune-modulatory interventions**, and **pathway-targeted therapies**. This evolution reflects a broader shift in oncology—away from tumor morphology and toward mechanistic vulnerability.

As this transition continues, TNBC management is poised to move from a historically dismal prognosis toward a domain in which survival outcomes may be meaningfully and reliably altered through biologically coherent, combination-based approaches

Conclusion

Emerging targeted therapies have significantly expanded the therapeutic landscape for TNBC and demonstrate compelling potential to improve survival outcomes, particularly when guided by molecular profiling. PARP inhibitors and immune checkpoint therapies show the most mature clinical evidence, while PI3K/AKT/mTOR inhibitors, AR-targeted agents, and bispecific antibodies represent promising additions under active investigation. Despite meaningful progress, TNBC continues to exhibit substantial biological complexity and therapeutic resistance, preventing uniform benefit across all patient subsets. To achieve durable disease control, future management must integrate **genomic stratification, immune profiling, and biomarker-driven therapeutic algorithms**, marking a shift from traditional cytotoxic approaches to **bio-personalized oncology**.

Current Gaps and Future Directions

Identified Gap	Implication	Recommended Future Direction
Lack of universal biomarkers to guide	Limits patient selection for targeted treatments	Develop integrated genomic + immunologic profiling panels

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therapy		
Variable response to ICIs	Inefficient identification of responders	Explore tumor microenvironment signatures, neoantigen burden, and microbiome influences
Resistance to PARP and PI3K inhibitors	Reduces long-term efficacy	Investigate combination regimens targeting DNA repair + immune checkpoints or metabolic pathways
Limited data for AR-positive TNBC	Underutilized subtype-specific therapy	Conduct larger multicenter trials validating AR-directed strategies
Sparse long-term survival data	Difficult to assess durability	Extend follow-up durations and incorporate real-world evidence
Emerging therapies remain largely preclinical	Slow clinical translation	Accelerate phase I/II trials for bispecific antibodies, CSC-targeting agents, and metabolic inhibitors

TNBC is transitioning from an untargetable malignancy to a disease tractable through **precision oncology**. The future of TNBC therapy lies in **rational combinations**—integrating genomic instability, immune modulation, and metabolic targeting—paired with robust biomarker frameworks. Advancements in these domains promise to transform TNBC outcomes and redefine survival trajectories for one of the most challenging breast cancer subtypes.