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Next-Generation Therapeutic Targets in Triple-Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) lacks estrogen and progesterone receptors, and estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 expression, and is associated with early relapse, visceral metastasis, and limited targeted options. High-throughput profiling supports TNBC as a collection of molecularly distinct diseases with exploitable vulnerabilities across DNA-damage response, cell-cycle control, receptor tyrosine kinase signaling, metabolism, and anti-tumor immunity. Clinically, immune checkpoint blockade has shifted standards of care in selected settings, and biomarker enrichment is increasingly central to trial design. In parallel, DNA repair-directed approaches, including poly(ADP-ribose) polymerase inhibitors in BRCA1/2-mutant and homologous recombination–deficient tumors, are being extended through rational combinations that intensify replication stress (e.g., ataxia telangiectasia and Rad3-related protein, WEE1, or checkpoint kinase 1 inhibition) to deepen responses and delay resistance. Additional candidate targets, including androgen receptor-driven disease biology, epidermal growth factor receptor, fibroblast growth factor receptor, vascular endothelial growth factor receptor signaling, and emerging antibody-drug conjugate antigens highlight the importance of matching therapy to subtype and tumor microenvironment context. Metabolic reprogramming (glycolysis, fatty-acid oxidation/synthesis, and amino-acid use) intersects with therapy resistance and may provide complementary combination opportunities. In this study, we synthesize recent advances in actionable TNBC pathways, summarize key preclinical and clinical evidence, and propose a pragmatic framework for biomarker-led combinations that integrate DNA repair, cell-cycle, metabolic, and immune vulnerabilities.

Keywords: Triple-negative breast cancer (TNBC); precision oncology; DNA damage response; cell-cycle/mitotic targets; metabolic reprogramming; immunotherapy; antibody-drug conjugates

KEY POINTS

- Triple-negative breast cancer (TNBC) is aggressive, heterogeneous, and lacks estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2, so targeted options are limited.
- Next-generation targets matter because profiling reveals distinct TNBC subgroups with actionable vulnerabilities.

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- Poly(ADP-ribose) polymerase (PARP) inhibitors work best in BRCA1/2-mutated and other homologous recombination deficiency (HRD) TNBC, and research is expanding beyond classic HRD.
- Pairing PARP inhibition with ataxia telangiectasia and Rad3-related protein, WEE1, or checkpoint kinase 1 inhibitors can raise replication stress and create synthetic lethality.
- These replication-stress combinations may also help overcome or delay treatment resistance.
- Cell-cycle and mitotic regulators like CDC25 and aurora kinase A are druggable nodes that disrupt abnormal proliferation.
- Protein-stability and oncogenic drivers such as heat shock protein 90, mouse double minute 2 homolog/MDM2 binding protein, and metadherin support survival and metastasis and may be biomarker-linked targets.
- Receptor tyrosine kinase targeting (epidermal growth factor receptor, fibroblast growth factor receptor, vascular endothelial growth factor receptor) can benefit selected TNBC patients when guided by biomarkers.
- Immunotherapy with programmed cell death protein 1/programmed death-ligand 1 (PD-L1) inhibitors improves outcomes in PD-L1-positive TNBC, and combination approaches aim to deepen responses.
- The best path forward is biomarker-driven, rational combinations that integrate DNA repair, cell-cycle, metabolic, and immune vulnerabilities.

Introduction

Breast cancer remains a major global health burden, with hundreds of thousands of deaths annually and persistent disparities in outcomes across regions and populations (1). Contemporary epidemiology underscores both the scale of the problem and the importance of sustained investment in early detection and improved systemic therapy (2, 3). Triple-negative breast cancer (TNBC) is defined clinically by the absence of estrogen receptor, progesterone receptor, and estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2). Although this definition is operationally useful, it encompasses multiple biologically distinct diseases that differ in immune infiltration, metastatic tropism, and therapy sensitivity. TNBC accounts for roughly 10–20% of breast cancers and is associated with higher rates of early relapse and visceral metastasis compared with hormone receptor-positive disease (4). Because surgery and endocrine therapy and HER2-directed therapy are ineffective (5), systemic management historically relied on chemotherapy, with newer targeted and immune-based strategies now expanding options, due to which we focus on next-generation therapeutic vulnerabilities in TNBC and the practical logic for combination regimens. We emphasize DNA-damage response and replication stress, cell-cycle and checkpoint dependence, growth factor and nuclear receptor signaling, inflammatory and stem-like programs that enable metastasis and drug resistance, and metabolic reprogramming as an adjunct target space. Throughout, we highlight biomarker contexts that can help match patients to therapies and prioritize the most actionable combinations for clinical translation (6-8).

Materials and Methods

Literature search was conducted in databases including PubMed/MEDLINE, Scopus, and Web of Science using key words "triple negative breast cancer", "targeted therapy", "precision therapy", "drug resistance", "metastasis". Target/pathway terms aligned with the review scope [poly(ADP-ribose) polymerase (PARP), p53, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor, PI3K/AKT/mammalian target of rapamycin (mTOR), immune checkpoint etc.]. Studies were included if they include clinical trials, *in vitro*/*in vivo* studies providing mechanistic support for a target's role in TNBC biology or systematic reviews or meta-analyses used primarily to contextualize clinical efficacy/safety trends. Exclusion criteria included non-TNBC breast cancer studies without extractable TNBC subgroup data or articles lacking primary data, and reports with insufficient methodological detail to interpret findings.

Results

TNBC Heterogeneity and the Evolving Treatment Landscape

Despite progress, TNBC management remains constrained by three recurring challenges: rapid emergence of resistance, limited durability of response in metastatic disease, and treatment-related toxicities that restrict intensification. Even when immune checkpoint blockade or targeted therapy is indicated, most regimens still rely on chemotherapy backbones that contribute neuropathy, myelosuppression, fatigue, and cumulative organ toxicities. Consequently, many reviews emphasize a shift from empiric escalation toward precision combination strategies that use biomarkers to select patients who can benefit from targeted agents while allowing chemotherapy de-escalation when deep responses occur (7-9). A practical implication is that target selection in TNBC often means selecting a combination rather than a single agent. Because the disease frequently uses parallel pathways [receptor tyrosine kinase (RTK) signaling, checkpoint dependence, inflammatory loops, and metabolic adaptation] to maintain survival, therapeutic programs that inhibit only one node are commonly bypassed. Drug development frameworks therefore prioritize identifying dominant dependencies in a given tumor state, pairing agents with complementary mechanisms (e.g., DNA damage plus checkpoint inhibition), and using on-treatment biomarkers to confirm that the intended pathway is suppressed *in vivo* (6, 10). TNBC heterogeneity has practical implications for therapy selection. Molecular subtyping

efforts consistently identify basal-like phenotypes enriched for DNA repair and cell-cycle abnormalities, as well as immune-enriched tumors and androgen receptor-driven subgroups that resemble luminal programs despite ER/PR negativity (11, 12). Clinically useful biomarkers now include germline/somatic *BRCA1/2* alterations, homologous recombination deficiency (HRD)-associated features, and immune markers such as programmed death-ligand 1 (PD-L1) expression and tumor-infiltrating lymphocytes. Guideline-based care increasingly integrates biomarker-driven strategies alongside chemotherapy, particularly in high-risk early-stage and metastatic settings (9, 13). Immune checkpoint blockade has shifted standards of care for selected patients. Atezolizumab combined with nab-paclitaxel has been reviewed as an approach for PD-L1-positive metastatic TNBC, with ongoing efforts to refine patient selection, sequencing, and management of immune-related adverse events (14, 15). More broadly, programmed cell death protein 1 (PD-1)/PD-L1 targeting in breast cancer is supported by an expanding clinical evidence base, and multiple lines of investigation aim to deepen and prolong responses through rational combinations (13, 16). At the same time, the therapeutic pipeline is broadening. Reviews of TNBC drug discovery emphasize DNA repair targeting, kinase pathway inhibitors, and emerging immune and antibody-based platforms as key growth areas (6, 10, 17). In particular, antibody engineering has enabled bispecific formats that can redirect immune effector functions or engage multiple tumor antigens, potentially overcoming pathway redundancy and tumor escape mechanisms (17).

DNA as Target: Repair Path, Replication Stress, and Synthetic Lethality in TNBC Cells

Platinum chemotherapy provides a clinically familiar example of DNA damage exploitation in TNBC, and it is often considered in HR- deficient or highly proliferative tumors. The rationale is conceptually aligned with PARP inhibition: both approaches increase DNA lesions that require high-fidelity repair. However, platinum sensitivity is not synonymous with HRD, and clinical benefit can vary depending on tumor subtype, prior exposure, and drug tolerance. For this reason, contemporary strategies frequently combine DNA crosslinking agents with targeted checkpoint inhibitors rather than relying on cytotoxic DNA damage alone (6, 18). Epigenetic modulation can also intersect with DNA repair targeting. Histone deacetylase (HDAC) inhibition may alter chromatin accessibility, transcription of repair genes, and replication stress responses. In TNBC cells, the HDAC inhibitor suberoylanilide hydroxamic acid has been reported to enhance the activity of PARP inhibitor olaparib, suggesting a potential strategy for sensitization in tumors where PARP inhibition alone is insufficient (4, 19). More recently, discovery-oriented work has described dual targeting of G-quadruplex structures and HDAC activity as a novel approach to disrupt proliferation and increase DNA damage burden (20). When considering these combinations, two principles are especially important. First, combinations should be built around a specific failure mode, e.g., restoring HR, checkpoint adaptation, or transcriptional rewiring rather than combining agents solely because each has modest single-agent activity. Second, the biomarker strategy should anticipate toxicity since multi-agent DNA damage and checkpoint regimens can increase hematologic adverse events, so early-phase development must establish schedules that preserve exposure while maintaining tolerability (7, 8). Defects in HR repair create a synthetic lethal opportunity for PARP inhibition. In HR-deficient tumors, PARP inhibition both impairs single-strand break repair and increases replication-associated lesions that evolve into unrepaired double-strand breaks, driving selective tumor cell death (6). However, resistance can emerge through restoration of HR function, replication fork protection, altered PARP trapping, or rewiring of cell-cycle checkpoints. Accordingly, a major thrust of next-generation therapy is to combine PARP inhibition with agents that amplify replication stress or prevent DNA damage tolerance. Checkpoint and replication-stress targeting provides a mechanistic route to deepen PARP responses. Ataxia telangiectasia and Rad3-related (ATR) protein kinase is involved in the DNA damage response and a master regulator of replication stress signaling, coordinating fork stabilization and S/G2 checkpoint enforcement. In phosphatase and tensin homolog (PTEN)-deficient breast cancers, ATR targeting has been proposed as a personalized therapy strategy, with preclinical evidence supporting increased DNA damage and vulnerability to DNA repair disruption (21). Similarly, WEE1 G2 checkpoint kinase inhibition can force premature mitotic entry, converting accumulated DNA lesions into mitotic catastrophe. Co-targeting DNA repair and checkpoint control has shown synergistic effects in TNBC models with Cyclin E or *BRCA1* alterations (22, 23). Clinical translation of replication-stress combinations is underway. One example is berzosertib (an ATR inhibitor) combined with cisplatin in advanced TNBC, evaluated in a phase 1b setting. Such regimens aim to exploit the reliance of highly proliferative tumors on checkpoint signaling when exposed to DNA crosslinking agents (18). These approaches also illustrate key implementation questions: identifying predictive biomarkers (e.g., HRD, PTEN loss, high replication stress signatures) and managing overlapping toxicities, including myelosuppression and fatigue.

DNA repair intersects with immune regulation. PARP inhibition has been reported to upregulate PD-L1 expression and increase cancer-associated immunosuppression, providing a biologic rationale for combining PARP inhibitors with checkpoint blockade (24). Depending on context, this PD-L1 increase could represent an adaptive immune-evasion response that becomes therapeutically actionable when PD-1/PD-L1 is blocked. Thus, replication-stress therapies may serve dual roles in direct

cytotoxicity through DNA damage and indirect immune modulation that enhances checkpoint inhibitor responsiveness.

Cell Cycle Checkpoint Targets in TNBC

Checkpoint dependence is not only a consequence of genomic instability; it can also be a compensatory adaptation to oncogene-driven hyperproliferation. In such states, tumor cells tolerate replication stress by engaging ATR-CHK1 (checkpoint kinase 1) signaling, enforcing G2/M arrest, and activating transcriptional programs that buffer damage. WEE1 and polo-like kinase 1 (PLK1) represent complementary nodes where WEE1 maintains G2 control, while PLK1 drives mitotic progression. Therefore, combinations that perturb both checkpoint enforcement and mitotic execution may be particularly effective when paired with DNA damage induction (22, 23, 25). Mutant p53 biology also links to inflammatory and RTK signaling. Mutant p53 can influence cytokine pathways and transcriptional outputs that promote invasion and survival, which may explain why mutant p53 targeting is viewed as a cross-cutting strategy that can affect both tumor-intrinsic growth and microenvironmental interactions (26). From a translational perspective, identifying mutant p53-dependent transcriptional states and mapping them to druggable dependencies, such as cyclin-dependent kinase 7 (CDK7) can create a more actionable precision framework than attempting universal p53 restoration (27). Beyond DNA repair, TNBC frequently depends on cell-cycle checkpoints and transcriptional programs that compensate for genomic instability. WEE1 inhibition represents one checkpoint-directed strategy, and preclinical work suggests synergy with capecitabine by increasing DNA damage and limiting repair capacity (23). PLK1 is another mitotic regulator implicated in TNBC; immunohistochemical studies in triple-negative breast carcinoma support PLK1 as a plausible therapeutic target and potential biomarker for aggressive biology (25). The p53 pathway is particularly relevant because tumor protein p53 (TP53) is mutated in a large fraction of TNBC. Comprehensive genetic profiling in triple-negative tumors has documented frequent TP53 alterations alongside other actionable changes, reinforcing the importance of pathway-based targeting strategies (28). Mutant p53 has been proposed as a novel therapeutic target in metastatic breast cancer, both because mutant p53 can gain pro-oncogenic functions and because p53 pathway disruption can create exploitable dependencies on alternative checkpoints (26). An emerging concept is to target mutant-p53 dependency rather than attempting direct p53 reactivation in every setting. For example, CDK7 inhibition has been explored as a way to exploit the transcriptional addiction of mutant p53-dependent TNBC cells, emphasizing that transcriptional regulation can be as critical as classical kinase signaling in sustaining tumor growth (27). These ideas complement checkpoint and DNA repair therapies: by reducing transcription of survival programs or DNA damage response genes, transcriptional inhibitors may lower the threshold for apoptosis when tumors are exposed to replication stress.

Growth Factor Signaling Molecules as Target for TNBC Treatment

RTK biology in TNBC is best understood as a signaling network rather than a single driver. EGFR can promote downstream mitogen-activated protein kinase and phosphatidyl inositol 3-kinase (PI3K) pathway activation, while MET proto-oncogene (cMET) provides a bypass route that preserves proliferative signaling under EGFR blockade. Accordingly, combinatorial approaches may include dual RTK inhibition, RTK inhibition plus PI3K/AKT/mTOR suppression, or RTK inhibition plus chemotherapy to increase tumor cell kill before adaptive reprogramming occurs (29, 30). Seven-in-absentia homologue (SIAH) pathway activity has been proposed as a functional readout of persistent EGFR/K-rat sarcoma family (RAS) signaling, which may be particularly relevant for identifying tumors that remain pathway-dependent despite chemotherapy exposure. If validated prospectively, such pathway activity markers could help stratify patients for RTK- or pathway-directed intensification, and could provide an on-treatment measure of whether resistance is emerging through pathway reactivation (31).

Angiogenesis inhibition occupies a similar niche: it is rarely sufficient as monotherapy but may contribute meaningful benefit in combinations that improve drug delivery, reduce hypoxia-driven adaptation, or reshape immune infiltration. Mechanistic reviews of anti-vascular endothelial growth factor (VEGF) therapy emphasize that the most effective use cases may be those where vascular normalization or immune-vascular interactions are explicitly targeted rather than expecting angiogenesis blockade to eradicate tumor cells directly (32). RTK signaling remains a major vulnerability for subsets of TNBC, but single-agent RTK inhibition has often been limited by pathway redundancy and compensatory signaling. EGFR is frequently expressed in TNBC, and combinations of antibodies to EGFR have inhibited TNBC models in preclinical work, supporting the premise that multi-epitope blockade or combination with cytotoxic agents can improve efficacy (29). Resistance mechanisms highlight why network-level strategies are required. cMET activation has been associated with EGFR-directed therapy resistance in TNBC, suggesting that dual RTK targeting or downstream pathway suppression may be needed to prevent bypass signaling (33). More recently, persistent activation of the EGFR/K-RAS/SIAH pathway has been linked to chemoresistance and early relapse in TNBC, reinforcing the importance of identifying durable pathway readouts (e.g., SIAH activity) that can track oncogenic signaling under treatment pressure (31). Downstream signaling inhibitors are therefore central to the next-generation landscape. The

PI3K/AKT/mTOR axis regulates growth, survival, and metabolism and is commonly altered or activated in TNBC through multiple upstream inputs. Drug discovery reviews emphasize both the promise and challenge of pathway inhibition, including feedback activation, metabolic adaptation, and toxicity that can limit dose intensity (30). Combination logic often pairs PI3K/AKT/mTOR pathway inhibitors with chemotherapy, RTK targeting, or immunotherapy to reduce adaptive signaling and increase tumor cell kill. Angiogenesis contributes to tumor growth and metastasis through VEGF receptor signaling, which can also shape immune contexture by influencing vascular permeability and immune cell trafficking. Recent reviews of anti-VEGF therapy in breast cancer summarize key molecular targets and therapeutic strategies, supporting continued exploration of angiogenesis inhibitors in biomarker-defined settings and rational combinations (32).

Inflammatory Signaling in TNBC, STAT3 Dependence and Cancer Stemness

The signal transducer and activator of transcription 3 (STAT3)-linked mechanisms also suggest a rationale for multi-layer targeting. For example, tumors that show leptin receptor (LEPR)-STAT3 dependence at hematological and neurological expressed 1-like protein (HN1L)-high states could, in principle, be co-targeted at the cytokine receptor level (to reduce upstream activation) and at downstream survival nodes such as PI3K/AKT/mTOR or checkpoint signaling, particularly when therapy exposure increases inflammatory cues from the microenvironment (30, 34). Similarly, cancer stem cell (CSC)-directed sensitization strategies illustrated by dasatinib-mediated chemosensitization may be most effective when coupled to a second agent that eradicates the bulk tumor population. This "two-compartment" logic (bulk tumor cytotoxicity plus CSC suppression) aligns with the clinical observation that initial responses can be followed by relapse driven by residual resistant clones or stem-like populations (4, 7, 34-36).

Inflammatory signaling supports TNBC progression by promoting proliferation, invasion, immune suppression, and therapy resistance. Interleukin-6 (IL-6)/STAT3 signaling is a recurrent theme: multiple TNBC regulators converge on STAT3 activation, which can sustain stem-like features and chemotherapy resistance. Mechanistically, gametogenetin-binding protein has been reported to suppress TNBC aggressiveness by inhibiting IL-6/STAT3 signaling activation, highlighting that negative regulators of STAT3 can function as tumor suppressors (37). Conversely, *HN1L* gene has been implicated in promoting TNBC stem cells through a LEPR-STAT3 pathway, linking inflammatory cues to stemness and metastatic potential (34). Pharmacologic disruption of IL-6/STAT3 signaling is therefore an active area of investigation. Bazedoxifene has been described as an IL-6/glycoprotein 130 kDa (GP130) inhibitor with activity in TNBC models, supporting GP130 as a druggable node in inflammatory signaling (38). These approaches may complement immunotherapy: By reducing cytokine-driven immune suppression and stem-like persistence, STAT3 pathway inhibition could improve both chemotherapy sensitivity and immune-mediated tumor clearance.

CSC phenotypes are linked to relapse and metastasis in TNBC, and CSC-directed strategies often overlap with inflammatory and RTK signaling. Dasatinib, a proto-oncogene tyrosine-protein kinase (SRC)-family kinase inhibitor, has been shown to sensitize TNBC cells to chemotherapy by targeting CSCs, exemplifying a sensitization approach that is not primarily cytotoxic as monotherapy but can amplify standard regimens (35). More broadly, reviews of CSC targeting in TNBC emphasize that successful translation will require robust CSC biomarkers and endpoints that capture residual disease biology (36).

Metabolic Reprogramming in TNBC Microenvironmental Context

Metabolic targeting is increasingly viewed as a way to constrain adaptability rather than to produce immediate tumor regression in all patients. Because metabolic pathways support multiple resistance phenotypes-drug efflux, antioxidant defense, and survival under hypoxia-metabolic interventions may be particularly useful as partners for DNA damage, RTK, or immune therapies. For instance, PI3K/AKT/mTOR signaling regulates glucose uptake and anabolic growth, so pathway inhibition can indirectly reshape metabolic state; conversely, tumors may compensate for pathway inhibition by switching fuel sources or increasing oxidative metabolism (30, 39). Serine biosynthesis illustrates how a relatively narrow metabolic vulnerability can connect to broad phenotypes such as metastasis. When phosphoserine aminotransferase 1 (PSAT1) is required for invasive behavior, targeting serine pathway enzymes may suppress dissemination even if primary tumor proliferation is only modestly affected. This supports a broader strategy: matching metabolic inhibitors to clinically relevant phenotypes (metastasis risk, stem-like persistence) and measuring endpoints beyond short-term tumor shrinkage (36, 40). Metabolic reprogramming enables TNBC cells to survive fluctuating nutrient supply, oxidative stress, and therapy-induced damage. A comprehensive review of metabolic remodeling in TNBC highlights glycolysis, mitochondrial adaptation, lipid metabolism, and amino-acid utilization as interconnected vulnerabilities that also influence immune function and drug resistance (39). Importantly, metabolic dependencies vary by subtype and microenvironment; therefore, metabolic targeting is most likely to succeed when guided by biomarkers such as pathway enzyme expression, metabolite signatures, or transcriptional programs. Metabolism also connects systemic physiology to tumor behavior. Adipokines and adiponectin-related signaling

have been investigated in relation to estrogen receptor-negative and triple-negative subtypes, suggesting that host metabolic state can shape tumor biology and potentially therapy response (41). While such associations do not immediately specify a drug target, they reinforce a practical point: metabolic and inflammatory context can influence the effectiveness of targeted and immune therapies, and should be considered in trial stratification and covariate adjustment. Specific metabolic enzymes can mediate invasion and metastasis. For example, selective loss of PSAT1 has been reported to inhibit invasion, migration, and experimental metastasis in TNBC, positioning serine biosynthesis as a candidate vulnerability in metabolically dependent tumors (42). Because metabolic interventions can have systemic effects, careful dose optimization and patient selection will be important, particularly when metabolic targeting is combined with chemotherapy or immunotherapy.

Emerging Platforms and Combination Design Principles

A useful way to operationalize combination selection is to map each patient's tumor to a small set of dominant liabilities and then choose combinations that cover complementary failure modes. Examples include HRD/BRCA-altered or high replication stress tumors: PARP ± ATR/WEE1, with optional checkpoint blockade when immune markers are present (18, 22, 24). In RTK/pathway-dependent tumors, EGFR/RTK-directed therapy plus downstream PI3K/AKT/mTOR suppression or chemotherapy is appropriate (29, 30, 33). In STAT3/CSC-enriched tumors, GP130/STAT3 targeting plus CSC sensitization to chemotherapy, with careful immune monitoring should be used (35, 38).

Because TNBC is clinically managed across distinct disease states (neoadjuvant, adjuvant, metastatic), the optimal endpoint also differs. In early-stage disease, pathologic complete response and event-free survival can be sensitive to intensification strategies. In metastatic disease, durable disease control and quality of life are paramount, and toxicity-limited regimens may need sequential rather than simultaneous combinations. These trade-offs argue for adaptive clinical trial designs that allow response-guided therapy modification and incorporate patient-reported outcomes alongside molecular biomarkers (7, 8, 13). Antibody engineering is enabling next-generation platforms that can complement small-molecule and cytotoxic strategies. Bispecific antibodies offer opportunities to co-engage immune cells and tumor antigens or to block multiple signaling inputs simultaneously, potentially reducing pathway redundancy and adaptive resistance (17). In parallel, new delivery and targeting strategies including peptide-derived agents continue to expand the druggable space in TNBC. For instance, gap junction protein connexin 26-derived cell-penetrating peptides have been used to target homeobox transcription factor, a stemness-associated factor NANOG and focal adhesion kinase (FAK, also called PTK2). FAK, illustrating a mechanism-driven strategy that links stemness programs to focal adhesion signaling (43). Combination design is increasingly informed by mechanistic complementarity: pair DNA damage with checkpoint blockade to convert damage into lethal events (22, 23), combine pathway inhibitors to prevent bypass signaling (31, 33), integrate immune modulation when tumor antigens and immune infiltration are present (13, 16), and target stem-like persistence or inflammatory loops to reduce relapse risk (34, 36). Early-phase clinical development of multi-agent regimens, such as kinase inhibition combined with immunotherapy and chemotherapy, demonstrates the feasibility of multi-node targeting but also emphasizes the need for toxicity-aware sequencing and adaptive dosing (44).

In practice, biomarker integration is the key enabling factor. Candidate biomarkers include: BRCA/HRD status (for PARP and replication-stress therapies), PTEN loss or high replication stress signatures (for ATR/WEE1 strategies), PD-L1 and immune gene signatures (for checkpoint blockade), and STAT3 pathway activity markers (for IL-6/GP130 or LEPR–STAT3 targeting). Developing trial designs that allow therapy adaptation based on early molecular response using circulating tumor DNA or serial biopsy may help reduce overtreatment while preserving efficacy (7, 8).

Conclusion

TNBC is a heterogeneous clinical entity that demands biologically guided therapy. Recent progress reflects two complementary trends: better matching of patients to therapies using biomarkers (e.g., PD-L1, HRD) and increasing use of rational combinations that anticipate resistance and exploit synthetic lethal interactions. Replication-stress strategies (ATR/WEE1/CHK pathways), RTK and downstream signaling blockade (EGFR/cMET/PI3K), inflammatory and stemness targeting (STAT3/CSC programs), and metabolic adjunct therapies together form a coherent next-generation toolkit. Continued advances will depend on integrating these tools into adaptive, biomarker-led clinical strategies that maximize durable control while minimizing cumulative toxicity.

Footnotes

Authorship Contributions

Concept: K.M.S., M.F.A., J.A.R., K.N.M., E.E.H., N.V.M.; Design: K.M.S., M.F.A., J.A.R., K.N.M., E.E.H., N.V.M.; Data Collection or Processing: K.M.S., M.F.A., J.A.R., K.N.M., E.E.H., N.V.M.; Analysis or Interpretation: K.M.S., M.F.A., J.A.R., K.N.M., E.E.H., N.V.M.; Writing: K.M.S., M.F.A., J.A.R., K.N.M., E.E.H., N.V.M.

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