Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD25832

The Evolving Landscape of Immunotherapy in Triple-negative Breast Cancer: Mechanisms, Biomarkers, and Future Horizons

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Abstract: Triple-negative breast carcinoma (TNBC) is an aggressive malignancy with a historical paucity of targeted therapies, but recent years have seen a therapeutic revolution. Its distinct immunogenic profile, with an elevated tumor mutational burden and dense lymphocytic infiltration, makes it a prime candidate for immuno-oncology. This review synthesizes impactful research from 2023–2025 that defines the contemporary treatment paradigm. The author provides a comprehensive evaluation of the pivotal results that establish the significance of immunological checkpoint inhibitors (ICIs) in both curative and palliative contexts, most notably, the establishment of a significant overall survival improvement with the perioperative administration of pembrolizumab in the initial stages TNBC, a finding validated by the KEYNOTE-522 trial. Additionally, the author examines the transformative effect of antibody-drug conjugates (ADCs) directed against Trophoblast cell-surface antigen 2 (TROP2). Specifically, agents like sacituzumab govitecan are now established as a new therapeutic standard in the metastatic context. The necessity for strong biomarkers for prediction beyond the therapeutic target of checkpoint blockade, programmed death-ligand 1 (PD-L1) is examined, emphasizing the potential of lymphocytes that infiltrate tumors (TILs) and the transition towards dynamic, integrated multi-omic methodologies. Finally, the author explores the next frontier of innovation to overcome resistance, including rational combination strategies, "armored" CAR-T cell therapies, and personalized neoantigen vaccines. This review underscores the clear shift towards more complex, personalized, and potentially curative immunotherapy strategies for TNBC.

Keywords: triple-negative breast cancer, immunotherapy, antibody-drug conjugates, predictive biomarkers, therapeutic resistance

1. Introduction

Triple-negative breast carcinoma (TNBC) constitutes roughly 15-20% of all instances of breast cancer, and is distinguished by the lack of expression of the receptors for estrogen (ER), the receptor for progesterone (PR), and the receptor for human epidermal growth factor-2 (HER2) [1]. An aggressive clinical trajectory is a distinguishing feature of this subtype. It carries a notable tendency for both early relapse and distant dissemination, which culminates in a less favorable prognosis

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when compared to other forms of breast cancer. Historically, the absence of defined molecular targets rendered systemic treatment reliant on cytotoxic chemotherapy, a significant limitation that underscored a critical unmet need for novel therapeutic strategies [2]. Furthermore, TNBC disproportionately affects younger women and exhibits significant demographic and racial disparities in both incidence and outcomes, adding layers of complexity to its management.

The advent of immuno-oncology has heralded a paradigm shift, providing a powerful new therapeutic pillar for TNBC. The rationale for applying immunotherapy to this subtype is rooted in its distinct biological features. In contrast to other breast cancer subtypes, a more pronounced immunogenic signature is evident in TNBC tumors. This profile is evidenced by indications like an elevated tumor mutational burden (TMB), an increased presence of lymphocytes that infiltrate tumors (TILs), and tumors exhibiting a PD-L1-positive phenotype [2]. These characteristics indicate a pre-existing, albeit repressed, anti-tumor immune system reaction that can be therapeutically reactivated. This inherent immunogenicity has positioned TNBC as a uniquely suitable candidate for therapies designed to modulate the host immune system. The advancement and successful validation in clinical investigations of immunological checkpoint inhibitors (ICIs), conjugates of antibody-drug (ADCs), and poly (ADP-ribose) the polymerase enzyme (PARP) inhibitors for germline BRCA-mutated conditions have collectively revolutionized the treatment paradigm, decisively surpassing a uniform chemotherapy strategy [3]. The findings from several decisive prospective investigations provided the evidentiary basis for new clinical practice guidelines covering the treatment of cancer across the disease continuum, from adjuvant to palliative settings, for the inaugural time, demonstrating that utilizing the body's immune system or targeting specific tumor antigens can lead to durable improvements in patient outcomes [2].

Despite this remarkable progress, considerable challenges persist. A notable subset of patients is refractory to initial immunotherapy, a state defined as primary resistance, while another cohort experiences disease progression following a period of clinical benefit, which is termed acquired resistance [2]. This reality has intensified the search for robust predictive biomarkers that can more accurately identify patients most likely to benefit, thereby personalizing treatment and mitigating unnecessary toxicity. This review critically synthesizes pivotal 2023-2025 advances in the immunobiology of TNBC that are reshaping treatment protocols. The author analyzes the evidence underpinning current therapeutic benchmarks, the trajectory of predictive biomarker development, emerging mechanisms of resistance, and the next wave of therapeutic innovations for this aggressive malignancy.

2. The current clinical landscape: approved immunotherapies and targeted agents in TNBC

The therapeutic armamentarium for TNBC has expanded dramatically beyond conventional chemotherapy, built upon a strong immunological rationale. TNBC's inherent characteristics, manifested as tumors with a high mutational load (TMB) and a robust immune infiltrate rich in lymphocytes (TILs), signify a pre-existing but suppressed anti-tumor immune response, rendering it an exemplary prospect for immuno-oncology [2,4]. This has led to the successful incorporation of ICIs and ADCs, and targeted DNA damage repair agents into the standard of care. The pivotal function of ICIs in the context of early-stage TNBC was firmly established with the concluding overall survival (OS) data from the Phase III KEYNOTE-522 study, which was showcased at the 2024 ESMO Congress [5]. This study randomized patients with high-risk, early-stage TNBC to neoadjuvant chemotherapy with either pembrolizumab or placebo, followed by adjuvant single-agent therapy. At a median follow-up of 75.1 months, a statistically significant and clinically meaningful improvement in OS was demonstrated with the perioperative pembrolizumab protocol.

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This resulted in a 34% decrease in mortality risk compared with chemotherapy only (Hazard Ratio=0.66). This regimen was designated as the definitive standard of therapy. A durable separation of the Kaplan-Meier survival curves was observed between the two treatment arms, culminating at the 5-year landmark with a 4.9 percentage point absolute difference in overall survival, favoring the pembrolizumab-based regimen (86.6%) over the placebo-controlled arm (81.7%) [5,6]. The pivotal findings from the KEYNOTE-355 investigation provided the evidentiary basis for a new first-line therapeutic benchmark in metastatic disease. Specifically, for the patient subpopulation whose tumors demonstrate high PD-L1 expression (CPS $\geq$ 10), the trial validated the integration of pembrolizumab with chemotherapy by demonstrating a significant overall survival advantage [2,7].

The second pillar of modern TNBC therapy is ADCs, which deliver potent cytotoxic payloads directly to cancer cells. The TROP2-directed ADC, sacituzumab govitecan (SG), was validated by the Phase III ASCENT trial. The agent's substantial efficacy was validated by the trial's concluding analysis in previously treated metastatic TNBC. Treatment conferred a marked improvement over chemotherapy, with median OS extended to 11.8 from 6.9 months, and median PFS increased to 4.8 from 1.7 months [8]. A second-generation TROP2-ADC, datopotamab deruxtecan (Dato-DXd), has also shown compelling activity, with results from the TROPION-PanTumor01 study reporting a 31.8% objective response rate in heavily pretreated patients [9]. The emergence of these two ADCs validates TROP2 as a target but also introduces clinical complexity due to differing toxicity profiles; the administration of SG correlates with an increased incidence of both neutropenia and diarrhea, while Dato-DXd is linked more to stomatitis, requiring careful patient selection and sequencing decisions [8,9]. Finally, for the cohort of patients possessing hereditary BRCA1/2 mutations, PARP inhibitors like olaparib and talazoparib are an established standard, exploiting the principle of synthetic lethality in tumors with deficient homologous recombination repair [1,3].

3. The critical quest for predictive biomarkers

The successful integration of powerful new therapies has created an urgent need for robust predictive biomarkers to personalize treatment, maximizing efficacy while sparing non-responders from unnecessary toxicity [4]. Although PD-L1 expression serves as the recognized benchmark for directing first-line pembrolizumab therapy in metastatic TNBC, its practical application is hindered by considerable limitations. The KEYNOTE-355 trial demonstrated that a significant survival benefit was confined to patients exhibiting a Combined Positive Score (CPS) of 10 or higher [7]. The prognostic capability of PD-L1 is, however, substantially compromised by a lack of concordance among the various immunohistochemistry assays that have received FDA approval (e.g., 22C3, SP142, SP263), which use different antibody clones and scoring algorithms; they are not interchangeable, and can yield conflicting results for the same patient [2,4]. Furthermore, PD-L1 expression is heterogeneous and dynamic, varying between primary and metastatic sites and changing over time, particularly after therapy [4]. Most notably, its predictive power is inconsistent, being crucial in the metastatic setting but not predictive of benefit in the neoadjuvant setting (KEYNOTE-522), suggesting context-dependent mechanisms of action [4,7].

In contrast, the assessment of tumor-infiltrating lymphocytes (TILs) has emerged as a more consistent and powerful biomarker. Within the context of the initial stages TNBC, elevated levels of the tumor stroma by lymphocytes stands as a well-documented and independent prognostic indicator for improved patient survival [2,7]. Beyond prognosis, TILs are also predictive of immunotherapy benefit, as ICIs are more effective in "hot" tumors with a pre-existing immune infiltrate. The International Immune-oncology biological markers Working Group's initiatives for standardizing TIL evaluation on H&E slides are essential for its wider clinical application [7]. Tumor Mutational

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Burden (TMB), an indicator of neoantigen quantity, has limited utility in TNBC as the overall median TMB is low, and it has shown more prognostic than predictive value in some trials [4]. The future of biomarker science is moving towards dynamic, multi-modal strategies. Liquid biopsies that analyze circulating tumor DNA (ctDNA) enable a minimally invasive strategy for identifying molecular residual disease (MRD). The c-TRAK-TN trial provided a proof-of-concept, showing ctDNA detection was a potent prognostic marker for relapse, though it also highlighted a narrow therapeutic window, as 72% of patients already had radiologically detectable metastases when their ctDNA became positive [2]. Ultimately, the future of biomarker development points toward integrative strategies. Such approaches are expected to merge genomic data, immune-related gene expression profiles (like the Tumor Inflammation Signature), and spatial transcriptomics to construct a comprehensive, predictive model of the tumor microenvironment.

4. Overcoming resistance and future therapeutic directions

Despite transformative advances, therapeutic resistance remains the foremost clinical challenge in TNBC. A complex array of mechanisms underpins therapeutic resistance. These can be broadly conceptualized along two primary axes: factors intrinsic to the tumor, such as the loss of antigen presentation machinery (e.g., mutations in B2M/HLA genes) that renders tumors "invisible" to T cells, and extrinsic factors that are mediated by the surrounding microenvironment. The microenvironment of tumors (TME) constitutes a significant obstacle， creating a profoundly immunosuppressive network. This is marked by the aggregation of inhibitory immune cells, including regulatory T cells (Tregs) and suppressor cells derived from myeloid cells (MDSCs) that actively limit the function of cytotoxic T cells and play a substantial role in immunotherapy resistance [2]. Confronting this complexity requires innovative strategies that can both enhance tumor immunogenicity and disarm the suppressive TME.

The next wave of therapeutics is focused on rational combinations and highly engineered modalities. Combining ICIs with PARP inhibitors is a promising strategy that aims to augment immunogenicity beyond the BRCA-mutated population. It is hypothesized that DNA damage resulting from PARP inhibition can, in turn, serve as a trigger for the cGAS-STING signaling cascade. This pathway functions by detecting cytosolic DNA, which in turn initiates a robust type I interferon response that promotes immune cell recruitment and enhances tumor sensitivity to ICIs. Similarly, combining ICIs with ADCs is being explored to leverage the immunogenic cell death (ICD) induced by the ADC payload, which releases tumor antigens and effectively turns "cold" tumors "hot". Beyond combinations, research is advancing on therapies targeting novel immune checkpoints like LAG-3 and TIM-3 to more comprehensively reverse T-cell exhaustion [2]. The most futuristic approaches involve nascent modalities with immense promise. These include next-generation ADCs carrying novel payloads like STING agonists to deliver a potent immune activator directly to the tumor [1]. Advanced cellular therapies, such as "armored" CAR-T cells, are being engineered to overcome the hostile TME. A 2023 preclinical study described MUC1-targeting CAR-T cells engineered to resist TGF-β and secrete pro-inflammatory IL-12 at the tumor site, demonstrating potent TME remodeling and tumor control [10]. Finally, personalized neoantigen-based therapeutic vaccines, which train a patient's immune system against their specific tumor mutations, represent the ultimate in personalized medicine. Recent Phase I trials of DNA-based neoantigen vaccines in high-risk TNBC have shown them to be safe, immunogenic, and associated with promising recurrence-free survival, charting a clear path toward a new era of bespoke cancer therapy [1].

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5. Conclusion

Over the past five years, the treatment paradigm for triple-negative breast carcinoma has undergone a fundamental and irreversible transformation. Once defined by a lack of targets and a reliance on conventional chemotherapy, TNBC is now at the forefront of immuno-oncology innovation. The amalgamation of immunological checkpoint inhibitors with conjugates of antibody-drug has established new standards of care, and for the first time, a perioperative immunotherapy regimen has demonstrated a definitive overall survival benefit in the curative setting for high-risk early-stage disease. This progress marks a pivotal shift in the clinical management of TNBC. It has prompted a fundamental reorientation of the therapeutic dialogue, moving the focus from palliative care toward the prospect of curative outcomes for a larger patient population.

Despite these triumphs, significant challenges remain. Therapeutic resistance, both primary and acquired, continues to limit the benefit of these powerful agents for many patients. The significance of how PD-L1 is expressed in the stratification of patients for immunotherapy, while its utility has been validated for the treatment of distant metastatic disease, is hampered by technical inconsistencies and a notable lack of predictive power in early-stage disease. This underscores the critical and ongoing need for more robust, reliable, and dynamic biomarker strategies that can capture the multifaceted dialogue between a tumor and its surrounding microenvironmental niche. The future of patient selection is unlikely to rest on a single marker but will instead evolve towards integrated, multi-modal approaches that combine spatial biology, liquid biopsies, and sophisticated computational models.

Looking forward, the next decade of progress will likely be defined by two parallel efforts: the intelligent optimization of existing therapies and the clinical maturation of highly personalized, engineered treatments. Rational combination strategies that pair ADCs, PARP inhibitors, and other targeted agents with ICIs are poised to further enhance immunogenicity and overcome resistance. Simultaneously, nascent modalities such as armored CAR-T cells and personalized neoantigen vaccines represent a paradigm shift towards "living drugs" and bespoke therapies. These approaches hold the promise of inducing highly specific, powerful, and durable anti-tumor immune responses. While formidable challenges in manufacturing, cost, and accessibility must be overcome, these innovative frontiers are moving the field ever closer to the ultimate goal of providing effective, long-term, and potentially curative outcomes for all patients with this aggressive disease.

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