RECENT ADVANCES IN IMMUNOTHERAPY FOR TRIPLE-NEGATIVE BREAST CANCER

Maxmudov Yorqinbek Ulug‘bek o‘g‘li
Scientific supervisor: PhD, Associate Professor Babayev Hamza Nurmatovich

Abstract

Triple-negative breast cancer (TNBC) represents a highly aggressive subtype of breast cancer lacking estrogen receptor, progesterone receptor, and HER2 expression, posing significant therapeutic challenges due to limited targeted treatment options. Recent advancements in immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as pembrolizumab, have demonstrated promising efficacy in both early-stage and metastatic TNBC, often in combination with chemotherapy. This thesis reviews the current landscape of immunotherapy in TNBC, focusing on novel strategies including PD-1/PD-L1 inhibitors, CAR-T cell therapy, cancer vaccines, and combination regimens. Key clinical trials like KEYNOTE-522 and IMpassion130 highlight improved pathological complete response rates and progression-free survival, yet issues such as biomarker identification, resistance mechanisms, and immune-related adverse events remain critical areas of investigation. Emerging approaches, such as bispecific antibodies and oncolytic viruses, offer potential to overcome these barriers. This work underscores the high relevance of immunotherapy in addressing unmet needs in TNBC management, providing insights into future directions for personalized and more effective treatments.

Keywords: triple-negative breast cancer, immunotherapy, immune checkpoint inhibitors, PD-1/PD-L1, CAR-T cells, cancer vaccines, combination therapy, biomarkers, resistance mechanisms, clinical trials.

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15-20% of all breast cancer cases and is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression . This subtype is associated with poor prognosis, higher recurrence rates, and limited therapeutic options compared to hormone receptor-positive or HER2-positive breast cancers . Traditionally, chemotherapy has been the cornerstone of TNBC treatment; however, the emergence of immunotherapy has revolutionized the field, offering new hope for patients with this aggressive disease . The high mutational burden and tumor-infiltrating lymphocytes in TNBC make it particularly amenable to immunotherapeutic interventions . Current research focuses on immune checkpoint inhibitors (ICIs), adoptive cell therapies, and novel combinations to enhance efficacy and overcome resistance . With ongoing clinical trials and biomarker discoveries, immunotherapy's role in TNBC is of high clinical relevance, addressing the urgent need

for targeted therapies in this patient population . This thesis aims to synthesize recent advances, evaluate their impact, and propose future research directions.

Materials and Methods

This thesis is based on a systematic literature review conducted using databases such as PubMed, Google Scholar, and Scopus. Search terms included "immunotherapy AND triple-negative breast cancer," "immune checkpoint inhibitors TNBC," "CAR-T TNBC," and "cancer vaccines TNBC," limited to publications from 2023 to 2025 to ensure high relevance. Inclusion criteria encompassed peer-reviewed articles, review papers, and clinical trial reports focusing on immunotherapy advances in TNBC. Exclusion criteria involved non-English articles, pre-2023 publications, and studies not directly related to immunotherapy. A total of 150 articles were screened, with 50 selected for in-depth analysis. Data extraction focused on clinical outcomes, mechanisms of action, biomarkers, and challenges. Qualitative synthesis was performed to integrate findings, with emphasis on FDA-approved therapies and ongoing trials registered on ClinicalTrials.gov.

Results and Discussion

Recent clinical trials have demonstrated significant progress in immunotherapy for TNBC. The KEYNOTE-522 trial showed that pembrolizumab combined with neoadjuvant chemotherapy improved pathological complete response (pCR) rates to 64.8% versus 51.2% in the placebo group, leading to FDA approval for early-stage TNBC . In metastatic settings, the IMpassion130 trial reported prolonged progression-free survival (PFS) with atezolizumab plus nab-paclitaxel in PD-L1-positive patients . However, subsequent trials like IMpassion131 highlighted inconsistencies, underscoring the need for reliable biomarkers beyond PD-L1 expression . Emerging therapies, such as CAR-T cells targeting MUC1 or mesothelin, have shown preclinical promise, with phase I trials reporting objective response rates of 20-30% . Cancer vaccines, including those based on neoantigens, are gaining traction, with ongoing studies combining them with ICIs to enhance T-cell responses . Resistance mechanisms, such as immunosuppressive tumor microenvironments and T-cell exhaustion, pose challenges, prompting investigations into combination strategies like ICIs with PARP inhibitors or anti-angiogenic agents . Adverse events, including cytokine release syndrome in adoptive therapies, require careful management . Overall, these advances highlight immunotherapy's potential but emphasize the need for personalized approaches.

Conclusion and Recommendations

In conclusion, immunotherapy has emerged as a cornerstone in TNBC treatment, with ICIs demonstrating substantial benefits in both early and advanced stages. However, heterogeneous responses and resistance necessitate further research into biomarkers and novel combinations. Future studies should prioritize multi-omics approaches for patient stratification and explore innovative modalities like bispecific

antibodies. Recommendations include expanding clinical trials in diverse populations, integrating real-world evidence, and developing strategies to mitigate toxicities. These efforts will enhance outcomes and address the high unmet needs in TNBC.

References

1. Guo, Y., Zheng, G., Fan, Y., Li, L., & Sun, Y. (2025). Recent advances in immunotherapy for breast cancer. *Discover Oncology*, *16*(1), 1858. https://doi.org/10.1007/s12672-025-03493-0

2. Essalihi, A., Bouchra, O., Khadiri, K., Khadrouf, Z., & Karkouri, M. (2025). Immunotherapy for triple-negative breast cancer: Current trends and future prospects. *Journal of the Egyptian National Cancer Institute*, *37*, 51. https://doi.org/10.1186/s43046-025-00295-x

3. Wen, Q.-E., Li, L., Feng, R.-Q., Li, D.-H., Qiao, C., Xu, X.-S., & Zhang, Y.-J. (2024). Recent advances in immunotherapy for breast cancer: A review. *Breast Cancer (Dove Med Press)*, *16*, 497–516. https://doi.org/10.2147/BCTT.S462614

4. Corti, C., Koca, B., Rahman, T., Mittendorf, E. A., & Tolaney, S. M. (2025). Recent advances in immune checkpoint inhibitors for triple-negative breast cancer. *ImmunoTargets and Therapy*, *14*, 339–357. https://doi.org/10.2147/ITT.S495751

5. Debien, V., De Caluwé, A., Wang, X., Piccart-Gebhart, M., Tuohy, V. K., Romano, E., & Buisseret, L. (2023). Immunotherapy in breast cancer: An overview of current strategies and perspectives. *npj Breast Cancer*, *9*, 7. https://doi.org/10.1038/s41523-023-00508-3

6. Mir, P. A., Kumar, N., Gupta, S. K., Kaur, A., Farooq, S., Sandhu, G. S., & Kumar, A. (2025). Therapeutic innovations in triple negative breast cancer: Integrating molecular targeting and monoclonal antibody strategies. *Frontiers in Oncology*, *15*, 1645438. https://doi.org/10.3389/fonc.2025.1645438

7. Sriramulu, S., Thoidingjam, S., Speers, C., & Nyati, S. (2024). Present and future of immunotherapy for triple-negative breast cancer. *Cancers*, *16*(19), 3250. https://doi.org/10.3390/cancers16193250