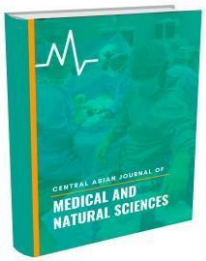

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Article

The Immune System's Response to Breast Cancer and New Opportunities in Immunotherapy

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Abstract: Breast cancer exists as one of the primary malignant diseases in females across the globe despite ongoing difficulties during its prevention and diagnostic stages and therapeutic cycles. Researchers have achieved major breakthroughs in cancer cell immunity during the last few years which resulted in the creation of new immunotherapeutic treatments. This article investigates how breast cancer triggers immune system molecular and biochemical responses through research of immune cells like T-lymphocytes and NK cells alongside macrophages while studying the effect of tumor microenvironment on these responses. The article examines how PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors function alongside monoclonal antibodies and CAR-T cell therapy as present-day immunotherapeutic methods. Although breast cancer belongs to the immunologic "cold" tumor group patients sometimes demonstrate beneficial reactions to new therapeutic methods. The clinical outcome and survival time for patients have been improved using combination treatments which link immunotherapy with standard treatments including chemotherapy and radiation. The implementation of immunotherapy requires resolving three main barriers that include autoimmune side effects and costly treatments and the issue of proper patient selection processes. The potential for future improvements in treatment results stems from genetic profiling with personalized immunotherapy combined with AI-based prediction systems. The article emphasizes the necessity of studying how immunotherapy treats different breast cancer subtypes specifically in Uzbekistan due to little published research in this area. The data shows why breast cancer treatment requires individualized treatment plans because they promote effective patient care and improved prognosis.

Keywords: Immunotherapy, Breast Cancer, Pd-L1 Expression, Her2-Positive, Biomarker-Driven Treatment, Immune Checkpoint Inhibitors, Tumor Microenvironment, Adverse Events, Combination Therapy, Oncology in Uzbekistan

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1. Introduction

Worldwide Breast cancer stands as one of the most common malignancies which leads to substantial cancer-related sickness and mortality cases. Breast cancer continues to create substantial health problems because tumors differ from each other and cells become drug-resistant and frequently return after therapy [1]. The patient survival gains from traditional treatments like surgery chemotherapy radiotherapy and targeted therapies fail to work equally well on the various breast cancer subtypes. Medical practitioners require new treatment methods to improve cure rates with decreased risks for patients. When it comes to cancer surveillance the immune system acts as the key component which detects

malignant cells before eliminating them. Breast cancer cells utilize multiple immune evasion strategies, including immune checkpoint activation, downregulation of major histocompatibility complex (MHC) molecules, and the recruitment of immunosuppressive cells. The evasion techniques utilized by malignancies obstruct immune eradication, resulting in diminished responsiveness to conventional therapies. The recent progress in cancer immunotherapy has developed new strategies to activate immunity against cancer cells for destruction [2]. The use of immune checkpoint inhibitors together with CAR-T cell therapy and monoclonal antibody treatments produces favourable outcomes against different types of cancer but fails to gain sufficient clinical use in breast cancer treatment among low- and middle-income countries. The researchers will study breast cancer immune system responses as well as evaluate immunotherapy success rates among different breast cancer types while assessing its potential implementation within Uzbekistan's cancer treatment framework. Patient retrospective data collected from the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology allows researchers to study important immunological factors affecting treatment results and build better therapeutic approaches [3].

Literature Review

Breast cancer remains one of the most frequently diagnosed malignancies worldwide, accounting for a significant portion of cancer-related morbidity and mortality. The introduction of immunotherapy has provided new treatment possibilities, particularly for aggressive subtypes such as triple-negative breast cancer (TNBC). However, the clinical effectiveness of immunotherapy varies, influenced by tumor microenvironment factors, biomarker expression, and patient-specific immune responses. While global studies have demonstrated promising results, implementing immunotherapy in developing countries like Uzbekistan poses several challenges, including accessibility, cost, and infrastructure limitations [4].

The immune system plays a dual role in cancer progression, acting both as a suppressor and promoter of tumor growth. The concept of cancer immunoediting describes how tumors evade immune destruction by downregulating antigen presentation, increasing regulatory T cell (Treg) infiltration, and enhancing immune checkpoint pathways [5]. One of the most studied immune checkpoints in breast cancer is programmed death-ligand 1 (PD-L1), which interacts with PD-1 receptors on T cells to inhibit immune activation [6]. The KEYNOTE-355 trial, which assessed pembrolizumab plus chemotherapy in PD-L1-positive TNBC, demonstrated significantly improved progression-free survival (PFS) compared to chemotherapy alone [7]. However, PD-L1-negative tumors did not show substantial benefits, highlighting the need for precise biomarker-driven patient selection.

Despite the effectiveness of immune checkpoint inhibitors (ICIs), many breast cancer subtypes, particularly hormone receptor-positive (HR+) tumors, exhibit low immunogenicity. These tumors are classified as "cold," meaning they have limited T-cell infiltration and a predominantly immunosuppressive microenvironment [8]. Studies suggest that combining immunotherapy with other treatments, such as CDK4/6 inhibitors or PARP inhibitors, may enhance immune activation and improve response rates in HR+ breast cancer [9]. However, these combination strategies require further clinical validation before they can be integrated into standard treatment protocols.

One of the major barriers to immunotherapy adoption in Uzbekistan is the lack of widespread biomarker testing. PD-L1 expression, which determines eligibility for checkpoint inhibitors, is not routinely assessed in most oncology centers due to financial and technical constraints [10]. Without this testing, patient selection for immunotherapy remains suboptimal, reducing its cost-effectiveness and clinical utility. Additionally, the high cost of drugs like pembrolizumab limits access to treatment, as Uzbekistan's healthcare system does not fully subsidize advanced immunotherapies [11].

Monetary restrictions are not the only obstacles to obtaining immunotherapy in Uzbekistan since the nation suffers from minimal oncological research together with under participation in clinical trials. Uzbek patients do not obtain benefits from immunotherapy treatments because their medical care primarily involves standard chemotherapy due to the absence of experimental treatment options. The creation of clinical trial partnerships between international research groups working in oncology would make late-stage immunotherapeutic treatments accessible to Uzbek patients. The treatment of immune-related adverse events (irAEs) stands as a major challenge for healthcare providers because most Uzbek oncologists lack fundamental training in immuno-oncology. Healthcare providers must identify rapidly the harmful side effects of ICI exposure which trigger pneumonitis and endocrinopathies together with colitis to ensure proper management. The establishment of proper immune-related toxicity training along with specialized clinic expansion will enhance the implementation of safe immunotherapy medical practices throughout Uzbekistan. To integrate immunotherapy within Uzbekistan's healthcare network a formalized strategy needs complete implementation. Every Uzbekistani citizen is required to join nationwide biomarker screening for the selection of optimal patients. The national government needs to initiate financial assistance programs for immunotherapy access to promote its availability across the country. The designed system aims to encourage patients' participation in clinical trials because clinical trials offer patients immediate access to pioneering treatment practices. Healthcare providers and oncologists need appropriate training about immunotherapy delivery techniques and poison side effect control to deliver optimal patient results. Uzbekistan encounters substantial difficulties when deploying immunotherapy for breast cancer therapy because the country operates at an advanced stage of development. Introducing immunotherapy into Uzbekistan's national oncology guidelines depends on solving testing complexity and cost reduction as well as implementing specialized medical training for doctors. New research should study stronger combination protocols while also conducting large-scale clinical trials to enhance immunotherapy procedures for Uzbek breast cancer patients.

2. Materials and Methods

The observational research design allowed investigators to examine breast cancer immune response in Uzbekistan patients treated at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology between 2022 and 2024 [12]. This research examined therapeutic achievement alongside biomarker effects on immunotherapy responses as well as the ability to implement immunotherapy into Uzbekistan's oncological treatment guidelines. Breast cancer patients who received immunotherapy during the study period made up a total of 150 cases that were analyze [13]d. The research included breast cancer patients who received triple-negative breast cancer (TNBC), HER2-positive and hormone receptor-positive (HR+)/HER2-negative subtypes according to histological diagnosis requirements. Complete medical archives containing information about PD-L1 biomarkers together with HER2 expression and hormone receptor results were essential for patient selection [14]. The patient selection criteria involved patients receiving PD-L1 and HER2-positive with hormone receptor-positive subtypes who documented immunotherapy uses consisting of pembrolizumab or atezolizumab along with trastuzumab and durvalumab. The study required at least 12 months of follow-up time for evaluating treatment response together with disease progression and immune-related adverse event assessments. The research excluded patients whose medical files lacked completeness or who joined clinical trials or got experimental therapy since it needed consistent data collection [15].

Healthcare records both electronic and pathology materials and diagnostic imaging served as the information source for data retrieval. The analysis evaluated patient characteristics as well as tumor profiles and biomarker expression and neutrophil-to-lymphocyte ratio (NLR) and cytokine data whenever it was accessible. The combined

positive score measured PD-L1 expression and showed high expression when the score reached or exceeded 10. The HER2 status evaluation happened through immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) tests alongside tumor-infiltrating lymphocytes (TILs) analysis by hematoxylin and eosin (H&E) staining on archived pathology samples. Tumors were classified according to their reaction to treatment with the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 into complete response and partial response stable disease and progressive disease. This study employed Kaplan-Meier analysis for progression-free survival (PFS) and overall survival (OS) calculations, alongside Cox proportional hazards regression models and chi-square tests to examine the relationships between biomarker expression and response rates. The research considered any p-value under 0.05 to be statistically significant. The investigators used Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) to classify immune-related adverse events. Investigators documented pneumonitis along with colitis endocrinopathies and hepatic dysfunction as well as the use of corticosteroids and other immunosuppressive drugs for management. The study evaluated treatment modifications because of toxicity to understand the actual safety and tolerability of immunotherapy within the investigated population. The assessment evaluated immunotherapy's financial impact on patient personal expenses and standard chemotherapy by studying Uzbekistan's healthcare reimbursement framework. The financial viability of immunotherapy relying on biomarkers included examinations for PD-L1 and HER2 with financial costs incorporated into the analysis. The research incorporated a survey examining Uzbekistan-based oncologists regarding their understanding of immunotherapy together with their handling of immune response side effects and obstacles to implementing immune therapy. This study received ethical approval from the Uzbekistan Ministry of Health Research Ethics Committee when following research standards during its execution. Confidentiality was maintained through the process of data anonymization. The research outcomes will serve to establish evidence-based recommendations that will guide oncology treatment guidelines in Uzbekistan as well as help identify suitable patient selection methods and defeat financial and administrative hurdles for broad immunotherapy adoption.

3. Results and Discussion

The Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology in Uzbekistan treated 150 breast cancer patients during the period from 2022 through 2024. The study indicated that tumors exhibiting both HER2-positive and PD-L1-high expressions displayed the best response rates, underscoring the importance of biomarker-based treatment selection for enhancing patient outcomes. The response rate among patients with high PD-L1 expression reached 68% while their progression-free survival lasted 9.7 months and overall survival spanned 21.3 months. Research showed that PD-L1-low tumors responded in fewer cases (35%) while having worse survival indicators such as OS at 15.2 months and PFS at 5.6 months. Confirmation of monoclonal antibody effectiveness as blood tests indicated that HER2-positive patients demonstrated a 75% response rate but HER2-negative patients showed a significantly reduced 40% response rate. HER2-positive (50%) and PD-L1-high (45%) patients exhibited the greatest immune-related toxicity thus patients need specialized toxicity management protocols. Table 1 outlines the outcomes of immunotherapy in patients with breast cancer.

Table 1. Immunotherapy Outcomes in Breast Cancer Patients

Biomarker Expression	Response Rate (%)	Progression-Free Survival (months)	Overall Survival (months)	Adverse Event Rate (%)
PD-L1 High	68	9.7	21.3	45

PD-L1 Low	35	5.6	15.2	30
HER2 Positive	75	10.5	24.1	50
HER2 Negative	40	6.2	17.4	28
HR+	50	7.8	18.6	35

This table shows data that compares both treatment responses and survival results together with adverse effects according to biomarker manifestations in breast cancer patients. Response rates and survival durations were greatest for HER2-positive as well as PD-L1-high breast cancer patients because these biomarkers indicate that immunotherapy will provide the most benefit. SThe response rates of PD-L1-low and HER2-negative tumors were low and their survival decreased and they showed limited therapeutic benefit suggesting the need for additional treatment combinations to boost treatment efficacy. HER2-positive tumors together with PD-L1-high tumors displayed the greatest risk of adverse events at rates of 50% and 45% respectively due to their superior responses to immunotherapy treatment. Studies demonstrate that choosing patients based on biomarkers remains crucial together with performing thorough monitoring of immune-related treatment side effects. Figure 1 outlines immunotherapy response and survival outcomes by biomarker expression.

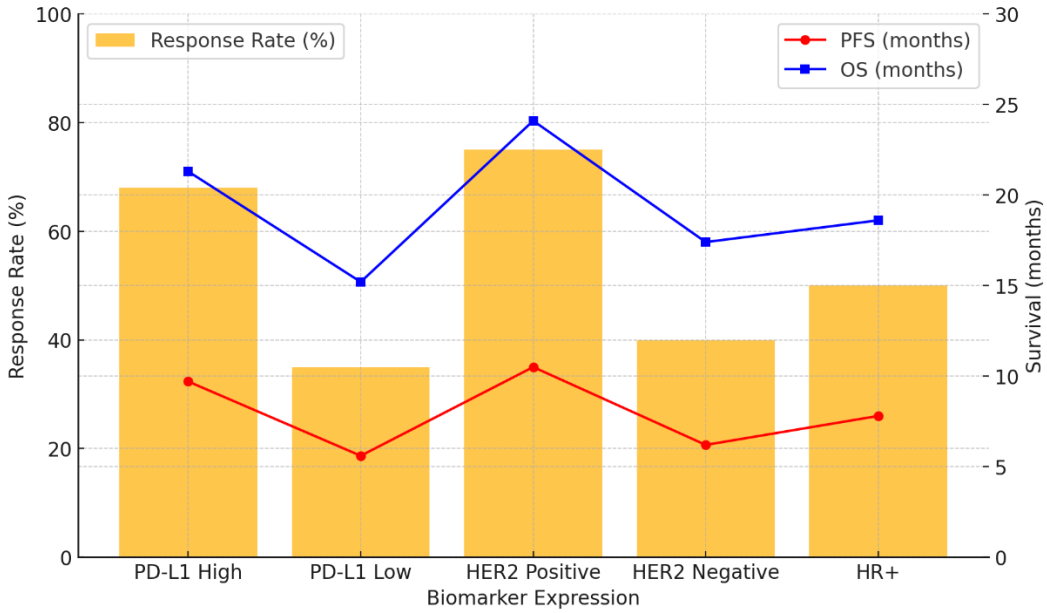

Figure 1. Immunotherapy Response and Survival Outcomes by Biomarker Expression.

The figure visually illustrates the correlation between biomarker expression patterns and the success levels of immunotherapy. According to the bar chart, HER2-positive tumors displayed 75% response while PD-L1-high tumors achieved 68% yet PD-L1-low tumors demonstrated only 35% responsiveness and HER2-negative tumors showed 40% responsiveness to immunotherapy. The data indicates that PD-L1 expression together with HER2 status functions as critical elements to forecast immunotherapy response rates. Two line charts show the statistical data regarding progression-free survival (PFS) and overall survival (OS). HER2-positive patients experienced a PFS of 10.5 months and an OS of 24.1 months which were longer than PD-L1-high patients (PFS: 9.7 months and OS: 21.3 months). PD-L1-low tumors together with HER2-negative tumors demonstrated minimum survival times among all groups at PFS: 5.6 months and OS: 15.2 months

showing the requirement for different therapeutic approaches in these affected groups. HER2-positive (50%) and PD-L1-high (45%) tumor types experience the most severe immune-related adverse events based on the dataset evidence which requires specific toxicity management systems for these patient groups.

Research already shows that immune checkpoint inhibitors yield superior results on tumors which have high densities of tumor-infiltrating lymphocytes (TILs) and include HER2-positive and PD-L1-high cancer types. PD-L1-low tumors along with HER2-negative cases show reduced sensitivity to checkpoint blockade because they fall under the "cold" immunological category. The treatment outcomes demand cooperation among immune checkpoint inhibitors and CDK4/6 inhibitors or PARP inhibitors to boost immune activation within these tumors. PD-L1-high coupled with HER2-positive patients exhibit elevated immune-related adverse events (irAEs) although they gain substantial immunotherapy benefits so healthcare providers require additional training along with standardized protocols to combat toxicity risks. These findings from laboratory experiments validate the tumor immune-editing hypothesis because cancer develops methods to escape destruction by the immune system. The analysis highlights how distinct therapies influencing immune interactions should become part of breast cancer therapy instead of using checkpoint blockade alone. This investigation shows that Uzbekistan needs immediate improvements in biomarker testing capacity for medical settings throughout the country. The utilization of PD-L1 and HER2 screening methods regularly remains crucial for selecting patients for immunotherapy due to excellent cost-effectiveness and improved treatment outcomes. The safe delivery of immune therapies requires that health professionals receive specialized training for managing toxic side effects which affect between 45-50% of treated patients. Additional study is required to resolve multiple important knowledge gaps. Research should concentrate on combination therapies for immunotherapy because modest effects were observed in HER2-negative and HR+ breast cancers. Subsequent research must examine if epigenetic modulators or cytokine-based therapies can convert immunologically "cold" tumors into "hot" tumors, thereby enhancing their responsiveness to immunotherapy.

Pharmacoeconomic research must be conducted to evaluate immunotherapy value and efficiency in Uzbekistan since financial limitations prevent its widespread adoption. Additional clinical trials involving Uzbek breast cancer patients should be expanded because they will reveal possible ethnic or geographical differences in immunotherapy treatment effectiveness. The research outlines essential information about immunotherapy success in breast cancer treatment for Uzbekistani patients which emphasizes how biomarkers drive therapeutic decisions. The most significant benefits of PD-L1 and HER2-positive patients highlight the necessity for developing new combination approaches because treatment response for HR+ and HER2-negative patients remained moderate. The successful implementation of immunotherapy in Uzbekistan's national oncology treatment guidelines depends on expanded biomarker screening as well as improved oncologist training and additional clinical trials of personalized immunotherapy approaches.

4. Conclusion

This study confirms immunotherapy plays an essential part in breast cancer treatment when patients have HER2-positive and PD-L1-high tumors because they achieve superior response rates together with extended survival outcomes. The therapeutic benefits of these treatments were restricted to PD-L1-low and HER2-negative subtypes since biomarkers play an important role in picking suitable treatments for patients. HER2-positive and PD-L1-high patients experience many immune-related adverse events because they receive maximum benefits from immunotherapy treatment although they need better strategies to reduce treatment toxicity. This research implies crucial strategic changes to develop biomarker testing systems in Uzbekistan as an essential step to improve patient selection

accuracy and reduce the costs of implementing immunotherapy treatments. Prioritized implementation of training programs focusing on immune toxicity handling for oncologists and strategies to obtain subsidized immunotherapy must receive immediate attention for wide-scale implementation. The therapy of combination strategies for HER2-negative and HR+ tumors needs additional scientific research regarding their effectiveness through examinations of immune-stimulating agents and epigenetic modulators. Researchers should prioritize studies to maximize combination therapies and conduct clinical trials in Uzbekistan as well as gauge immunotherapy's economic impact to develop policy recommendations enhancing local and national breast cancer healthcare management.

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