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Prognostic significance of PD-L1 expression and efficacy of immunotherapy in the Georgian population with non-small cell lung cancer

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Abstract:

Introduction: Prevention, early diagnosis and treatment of oncological diseases remain a significant challenge for modern medicine. The discovery of immune checkpoint inhibitors, including programmed death protein and programmed death ligand 1 (PD-1/PD-L1), has made a significant breakthrough in modern approaches to the treatment of oncological diseases. These monoclonal antibodies block the “braking” mechanisms of the immune system, which allows T-lymphocytes to recognize and destroy tumor cells.

This research paper aims to analyze the characteristics of PD-L1 expression in a cohort of 108 patients with non-small cell lung cancer (NSCLC) in Georgia;

Methods: An observational and quantitative study was conducted, which included 108 patients with NSCLC registered in 2025 at the “Todua” and “Healthycore” clinics in Georgia. Clinical data were obtained from laboratory records and electronic medical databases. PD-L1 expression was assessed using standard clinical protocols. Patients were categorized according to the level of expression: <1%, 1–49% and ≥50%. The data were processed retrospectively, using descriptive statistics. The use of this methodology ensures the reliability, reproducibility and generalizability of the study results to the Georgian population in a national context.

Results: The analysis showed that only 18.5% of the studied cohort had high PD-L1 expression (TPS, CPS ≥ 50%), which makes them optimal candidates for first-line monotherapy. The majority of the population (76.8%) had low or negative expression, indicating that monotherapy alone is insufficient for adequate clinical response in these patients. The study showed a low test-miss rate (4.6%). In

addition, it was noted that atezolizumab, despite funding from government programs, is rarely used compared to other drugs in NSCLC due to its low clinical efficacy.

Conclusion: Although the discovery of PD-1/PD-L1 inhibitors has revolutionized oncology, their efficacy is not universal and requires a personalized, multidisciplinary approach. The “biomarker dilemma” remains a subject of research, as high PD-L1 expression does not always provide an absolute guarantee of success. Some patients with negative expression levels still receive positive therapeutic benefits. Patients with low expression for most, multimodal strategies, such as combining immunotherapy with chemotherapy or targeted therapy, are necessary to transform “cold” tumors into “hot,” immunoactive forms. Further development of anti-PD-1/PD-L1 immunotherapy is fully based on personalized medicine – targeted treatment tailored to the individual patient. Further refinement of personalized treatment models requires future large-scale, prospective clinical trials in the Georgian population.

Keywords: immunotherapy, immune checkpoint inhibitors (ICIs), PD-1/PD-L1 inhibitors, non-small cell lung cancer (NSCLC), tumor heterogeneity, biomarkers, prognostic value, personalized medicine.

Introduction:

Treatment of oncological pathologies remains a top priority of modern medicine, which is due to the high morbidity and mortality rates. Traditional treatment methods - surgery, chemotherapy, radiation therapy - are the fundamental pillars of modern oncology, however, their use in some oncological pathologies is often limited by insufficient clinical response, pronounced systemic toxicity and high rates of disease recurrence [2].

An innovative breakthrough in medicine is associated with the development of the field of immuno-oncology, the goal of which is to mobilize the immune system to identify and eliminate malignant cells. The central molecular basis of this change is the PD-1/PD-L1 signaling system, which under physiological conditions provides immune homeostasis and prevents the development of autoimmune diseases. However, various neoplasms, especially melanoma, non-small cell lung cancer and triple hormone-negative breast cancer (TNBC), use this pathway to escape immune surveillance [1]. These tumors are characterized by high expression of PD-L1 and immune sensitivity. PD-L1 binds to the PD-1 receptor on T cells, thereby reducing T-cell activation, proliferation and cytokine production. Ultimately, cytotoxic activity against tumor cells is inhibited. This binding leads to “braking” of the immune system, T-cell anergy, exhaustion and apoptosis, which allows the tumor to evade immune surveillance [3].

In addition, therapeutic reactivation of the immune system often leads to a cascade of immune-related adverse events (irAEs), manifested in the form of acute autoimmune pathologies.

Although the pharmacological inhibitors of immune checkpoints (ICIs), pembrolizumab and nivolumab, have radically changed the current standard of care [1], their therapeutic efficacy is not

universal. While the objective response rate (ORR) in melanoma reaches 45–60%, in most solid tumors this figure is much lower and varies within 15–30% [4] [3]. This figure once again confirms that the therapeutic response of tumors is largely determined by their molecular and immune heterogeneity.

The molecular mechanisms of primary and acquired resistance remain an active subject of research in science. The “biomarker dilemma” remains a significant challenge: The Society for Immunotherapy of Cancer (SITC) highlights the importance of key biomarkers in immunotherapy clinical trials to better match patients with personalized treatments

PD-L1 expression is one of the key biomarkers included in the required panel of studies, which also includes the neutrophil-to-lymphocyte ratio (NLR), serum lactate dehydrogenase (LDH), microsatellite stability, and tumor mutational burden (TMB). Although the standardization of the PD-1/PD-L1 score is still under criticism in different countries, the European Society for Medical Oncology (ESMO) and the College of American Pathologists (CAP) have recognized the effectiveness of this score and are working to reduce interassay variability and ensure its accuracy [3]. Modern medicine emphasizes the importance of moving from monotherapy to a new generation of combined and individually tailored treatment strategies. If early studies focused on the PD-1/PD-L1 complex as only a limiting mechanism. Promising ways to overcome resistance are actively being discussed - the conversion of immunologically “cold” non-inflammatory tumors to “hot”, i.e. inflammatory forms [1] [6]. This path involves artificial stimulation of T-cell infiltration and increasing sensitivity to PD-1/PD-L1 blockade.

This research paper aims to analyze the features of PD-L1 expression in a cohort of 108 patients with non-small cell lung cancer (NSCLC) in Georgia; to review the pharmacotherapeutic agents commonly used for the treatment of patients with high expression (TPS, CPS $\geq$ 50%); to assess the effectiveness of financial mechanisms within the framework of the state program to improve access to therapeutic interventions.

The study identified a small group with PD-L1 TPS, CPS >50%, which raised the hypothesis that these patients may be potential candidates for long-term monotherapy. However, it was found that the majority require multimodal strategies, since monotherapy alone does not provide sufficient immune activation. In addition, it is doubtful that a high level of PD-L1 will be an absolute predictor of success, and additional biomarkers and immunoinhibitory pathways should be considered for a more accurate prediction of therapeutic efficacy.

Methodology:

We conducted an observational and quantitative study on a selected cohort of the Georgian population. We analyzed the data of the study conducted in the "Healthycore" and "Todua" clinics, which reflect the sensitivity of PD-L1 in registered patients with non-small cell lung cancer in 2025. Clinical data were obtained from routine laboratory records and electronic medical databases, where each value was

recorded based on the corresponding measurement. Oncopatients were categorized according to various clinical parameters.

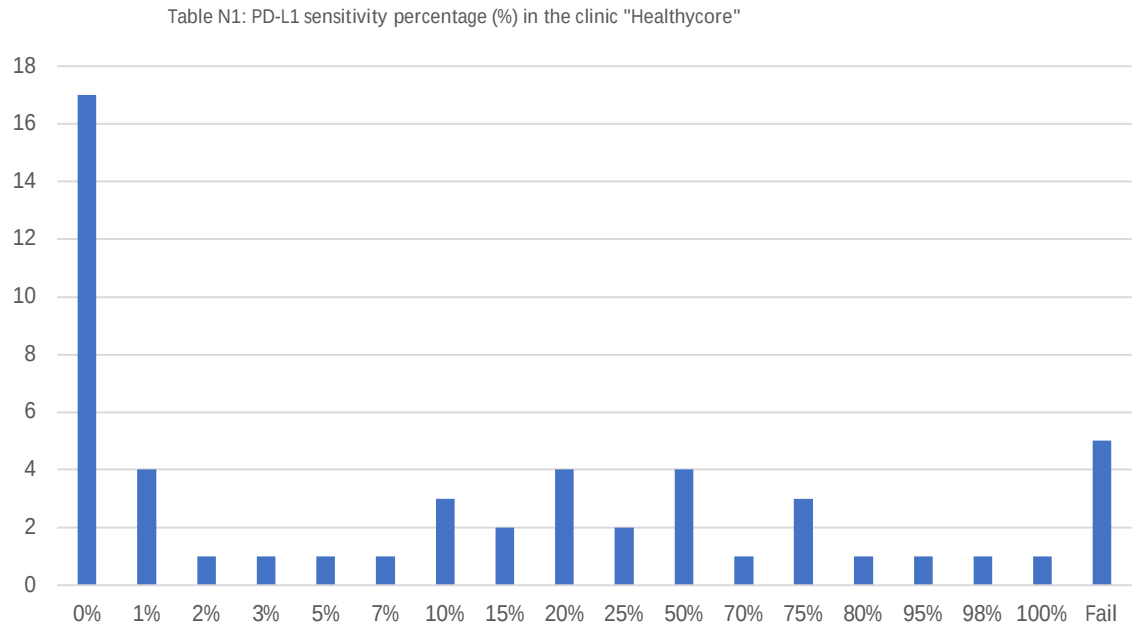
The study was conducted with full respect for patient confidentiality; personal information is anonymous, which excludes the identification of individual patients.

The data were analyzed retrospectively, using descriptive statistics methods. Categorical variables are presented as absolute frequencies (n) and percentages (%). PD-L1 expression was assessed according to standardized clinical protocols, using TPS (Tumor Proportion Score) and CPS (Combined Positive Score). This ensures the accuracy, reliability and parallelism of the results with international studies. The obtained values were classified into three categories: <1%, 1–49% and ≥50%, reflecting the clinically applicable cut-off values of low and high expression. The use of this methodology ensures the reliability, reproducibility and generalizability of the study results to the Georgian population in a national context.

Results:

Clinic "Helsicor" provided accurate PD-L1 sensitivity percentages for 53 patients, allowing for a deeper analysis of variance in the data.

Diagram 1: PD-L1 sensitivity percentage (%) at Clinic "Healthycore".



According to the medical databases available at the “Todua” Clinic, the results of 55 patients were categorized based on a 50% clinical sample, which is in line with international protocols.

Diagram 2: PD-L1 sensitivity percentage (%) at the “Todua” Clinic

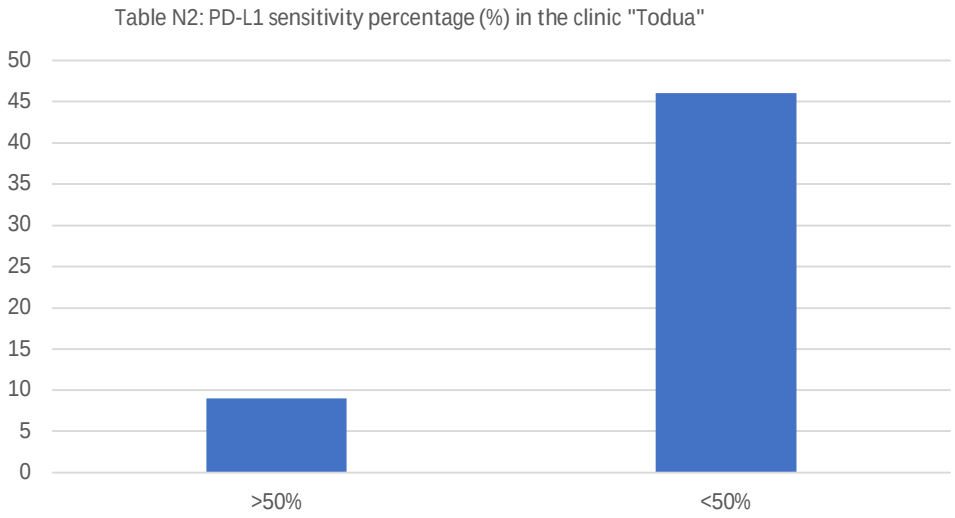


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Figure 3: PD-L1 expression rates by clinical basis

These trends provide important information on the prospects for the therapeutic management of non-small cell lung cancer in the local population. The analysis revealed that only 18.5% of the study cohort had high expression of PD-L1 (TPS, CPS ≥ 50%). Based on international clinical guidelines, this category of patients is considered an optimal candidate for first-line monotherapy. This indicator indicates that in this small part of patients it is possible to achieve high clinical efficacy with a less toxic, targeted approach, which fundamentally improves the quality of life.

At the same time, the majority of the study population (76.8%) is characterized by low or negative expression of the biomarker, which clearly emphasizes the importance of multimodal therapeutic

strategies. For this category of patients, the use of PD-1/PD-L1 inhibitors as monotherapy is usually not sufficient to obtain an adequate clinical response.

It was observed that “atezolizumab”, which is financed within the framework of Georgian healthcare programs, is rarely used in the treatment of non-small cell lung cancer due to its relatively low clinical efficacy.

The reliability and practical value of the study results are determined by the accuracy and validity of the diagnostic methodology used. The minimal share of test failures (4.6%) indicates the high technological and procedural soundness of the clinical databases. The obtained statistical picture provides a solid basis for future clinical forecasting and more effective, targeted allocation of healthcare resources to innovative pharmacotherapeutic courses.

Discussion:

When interpreting the data obtained, it is particularly important to take into account several circumstances. PD-L1 expression varies not only between different tumors, but also within the same neoplasm. Such results are consistent with international literature and clinical guidelines. This variability is due to heterogeneity, where the same tumor site has different genetic mutations, immune cell infiltration, testing conditions and stage progression [3]. A single biopsy often cannot reflect the molecular picture of the entire neoplasm, since PD-L1 expression varies significantly both in different areas of the same tumor and between the primary focus and its metastases. International studies confirm that the discordance rate between surgical specimens and biopsies reaches 48% [5]. Accordingly, 100% expression in one part of the tumor does not exclude its complete absence in other areas, which leads to erroneous predictions of treatment effectiveness.

A review of the international scientific literature showed that patients with high PD-L1 expression (CPS ≥50%) exhibit higher sensitivity to immunotherapy [5]. However, according to the assessment of experienced oncologists in Georgia, high expression does not represent an absolute guarantee of treatment success. This discrepancy is known in the scientific literature as the “biomarker dilemma”: there are cases when patients with 100% PD-L1 sensitivity do not respond to treatment, while in some patients with a negative indicator, the therapeutic effect is noticeable [3].

Accordingly, to optimize the clinical outcome, it is necessary to combine immunotherapy with cytotoxic chemotherapy or specific targeted drugs. This synergistic approach contributes to the transformation of the immunologically passive, “cold” tumor microenvironment and the effective reactivation of the body’s immune surveillance. Despite the importance of the study, there are several limitations that must be considered when discussing the results. First, the study is of retrospective design, which limits the possibility of making unambiguous conclusions about causal relationships. The data were obtained from electronic databases of two leading clinics in Georgia, which, on the one hand, allows for generalization to the Georgian population, but on the other hand, requires larger-scale

analyses. The second factor is related to methodologically different approaches to biomarker assessment, which leads to some variability in the results. This problem has been discussed in international studies and represents one of the main challenges in standardizing biomarkers and determining accurate indicators [3, 5].

In the future, it is advisable to conduct larger-scale, prospective clinical trials in the Georgian population, which will allow researchers to more accurately assess the effectiveness of immunotherapy.

Conclusion:

The discovery of the PD-1/PD-L1 signaling pathway and its inhibitors has fundamentally revolutionized modern oncology, due to the unique mechanism of reactivation of the immune system against malignant cells. The main result of this study emphasizes that, despite a significant increase in survival rates, the effectiveness of this therapy is not guaranteed and requires a personalized, multidisciplinary approach. This is due to the high heterogeneity of the tumor, the high rate of discordance (inconsistency) between biopsies and the actual molecular landscape of the tumor (up to 48%).

In a cohort study of 108 patients with non-small cell lung cancer across Georgia, it was found that 18.5% of the study group had high PD-L1 expression (TPS, CPS ≥ 50%), making them candidates for immunotherapy.

The need for combination strategies is driven by the fact that the majority of the cohort, 76.5%, has low or negative expression. This fact confirms that multimodal treatment is a priority to improve clinical outcomes. This includes immunotherapy in combination with chemotherapy or the use of targeted agents to transform “cold” tumors into active, “hot” forms.

That is why there is no universal or unified approach to PD-1/PD-L1 immunotherapy. Effective management requires an individualized, patient-centered strategy. This approach leads us to the need to develop a more personalized oncoimmunological model.

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