PD-1 and PD-L1 in Single-Target and Multi-Target Combination Therapies for Non-Small Cell Lung Cancer (NSCLC)

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Abstract. Lung cancer ranks as the most prevalent malignant tumor, exhibiting a higher annual incidence rate compared to other cancers. In clinical practice, treatment approaches currently encompass traditional chemotherapy alongside newer strategies such as immune checkpoint inhibitors, notably PD-1 and PD-L1 inhibitors, to manage patient care. While conventional chemotherapy has been widely adopted in clinical settings as a standard method to combat tumors, its effectiveness in treating non-small cell lung cancer (NSCLC) remains limited and often falls short of expectations. In contrast, emerging therapies involving PD-1 or PD-L1 inhibitors, either as single-target treatments combined with chemotherapy or as dual-target regimens combining both PD-1 and PD-L1 inhibitors, have been explored in clinical trials and have demonstrated promising outcomes. These innovative approaches appear to offer improved efficacy over traditional methods, sparking interest in their potential to transform NSCLC management. This article provides a comprehensive summary of the current landscape of PD-1 and PD-L1 therapies for NSCLC, drawing on an extensive review of existing literature. By synthesizing findings from recent studies, it aims to shed light on the advancements, challenges, and future directions of these immunotherapeutic strategies in the context of NSCLC treatment, contributing to a deeper understanding of their role in modern oncology.

Keywords: PD-1, PD-L1, non-small cell lung cancer (NSCLC), Immune checkpoints targeted therapy.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases, with about half of these patients eventually developing distant metastases [1]. Among the established clinical treatment options, targeted therapies directed at programmed cell death receptors and their ligands have markedly improved outcomes in the management of small cell lung cancer [2-3]. Increasingly, research into immune checkpoint inhibitors for NSCLC has gained momentum. A key focus of these studies is the programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) axis, which is implicated in T-cell exhaustion during chronic infections and tumor progression. This pathway has been extensively investigated, positioning PD-1 and PD-L1-targeted drugs as some of the most widely utilized agents against NSCLC in current clinical practice [4]. A prominent therapeutic strategy involves combining traditional chemotherapy with immune checkpoint inhibitors. This approach, now a standard in NSCLC treatment, employs drugs such as atezolizumab to block the interaction between PD-1 receptors on immune cells and PD-L1 receptors on tumor cells [5].

PD-1/PD-L1 inhibitors represent one of the most advanced targets in immune checkpoint. therapy. The PD-1 surface protein, expressed on activated T cells, interacts with its ligands PD-L1 and PD-L2 on tumor cells, suppressing T-cell receptor (TCR)-mediated immune functions [6]. Upon binding of PD-1 to PD-L1 or PD-L2, the intracellular domain of PD-1 undergoes phosphorylation by the Lck tyrosine kinase. This phosphorylation event triggers the targeted recruitment of the tyrosine phosphatase Shp2, which in turn facilitates the dephosphorylation of the CD28 co-stimulatory molecule. Through this cascade, the signaling pathways mediated by TCR and CD28 co-stimulation are significantly dampened, ultimately impairing the signal transduction required for T-cell activation [4, 7-9]. In the context of cancer immunotherapy, disrupting the PD-1/PD-L1 interaction between immune T cells and tumor cells can restore T-cell immune activity, thereby unleashing its tumor-killing potential [6, 10].

Immune checkpoints are a class of immunosuppressive factors primarily expressed on immune cells, serving as a mechanism for the body to regulate its immune responses. These are essentially small protein molecules produced by immune cells to modulate their own immune functions. During tumor immune evasion, tumor cells exploit this system by expressing immune checkpoint ligands that bind to T cells, thereby inhibiting their tumor-killing effects [5]. Immune checkpoint therapies counteract this process by leveraging co-stimulatory or co-inhibitory signals to maintain an optimal level of T-cell tumoricidal activity. This ensures that the immune system remains balanced—neither overly activated, which could lead to autoimmunity, nor excessively suppressed, which would allow tumor progression.

The integration of immune checkpoint inhibitors with conventional treatments has revolutionized NSCLC management, offering a dual-pronged approach that enhances efficacy. By targeting the PD-1/PD-L1 axis, these therapies reinvigorate the immune system's ability to recognize and destroy cancer cells, addressing a critical limitation of traditional chemotherapy, which often lacks specificity and yields suboptimal results in NSCLC. Ongoing research continues to refine these strategies, exploring combination regimens and novel inhibitors to overcome resistance and expand therapeutic benefits. This evolving landscape underscores the transformative potential of immune checkpoint therapies in oncology, particularly for NSCLC, where they have become a cornerstone of modern treatment.

2. Combination Therapy in NSCLC

2.1. Single-Target PD-1 and PD-L1 Combination Therapy in NSCLC

A review of relevant literature reveals that low-dose radiotherapy can upregulate PD-L1 expression on tumor cells, while platforms such as platinum- and gadolinium-palladium-based nanoparticles have been explored in conjunction with single-target PD-1 or PD-L1 inhibitors [9]. Among commonly used agents—atezolizumab, camrelizumab, sintilimab, sugemalimab, tislelizumab, and toripalimab—atezolizumab demonstrates superior efficacy in patients with PD-L1-expressing tumors, correlating with enhanced tumor suppression. Clinical studies further suggest that incorporating PD-1 or PD-L1 inhibitors into neoadjuvant chemotherapy regimens may improve survival outcomes in patients with resectable NSCLC [10, 11]. Although PD-1, a well-studied immune checkpoint, has been extensively applied in clinical practice, its standalone efficacy in NSCLC is limited, with an objective response rate of approximately 40% and a relatively short duration of effectiveness [12]. While single-target combination therapies outperform traditional chemotherapy, their durability and efficacy fall short of multi-target approaches [13]. Single-agent PD-1 or PD-L1 therapies combined with chemotherapy effectively sustain T-cell tumoricidal activity by binding PD-1 on T cells or PD-L1 on tumor cells, bolstering immune-mediated tumor clearance. However, NSCLC patients treated with these agents often exhibit increased PD-L1 expression, which diminishes the efficacy of single-target therapies. Current evidence indicates that prolonged use of single-target PD-1 or PD-L1 inhibitors leads to reduced therapeutic potency, weakened tumor suppression, and limited benefits in post-resection NSCLC recovery.

2.2. Multi-Target Combination Therapy in NSCLC

In clinical practice, the prolonged use of single-drug, single-target therapies to sustain the tumor-immune effects of autologous T cells has often led to diminished efficacy over time. To address this challenge, researchers have explored multi-target therapeutic strategies. The combined application of PD-1 and PD-L1 multi-target therapies has been shown to enhance the objective response rate (ORR) [14-16] and improve the management of checkpoint inhibitor pneumonitis (CIP) symptoms associated with non-small cell lung cancer (NSCLC) [17]. Furthermore, the integration of PD-1 and PD-L1 inhibitors has proven particularly effective in patients with high tumor mutational burden (TMB) within the tumor microenvironment [18]. In cases where long-term single-target combination therapies result in elevated PD-L1 expression, multi-target approaches demonstrate superior

therapeutic outcomes. Notably, the efficacy of these treatments correlates strongly with the level of PD-L1 expression on tumor cells, which is regulated by the gene B4GALT1 [19]. Multi-target regimens exhibit enhanced effectiveness in patients with high PD-L1 expression, offering a broader applicability and greater benefit compared to single-drug therapies.

Several biomarkers, including PD-L1 expression, TMB, microsatellite instability (MSI), the microbiome, hypoxia, interferon-gamma (IFN-γ), and extracellular matrix components, have been identified as predictors of improved responses to immune checkpoint inhibitors (ICIs) [20]. Patients with high TMB (>14 mutations/Mb) exhibit significantly better responses to PD-1/PD-L1 inhibitors ($P=6\times10^{-9}$), and those with elevated TMB levels also show improved survival rates under combination therapies [18]. Additionally, studies have demonstrated that blocking the interaction between CTLA-4 and CD80/CD86 enhances T-cell activation. The dual blockade of PD-1 and CTLA-4 markedly improves ORR and progression-free survival (PFS) [20]. PD-1PD-L1 inhibitors are generally well-tolerated, with a low incidence of neurological toxicities such as radiation necrosis. In patients with brain metastases (BM), combination regimens have been associated with higher disease control rates and survival advantages.

Multi-target therapies exhibit a more robust therapeutic impact on NSCLC, primarily by more effectively counteracting the immunosuppressive effects of tumor-derived PD-L1 on T-cell-mediated tumor immunity. However, this approach is not without drawbacks, as it is also associated with an increased incidence of adverse effects in patients. The enhanced efficacy of multi-target strategies stems from their ability to simultaneously address multiple immune evasion pathways exploited by tumors, thereby restoring and sustaining T-cell activity more effectively than single-target interventions. For instance, while single-target therapies may lead to compensatory upregulation of PD-L1, multi-target treatments can mitigate this resistance mechanism, particularly in tumors with high PD-L1 expression driven by genetic regulation. Moreover, the synergy between PD-1 and PD-L1 blockade, and in some cases CTLA-4 inhibition, amplifies the immune response, offering a more comprehensive attack on the tumor microenvironment.

Despite these advances, the increased complexity of multi-target regimens necessitates careful consideration of patient-specific factors, such as biomarker profiles and tolerance to potential side effects. High TMB, in particular, has emerged as a critical indicator of responsiveness, guiding the selection of patients likely to benefit from these intensified therapeutic approaches. As research progresses, the refinement of multi-target strategies, coupled with the identification of additional predictive biomarkers, holds promise for further optimizing outcomes in NSCLC while balancing efficacy and safety.

2.3. Comparative Clinical Data: Single-Target vs. Multi-Target Combination Therapies

This study conducted a literature search on PubMed using keywords such as "clinical treatment," "PD-1," "PD-L1," "combination therapy," "single-target therapy," and "multi-target therapy," identifying four highly relevant analytical articles. Key findings include the following: ZPatients receiving dual immunotherapy exhibited significantly higher PFS, with subgroup analysis based on PD-L1 expression levels revealing greater PFS benefits in the PD-L1 <25% subgroup. However, dual immunotherapy was associated with an increased incidence of immune-related adverse events (irAEs) across all grades compared to single ICI therapy [20]. A Phase II randomized controlled trial evaluating sintilimab or pembrolizumab, with or without platinum-based doublet chemotherapy, in untreated advanced NSCLC demonstrated that PD-L1 expression-guided monoclonal antibody therapy or combination chemotherapy is feasible as a first-line treatment. No significant differences in efficacy or safety were observed between sintilimab and pembrolizumab [12].

When used alone or in combination with chemotherapy, PD-1/PD-L1 inhibitors significantly improve outcomes in small cell lung cancer (SCLC). In patients receiving combination regimens, PFS varied significantly across PD-L1 expression strata. Combination therapies increased chemotherapy-induced adverse events (AEs), whereas standalone PD-1/PD-L1 inhibitor use was associated with a lower incidence of treatment-related AEs (TRAEs) of any grade [13]. Compared to

chemotherapy alone, neoadjuvant immunotherapy and standalone neoadjuvant ICI regimens significantly improved event-free survival (EFS). However, adding PD-1 or PD-L1 inhibitors to neoadjuvant chemotherapy did not enhance survival outcomes in resectable NSCLC patients and was potentially linked to increased AEs [10].

3. Discussion

While research into multi-target therapies remains in the refinement stage, the suboptimal outcomes of single-target PD-1 or PD-L1 receptor blockade have driven the adoption of multi-target strategies in clinical practice. Approaches such as combined PD-1 and PD-L1 inhibition, or their integration with chemotherapy, have shown improved efficacy against tumors compared to single-target therapies or chemotherapy alone. These multi-target regimens exhibit prolonged antitumor activity, and in small cell lung cancer (SCLC), they are less prone to efficacy attenuation or the development of resistance. Furthermore, they effectively mitigate SCLC-related complications, such as checkpoint inhibitor-induced pneumonitis (CIP), and demonstrate enhanced benefits in patients with elevated tumor mutational burden (TMB) in specific immune cell populations. However, dual-target therapies are associated with a higher incidence of adverse effects, and in certain cases, their therapeutic advantage over other options is not markedly superior, posing challenges to their broad application.

Drawing from the literature reviewed in this study, clinical recommendations lean toward single-agent PD-1 or PD-L1 therapy, or their use in combination with chemotherapy, rather than dual-target immunotherapy. For patients receiving chemotherapy, a single-agent adjunct alongside chemotherapy is advised. The evidence compiled here does not endorse the widespread implementation of dual-drug immunotherapy. Particular caution is urged when considering single-agent therapy for patients with low PD-L1 expression, given its diminished efficacy in this subgroup.

In conclusion, although multi-target treatments hold potential, especially for complex diseases like SCLC, their use must be balanced against the risk of increased toxicity and the absence of consistent superiority across all contexts. Current data favor single-agent approaches, either standalone or paired with chemotherapy, as a more dependable option, tailored to factors such as PD-L1 expression and TMB levels. Additional investigation is needed to optimize these strategies and clarify their most effective clinical applications, ensuring precision in patient management while minimizing drawbacks.

4. Summary

This article offers an in-depth review of recent progress in immune checkpoint therapies, focusing on studies involving PD-1 and PD-L1 inhibitors as monotherapies and in combination with chemotherapy. A meta-analysis of several clinical trials indicates that the use of dual-drug regimens in clinical settings should be approached with caution. Experimental data suggest that multi-modal immunotherapies may yield better outcomes, particularly in patients with low PD-L1 expression and in improving progression-free survival (PFS). However, these approaches carry a greater risk of adverse effects compared to single-agent therapies. Current clinical trial evidence remains limited, highlighting the need for further research to provide clearer insights and distinguish the therapeutic effectiveness of dual immune combination treatments from monotherapies. Despite these uncertainties, clinical practice has shown promising results, with single-drug immunotherapy combined with chemotherapy proving effective in managing non-small cell lung cancer (NSCLC). This combination demonstrates superior efficacy and tolerability compared to chemotherapy alone. Consequently, for guiding clinical drug use, the preferred strategy remains the integration of chemotherapy with single-agent immunotherapy or the use of single-agent immunotherapy as a supportive treatment. In cases where patients show limited response to these standard options, multi-target, multi-modal immunotherapies may be considered, though only with careful evaluation. More

robust research data are required to formulate precise therapeutic recommendations and enhance treatment accuracy. In summary, while multi-target immunotherapies offer potential for specific patient groups, their widespread adoption demands a better understanding of their benefits versus risks. The heightened possibility of side effects with these complex treatments calls for a prudent approach, balancing efficacy with patient safety. Meanwhile, the combination of single-agent immunotherapy and chemotherapy emerges as a dependable and well-tolerated choice, forming a key component of current NSCLC treatment protocols. Future investigations should focus on identifying predictive biomarkers and patient-specific characteristics to refine treatment decisions, paving the way for personalized strategies that optimize outcomes while reducing adverse effects. Until such evidence is available, clinicians should prioritize the proven benefits of single-drug immunotherapy alongside chemotherapy, reserving multi-target approaches for carefully selected cases where conventional treatments fall short.

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