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Advances in PD-1 inhibitor combination therapy for non-small cell lung cancer

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Abstract:

Non-small cell lung carcinoma (NSCLC), characterized by its rapid progression and absence of clear initial symptoms, represents the most common variant of pulmonary malignancies. Therapeutic approaches focusing on PD-1/PD-L1 immune checkpoint blockade have dramatically transformed NSCLC management strategies. However, single-agent treatments continue to demonstrate constrained efficacy, with observable response rates fluctuating between 15% and 30%, while also facing challenges from both intrinsic and acquired resistance mechanisms. Thus, there are ongoing clinical trials involving multimodal interventions for PD-1 inhibitor combination therapy (for example, radiotherapy causing immunogenic tumor cell death, chemotherapy perturbing the tumor microenvironment, targeted drugs to inhibit oncogenic signaling, and TCM reversion of multidrug resistance); the studies also demonstrated the potential of these combination strategies to significantly improve the survival endpoints (PFS/OS). Nevertheless, it is difficult to combine therapies, and these combinations are often plagued by heterogeneous treatment responses, an absence of evidence-based rationale for treatment subdivisions (for example, patients with an EGFR mutation), and insufficient dynamic safety assessment. We must pursue a future where biomarker-driven precision interventions represent our gold standard (such as using single-cell sequencing to screen for sensitive subpopulations), where "molecular mechanism-based" synergistic therapies are the norm (for instance, combining bispecific antibodies with epigenetic modulation), where toxicity risk stratification modeling is established, and where optimization of healthcare economics is proven effective. Ultimately, we need to achieve the transformation of empirical combinations to molecular mechanism-driven precision therapies through real-world data integration and benefit patients by increasing their survival benefit.

Keywords: NSCLC, PD-1, combination therapy, multi-modal intervention, precision therapy

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1. Introduction

Non-small cell lung carcinoma (NSCLC) represents approximately 85% of global lung cancer cases according to recent epidemiological data (WHO/IARC, 2020). This malignancy exhibits pronounced heterogeneity in its metastatic behavior and demonstrates aggressive progression patterns, frequently presenting with nonspecific clinical manifestations during initial phases. Consequently, nearly 70% of affected individuals are diagnosed at either regionally advanced (stage III) or disseminated (stage IV) disease states. While standard therapeutic interventions including definitive surgical resection, targeted radiation therapy, and platinum-containing combination chemotherapy remain cornerstone treatments, they have failed to significantly improve overall prognosis. The five-year survival probability for stage III-IV NSCLC patients generally remains below 20% in clinical observations8[1]. The emergence of immunotherapeutic agents targeting immune checkpoints has revolutionized management strategies for advanced NSCLC cases. These inhibitors, particularly those directed against the PD-1/PD-L1 axis, demonstrate notable clinical efficacy by interfering with T-cell inhibitory mechanisms and modifying the immunological landscape within tumor microenvironments[2]. Mechanistic studies have shown that ICIs can reverse the T cell depletion phenotype by blocking the ligand binding of PD-1 to PD-L1/PD-L2 and rebuild the anti-tumour immunosurveillance function, thus inducing a durable anti-tumour response[3]. However, single-agent ICI therapy still has significant limitations: the objective response rate (ORR) is mostly lower than 30%, and primary/secondary drug resistance is prominent[4]. Based on this, PD-1/PD-L1 inhibitor combination therapy has gradually become the focus of clinical research, which can synergise with the immunogenic cell death (ICD) effect of chemotherapy, the distal immune activation (abscopal effect) of radiotherapy, and the neoantigenic exposure of targeted drugs to achieve multidimensional immune microenvironment modulation[5]. Recent findings demonstrate that therapeutic combinations significantly improve both median progression-free survival (mPFS) and overall survival (OS) in patients diagnosed with advanced non-small cell lung carcinoma (NSCLC), Some clinical studies report these interventions achieving more than double the objective response rate (ORR) compared to conventional treatments[6]. This review integrates evidence-based advancements and biomarker exploration to analyze the mechanistic innovations and clinical applicability of PD-1 inhibitor-based combination therapy in NSCLC, aiming to advance precision immunotherapy through translational medicine perspectives.

2. Overview of PD-1 inhibitors

Programmed death-1 (PD-1) serves as a pivotal immune regulatory receptor belonging to the CD28 superfamily. The gene encoding PD-1 is situated in the q37 region of chromosome 2 in humans. This transmembrane glycoprotein of type I consists of 268 amino acid residues, demonstrating roughly 20% sequence homology with cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)[7].

The PD-1 molecule consists of three structural domains: the extracellular region, the transmembrane region and the intracellular region, which form a functional complex. The extracellular portion specifically binds to PD-L1 and PD-L2 molecules through a configuration that mimics the variable domain of immunoglobulins (IgV). The nonpolar transmembrane section securely embeds itself within the cellular membrane structure.The cytoplasmic segment contains two key structural elements: an N-terminal immunoreceptor tyrosine-based inhibitory sequence (ITIM, Y223) and a C-terminal immunoreceptor tyrosine-based switch sequence (ITSM, Y248). These domains experience differential phosphorylation states, establishing a fluid signaling cascade. Following PD-1/ligand engagement, tyrosine residues located in the ITSM region become phosphorylated. This modification recruits phosphatase enzymes including SHP-2 and SHP-1, which subsequently remove phosphate groups from essential nodes within both the PI3K-AKT-mTOR cascade and TCR signaling molecules like SYK and ZAP70. As a direct consequence, the stimulation of transcriptional regulators such as ERK and NF-κB gets attenuated. Such suppression effectively halts the generation of key immune mediators including IL-2 and IFN-γ, culminating in the cessation of T cell proliferation. The temporal and spatial regulation of this signalling pathway is highly specific: in the temporal dimension, PD-1 expression is regulated by transcription factors such as NFATc1 and reaches its peak 48-72 hours after T cell antigen recognition; in the spatial dimension, its membrane localisation is dependent on the immune synaptic microenvironment formed by the TCR-pMHC interactions, which can selectively inhibit the antigen-activated T cell subsets such as tumour-infiltrating lymphocytes, and achieve immune responses to peripheral tissues. and achieve precise negative regulation of the immune response in peripheral tissues[3][8][9].

Tumour cells synergistically upregulate PD-L1 expression through multiple molecular mechanisms: in the tumour-intrinsic signalling network, aberrant activation of the EGFR/MAPK/PI3K-Akt pathway enhances the transcriptional activity of STAT3 and HIF-1α through phosphorylation modification, driving PD-L1 gene amplification; EBV can induce PD -L1 epigenetic reprogramming; and pro-inflammatory cytokine storms such as IFN-γ in the tumour

microenvironment trigger adaptive high expression of PD-L1/L2 through the JAK-STAT-IRF1 signalling axis[10]. The attachment of these ligands to the PD-1 receptor on T cells hinders the TCR-CD28 co-stimulatory signaling by disrupting the phosphorylation cascade within the ITSM structural domain. This interference results in the suppression of T-cell proliferation and the deactivation of their effector functions, thereby facilitating immune evasion. PD-1/PD-L1 inhibitors disarm PD-1-mediated immune checkpoint inhibition by spatially competitively blocking ligand-receptor interactions, inducing tumour infiltrating CD8+ T cells oligoclonal expansion, specifically recognising new antigenic epitopes generated by tumour mutational load (TMB); meanwhile, reversing T cell depletion, restoring perforin-granzymes-mediated cytotoxicity killing, and enhancing cross-sensitisation of antigen-presenting cells by reshaping the immune-suppressive microenvironment to ultimately reestablish a systemic anti-tumour immune response[3][5].

The extent of PD-L1 presence serves as a primary biomarker for evaluating the therapeutic response to PD-1/PD-L1 blockade agents across numerous clinical studies. Therefore, the frequency of PD-L1 detection in metastatic NSCLC holds significant importance. In the KEYNOTE-001 study, 824 NSCLC patients were assessed for PD-L1 levels, revealing that 60.8% had expression ≥1%, and 23.2% had expression ≥50%[11]. The KEYNOTE-010 study included 2,222 patients, with 66% having expression ≥1% and 28% having expression ≥50%[12]. In the KEYNOTE-024 study, 1,653 patients were evaluated, and 30.2% exhibited expression ≥50%[13]. The results demonstrate elevated PD-L1 levels in individuals diagnosed with late-stage (phase IIIB/IV) non-small cell lung carcinoma. Consequently, PD-1/PD-L1 blocking agents enhance immune-mediated tumor destruction through interference with checkpoint pathways, a finding validated by experimental and human trial data in NSCLC cases, highlighting their role in optimizing immunotherapeutic strategies.

Currently, multiple PD-1 blocking agents have reached commercialization: Pembrolizumab by Merck Sharp & Dohme, Nivolumab from Bristol-Myers Squibb, Atezolizumab manufactured by Roche, Avelumab developed by Merck, Durvalumab produced by AstraZeneca, Toripalimab created by Junshi Biotech, Camrelizumab from Hengrui Medicine, Tislelizumab by Baizi Shinshu, Sintilimab from Cinda Biopharma, Cetrelimab by Goodwill Pharmaceuticals, and Pucotenlimab developed by Lepus Biologics. Such inhibitors have demonstrated significant anti-tumour activity in the clinical treatment of melanoma, NSCLC and renal cell carcinoma[3].

3. PD-1 inhibitor combination therapy

The clinical efficacy of PD-1 inhibitors for NSCLC is limited by drug resistance and response heterogeneity. Combination therapies can enhance the efficacy of NSCLC through multimodal approaches: release of neoantigens by radiotherapy, reversal of the immune-suppressive microenvironment by chemotherapy, modulation of PD-L1 expression by targeted agents, and modulation of multidrug resistance by Chinese herbal components. Combination therapy has been clinically proven to improve ORR and PFS, and its mechanism involves remodelling of the immune microenvironment and epigenetic regulation. In the future, individualised combination regimens should be optimised based on multi-omics markers[3].

3.1 PD-1 inhibitors in combination with radiotherapy

Radiotherapy exerts anti-tumour effects in NSCLC treatment through multidimensional mechanisms. First, ionizing radiation directly induces DNA damage and apoptosis in tumour cells, while up-regulating the expression of MHC-I-like molecules and tumour-associated antigens, which promotes recognition by antigen-presenting cells and activation of T-cell responses; second, radiotherapy induces immunogenic cell death (ICD), which is characterized by the release of damage-associated molecular patterns (DAMPs) like high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP). These DAMPs, when released, work together to activate an anti-tumor immune response, especially when tumor-specific antigens are exposed. This molecular mechanism enables optimization of treatment strategies by significantly modifying the tumor's immunological landscape. Dendritic cells mediate this effect through CD8+ T cell stimulation and enhanced secretion of inflammatory mediators including IFN-γ. Furthermore, radiation therapy transforms the tumor microenvironment by limiting regulatory T cell (Treg) and myeloid-derived suppressor cell (MDSC) penetration. It also downregulates immunosuppressive molecules such as TGF-β and IL-10, effectively counteracting tumor-induced immune suppression. This offers crucial therapeutic targets to boost the effectiveness of both radiotherapy and immunotherapy, such as targeting TGF-β[5]; and fourth, radiotherapy up-regulates PD-L1 through activation of the JAK-STAT-IRF1 signalling pathway expression and enhances tumour sensitivity to PD-1 inhibitors, a mechanism that has been shown to improve patient survival outcomes in the PACIFIC model of stage III unresectable NSCLC[12].

The synergistic effect of radiotherapy and immunotherapy relies on multiple molecular mechanisms acting in concert. Radiation enhances tumour immunogenicity by up-

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regulating ICAM-1 and HMGB1, while activating DNA damage response pathways such as ATM-CHK1 and promoting PD-L1 epigenetic modification[14].Studies indicate that PD-L1 levels strongly correlate with immunotherapy efficacy. Additionally, the increase in PD-L1 levels triggered by radiation therapy boosts the effectiveness of immune checkpoint inhibitors. In addition, radiotherapy can also modulate immune cell function through the IFN signalling pathway, inhibit the immunosuppressive microenvironment and promote effector T cell infiltration. Dose-dependent studies have confirmed that radiotherapy dose is positively correlated with the levels of tumour markers and immune activation effects, suggesting that optimisation of radiotherapy parameters is of key significance in increasing the efficacy of combination therapy[3].

Current clinical practice for locally advanced non-small cell lung carcinoma patients commonly incorporates PD-1 blockade continuation treatment after synchronous radiation therapy. Research from the KEYNOTE-001 trial demonstrated superior outcomes, with subjects administered pembrolizumab during radiation showing prolonged disease-free intervals (4.4 months) and enhanced median survival duration (10.7 months). Comparative analysis revealed significantly inferior results in the control cohort, exhibiting only 2.0 months progression-free interval and 5.3 months median survival period without combination therapy[11]. Additionally, in the LUN14-179 clinical trial, which focused on stage III unresectable NSCLC, the main outcome measure was the time to metastatic disease or death (TMDD). The median TMDD for participants who received radiotherapy followed by pembrolizumab was 30.7 months, surpassing the initial hypothesis of 12 months. PD-1 inhibitors in combination with radiotherapy could PD-1 inhibitors and radiotherapy have different mechanisms of action and therapeutic ranges[15]. Combination therapy not only has a synergistic effect and enhances the immune response, but also achieves an organic combination of local control and systemic therapy, reducing recurrence and metastasis. It can significantly improve the survival and remission rates of patients.

3.2 PD-1 inhibitors in combination with chemotherapy

Chemotherapeutic agents such as paclitaxel, doxorubicin and methotrexate are the traditional means of tumour treatment by inhibiting cell proliferation and inducing cell death by affecting key biological processes such as DNA replication, transcription and microtubule stability in tumour cells. These pharmaceutical agents induce immunogenic cellular destruction, heighten the susceptibility of malignant cells to immunological attack, and deplete immunosuppressive components including myeloid-derived suppressor cells (MDSCs) and regulatory T lymphocytes (Tregs). Additionally, chemotherapeutic compounds modify the tumor's surrounding environment to create more favorable immunological circumstances for PD-1 blockade therapies. The combined application of PD-1 inhibitors with cytotoxic drugs enables multi-mechanistic targeting of neoplastic cells, significantly improving treatment efficacy[5].

The EYNOTE -024 revealed that for NSCLC patients with substantial PD-L1 expression (TPS ≥ 50%), those receiving pembrolizumab exhibited a prolonged progression-free survival of 4.3 months (10.3 months versus 6.0 months, hazard ratio=0.50, P<0.001) relative to those undergoing conventional platinum-based chemotherapy. Additionally, the pembrolizumab cohort experienced a 40% decrease in mortality risk. In terms of overall response rate (ORR), the pembrolizumab group achieved an ORR of 44.8%, while the chemotherapy group had an ORR of 27.8%[13].

KEYNOTE-021 investigated pembrolizumab combined with pemetrexed and carboplatin as first-line therapy for advanced lung adenocarcinoma. Efficacy analysis revealed a 55% objective response rate (ORR) in the pembrolizumab-chemotherapy arm versus 29% with chemotherapy alone. Median progression-free survival (PFS) demonstrated 13 months for combination treatment compared to 8.9 months for standard chemotherapy (HR=0.53; P=0.01), showing clinically meaningful improvement. Stratified by PD-L1 expression, combination therapy yielded ORRs of 57%, 26%, and 80% in patients with <1%, 1-49%, and ≥50% PD-L1 levels respectively, contrasting with 13%, 39%, and 35% in the chemotherapy cohort. The most pronounced therapeutic advantage emerged in subjects exhibiting ≥50% PD-L1 expression[16].

Compared with the KEYNOTE-024 study: the combination chemotherapy regimen resulted in a 2.6-month prolongation of PFS (10.4 months vs. 13 months) and a 10.2-percentage-point improvement in ORR (44.8% vs. 55%) compared with Pembrolizumab monotherapy. Significantly, among individuals demonstrating elevated PD-L1 levels (TPS ≥50%), the combination therapy achieved an 80% objective response rate. The integration of pablicizumab with chemotherapy shows promising potential to enhance the quality of life and extend survival for individuals with advanced lung adenocarcinoma, particularly in those with elevated PD-L1 levels[13].

3.3 PD-1 inhibitors combined with targeted drugs

Small molecule targeted therapies preferentially eliminate cancer cells while sparing normal cells, thereby minimizing collateral damage and side effects. Numerous special-

ized compounds can modulate different aspects of tumor immunity, including disrupting cancer cells' inherent immune escape pathways, enhancing antigen presentation, and directly affecting immunostimulatory as well as immunosuppressive cellular components. Specific targeted agents can make tumors more sensitive to immunotherapy by inhibiting immune escape programs within tumor cells or enhancing antigenicity. In addition, certain targeted drugs can upregulate the expression of natural immunosuppressive receptors (e.g., CD47 and PD-L1) by acting on specific genes (e.g., MYC), thereby promoting tumor progression and the formation of an immunosuppressive tumor microenvironment[17].

Targeted therapies are initially effective in some patients, improving response rates and survival. However, drug resistance is often a barrier to long-term efficacy. Meanwhile, immunotherapy has been able to achieve long-term therapeutic effects in some patients. Therefore, combination therapy strategies have the potential to bring synergistic and durable therapeutic outcomes for patients[18].

Min Zhu et al conducted research evaluating therapeutic outcomes in 32 individuals diagnosed with advanced lung adenocarcinoma harboring EGFR-sensitive mutations. These patients received combined treatment involving PD-1 inhibitors administered alongside either chemotherapy or anti-angiogenic medications after experiencing unsuccessful responses to targeted therapies. The patients were given various PD-1 antibodies along with pemetrexed and cisplatin after developing resistance to targeted treatment. Subsequently, a subset of these patients also received bevacizumab as part of their anti-angiogenic therapy. Analysis revealed a comprehensive objective response rate reaching 43%, with disease stabilization achieved in 67% of cases. The median duration without disease progression stood at 7.1 months, while median survival time was documented as 11.7 months. It was found that there was no significant correlation between different EGFR mutation types, types of PD-1 inhibitors, combination therapy regimens, and whether or not radiotherapy was administered during treatment and PFS ($P>0.05$)[19]. Ma Li et al investigated 27 individuals with advanced lung adenocarcinoma harboring EGFR mutations. These patients, following targeted therapy, received a combination of PD-1 inhibitors, chemotherapy, and anti-angiogenic medications as their primary treatment. The results showed that 19 patients (70.4%) were negative for the T790M mutation and 8 patients (29.6%) were positive, with an overall objective remission rate of 40.7%[20].

3.4 PD-1 inhibitors combined with Chinese medicine

Excessive expression of specific transport proteins, particularly P-glycoprotein (ABCB1), multidrug resistance-linked protein (MRP1/ABCC1), and the breast cancer resistance transporter (ABCG2), results in the active removal of anticancer medications from cellular interiors. This process reduces the intracellular drug concentration below the effective threshold. These exocytosis "pumps" expel the antitumor drugs from the cells, diminishing intracellular drug levels below the minimum effective concentration (MEC) compromises therapeutic efficacy by failing to sustain target engagement or biochemical activity which will result in drug resistance. Secondly, the alteration or activation of specific oncogenes can decrease the sensitivity of tumor cells to chemical drugs. For instance, a mutation in the p53 gene might result in a failure of apoptosis, thereby leading to drug resistance. Furthermore, the DNA repair enzyme XPF along with its partner protein ERCC1 serve as essential components within the nucleotide excision repair mechanism. These proteins help maintain genomic stability by recognizing and removing DNA adducts, such as pyrimidine dimers. Its overexpression is associated with resistance to platinum-based chemotherapy, suggesting that targeting the NER pathway may reverse tumor resistance.are overexpressed in drug-resistant tumor cells, which enhances the role of DNA repair, resulting in treatment-resistant tumor cells ,cross-linking and platinum drug resistance, among others, contribute to the problem of tumor drug resistance[21].

TCM can ameliorate tumor multidrug resistance (MDR) through multiple mechanisms, including modulation of drug resistance-related proteins, inhibition of signaling pathways, induction of apoptosis, modulation of immune responses, and reversal of the tumor microenvironment[21]. Moreover, TCM can influence the expression of PD-1/PD-L1, modulate immune cells, enhance the immune microenvironment, and boost the presentation of tumor cell antigens. The strategic integration of TCM with immunotherapy not only boosts T cell activity and stimulates their proliferation but also enhances the release of cytokines such as IL-2 and IFN-γ. This combination results in a synergistic effect, thereby improving the overall therapeutic outcome. In addition, based on the principle of evidence-based treatment, TCM provides non-NSCLC patients with precise and personalized treatment plans to reduce the incidence of adverse reactions. For instance, Luo Yueqiong employed a spleen-strengthening and lung-nourishing formula in conjunction with a PD-1 monoclonal antibody and DP regimen for NSCLC, yielding favorable clinical outcomes[22].

The study's findings indicated that the overall efficacy rate of the combined treatment group using the spleen-strengthening and lung-nourishing formula was

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70.45%. Compared with the DP regimen combined with PD-1 inhibitor monoclonal antibody group, the IL-6 and TNF-α levels as well as the TCM clinical symptom scores were lower in this combination therapy group. Moreover, the frequency of neutropenia and gastrointestinal side effects in the combined treatment group was 68.18% and 59.09%, respectively, notably lower than the 86.36% and 81.81% observed in the monoclonal antibody group. This suggests that the combination therapy of spleen-enhancing and lung-tonifying formula can effectively improve the immunocompetence of patients, reduce the occurrence of adverse reactions, and exert a synergistic effect[22].

4. Summarizing and looking forward

Combining PD-1 blockade with complementary therapeutic approaches demonstrates measurable enhancements in progression-free intervals, tumor response metrics, and extended survival durations among NSCLC patients. This synergistic effect stems from integrating radiation protocols, cytotoxic agents, molecularly targeted interventions, and herbal medicinal components, offering an alternative paradigm to overcome limitations inherent in conventional treatment modalities[18]. However, this strategy faces significant challenges, including the need to address issues of response rate and drug resistance. Single-agent treatment with PD-1/PD-L1 blocking agents achieves sustained clinical responses in merely 15% to 30% of individuals with progressive malignancies, while the fundamental mechanisms driving primary and acquired resistance continue to present multifaceted challenges(e.g., inactivation of the JAK/STAT pathway, defective interferon gamma signaling, etc.) require further elucidation. Secondly, there is an absence of sufficient clinical data concerning special populations[3]. For instance, there is a paucity of clinical data on patients with EGFR-sensitive mutations treated with PD-1 inhibitor combination therapy after targeted resistance. Furthermore, the timing selection and risk of toxicity stacking between TKI and immunotherapy have not been elucidated. Furthermore, there is an urgent need for safety management. The combination of these treatment approaches has been observed to result in an increased occurrence of immune-mediated side effects (irAEs) alongside radiation-triggered complications, particularly esophageal inflammation.Consequently, the development of a dynamic monitoring system has been advocated to ensure the safety of patients undergoing this therapy[19]. Finally, the biomarker system is not yet perfected. Although PD-L1 expression level, tumor mutational load (TMB), and microsatellite instability (MSI) have been partially used for efficacy prediction, their heterogeneity and dynamic changes limit clinical application.

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