Biomedical Data Science
2025, VOL. 5, NO. 2, 136-141
DOI: 10.47297/wspbdsWSP2752-630525.20250502

Research Progress of PD-1 and Its Inhibitors in Tumor Immunotherapy

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ABSTRACT
Programmed cell death protein 1 (PD-1) and its ligands PD-L1/PD-L2 serve as critical immune checkpoint molecules that execute core regulatory functions in tumor microenvironment-mediated immune evasion mechanisms. Recent clinical investigations have revealed that monoclonal antibody-based agents targeting this signaling axis demonstrate substantial antitumor efficacy across multiple malignancies. These therapeutic agents specifically block the PD-1/PD-L2 immunosuppressive pathway, thereby reversing the functional suppression of T lymphocytes. This discovery has translated into clinically validated immunotherapeutic strategies for diverse neoplastic diseases, including both solid tumors and hematologic malignancies. However, challenges such as drug resistance, cumulative toxicity, high treatment costs, and biomarker heterogeneity limit their widespread application. This article systematically reviews the structure of PD-1, the molecular mechanisms of the PD-1/PD-L1 signaling pathway, clinical treatment strategies (monotherapy, combined immunotherapy, combined traditional therapy, personalized treatment, and integration of novel therapies) and their challenges, while outlining future research directions to provide a theoretical basis for optimizing tumor immunotherapy.

KEYWORDS
PD-1/PD-L1 inhibitors; tumor immune evasion; immunotherapy; combination therapy; drug resistance; biomarkers; personalized treatment; tumor immunotherapy

1 Introduction

According to WHO epidemiological surveillance data, malignant neoplasms have become the second-largest contributor to the global disease burden. The 2022 statistics revealed that worldwide cancer incidence surpassed 2×10^7 cases, with mortality approaching the decamillion threshold (9.7×10^6 deaths). These figures underscore that oncology prevention and treatment remain critical challenges for public health systems. (IARC, 2022). Although traditional therapies (surgery, radiotherapy, chemotherapy, and targeted therapy) are effective for local control, they often face limitations such as metastasis recurrence, systemic toxicity, and drug resistance. Therapeutic strategies harnessing endogenous antitumor immunity, particularly those inducing sustained tumoricidal responses through systemic immune activation, demonstrate distinct clinical merits in contemporary oncology practice.[1] As prototypical agents in the immune checkpoint inhibitor (ICI) class, pharmacological modulators targeting the PD-1/PD-L1 axis have undergone substantial clinical validation. Following initial regulatory approval in 2014 for advanced malignancies, these biologics have been progressively incorporated into standardized clinical protocols, establishing themselves as first-line therapeutic regimens for multiple advanced malignancies spanning diverse histological subtypes. However, drug resistance and side effects restrict their broad application. By analyzing multiple studies, this article categorizes the clinical applications of PD-1 and its inhibitors into five treatment strategies, compares their advantages and disadvantages, and comprehensively examines the scientific value and translational potential of PD-1/PD-L1 inhibitors from molecular mechanisms to clinical practice, aiming to identify new directions for future research.

1 Structure and Function of PD-1

1.1 Structural Features of PD-1

From a structural topology perspective, the PD-1 protein can be compartmentalized into three distinct domains: an extracellular ligand-binding domain, a transmembrane helical segment, and a cytoplasmic functional domain. Notably, the extracellular region exhibits a canonical immunoglobulin variable (IgV) -like fold structure, wherein a conserved disulfide bridge between Cys54 and Cys123 maintains its spatial conformation. This structural motif is biochemically characterized as comprising approximately 124 amino acid residues. This domain specifically mediates the molecular recognition process with B7 family ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). X-ray crystallography studies reveal that the domain adopts the canonical β-sandwich fold topology characteristic of the immunoglobulin superfamily (IgSF). Its ligand-binding epitope features a molecular architecture comprising three hypervariable loop domains (corresponding to BC, C'C", and FG loops) that collectively form a spatially complementary interface. These structural

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elements mimic both the spatial conformation and functional properties of the antigen-binding mode observed in antibody complementarity-determining regions (CDR). Residues such as Asn58, Gln75, and Thr76 participate in binding through hydrogen bonds and hydrophobic interactions [2-3].

The transmembrane domain of PD-1 consists of approximately 25 hydrophobic amino acids, forming a single α-helix structure that anchors it to the cell membrane. This region is crucial for the membrane localization of PD-1 and its interaction with neighboring signaling molecules [2].

The intracellular signaling domain of PD-1 demonstrates a structurally condensed architecture, wherein its C-terminal effector region contains two phylogenetically conserved tyrosine residues (Tyr^{223} and Tyr^{248}). These residues form distinct functional domains: the immunoreceptor tyrosine-based inhibitory motif (ITIM) and the immunoreceptor tyrosine-based switch motif (ITSM), which mediate specific inhibitory signaling functions, respectively. Notably, the ITSM domain centered at Tyr^{248} serves as a critical molecular docking platform. Through specific binding with the SH2 domain-containing phosphatase SHP-2, it activates downstream immunosuppressive signaling cascades. This molecular mechanism concurrently disrupts T cell receptor signaling and suppresses the CD28 co-stimulatory pathway, thereby executing immune checkpoint regulatory functions[2].

1.2 Biological Functions of PD-1

The PD-1/PD-L1 signaling pathway regulates immune responses through the following mechanisms:

1.2.1 Maintaining peripheral tolerance

Suppressing the activation of autoreactive T cells to prevent autoimmune diseases.

1.2.2 Inhibiting T cell activation

Blocking downstream TCR signaling (e.g., ZAP70 dephosphorylation) and the CD28 co-stimulatory pathway.

1.2.3 Inducing T cell exhaustion

Under prolonged antigen exposure, PD-1 signaling leads to T cell functional exhaustion.

1.2.4 Modulating the tumor microenvironment

Enhancing the functional upregulation of immunosuppressive regulatory T lymphocytes (Tregs) while concurrently facilitating the tissue infiltration of myeloid-derived suppressor cell populations (MDSCs), thereby establishing an immunosuppressive microenvironment.

1.3 Mechanisms of PD-1-Mediated Tumor Immune Evasion

The tumor microenvironment (TME) employs PD-L1 as a master regulator of immune evasion through dynamic expression mechanisms spanning genomic, transcriptional, and post-translational levels. Molecular pathology studies delineate three-tiered PD-L1 regulation: 1) Genomic aberrations such as CD274 (9p24.1) copy number gain or promoter demethylation elevate baseline PD-L1 expression (validated by Western blot) in NSCLC and melanoma. [4] TME-derived cytokines (IFN- γ, TNF- α) activate JAK/STAT and canonical NF- κB pathways via phosphorylation-dependent STAT1/3 dimerization and p65 nuclear translocation, respectively, binding to ISRE and κB enhancer elements in the PD-L1 promoter. [5] Oncogenic PI3K/AKT/mTOR signaling triggered by PTEN loss promotes cap-dependent PD-L1 mRNA translation through eIF4E phosphorylation, increasing protein synthesis [6] . PD-L1 exhibits dual immunosuppressive modes: 1) PD-1 engagement recruits SHP2 phosphatase to dephosphorylate ZAP70/Lck kinases, attenuating proximal TCR signaling [7]PD-L1-CD80 cis-binding on APCs disrupts CD28 costimulation, inducing T cell anergy. [8] Clinically, humanized anti-PD-1 IgG4 antibodies (e. g., pembrolizumab) targeting the PD-1 N-loop epitope demonstrate survival benefits in KEYNOTE trials, extending median overall survival (mOS) beyond 30 months in advanced NSCLC. Nevertheless, immunologically "cold" tumors (e. g., pancreatic adenocarcinoma, glioblastoma) require multimodal approaches combining PD-1 blockade with radiotherapy (abscopal effect), bispecific antibodies (PD-1/CTLA-4), or oncolytic viruses to overcome resistance mediated by tumor immunoediting.

2 Clinical Application Strategies for PD-1/PD-L1 Inhibitors

2.1 Monotherapy

Biomarker-dependent patient selection is crucial for monotherapy success: This strategy heavily relies on precise biomarker screening to identify the population most likely to benefit. The KEYNOTE-024 study (2016) first established PD-L1 as the core biomarker for monotherapy. In the field of first-line treatment for metastatic non-small cell lung cancer, researchers conducted a prospective randomized controlled study (KEYNOTE-024 expanded cohort) targeting the PD-L1 high-expression subgroup (TPS≥50%). This phase III registration clinical trial utilized the centrally validated 22C3 antibody assay to confirm PD-L1 status. Eligible subjects meeting the protocol criteria were ultimately enrolled and assigned via stratified randomization to receive pembrolizumab (a humanized anti-PD-1 IgG4 monoclonal antibody) or standard chemotherapy regimens. Survival endpoint data assessed per RECIST 1.1 criteria demonstrated that the monoclonal antibody treatment group exhibited significant survival benefits, with a median overall survival of 30.0 months (95% CI 25.8-34.1), achieving a clinically meaningful doubling of survival time compared to the chemotherapy group, significantly superior to chemotherapy's 14.2 months (HR=0.60, p<0.001), with lower grade 3-5 adverse events (26.6% vs. 53.3%)[9]. Five-year follow-up data further revealed 31.9% survival in the Pembrolizumab group versus 16.3% in chemotherapy[10]. These outcomes not only established Pembrolizumab as first-line standard care for PD-L1-high NSCLC but also validated PD-L1's clinical predictive value. Another immunotherapy biomarker is MSI-H/dMMR - the first pan-cancer immunotherapy biomarker, whose scientific basis lies in DNA mismatch repair deficiency causing high tumor mutational burden (TMB) and consequent neoantigen production. The KEYNOTE-158 study (2020) included 233 MSI-H/dMMR patients across 27 cancer types, showing Pembrolizumab's objective response rate (ORR) of 34.3% (complete response: 7.3%, partial response: 27.0%), with disease control rate (DCR) reaching 52.4%. Median duration of response (DOR) was not reached (indicating most responses lasted beyond observation), with 63% maintaining ≥24-month responses, demonstrating durable efficacy. Only 14.6% experienced grade 3-5 treatment-related adverse events[11] Based on this, Pembrolizumab became the first immunotherapy approved for all MSI-H/dMMR solid tumors regardless of primary site.

However, monotherapy has limitations: narrow applicability (only minority of NSCLC patients have high PD-L1 expression, while MSI-H/dMMR occurs rarely in solid tumors), complex resistance mechanisms, and biomarker detection challenges.

2.2 Combination Immunotherapy

The cutting-edge strategies in the field of tumor immunotherapy currently focus on multi-target synergistic regulatory mechanisms, achieving complementary inhibition of different signaling pathways through combined blockade of the PD-1/PD-L1 axis with other immune checkpoint molecules (including but not limited to CTLA-4, LAG-3, and TIGIT). This combination intervention model demonstrates significantly enhanced anti-tumor immune activation effects compared to monotherapy, particularly showing breakthrough efficacy in PD-L1-negative solid tumors, though the accompanying toxicity management challenges cannot be overlooked. The landmark CheckMate 067 study (NCT01844505, 2015) was the first to systematically evaluate the clinical value of dual PD-1/CTLA-4 inhibition: this Phase III randomized controlled trial enrolled patients with unresectable stage IIIc-IV melanoma, employing a three-arm parallel design (nivolumab monotherapy at 3mg/kg Q2W, ipilimumab monotherapy at 3mg/kg Q3W, and acombination regimen of nivolumab 1mg/kg ipilimumab 3mg/kg Q3W×4 followed by nivolumab maintenance). Extended follow-up data revealed a 5-year overall survival rate of 52% (95% CI 47-57) in the combination group, with a 32% and 58% reduction in mortality risk compared to the nivolumab monotherapy group (44%, HR=0.84) and ipilimumab monotherapy group (26%, HR=0.42), respectively (stratified log-rank p<0.001). In terms of disease control metrics, the combination group achieved a median progression-free survival of 11.5 months (95% CI 8.9-16.7), nearly tripling the duration of monotherapy groups (nivolumab group 6.9 months, ipilimumab group 2.9 months), while the objective response rate increased to 61% (CR rate 22% vs. nivolumab group 44%/CR 9%). However, the combination therapy group reported a ≥3grade immune-related adverse event (irAE) incidence as high as 54% (vs. nivolumab group 22.4%), primarily involving colitis (13%), hepatitis (10%), and hypophysitis (8%) [12.13]. Breakthroughs in novel combination strategies were achieved in the RELATIVITY-047 study (NCT03470922, 2022): this global multicenter Phase III trial first confirmed the clinical synergistic effect of LAG-3 inhibitors, demonstrating a median PFS of 10.1 months (monotherapy group 4.6 months; HR=0.75, p=0.005) in treatment-naïve advanced melanoma patients receiving a fixed-dose regimen of relatlimab (160mg) + nivolumab (480mg) Q4W, with an ORR increase to 43.1% (monotherapy 32.6%, p=0.013). Notably, the 3-4 grade irAE incidence for this combination was only 18.9%, significantly lower than traditional CTLA-4 combination regimens (p<0.001), suggesting that LAG-3 pathway inhibition may offer a superior safety profile. [14]. Based on this, the FDA approved Opdualag® (Relatlimab + Nivolumab) for advanced melanoma in 2022.

2.3 Combination with Traditional Therapy

Combination with traditional therapies (chemotherapy, radiotherapy, targeted drugs) aims to overcome the tumor immunosuppressive microenvironment through synergistic mechanisms, expanding the beneficiary population. It is particularly suitable for patients requiring rapid tumor control or those with insufficient response to immunotherapy alone, though it also presents the issue of increased toxicity.

The landmark KEYNOTE-189 trial (2018) established a new therapeutic paradigm in the management of advanced non-squamous non-small cell lung cancer (NSCLC). This phase III multicenter randomized controlled trial, conducted in a cohort of treatment-naïve patients diagnosed with advanced non-squamous NSCLC, employed a comparative design where participants were randomized in a 1:1 ratio to receive either pembrolizumab in combination with pemetrexed-platinum doublet chemotherapy or platinum-based chemotherapy monotherapy. Survival analysis demonstrated a statistically significant improvement in median overall survival (22.0 months versus 10.7 months; HR 0.56, 95% CI 0.45-0.70) favoring the investigational arm. The 5-year survival analysis revealed a near doubling of long-term outcomes (18.4% versus 9.7%) in the combination therapy cohort compared to conventional chemotherapy. [15]

Efficacy assessments demonstrated superior antitumor activity in the experimental group, with objective response rates reaching 47.6% as per RECIST criteria versus 18.9% in the control arm ($p<0.001$). Notably, subgroup analysis identified clinical benefit extending to PD-L1 negative populations (tumor proportion score <1%), with hazard ratios for mortality risk reduction comparable to PD-L1 positive subgroups. This observation supports the proposed mechanistic hypothesis involving chemotherapy-induced immunogenic cell death (ICD) leading to enhanced tumor antigen exposure and subsequent immune activation through checkpoint inhibition.

Safety profiling revealed comparable incidence rates of grade ⩾3 treatment-emergent adverse events between study arms (67.2% versus 65.8%), suggesting that the addition of immune checkpoint inhibition to platinum-based chemotherapy did not significantly amplify conventional toxicity profiles. These findings collectively validate the immunochemotherapy combination as a clinically meaningful advancement in first-line NSCLC treatment, particularly notable for demonstrating survival benefits across all PD-L1 expression subgroups. [16]

2.4 Personalized Therapy

Whether monotherapy, combination immunotherapy, or traditional combination therapy, all face challenges with biomarker detection difficulties or absence, leading to ineffective treatment. Personalized therapy leverages multidimensional biomarkers (e.g., PD-L1, TMB, MSI-H, genetic signatures) to identify optimal patient populations, aiming to avoid ineffective treatments and optimize healthcare resource allocation.

The KEYNOTE-158 study (2020) first prospectively validated TMB's value as a pan-cancer biomarker across 10 tumor types.This trial enrolled 790 patients with advanced solid tumors receiving Pembrolizumab treatment, This cohort analysis demonstrated that 102 patients (13%) exhibited elevated tumor mutational burden (tTMB ⩾10 mutations/megabase), compared with 688 cases (87%) in the non-high tTMB subgroup (<10 mut/Mb). The high TMB population achieved superior clinical outcomes, with an objective response rate of 29% versus 6% in low-TMB counterparts, alongside improved progression-free survival (median PFS 2.1 vs. 2.0 months; hazard ratio 0.58). Safety evaluation across 105 treated subjects revealed treatment-related serious adverse events in 11 patients (10%) and grade 3-5 toxicities in 16 participants (15%). [17]These pharmacodynamic and safety profiles supported the 2020 FDA accelerated approval of pembrolizumab for TMB-high (⩾10 mut/Mb) metastatic solid tumors lacking alternative therapies, establishing the first tissue-agnostic regulatory endorsement utilizing TMB rather than tumor histology as a predictive biomarker. However, TMB's clinical application faces challenges: threshold heterogeneity (discrepancies across platforms like FoundationOne CDx vs. MSK-IMPACT) and tissue specificity (high predictive value in melanoma/lung cancer but confounded by MSI status in colorectal cancer)[18].

2.5 Integration of Novel Therapies

The integration of novel therapies aims to overcome immunotherapy resistance and achieve potential cures by combining cutting-edge technologies such as cell therapy, oncolytic viruses, and bispecific antibodies. However, its development is limited by high costs and technical complexity.

Addressing therapeutic challenges in end-line treatment of large B-cell lymphoma, the ZUMA-1 expanded clinical trial systematically analyzed the clinical value of second-generation CD19-specific CAR-T (axi-cel). Within the evaluable cohort of 111 patients, cell product manufacturing success rate reached 99% (110/111), with 91% (101/111) completing therapeutic infusion. Efficacy metrics demonstrated 82% of patients attaining objective responses, including 54% achieving pathological complete remission. However, the study highlighted limitations—subsets of CAR-T recipients developed primary resistance or experienced secondary relapse post-infusion [19].

ZUMA-1 data showed that approximately 50-60% of patients relapsed within one year, indicating the need for optimized treatment strategies. A 2022 study explored the potential synergistic effects of sequential PD-1 inhibitor pembrolizumab (Keytruda) following CAR-T therapy (axicabtagene ciloleucel). The scientific hypothesis was: Post-CAR-T therapy, The immunosuppressive tumor microenvironment has been shown to induce activation of inhibitory signaling axes, particularly the programmed cell death protein 1 and its ligand pathways (PD-1/PD-L1), which may culminate in functional impairment of effector T lymphocytes through exhaustion mechanisms. Mechanistically, therapeutic blockade of PD-1 receptors using Pembrolizumab demonstrates potential to augment chimeric antigen receptor T-cell therapies by preserving their proliferative capacity and enhancing tumoricidal activity through immune checkpoint modulation..

This study reported a lower CR rate compared to the ZUMA-1 extension trial. However, some patients achieved conversion from partial response (PR) to CR through sequential pembrolizumab treatment. Patients with high PD-L1 expression or early relapse post-CAR-T therapy may benefit more significantly from combination therapy. In relapsed/refractory LBCL patients, axicabtagene ciloleucel and pembrolizumab demonstrated manageable safety and encouraging efficacy [20]. Therapeutic synergy between these agents could augment the proliferative capacity of chimeric antigen receptor T cells; concurrent modulation of inhibitory pathways may prolong their functional persistence in vivo, laying the groundwork for Phase III trials.

3 Discussion

Therapeutic deployment of programmed death-1/programmed death-ligand 1 axis blockade has catalyzed a paradigm shift in onco-immunotherapeutic strategies, demonstrating transformative clinical efficacy across multiple malignancies, but their efficacy and widespread use still face multiple challenges. Monotherapy with biomarker screening (e.g., high PD-L1 expression, MSI-H/dMMR, or high TMB) can precisely identify beneficiary populations. For instance, NSCLC patients with PD-L1 TPS ≥ 50% achieved a 5-year survival rate of 31.9% with pembrolizumab monotherapy, significantly outperforming chemotherapy (KEYNOTE-024) [9-10]. However, monotherapy is applicable to a narrow population (e.g., MSI-H/dMMR accounts for less than 5% of solid tumors), and resistance mechanisms are complex (e.g., T-cell exhaustion or tumor microenvironment remodeling) [11], necessitating combination strategies to break through these bottlenecks.

Combination immunotherapy achieves synergistic effects by targeting multiple pathways. For example, The therapeutic combination of anti-PD-1 agent Nivolumab with CTLA-4 blockade (Ipilimumab) demonstrated a significant survival advantage in metastatic melanoma, with phase III CheckMate 067 trial data revealing durable 5-year survival outcomes in 52% of treated cohort participants [12-13].

However, the additive toxicity (grade 3-4 irAEs reaching 54%) limits its application. Novel combination regimens like Relatlimab (a LAG-3 inhibitor) with Nivolumab exhibit lower toxicity (grade 3-4 irAEs at 18.9%), suggesting the need to balance efficacy and safety in target selection [14]. Combining traditional therapies (e.g., chemotherapy or radiotherapy) enhances antigen release by inducing immunogenic cell death (ICD), significantly benefiting PD-L1-negative patients (KEYNOTE-189) [15-16], but chemotherapy-related toxicity still requires optimized management.

Personalized therapy relies on multidimensional biomarkers (PD-L1, TMB, genetic signatures) to identify responsive populations. However, the heterogeneity of TMB thresholds (e.g., differences in detection platforms) and tissue specificity (e.g., interference from MSI status in colorectal cancer) reduce its universality[17-18]. Although novel therapy integrations (e.g., CAR-T combined with PD-1 inhibitors) can reverse T T-cell exhaustion (ZUMA-1 extension trial) [19-20], technical complexity and high costs limit clinical translation.

Future research should focus on: ① developing standardized, dynamically monitored biomarker systems; ② optimizing combination strategies to reduce toxicity (e.g., sequential dosing or dose adjustment); ③ exploring novel mechanisms like epigenetic regulation and metabolic reprogramming to overcome resistance; ④ promoting cost-effective personalized treatment models. Through interdisciplinary collaboration and technological innovation, PD-1/PD-L1 inhibitors are expected to achieve broader and more durable clinical benefits in cancer immunotherapy.

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