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Real-World Toxicity Profiles of PD-1 Inhibitors: A Critical Analysis

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Abstract: PD-1/PD-L1 inhibitors have reshaped modern oncology by restoring antitumor T-cell activity and producing durable clinical responses across diverse malignancies. Yet, their therapeutic benefits are tempered by a wide and often unpredictable spectrum of immune-related adverse events (irAEs). Real-world data consistently demonstrate a broader and more heterogeneous toxicity profile than that reported in clinical trials, with approximately 43% of treated patients developing irAEs—most commonly endocrine, hepatic, and hematologic. Although many events are manageable, rare but severe toxicities such as myocarditis, cholestatic liver injury, aseptic meningitis, and neuromuscular syndromes underscore the need for heightened vigilance and rapid intervention. Baseline factors, including age, ECOG performance status, and comorbidities, significantly influence irAE risk and may explain higher toxicity rates in real-world populations. Rechallenge after an irAE remains challenging, with recurrence rates of 28–32% and contraindications in serious cardiac or neurologic toxicities. Real-world datasets provide important advantages by capturing diverse patient groups, identifying rare or delayed toxicities, and reflecting heterogeneous clinical practice. Nonetheless, limitations such as under-reporting, inconsistent case definitions, and lack of denominator data restrict precise incidence estimation. Future priorities include standardized multicentre registries, biomarker-guided risk stratification, and AI-assisted monitoring to improve early detection and management. Overall, real-world evidence is essential for defining the full safety profile of PD-1/PD-L1 inhibitors and guiding safer, individualized immunotherapy.

Keywords: *PD-1 Inhibitors, Immune Checkpoint Inhibitors, Immune-Related Adverse Events (irAEs), Real-World Evidence (RWE), Real-World Toxicity, Pharmacovigilance, Post-Marketing Surveillance, Safety Profile, Toxicity Patterns.*

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I. INTRODUCTION

PD-1/PD-L1 inhibitors have become central to modern cancer therapy, producing durable responses across multiple malignancies by blocking inhibitory immune checkpoints and restoring T-cell activity.[1] Although these agents have expanded treatment possibilities beyond what traditional therapies could achieve, their clinical utility is tempered by immune-related adverse events (irAEs), which arise from therapeutic immune activation and may limit treatment continuation or affect long-term quality of life.[1]

PD-1 is a key regulator of immune homeostasis, preventing excessive T-cell activation under physiological conditions.[2] In cancer, persistent PD-1 signaling suppresses antitumor immunity; therapeutic blockade reverses this dysfunction but disrupts regulatory balance, leading to autoimmunity-like inflammation.[2] Consistent with this mechanism, clinical studies and pharmacovigilance data document irAEs affecting endocrine, hepatic, dermatologic, pulmonary, cardiac, and neurologic systems.[5,6] Although many events are manageable, rare but severe complications—such as myocarditis, cholestatic hepatitis, aseptic meningitis, and neuromuscular syndromes—require rapid recognition and specialist involvement.

Real-world evidence provides crucial insight into PD-1/PD-L1 toxicity beyond clinical trial settings. Retrospective melanoma data show meaningful clinical benefit but also highlight variability in outcomes and toxicity patterns among unselected patients.[3] A large systematic review similarly confirmed broad efficacy while emphasizing a distinct immunologic toxicity profile, including endocrinopathies and colitis.[4] Pharmacovigilance systems, including FAERS,

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capture rare, delayed, or multi-organ irAEs and clarify timing, recurrence risk, and organ involvement.[6,7,8]

Baseline assessments—such as ECOG performance status, organ function evaluation, and targeted cardiac testing—help identify patients at heightened risk for severe irAEs.[21] Real-world monitoring strategies, including periodic liver and thyroid function testing, reflect the frequency of hepatic and endocrine involvement.[6] Despite advances, uncertainties remain regarding the true population-level incidence of organ-specific irAEs, the safety of rechallenge after severe events, and outcomes in underrepresented groups such as older adults and those with autoimmune disease.

Given the growing reliance on immunotherapy, a clear understanding of real-world toxicity patterns is fundamental to safe and effective clinical practice. The present study synthesizes current real-world evidence to characterize the incidence, spectrum, timing, severity, and clinical impact of irAEs associated with PD-1/PD-L1 inhibitors, while highlighting key factors influencing toxicity risk and outlining implications for monitoring, management, and future research.

II. METHODS

This study synthesized real-world evidence on PD-1/PD-L1 inhibitor–associated immune-related adverse events (irAEs) using data from retrospective cohorts, pharmacovigilance databases, and published observational studies. Key sources included FAERS analyses, global registry data, and real-world clinical cohorts evaluating toxicity incidence, organ-specific patterns, and rechallenge outcomes. Relevant studies.

Were identified through targeted searches of peer-reviewed literature and safety databases. Extracted variables included patient demographics, baseline characteristics, organ systems affected, time-to-onset, severity, and outcomes. Findings were narratively integrated to compare real-world toxicity patterns with clinical trial data and to identify risk factors, rare events, and gaps requiring further research.

III. DISCUSSION

PD-1/PD-L1 inhibitors have become essential components of modern cancer therapy, offering meaningful clinical benefit across a broad range of malignancies. By blocking inhibitory immune checkpoints and restoring T-cell activity, these agents have enabled durable responses rarely achievable with conventional treatments. However, their clinical utility is limited by the frequency and unpredictability of immune-related adverse events (irAEs). [1] Although these toxicities stem from therapeutic immune activation, they may restrict treatment continuation, impair quality of life, and underscore the need for safer therapeutic strategies and a deeper understanding of real-world toxicity patterns.

PD-1 is a key regulator of T-cell activation, maintaining immune homeostasis and preventing excessive tissue damage. Under physiological conditions, this inhibitory pathway protects against immunopathology, but in chronic infection and cancer, persistent PD-1 expression suppresses protective immunity. Therapeutic blockade restores antitumor function but disrupts regulatory balance, predisposing patients to autoimmunity-like complications, as demonstrated in mechanistic immunology studies. [2]

Real-world outcomes further elucidate the performance of PD-1 inhibitors outside controlled clinical trials. A retrospective analysis of 116 patients with unresectable stage III–IV melanoma treated with single-agent PD-1 inhibitors reported a median overall survival of 27.9 months (95% CI: 19.8–36.0), a 12-month survival rate of 70.2%, and a median real-world progression-free survival of 5.7 months (95% CI: 3.7–7.1). [3] Complementing these findings, a systematic review of phase I–III trials including 11,130 records and 28,304 patients confirmed meaningful clinical benefit but highlighted a distinct toxicity profile marked by immune-related endocrinopathies, hepatitis, dermatitis, and colitis, emphasizing the importance of early recognition and proactive management in routine practice. [4]

Mechanistic and clinical evidence shows that PD-1 blockade induces systemic immune activation, leading to multi-organ inflammation and cytokine elevation. Clinically, irAEs most commonly affect the endocrine, hepatic, dermatologic, pulmonary, and cardiac systems, while real-world reports also describe rare but severe events such as myocarditis, cholestatic hepatitis, aseptic meningitis, and neuromuscular syndromes. [5] These findings reinforce the need for vigilant monitoring and timely intervention.

Pharmacovigilance datasets, including FAERS, similarly identify rare but serious toxicities such as myocarditis, cholestatic hepatitis, pneumonitis, and neuromuscular complications. Although limited by under-reporting and variable data quality, these findings—supported by preclinical and clinical evidence—underscore the systemic nature of PD-1-related toxicities and the necessity of comprehensive organ-specific monitoring. [6] Pembrolizumab-focused analyses provide further insight into timing, affected organ systems, hospitalization outcomes, reporting odds ratios (RORs), and time-to-onset patterns, which together clarify the onset windows of key toxicities. [7] Hepatic toxicity signals are particularly prominent, prompting consideration of diagnostic differentiation between hepatitis and cholestasis and highlighting distinctions from PD-L1-targeted therapies. [8] Real-world data also help characterize cardiac irAEs in PD-1-treated cohorts and identify baseline characteristics associated with specific toxicities. [9]

Prior to initiating PD-1 therapy, baseline evaluations—such as ECOG performance status, medication review, organ function testing, and targeted cardiac assessment for high-risk patients—can help identify individuals at increased risk for severe irAEs and distinguish pre-existing abnormalities from treatment-related injury. [21] Monitoring strategies informed by real-world toxicity patterns include liver function tests every 2–4 weeks, thyroid function tests every 4–6 weeks, inflammatory markers as appropriate, and baseline or

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symptom-triggered cardiac assessment. [6] Such proactive, organ-specific monitoring is supported by both cohort studies and pharmacovigilance data.

Real-world evidence consistently documents endocrine, hepatic, pulmonary, cardiac, and neurologic toxicities in PD-1-treated populations, including rare, high-morbidity complications such as myocarditis. [6] Optimal management relies on structured assessments, rapid specialist referral, judicious corticosteroid use, multidisciplinary care, and robust long-term follow-up. When atypical irAEs occur—including myocarditis, cholestatic liver injury, aseptic meningitis, or neuromuscular syndromes—rapid triage, targeted diagnostics, and specialist involvement are essential for minimizing delays in identifying life-threatening events. [10]

Rechallenge after an irAE remains a complex clinical decision. [11] Real-world data suggest recurrence rates of 28–32%, especially for colitis, pneumonitis, and hepatitis, whereas severe neurologic toxicities and myocarditis generally contraindicate rechallenge. When rechallenge is attempted, intensified monitoring is critical. [11]

Real-world evidence offers unique advantages in evaluating PD-1 toxicity, including the ability to capture outcomes in diverse, unselected populations reflective of routine practice, as demonstrated by FAERS-based endocrine toxicity studies. [12] These datasets include patients frequently excluded from clinical trials and enable the detection of rare or delayed irAEs through large sample sizes and extended follow-up, enhancing the external validity of safety assessments and informing clinical decision-making. [13] Real-world findings complement randomized trial data by refining toxicity estimates and supporting evidence-based management. [12] Nonetheless, limitations persist: spontaneous reporting systems and registries suffer from under-reporting, inconsistent definitions, incomplete follow-up, and lack of denominator data, reducing the accuracy of incidence estimates. [15] Confounding is inherent to non-randomized studies, as disease severity, comorbidities, and concurrent therapies influence outcomes—an issue noted in the Khozin review. [14] Differences in coding and regional reporting practices further complicate cross-study comparisons. [16]

Real-world toxicity patterns mirror those observed in pharmacovigilance and registry analyses. Endocrine, hepatic, and dermatologic irAEs consistently emerge as the most common events. [17] Although rare, myocarditis and pneumonitis remain notable severe complications. [18] Compared with clinical trial populations, real-world patients experience higher rates of hepatic and endocrine irAEs and a broader range of delayed toxicities, likely reflecting greater age, comorbidity burden, and clinical heterogeneity. [18] These trends align with pharmacovigilance findings showing more varied onset patterns and higher-than-anticipated rates of key toxicities. [18]

Despite advances, substantial knowledge gaps remain. [19] Reviews of irAEs and real-world evidence emphasize ongoing uncertainties that complicate clinical decision-making, including the lack of reliable population-level incidence estimates for many organ-specific toxicities. [14] Evidence guiding safe rechallenge is limited, particularly for high-risk groups typically excluded from clinical trials, such as older adults, patients with autoimmune disease, and individuals with underlying organ dysfunction. [20]

Future progress will depend on developing standardized, multicentre real-world registries that integrate clinical, laboratory, and pharmacovigilance data to generate more reliable toxicity estimates. [14] Such registries should incorporate biomarker research, systematically track rechallenge outcomes, and intentionally include underrepresented patient groups. Digital monitoring tools and AI-enhanced surveillance systems may further improve early detection of serious irAEs. [14] Ultimately, coordinated international data-sharing networks will be essential for translating real-world observations into practical, evidence-based guidance for clinical care.

Across real-world cohorts, approximately 43% of patients receiving PD-1 inhibitors experience irAEs, most frequently endocrine, hepatic, and hematologic. Risk is influenced by age, ECOG status, and comorbidities. Thyroid dysfunction and liver injury are common, highlighting the importance of routine monitoring. Combination treatment with angiogenesis inhibitors may reduce irAE incidence and severity. The development of irAEs is also associated with improved outcomes, including in NSCLC. Rare, high-morbidity toxicities such as myocarditis and multi-organ inflammatory syndromes highlight the limitations of clinical trials and the importance of real-world evidence in defining the full safety profile of PD-1/PD-L1 inhibitors.

Overall, PD-1/PD-L1 inhibitors have transformed cancer therapy, yet real-world data reveal a broader and more variable toxicity spectrum than clinical trials alone suggest. Nearly half of patients develop irAEs—most commonly thyroid, hepatic, and hematologic—with risk shaped by age, comorbidities, and performance status. The occurrence of irAEs may correlate with improved survival, particularly in NSCLC, and combining checkpoint inhibitors with angiogenesis inhibitors may reduce toxicity. Persistent knowledge gaps surrounding incidence, monitoring, and safe rechallenge underscore the need for standardized reporting and prospective registries. Real-world evidence remains essential for guiding the safe and effective use of PD-1/PD-L1 inhibitors in everyday oncology practice.

IV. LIMITATIONS

This study has several limitations inherent to real-world evidence. Pharmacovigilance databases, including FAERS, rely on voluntary reporting, which can result in under-reporting, inconsistent case definitions, incomplete clinical information, and variable follow-up, limiting precise incidence estimation [11, 15]. Non-randomized observational cohorts introduce confounding due to differences in baseline characteristics, comorbidities, disease severity, and concomitant treatments[14]. Heterogeneity in reporting practices, coding systems, and regional documentation further complicates comparisons across studies[16].High-risk

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populations, including older adults, patients with autoimmune conditions, and those with organ impairment, are often underrepresented, reducing generalizability[20]. Rare, delayed, or multi-organ irAEs may remain unrecognized even in large datasets[6,17]. Additionally, evidence on safe rechallenge after severe organ-specific irAEs remains limited [10,19]. Finally, reliance on previously published datasets may introduce publication bias, emphasizing the need for standardized, multicentre registries and AI-supported monitoring tools to generate more accurate real-world safety data [14, 15].

V. CONCLUSION

PD-1/PD-L1 inhibitors have revolutionized cancer therapy, delivering durable clinical responses across multiple tumor types [1, 4]. Real-world evidence, however, highlights a broader and more heterogeneous toxicity profile than reported in clinical trials, with up to 43% of patients developing immune-related adverse events (irAEs), most frequently involving endocrine, hepatic, and hematologic systems [6, 17]. Risk is influenced by age, ECOG status, and comorbidities [6, 18]. While most irAEs are manageable, rare but severe complications—such as myocarditis, cholestatic hepatitis, aseptic meningitis, and neuromuscular syndromes—require early recognition and specialist-driven management [5, 9, 10]. Rechallenge after irAEs remains complex, with recurrence rates of 28–32% and contraindications for severe cardiac or neurologic toxicities [10]. Combining PD-1/PD-L1 inhibitors with angiogenesis-targeted therapies may improve efficacy and reduce toxicity in selected patients, though data are limited [1, 4]. Moving forward, multicentre real-world registries, standardized reporting, biomarker-guided risk stratification, and AI-assisted monitoring are essential to optimize safety and support evidence-based clinical decision-making [14, 15, 16]. Real-world data are indispensable for capturing true toxicity patterns and guiding safe, individualized immunotherapy in routine oncology practice [6, 17, 20].

- *Conflicts of Interest*

  There is no conflicts of interest.

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- *Ethical Approval*

  Ethical approval was not required for this study.

- *Declaration of Patient Consent*

  Patient consent is not required as there is no patient in this study.

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