e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 13, Issue 03; 2025, 37-46

A Review on Immuno-oncology agents for cancer therapy

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Received: 17-02-2025 / Revised: 20-03-2025 / Accepted: 22-04-2025
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Conflict of interest: No conflict of interest.

Abstract:

Immuno-oncology (IO) leverages the immune system to attack cancer and has revolutionized therapy across many tumor types [1,2]. Among IO agents, immune checkpoint inhibitors (ICIs) that block CTLA-4 or PD-1/PD-L1 restore cytotoxic Tcell activity [6] and have shown remarkable efficacy in diverse malignancies [1,2]. To date, over a dozen ICIs are FDA-approved for multiple cancer indications, including tissue-agnostic approvals [2]. Adoptive cellular therapies such as chimeric antigen receptor (CAR) T cells (e.g. anti-CD19 or anti-BCMA constructs) have induced high remission rates in hematologic cancers [2]. Therapeutic cancer vaccines aim to prime T-cell responses by delivering tumor-specific antigens to antigen-presenting cells [3]. Despite decades of research, clinical efficacy of cancer vaccines in advanced disease has been modest [3], although prophylactic vaccines (e.g. HPV, HBV) successfully prevent virus-associated cancers. Recent vaccine platforms (e.g. mRNA, dendritic-cell, neoantigen-based) have shown promise, especially in combination with other IO modalities [3]. Oncolytic viruses (OVs) represent another modality: these engineered viruses selectively infect and lyse tumor cells while sparing normal tissues [4]. OVs also release tumor antigens and induce local inflammation, potentially converting immunologically “cold” tumors to “hot” [4]. Talimogene laherparepvec (T-VEC) for melanoma exemplifies OV approval, and many other OVs are in clinical trials [4]. Bispecific Tcell engagers Bispecific T-cell Engagers (BiTEs) are antibody-derived constructs that simultaneously bind a T-cell (via CD3) and a tumor antigen. BiTEs force formation of an immunologic synapse and trigger perforin/granzyme-mediated killing [5]. Blinatumomab (anti-CD19×CD3) was the first FDA-approved Bispecific T-cell Engagers. Bispecific T-cell Engagers (BiTEs) for B-cell acute lymphoblastic leukemia [5]; since then, several others (e.g. CD3×CD20, CD3×BCMA bispecifics) have reached late-stage trials or approval [5]. Despite these advances, IO therapies face significant challenges. Only a minority of patients achieve durable responses, as many tumors evade immunity via suppressive microenvironmental pathways and antigen loss [2]. IO agents can elicit serious immune-related toxicities (autoimmunity, cytokine release syndrome) and incur high cost [1]. Future efforts focus on rational combinations and predictive biomarkers to improve efficacy and safety of IO therapies.

Keywords: immuno-oncology; checkpoint inhibitor; CAR T-cell therapy; cancer vaccine; oncolytic virus; bispecific T-cell engager.

1. Introduction

Cancer remains a leading cause of global morbidity and mortality, with nearly 10 million deaths reported in 2022 according to WHO statistics ([28]). Traditional treatments like chemotherapy and radiation have been cornerstone modalities for decades. However, immuno-oncology has emerged as a transformative paradigm, seeking not to directly kill cancer cells but to empower the host immune system to identify and eliminate malignancies more effectively ([2]). The concept of leveraging immune mechanisms dates back to the 1890s with William Coley's use of bacterial toxins in osteosarcoma, but it was not until the late 20th and early 21st centuries that the field matured into viable therapeutic modalities ([1]). The introduction of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 marked a pivotal breakthrough, followed by the development of monoclonal antibodies, CAR-T cell therapies, and cytokine compounds. Today, the I-O drug development pipeline comprises thousands of agents in various stages of preclinical and clinical evaluation ([3]). This review will explore the mechanistic foundations, clinical applications, technological advances, and future directions of immuno-oncology agents, emphasizing data and developments through early 2025.

2. Mechanisms of Action of Immuno-Oncology Agents

2.1 Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints are regulatory pathways that maintain self-tolerance and modulate immune responses to prevent autoimmunity. Tumors exploit these checkpoints to evade immune detection by inhibiting T-cell activity. ICIs disrupt these inhibitory signals, thereby restoring cytotoxic T-cell function against cancer cells ([4]). PD-1/PD-L1 Axis: PD-1 is an inhibitory receptor on T cells, and its ligands PD-L1/PD-L2 are often upregulated on tumor cells or within the tumor microenvironment. Antibodies such as pembrolizumab and nivolumab block PD-1 or PD-L1, reactivating T-cell-mediated tumor eradication ([5]). CTLA-4: CTLA-4 competes with CD28 for binding to B7 ligands on antigen-presenting cells, suppressing T-cell priming. Ipilimumab, a CTLA-4 inhibitor, enhances T-cell activation at an earlier stage than PD-1 blockade ([1]).

Combination regimens targeting both pathways have shown synergistic effects, leading to FDA approvals for advanced malignancies such as melanoma and colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) status ([6]).

2.2 Monoclonal Antibodies (mAbs)

Monoclonal antibodies represent a versatile class of therapies that either block tumor-promoting pathways or engage immune effector mechanisms. Direct Targeting: mAbs can recognize tumor-specific antigens, facilitating antibody-dependent cellular cytotoxicity (ADCC), complement activation, or direct apoptosis induction. Immune Modulation: Immune checkpoint blockade mAbs restore T-cell function, while antibody-drug conjugates (ADCs) deliver cytotoxic payloads selectively to tumor cells, minimizing systemic toxicity ([5]). Bispecific Antibodies: Emerging bispecific antibodies simultaneously engage tumor antigens and immune cells, enhancing cytotoxic synapse formation ([5]).

2.3 Adoptive Cell Therapies (ACTs)

ACTs, particularly CAR-T cell therapies, involve ex vivo genetic modification of patient-derived T cells to express synthetic

receptors that recognize tumor antigens, followed by reinfusion.

CAR constructs typically combine an extracellular antigen-recognition domain (scFv) with intracellular T-cell activation domains (CD3ζ, co-stimulatory domains such as CD28 or 4-1BB).

CAR-T therapies have demonstrated remarkable efficacy in hematologic malignancies (e.g., CD19-directed therapies in B-cell lymphomas and leukemias) and are under investigation for solid tumors such as head and neck squamous cell carcinoma (HNSCC) with promising early data ([7]).

Table 1: Shows details of selected CAR-T therapies in clinical use or trials.

Therapy	Target Antigen	Cancer Type	Clinical Status	Notable Features
Tisagenlecleucel	CD19	B-cell ALL, lymphoma	FDA approved	First CAR-T approval (2017)
Axicabtagene ciloleucel	CD19	Large B-cell lymphoma	FDA approved	High response rates in refractory patients

2.4 Cytokine-Based Therapies

Cytokines such as IL-2 and interferons were early immunotherapies but had limited success due to toxicity. The recent FDA approval (2024) of IL-15 superagonist N-803 (nogapendekin alfa inbakicept-pmln) for bladder cancer marks a new era, providing potent immune stimulation with improved safety profiles ([8]).

IL-15 enhances natural killer (NK) and CD8+ T-cell proliferation without the activation-induced cell death associated with IL-2. Ongoing trials investigate recombinant proteins and genetically encoded constructs to optimize cytokine delivery and efficacy.

2.5 Cancer Vaccines and Oncolytic Viruses

Cancer vaccines aim to prime the immune system against tumor-specific or associated antigens, including neoantigens derived from somatic mutations. Personalized neoantigen vaccines have shown promise in preventing recurrence post-surgery in small trials ([6]). Oncolytic viruses selectively infect tumor cells, inducing immunogenic cell death and stimulating endogenous antitumor immunity ([9]). Their combination with ICIs is an active area of research.

3. Preclinical Models and Biomarker Development

3.1 Preclinical Models

Reliable preclinical models are critical for drug development, enabling evaluation of efficacy and toxicity. Mouse models remain predominant, Syngeneic models with immunocompetent mice allow for intact immune interactions but lack human tumor heterogeneity.

Humanized mouse models, incorporating human immune cells (e.g., hCD34+ hematopoietic stem cells), provide improved translational relevance for immunotherapies ([10]). Genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDXs) offer complementary insights. Challenges include recapitulating the tumor microenvironment (TME) complexity and immune suppression mechanisms.

3.2 Biomarkers for Immunotherapy

Biomarkers guide patient selection, predict response, and monitor therapy efficacy, PD-L1 Expression: Widely used but imperfect; expression heterogeneity and dynamic regulation limit reliability. Tumor Mutational Burden (TMB): High TMB correlates with neoantigen load and ICI responsiveness. Microsatellite Instability (MSI): MSI-H/dMMR tumors respond favorably to ICIs, leading to tissue-agnostic approvals ([11]).Liquid

Biopsies: Circulating tumor DNA (ctDNA) and immune cell profiling offer minimally invasive monitoring ([12]).Immune Gene Signatures and TME Profiling: Multiparametric assays assess T-cell infiltration, cytokine milieu, and suppressive cell populations. Ongoing efforts seek to identify robust combinatorial biomarkers to overcome current limitations ([3]).

4. Clinical Trials and Regulatory Landscape

The clinical and regulatory progression of immuno-oncology (IO) agents has played a pivotal role in shaping modern cancer therapy. Over the past two decades, a paradigm shift has occurred from conventional cytotoxic treatments to immunotherapies that harness the host immune system for sustained antitumor responses. This transition has been enabled by a growing number of well-designed clinical trials and adaptive regulatory frameworks that accelerate the approval of promising IO agents.

A landmark in the IO field was the approval of ipilimumab, an anti-CTLA-4 monoclonal antibody, for metastatic melanoma in 2011 following results from a phase III clinical trial demonstrating improved overall survival (OS) compared to conventional therapy [1]. This was followed by the rapid development and approval of anti-PD-1 and anti-PD-L1 agents such as nivolumab, pembrolizumab, atezolizumab, and durvalumab, which have shown remarkable efficacy across diverse malignancies including non-small cell lung cancer (NSCLC), renal cell carcinoma, head and neck squamous cell carcinoma, and urothelial carcinoma [2]. These approvals were largely based on robust evidence from randomized clinical trials and were often granted accelerated approval under designations such as Breakthrough Therapy or Fast Track.

The regulatory environment has been increasingly adaptive, particularly with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) implementing mechanisms like Priority Review, Accelerated Approval, and the EMA's PRIME (PRIority MEdicines) scheme. These programs aim to expedite the development and review of drugs that address unmet medical needs [3]. A landmark regulatory milestone was the approval of pembrolizumab for any solid tumor with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), making it the first tissue-agnostic cancer therapy approved based on a molecular biomarker rather than tumor origin [4].

In parallel, cellular immunotherapies such as chimeric antigen receptor (CAR) T-cell therapies have undergone accelerated development and approval due to their groundbreaking clinical results in hematologic malignancies. Agents such as tisagenlecleucel and axicabtagene ciloleucel were approved for relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and large B-cell lymphoma based on high response rates and durable remissions in early-phase trials [5]. The FDA's Regenerative Medicine Advanced Therapy (RMAT) designation has been instrumental in facilitating the approval of such personalized cell-based therapies.

Moreover, bispecific T-cell engagers (BiTEs), like blinatumomab (CD19×CD3), have expanded immunotherapy options by providing an "off-the-shelf" method to engage cytotoxic T cells against tumor cells without the need for individualized manufacturing [6]. Numerous ongoing clinical trials are exploring newer BiTEs targeting BCMA, CD20, and other tumor antigens.

Regulatory agencies have also recognized the necessity of dynamic trial designs. The

emergence of adaptive trial designs, umbrella and basket trials (e.g., NCI-MATCH, KEYNOTE studies), and real-world evidence integration is reshaping the IO trial landscape. These designs enable the simultaneous evaluation of multiple therapies and biomarkers, expediting the generation of clinically meaningful data [7].

Nonetheless, several challenges persist. Managing immune-related adverse events (irAEs) such as autoimmune pneumonitis, colitis, and endocrinopathies requires stringent safety monitoring in clinical trials [8]. Furthermore, trial design complexities—including appropriate endpoint selection, biomarker validation, and patient stratification—demand careful regulatory oversight. Additionally, cell therapy manufacturing scalability, quality control, and global regulatory harmonization remain significant hurdles, especially in low- and middle-income countries.

To support innovation, the FDA's Oncology Center of Excellence (OCE) has launched initiatives like Project Orbis and Real-Time Oncology Review (RTOR), promoting international collaboration and faster review timelines while maintaining safety and efficacy standards [9]. These efforts are critical as new IO agents, including personalized vaccines, oncolytic viruses, and novel immune modulators, enter early-phase clinical trials.

5. Combination Therapies and Optimization Pathways

Combining immuno-oncology agents with chemotherapy, targeted therapies, or radiation can enhance antitumor efficacy by modulating the TME and overcoming resistance. Chemotherapy may induce immunogenic cell death, increasing tumor antigen availability. Radiation can enhance antigen presentation and T-cell infiltration. Targeted therapies may normalize tumor vasculature or inhibit immunosuppressive pathways.

Optimization techniques include:

FP8 Quantization: Reduces computational load in AI-based biomarker analysis (AI Oncology Review, 2023). Bias Mitigation via Reinforcement Learning with Human Feedback (RLHF): Improves predictive fairness in therapy response models.

6. Challenges and Future Directions

Introduction

Immuno-oncology has emerged as a revolutionary approach in cancer therapy, harnessing the body's immune system to fight cancer. Despite significant advancements, several challenges remain that hinder the full potential of immuno-oncology agents. This section discusses these challenges and outlines future directions for research and clinical application.

Challenges in Immuno-Oncology

Tumor Heterogeneity

Description: Tumors are composed of diverse cell populations with varying genetic and phenotypic characteristics. This heterogeneity can lead to differential responses to immuno-oncology agents.

Impact: The presence of various subclones within a tumor can result in some cells being resistant to treatment, leading to tumor recurrence and metastasis.

Future Direction: Research should focus on personalized medicine approaches, utilizing genomic and proteomic profiling to tailor immuno-oncology therapies to individual tumor characteristics.

Immune Evasion Mechanisms

Description: Tumors can develop mechanisms to evade immune detection, such as downregulating antigen presentation or secreting immunosuppressive factors.

Impact: These mechanisms can significantly reduce the efficacy of immuno-oncology agents, leading to treatment failure.

Future Direction: Investigating the tumor microenvironment and identifying specific immune evasion pathways can help develop

combination therapies that enhance immune recognition and response.

Adverse Effects and Toxicity

Description: While immuno-oncology agents can be effective, they can also lead to immune-related adverse events (irAEs) due to the activation of the immune system against normal tissues.

Impact: The management of irAEs can complicate treatment regimens and affect patient quality of life.

Future Direction: Developing predictive biomarkers for irAEs and strategies for early intervention can help mitigate these risks, allowing for safer and more effective treatment protocols.

Limited Response Rates

Description: Not all patients respond to immuno-oncology therapies, and the reasons for this variability are not fully understood.

Impact: The limited response rates in certain cancer types or patient populations highlight the need for improved patient selection and treatment strategies.

Future Direction: Research into biomarkers that predict response to immuno-oncology agents, such as PD-L1 expression or tumor mutational burden, can enhance patient stratification and improve outcomes.

Cost and Accessibility

Description: The high cost of immuno-oncology agents can limit access for many patients, particularly in low-resource settings.

Impact: Economic barriers can lead to disparities in treatment access and outcomes among different populations.

Future Direction: Efforts should be made to develop cost-effective immuno-oncology therapies and to implement policies that ensure equitable access to these treatments.

Future Directions in Immuno-Oncology

Combination Therapies

Description: Combining immuno-oncology agents with other treatment modalities, such as chemotherapy, targeted therapy, or radiation, may enhance therapeutic efficacy.

Rationale: Synergistic effects can lead to improved tumor control and reduced resistance.

Future Direction: Clinical trials should focus on identifying optimal combinations and sequencing of therapies to maximize patient benefit.

Adoptive Cell Transfer and CAR-T Therapy

Description: Techniques such as CAR-T cell therapy have shown promise in treating hematological malignancies and are being explored for solid tumors.

Future Direction: Research should focus on improving the efficacy of CAR-T cells in solid tumors, including strategies to enhance T cell infiltration and persistence within the tumor microenvironment.

Neoantigen Targeting

Description: Neoantigens, which are unique to tumor cells, represent promising targets for personalized cancer vaccines and therapies.

Future Direction: Developing personalized vaccines that target neoantigens can enhance the specificity and effectiveness of immuno-oncology treatments.

Microbiome Influence

Description: Emerging evidence suggests that the gut microbiome can influence the efficacy of immuno-oncology therapies.

Future Direction: Investigating the role of the microbiome in modulating immune responses can lead to novel strategies for enhancing treatment outcomes through microbiome manipulation.

Global Collaboration and Data Sharing

Description: The complexity of cancer and the variability in patient responses necessitate a collaborative approach to research and data sharing.

Future Direction: Establishing global networks for data sharing and collaboration can accelerate the discovery of new

biomarkers, treatment strategies, and improve patient outcomes.

6.1 Resistance and Toxicity

Primary and acquired resistance to ICIs remain significant hurdles, driven by mechanisms such as:Tumor antigen loss Immunosuppressive TME, Regulatory T-cell and myeloid-derived suppressor cell (MDSC) expansion Management of irAEs requires multidisciplinary approaches to balance efficacy and safety ([3]).

6.2 Economic and Societal Considerations

High costs limit access in low- and middle-income countries, exacerbating health disparities. WHO initiatives emphasize affordability and inclusion in clinical trials to improve global equity ([28]).

6.3 Emerging Technologies

Artificial intelligence, multi-omics profiling, and nanomedicine promise to refine patient selection and therapeutic delivery ([24]; [25]).

7. Case Studies

7.1 CAR-T Therapy in Hematologic Malignancies

Tisagenlecleucel has transformed treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), achieving complete remission rates exceeding 80% in pediatric patients ([22]). Despite successes, challenges include cytokine release syndrome and neurotoxicity.

7.2 Immune Checkpoint Inhibitors in NSCLC

Pembrolizumab monotherapy in PD-L1 high-expressing NSCLC improved overall survival versus chemotherapy in multiple trials ([23]). Combination with chemotherapy has broadened indications.

7.3 Personalized Neoantigen Vaccines

Small trials in pancreatic and kidney cancers demonstrated safety and potential recurrence prevention by tailoring vaccines to tumor-specific mutations ([6]).

8. Data Visualization

Table 2: Shows Summary of FDA-Approved Immuno-Oncology Agents as of 2025

Agent	Class	Indications	Mechanism	Approval Year
Pembrolizumab	PD-1 inhibitor	NSCLC, melanoma, MSI-H colorectal	Immune checkpoint blockade	2014
Ipilimumab	CTLA-4 inhibitor	Melanoma, colorectal (MSI-H)	Immune checkpoint blockade	2011
Nivolumab	PD-1 inhibitor	NSCLC, RCC, colorectal (MSI-H)	Immune checkpoint blockade	2014
Tisagenlecleucel	CAR-T cell therapy	B-ALL, lymphoma	Genetically modified T cells	2017
N-803 (IL-15 superagonist)	Cytokine	Bladder cancer	Immune stimulation	2024

Table 2: shows Clinical Trial Response Rates for Selected Immuno-Oncology Agents

Agent	Cancer Type	Response Rate (%)	Median Overall Survival (Months)	Source
Pembrolizumab	NSCLC (PD-L1 >50%)	45	30	Garon et al., 2015
Ipilimumab + Nivolumab	Melanoma	58	48	Cancer Currents, 2025
CAR-T (Tisagenlecleucel)	B-ALL	81	24	Mayo Clinic, 2023

9. Cross-Disciplinary Insights

Technology: AI advances facilitate neoantigen prediction, biomarker discovery, and optimize clinical trial designs ([24]). Health: Immuno-oncology improves survival but requires management of toxicities and quality-of-life considerations ([3]). Law: Regulatory pathways for combination therapies and biomarker-driven approvals require adaptation ([26]). Finance: The oncology drug market is projected to reach USD 548.7 billion by 2033, driven largely by immunotherapies ([29]). Education: Increasing need for clinician education on IO agents' mechanisms, toxicities, and patient communication ([27]).

10. Conclusions

The advent of immuno-oncology (IO) has redefined the therapeutic paradigm in oncology, offering unprecedented advances in the treatment of multiple malignancies. Agents such as immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies, bispecific T-cell engagers (BiTEs), cancer vaccines, and oncolytic viruses have collectively contributed to significant improvements in clinical outcomes across a variety of tumor types. Checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have demonstrated durable responses in cancers previously considered refractory to treatment, including melanoma, non-small cell lung cancer, and renal cell carcinoma [1,2]. CAR T-cell therapies have revolutionized the management of hematological malignancies such as B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma [3]. BiTEs and other multispecific engagers have further expanded the scope of IO by facilitating T-cell redirection without the need for antigen processing or MHC presentation [4]. Despite these milestones, significant challenges remain. Many patients fail to respond to IO therapies due to primary or acquired resistance mechanisms, such as loss of antigen expression, immune suppressive tumor microenvironments, and T-cell exhaustion [5]. Additionally, immune-related adverse events, such as cytokine release syndrome and autoimmune manifestations, necessitate careful patient selection and monitoring [6]. The high cost and complex logistics of advanced therapies like CAR T cells also pose accessibility issues on a global scale. Future research is focused on overcoming these limitations through rational combination strategies (e.g., IO plus chemotherapy or targeted therapy), identification of robust predictive biomarkers, and development of next-generation agents with improved safety and efficacy profiles. Personalized immunotherapy approaches that consider tumor genomics, host immunity, and microbiome interactions are likely to become central in the next phase of cancer treatment innovation. Thus, while immuno-oncology has already transformed cancer therapy, its full potential remains to be realized through ongoing scientific and clinical advancements.

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