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IMMUNO-ONCOLOGY: A NOVEL AND TARGETED STRATEGY IN CANCER THERAPEUTICS

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Abstract:

Over the last two decades, immuno-oncology has transformed the landscape of cancer therapy by unlocking the body's own immune system to fight malignancies. Unlike conventional treatments that target tumors directly, immunotherapies such as immune checkpoint inhibitors, CAR-T cell therapies, cytokine-based approaches, and oncolytic viruses work by enhancing or restoring immune function against cancer cells. These agents have shown remarkable success in multiple cancer types—including melanoma, non-small cell lung cancer, renal cell carcinoma, and hematologic malignancies—offering not only improved survival but also durable, sometimes lifelong, responses. This review explores the historical milestones, underlying mechanisms, clinically approved therapies, and expanding applications of immuno-oncology. It also highlights key advantages, such as reduced toxicity and long-lasting immune memory, while discussing current limitations and emerging strategies aimed at broadening effectiveness. With continued innovation in biomarker development, combination therapies, and personalized immunotherapeutic approaches, immuno-oncology holds the promise to redefine cancer care in the years ahead.

keywords:
Immuno-oncology, immune checkpoint inhibitors, CAR-T cell therapy, cytokine therapy, oncolytic virus, cancer immunotherapy, tumor microenvironment, PD-1, CTLA-4, immune response, cancer treatment, personalized therapy, immune evasion, durable response, cancer vaccines.

Introduction:

Over the past two decades, cancer mortality rates have significantly decreased, whereas incidence rates have gradually increased (1,2). Alongside conventional surgical and radiation-based approaches, systemic therapies such as chemotherapy and targeted drugs are widely employed in cancer treatment. However, these modalities often suffer from toxicity, non-specificity, and resistance, which limit their long-term effectiveness (3,4).

In response to these challenges, immuno-oncology has emerged as a promising therapeutic strategy. By harnessing the body's immune system, this approach offers durable responses in malignancies that were once considered incurable, including non-small cell lung cancer (NSCLC) and metastatic melanoma (5-7). Despite advancements in non-surgical modalities like radiotherapy and molecular-targeted therapies, limitations persist due to low target specificity, drug resistance, inadequate control of metastases, and severe side effects (3,4,8).

Immunotherapeutic agents—particularly immune checkpoint inhibitors targeting CTLA-4 and PD-1/PD-L1 pathways—have demonstrated substantial clinical benefit by stimulating host immunity to mount a systemic anti-tumor response (5,6). While natural killer (NK) cells and T lymphocytes play essential roles in tumor surveillance, cancer cells can develop genetic instability and acquire molecular "hallmarks" that facilitate immune evasion and long-term proliferation (9,10). Nonetheless, studies have shown that host immunity can recognize tumor-specific "neoantigens" in vitro, which forms the basis for next-generation, personalized immunotherapies (11-13).

History of Immuno active agents:

The foundation of immuno-oncology dates back to the late 19th century, when physicians first observed that certain infections could shrink tumors, hinting at a connection between the immune system and cancer control. Dr. William Coley, often referred to as the father of cancer immunotherapy, experimented with bacterial toxins (Coley's toxins) to trigger immune responses in cancer patients—marking the earliest documented attempt to use immune activation as a therapeutic strategy (14). For much of the 20th century, the focus remained on surgery, radiation, and chemotherapy. However, sporadic efforts continued to explore immunological approaches, such as BCG (Bacillus Calmette–Guérin) for bladder cancer, which received FDA approval in 1990 and remains a key example of early immunotherapy success (15).

A turning point arrived in the 1990s with a deeper understanding of immune checkpoints—mechanisms that tumors exploit to avoid immune destruction. This led to the development of checkpoint inhibitors, with ipilimumab (anti-CTLA-4) becoming the first such agent approved by the FDA in 2011 for metastatic melanoma (16). This breakthrough was followed by PD-1 and PD-L1 inhibitors such as nivolumab, pembrolizumab, and atezolizumab, which significantly expanded treatment options for several cancers including lung, kidney, and bladder (17,18).

Another milestone came with the emergence of CAR-T cell therapy, a personalized treatment in which a patient's own T cells are engineered to better recognize and attack cancer cells. The first CAR-T therapy, tisagenlecleucel, was approved in 2017 for certain types of leukemia and lymphoma (19). Today, immuno-oncology continues to evolve rapidly, integrating novel agents, combination therapies, and personalized approaches that harness the body's own defenses against malignancies. This therapeutic revolution has not only redefined cancer treatment paradigms but has also provided lasting responses in cases previously considered untreatable (20).

Mechanism of action:

Immuno-oncology agents work by modulating the body's immune system to recognize and eliminate cancer cells more effectively. Unlike traditional chemotherapy, which directly targets and kills rapidly dividing tumor cells, these therapies enhance the natural immune surveillance mechanisms that can detect and destroy malignant cells. A major class of immuno-oncology agents is immune checkpoint inhibitors. Under normal conditions, immune checkpoints such as CTLA-4 (cytotoxic T-lymphocyte–associated antigen 4) and PD-1/PD-L1 (programmed death receptor-1 and its ligand) act as "brakes" on immune responses to prevent autoimmunity. Tumors exploit these pathways by expressing PD-L1 or inducing T-cell exhaustion, thereby avoiding immune attack. Checkpoint inhibitors—such as ipilimumab (anti-CTLA-4), nivolumab, and pembrolizumab (anti-PD-1)—work by blocking these inhibitory signals, thus reactivating cytotoxic T cells to attack tumor cells (21,22).

Another innovative strategy is CAR-T cell therapy (Chimeric Antigen Receptor T-cell therapy). In this approach, a patient's T cells are collected and genetically modified in the laboratory to express a receptor that specifically binds to an antigen on tumor cells (e.g., CD19 in B-cell malignancies). Once reinfused, these engineered T cells actively seek out and destroy cancer cells expressing the target antigen (23).

Cytokine-based therapies, such as interleukin-2 (IL-2) and interferons, boost the immune system more broadly by promoting the proliferation and activation of immune effector cells, including T cells and natural killer (NK) cells (24).

Cancer vaccines and oncolytic viruses represent additional modalities. Vaccines aim to stimulate an immune response against specific tumor antigens, while oncolytic viruses selectively infect and lyse tumor cells, releasing antigens that trigger immune activation (25,26).

Overall, immuno-oncology agents do not attack cancer cells directly; instead, they empower and reprogram the host's immune system to identify, target, and eliminate tumors with greater precision and durability.

Overview of Clinically Approved Immuno-Oncology Therapies and Their Targets

1. Immune Checkpoint Inhibitors

These drugs remove inhibitory signals (immune checkpoints) that prevent T cells from attacking cancer (27,28).

Drug	Target	Indications
Ipilimumab	CTLA-4	Metastatic melanoma, RCC, NSCLC (27)
Nivolumab	PD-1	Melanoma, NSCLC, RCC, Hodgkin lymphoma, esophageal cancer (27)
Pembrolizumab	PD-1	Melanoma, NSCLC, gastric cancer, TNBC, MSI-H tumors (27)
Atezolizumab	PD-L1	NSCLC, urothelial carcinoma (28,30)
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma (31)
Durvalumab	PD-L1	NSCLC, bladder cancer (31)
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma, NSCLC (28)

2. CAR-T Cell Therapies

These involve genetically modifying patient T cells to express chimeric antigen receptors targeting tumor-specific antigens (32).

Therapy	Target	Indications
Tisagenlecleucel	CD19	B-cell ALL, DLBCL (32)
Axicabtagene ciloleucel	CD19	Large B-cell lymphoma, follicular lymphoma (32)
Lisocabtagene maraleucel	CD19	Relapsed/refractory large B-cell lymphoma (33)
Idecabtagene vicleucel	BCMA	Multiple myeloma (33)
Ciltacabtagene autoleucel	BCMA	Relapsed/refractory multiple myeloma (33)

3. Cytokine-Based Immunotherapy

Boosts proliferation and activation of immune effector cells (30).

Drug	Type	Indications
Aldesleukin	IL-2	Metastatic RCC, melanoma (30)
Interferon-α2b	Cytokine	Melanoma, CML, Kaposi's sarcoma (30)

4. Oncolytic Virus Therapy

Viruses engineered to lyse tumor cells and stimulate immune activation; includes cancer vaccines (31).

Drug	Antigen Target	Indication
Sipuleucel-T	PAP	Metastatic prostate cancer (31)

Clinical Application:

Over the past decade, immuno-oncology (I-O) agents have revolutionized cancer treatment by empowering the immune system to recognize and eradicate tumors in settings where traditional therapies struggled. In melanoma, checkpoint inhibitors like ipilimumab, nivolumab, and pembrolizumab have delivered unprecedented survival benefits—offering durable responses well beyond what chemotherapy could achieve (34). In NSCLC, PD-1/PD-L1 inhibitors, including atezolizumab, durvalumab, and nivolumab, have become cornerstone first-line or maintenance therapies in PD-L1–high patients—extending overall survival while avoiding chemo toxicity (35,36).

Hematologic oncology has seen a breakthrough with CAR-T therapies. New data on obecabtagene autoleucel show deep, sustained remissions in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), reinforcing previously reported durable responses (37). In genitourinary cancers, the frontline combination nivolumab + ipilimumab has demonstrated impressive long-term outcomes in advanced RCC, maintaining superiority over sunitinib at 8 years (38,39). Meanwhile, the tissue-agnostic use of pembrolizumab for MSI-H/dMMR cancers continues to expand, showing high complete response rates across tumor types in real-world analyses (40,41).

While not universal, patient responses are increasingly guided by tumor mutational burden, immune microenvironment, and PD-L1 expression. Today's therapeutic frontier is exploring tailored combinations of immunotherapy, targeted agents, and radiation to enhance efficacy and overcome resistance.

Advantages:

The advent of immuno-oncology (I-O) has introduced a profound shift in the way we approach cancer treatment. Unlike conventional therapies that directly target the tumor, I-O agents empower the immune system to recognize and combat malignancies. This immunologically driven approach offers a range of distinct and clinically meaningful advantages.

1.Durable and Long-Lasting Responses
One of the most striking benefits of immuno-oncology therapies is their potential to produce long-term tumor control—even in patients with advanced-stage disease. Unlike chemotherapy, which often yields transient effects, agents such as checkpoint inhibitors have demonstrated sustained remissions, sometimes lasting years post-treatment cessation. This has been particularly notable in melanoma and NSCLC, where a subset of patients may achieve what is now referred to as a "functional cure" (42).

2. Broad Applicability Across Cancer Types
Immuno-oncology agents have demonstrated efficacy across diverse malignancies, including melanoma, lung, renal, bladder, various lymphomas, and MSI-H colorectal cancer. The tissue-agnostic approval of PD-1 inhibitors for MSI-H/dMMR tumors further underscores their versatility, irrespective of the tumor's tissue of origin (43).

3. Favorable Side Effect Profile
While immune-related adverse events (irAEs) can occur, most patients tolerate I-O therapies better than conventional chemotherapy. These agents typically avoid common cytotoxic complications like nausea, alopecia, or myelosuppression, thereby improving patient quality of life during long-term treatment (44).

4. Potential for Combination Therapies
Immuno-oncology agents can synergize with chemotherapy, targeted treatments, or radiation. For example, combining PD-1 inhibitors with chemotherapy has shown enhanced efficacy in multiple cancers. Ongoing studies are investigating how such regimens may overcome resistance and expand response rates.

5. Immunological Memory and Relapse Prevention
I-O therapies can generate durable immunological memory, training the immune system to recognize and suppress tumor antigens long after therapy ends. This lasting immunity helps prevent recurrence in some patients.

6. Less Tumor Resistance
Unlike chemotherapy, which directly targets tumor cells and may prompt resistant clones via selective pressure, immunotherapy modulates the immune landscape. The adaptive nature of immune responses counters resistance more effectively, thereby extending the duration of benefit (45).

Future direction of immuno oncology agents:

The future of immuno-oncology is driven by innovative strategies poised to overcome current limitations and benefit more patients.

1. Personalized Immunotherapy through Biomarkers
Advances in multi-omic profiling including genomics and transcriptomics—are refining the prediction of responders and guiding therapy selection in immuno-oncology.

2. Novel Immune Checkpoint Targets
Emerging immune checkpoints like LAG-3, TIM-3, and TIGIT are being explored in early-phase trials. Bispecific antibodies targeting LAG-3 and TIGIT show promise in rekindling exhausted T cells when combined with PD-1 blockade.

3. Combination Strategies with Other Modalities
Synergistic approaches combining checkpoint inhibitors with VEGF inhibitors, chemotherapy, and radiation can enhance immune activation. Radiation, for example, appears to convert "cold" tumors to "hot" by improving antigen presentation (46).

4. Cell-Based Therapies and Beyond
Next-generation cell therapies—such as TCR-T, NK-cell, and macrophage-based platforms—are being developed to improve targeting, persistence, and tumor infiltration, expanding beyond current CAR-T applications.

5. Addressing Immune-Related Toxicities
Understanding mechanisms underlying irAEs is critical. Novel biomarkers and therapeutic strategies aim to predict and manage toxicities without impairing immune efficacy.

6. Exploring the Microbiome's Role
Gut microbiome composition correlates with I-O response. Interventions such as dietary modulation, probiotics, and fecal microbiota transplant are now being investigated to improve immunotherapy outcomes (47).

Conclusion:

Immuno-oncology has moved from experimental curiosity to a central pillar in the fight against cancer. By shifting focus from attacking the tumor directly to empowering the immune system, this approach has already changed the course of treatment for many patients once considered untreatable. From the approval of the first checkpoint inhibitor to the emergence of cell-based and personalized therapies, the journey of immuno-oncology is marked by scientific breakthroughs and real-world clinical impact. As we look to the future, the field is poised for even greater strides—guided by deeper understanding of immune biology, improved biomarkers for patient selection, and novel combinations that push beyond current limitations. While challenges like immune-related toxicities and resistance remain, ongoing research into next-generation targets, the tumor microenvironment, and the gut microbiome continues to expand the therapeutic possibilities. Ultimately, immuno-oncology represents more than just another treatment option—it is a paradigm shift that continues to bring new hope to patients and clinicians alike.

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