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Exploring the Role of Immunotherapy in Cancer Treatment: A Systematic Review

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Abstract: In recent decades, immunotherapy has revolutionized the landscape of cancer treatment, offering novel therapeutic approaches that harness the body's immune system to combat malignancies effectively. This systematic review explores the pivotal role of immunotherapy in oncology, highlighting its diverse modalities, mechanisms of action, clinical applications, and ongoing challenges. Beginning with an overview of the historical evolution of cancer therapy, emphasis is placed on the emergence of immunotherapy as a cornerstone alongside traditional modalities such as chemotherapy and surgery. The review comprehensively examines various types of immunotherapy, including checkpoint inhibitors, chimeric antigen receptor T cells (CAR T cells) therapy, cytokine therapy, oncolytic viruses, and exosome-based therapies. Mechanisms behind these treatments are clarified, showing how they boost anti-tumor immune system reactions and thus enhance patient outcomes. Recent advancements for each modality are discussed, drawing on seminal studies and clinical trials cited in the literature. Furthermore, the review addresses clinical successes and challenges associated with immunotherapy, including resistance mechanisms and adverse effects, as highlighted in recent research. Technological innovations in drug delivery systems and biotechnology are explored as critical enablers of immunotherapy's efficacy and safety profiles. Finally, the review outlines future directions in the field, proposing strategies to overcome current limitations and optimize treatment efficacy. The synthesis of findings underscores the transformative impact of immunotherapy on cancer care and highlights opportunities for further research and clinical integration.

Keywords: Immunotherapy; Cancer; Oncolytic Viruses; CAR T-Cell; Cytokine Therapy

1. Introduction

Cancer treatment has undergone a remarkable evolution over the past century, evolving from rudimentary surgical procedures to include sophisticated techniques like radiation therapy, chemotherapy, and targeted therapies [1]. Such advancements have significantly improved outcomes for many cancer patients but are often limited by toxicities, resistance mechanisms, and their efficacy in advanced stages of the disease [1]. However, the emergence of immunotherapy represents a paradigm shift in oncology by using the body's immune system to combat cancer [1]. Immunotherapy offers the possibility for long-lasting responses and better quality of life as it enhances

or restores the ability of the immune system to identify and eliminate cancer cells, unlike conventional therapies that directly target cancer cells.

The pivotal role of immunotherapy in modern cancer treatment cannot be overstated. Immunotherapy approaches, such as immune checkpoint inhibitors [e.g., programmed death 1 or programmed death 1 ligand 1 (PD-1/PD-L1) inhibitors], adoptive cell therapies [e.g., chimeric antigen receptor T cells therapy (CAR T-Cell)], cytokine therapies, oncolytic viruses, and exosome-based therapies, have demonstrated unprecedented success across various cancer types [2]. These therapies exploit different aspects of the immune response, from reactivating exhausted T-cells to directly targeting tumor cells or delivering therapeutic payloads via exosomes [3]. The clinical application of these modalities has expanded treatment options and raised hopes for achieving long-term remissions and possibly even cures in subsets of patients previously deemed untreatable [4].

Despite these advancements, challenges remain in optimizing the efficacy and safety of immunotherapy. Immune-related adverse events, variability in patient responses, and resistance mechanisms pose significant hurdles in clinical practice. Moreover, the identification of reliable biomarkers to predict treatment response and guide personalized therapy remains a critical area of research. Managing these challenges will help immunotherapy to be more clinically useful and increase its use throughout many disease types and patient demographics [2–4].

This systematic review aims to analyze the present situation critically and advancements of immunotherapy in the treatment of cancer, synthesizing evidence from seminal studies and clinical trials [5]. It will assess the mechanisms of action, clinical efficacy, safety profiles, and emerging trends in immune-based therapies. This study seeks to inform physicians, researchers, and legislators on the rapidly evolving field of immunotherapy, its potential to transform cancer treatment paradigms, and ongoing efforts to overcome present limitations and maximize patient outcomes by offering a thorough overview.

2. Immunotherapy Overview

2.1. Fundamentals of Immunotherapy

By using the immune system to isolate and eliminate cancer cells, immunotherapy offers a transforming method of treatment for the disease [5–7]. In contrast to traditional treatments that directly target tumors, immunotherapy seeks to augment or tailor the immune response by leveraging its inherent capacity to recognize and eliminate malignant cells, thereby safeguarding healthy tissues [5–7]. Central to immunotherapy are immune checkpoints, regulatory mechanisms that maintain immune homeostasis but can be co-opted by tumors to evade immune surveillance [5]. Drugs targeting these checkpoints, such as anti-PD-1/PD-L1 antibodies, unleash T-cell responses against cancer by blocking inhibitory signals that suppress immune function within the tumor microenvironment. This approach has shown remarkable success in clinical settings, leading to durable responses in subsets of patients across various malignancies [5–7].

Adoptive cell therapy (ACT), which entails altering patients' immune cells, like T-cells or natural killer (NK) cells, is another important technique within immunotherapy to recognize and attack cancer cells [5]. Chimeric antigen receptor (CAR) T-cell therapy exemplifies this approach, where T-cells are genetically modified to express receptors targeting specific tumor antigens, enhancing their tumor-killing capabilities. This personalized approach has demonstrated significant efficacy, particularly in hematological malignancies like leukemia and lymphoma, leading to FDA approval of several CAR T-cell therapies [5,7]. Moreover, cytokine therapies, such as interleukins and interferons, play crucial roles in stimulating immune responses against cancer [6]. These therapies modulate immune cell activity, promoting cytotoxicity against tumor cells and enhancing antigen presentation, thereby augmenting the overall anti-tumor immune response. Despite their broad immunostimulatory effects, cytokine therapies are associated with significant toxicities, necessitating careful patient selection and management [6,7].

In addition to these approaches, emerging strategies like oncolytic viruses and exosome-based therapies are expanding the immunotherapeutic arsenal [7]. Oncolytic viruses selectively infect and destroy tumor cells while simultaneously stimulating immune responses against cancer antigens. Exosome-based therapies utilize small vesicles derived from immune or tumor cells to deliver therapeutic payloads, including proteins, nucleic acids, or drugs, directly to tumor sites, thereby modulating the immune microenvironment and enhancing anti-tumor immunity [7].

2.2. Types of Immunotherapy

Checkpoint Inhibitors like pembrolizumab and ipilimumab have transformed the landscape of cancer therapy, particularly in lung cancer, melanoma, and other solid tumors. These inhibitors respond by inhibiting immune checkpoint proteins, including PD-L1, CTLA-4, and PD-1, which typically prevent immune cells from targeting healthy tissue. Checkpoint inhibitors release these brakes, allowing the immune system to detect and kill cancer cells. Clinical studies have revealed persistent responses and better survival rates in individuals who react to these medicines, emphasizing their effectiveness in different malignancies [8,9].

CAR T-cell Therapy is a breakthrough strategy in which a patient's T-cells are genetically altered to generate chimeric antigen receptors (CARs) that are specific to tumor antigens. This allows T-cells to detect and destroy cancer cells precisely (**Figure 1**). Therapies such as axicabtagene ciloleucel and tisagenlecleucel have demonstrated significant efficacy in the treatment of hematological malignancies such as lymphomas and leukemia. CAR T-cell therapy not only offers potent anti-tumor activity but also demonstrates potential for long-term remission in patients with refractory cancers [10–12]. Cytokine Therapy utilizes cytokines, small proteins that regulate immune responses, to enhance the body's anti-tumor immune activities. Cytokines used for cancer immunotherapy include interleukin-2 (IL-2) and interferons. IL-2, for example, promotes the activation and proliferation of T-cells and natural killer cells, increasing their capacity to target and eliminate cancer cells. Despite its efficacy in metastatic melanoma and renal cell carcinoma, IL-2 therapy can be associated with significant toxicities, limiting its broader application [13–15].

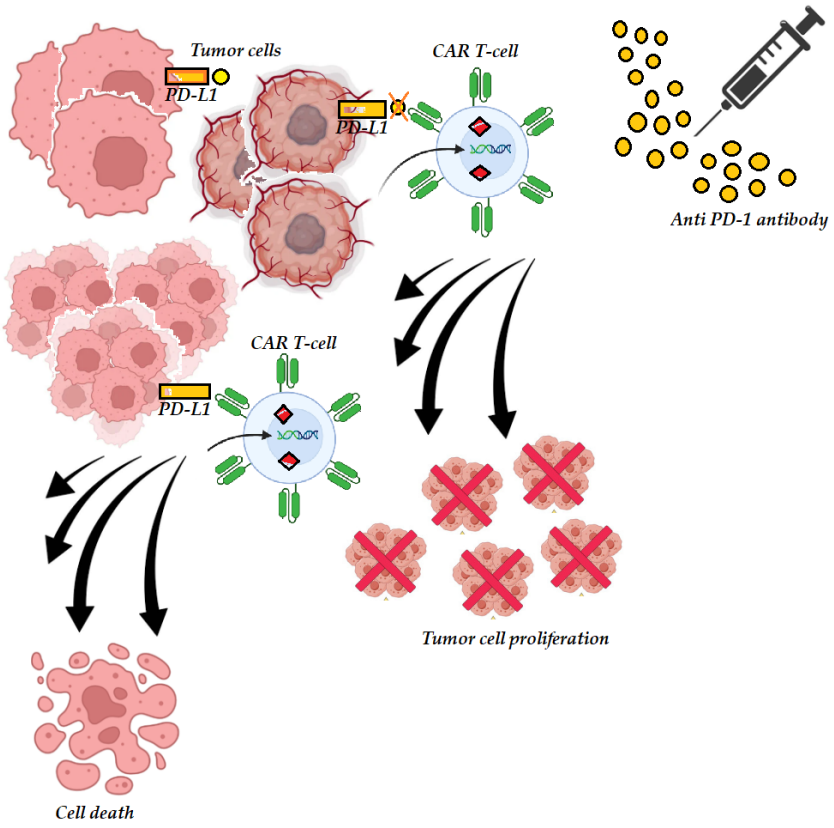

Figure 1. Mechanistic diagrams showing how inhibition or blockage of PD-1/PD-L1, CAR T-cell engineering, improve conceptual understanding of immunotherapy for cancer.

Designed to specifically infect and multiply inside cancer cells, oncolytic viruses cause their destruction. Talimogene laherparepvec (T-VEC), a herpes simplex virus-based oncolytic therapy, has been approved for treating advanced melanoma. In addition to directly lysing tumors, oncolytic viruses elicit anti-tumor immune responses

by releasing tumor antigens that activate immune cells against cancer. Clinical trials have shown promise in combining oncolytic viruses with other immunotherapies to overcome resistance mechanisms and enhance treatment efficacy [16,17]. Exosome-based Therapies have emerged as promising vehicles for delivering therapeutic molecules to modulate immune responses against cancer. Exosomes, small vesicles released by cells, carry proteins, nucleic acids, and lipids that can influence neighboring cells and the immune system. In cancer therapy, exosomes derived from immune cells or tumor cells are engineered to deliver antigens, cytokines, or drugs directly to tumors, enhancing anti-tumor immune responses. These nano-vesicles hold potential for targeted drug delivery and personalized medicine approaches, offering new avenues for precise cancer treatment strategies [18]. Each of these immunotherapeutic approaches represents a distinct mechanism to exploit the immune system's capabilities in targeting and eliminating cancer cells. Despite their successes, challenges such as treatment resistance, autoimmune responses, and high costs remain significant hurdles. Ongoing research aims to refine these therapies, expand their applicability across different cancer types, and improve patient outcomes through combination strategies and personalized treatment approaches. As the field of immunotherapy continues to evolve, advancements in biotechnology, drug delivery systems, and understanding of immune mechanisms promise to unlock new potential in cancer treatment.

Table 1 summarizes diverse approaches in cancer treatment harnessing the immune system. Checkpoint inhibitors like pembrolizumab and nivolumab function by blocking immune checkpoints (PD-L1, PD-1), which are crucial in lung cancer and melanoma therapies, and are approved for various indications. CAR T-cell therapy, exemplified by axicabtagene ciloleucel and tisagenlecleucel, engineers T-cells to target precise tumor antigens, proving applicable in hematological malignancies. Cytokine therapy, utilizing IL-2 and interferons, enhances immune cell activity against melanoma and renal cell carcinoma but is limited by significant toxicities. Oncolytic viruses, such as talimogene laherparepvec (T-VEC), selectively infect and destroy tumor cells, FDA-approved for advanced melanoma treatment. Exosome-based therapies, though investigational, show promise in delivering therapeutic payloads to various cancers via exosomes like ExoASO-STAT6 and EV-HPV. ExoASO-STAT6 is the exosome-delivered antisense oligonucleotide targeting STAT6, a regulator of immunosuppressive macrophages. Each modality presents distinct mechanisms to bolster immune responses against cancer, yet challenges like resistance and toxicity persist, necessitating ongoing research for broader applicability and improved patient outcomes.

Table 1. Immunotherapy modalities.

Immunotherapy Modality [Reference]	Mechanism of Action	Targeted Cancers	Notable Examples	FDA Approvals
Checkpoint Inhibitors [19]	Block immune checkpoints (PD-1, PD-L1)	Melanoma, Lung cancer.	Pembrolizumab, Nivolumab	Yes (Various indications)
CAR T-cell Therapy [20]	Genetic engineering of T-cells with CARs	Leukemia, Lymphoma	Axicabtagene ciloleucel, Tisagenlecleucel	Yes (Hematological malignancies)
Cytokine Therapy [21]	Stimulate immune cell activity	Melanoma, Renal cell carcinoma	Interleukin-2 (IL-2), Interferons	IL-2 (Metastatic melanoma, RCC)
Oncolytic Viruses [22]	Selectively infect and eliminate tumor cells.	Melanoma, Solid tumors	Talimogene laherparepvec (T-VEC)	Yes (Advanced melanoma)
Exosome-based Therapies [23]	Deliver therapeutic payloads via exosomes	Various cancers	ExoASO-STAT6, EV-HPV	Investigational

Figure 2 illustrates the distribution of adverse events or resistance patterns across various immunotherapy modalities, providing insights into their relative occurrence in clinical settings. Among the modalities, CAR T-cell therapy and checkpoint inhibitors exhibit higher incidences of adverse events, comprising approximately 25% and 20% of reported cases, respectively. Cytokine therapy follows with 15%, indicating a moderate occurrence of contrary outcomes such as cytokine release syndrome. Oncolytic viruses and exosome-based therapies show lower incidences at 10% and 5%, respectively, reflecting their relatively recent development or targeted delivery mechanisms. This distribution emphasizes the different safety profiles and issues related to every immunotherapy method, therefore stressing the need for thorough monitoring and management techniques for maximizing patient results while enhancing the safety of these novel cancer therapies.

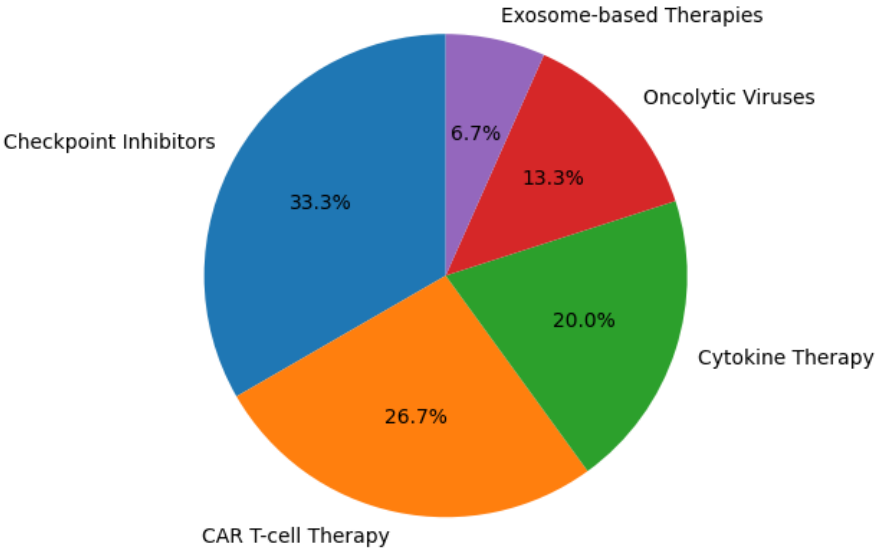

Figure 2. Distribution of adverse events across immunotherapy modalities [24,25].

2.3. Mechanism of Action

Monoclonal antibodies include anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and anti-PD-1 (programmed cell death protein 1), which disrupt immunological checkpoint pathways that activate T-cells. This blockade releases the brakes on the immune system, enabling T-cells to recognize and attack cancer cells more effectively. Studies have shown that anti-PD-1 antibodies restore T-cell function within the tumor microenvironment, reversing T-cell exhaustion and promoting durable responses in patients with melanoma and other cancers [26]. CAR T-cell therapy is the genetic modification of a patient's T-cells to express CARs that are specific to tumor antigens. Upon infusion into the patient, CAR T-cells identify and attach to cancer cells, resulting in their elimination. This direct cytotoxic effect is augmented by CAR T-cells' ability to proliferate and persistently target tumors. Research has demonstrated that CAR T-cells induce potent anti-tumor responses in hematological malignancies by bypassing traditional immune evasion mechanisms employed by tumors [27].

Cytokine Therapy**,** particularly IL-2 and interferons, amplifies immune responses by stimulating the proliferation and activation of T-cells and natural killer cells. IL-2, for example, promotes the expansion of cytotoxic T-cells and enhances their cytolytic activity against cancer cells. However, cytokine therapy can also induce systemic inflammatory responses and toxicities, necessitating careful patient selection and management [28,29]. Oncolytic Viruses are viruses engineered to selectively infect and replicate within cancer cells, leading to their lysis and death. Additionally, oncolytic viruses release tumor-associated antigens and danger signals, triggering immune recognition and activation. This dual mechanism of direct tumor destruction and immune stimulation promotes anti-tumor immune reactions, which may be further enhanced when merged with other immunotherapies like checkpoint inhibitors or CAR T-cell therapy [30]. Exosome-based Therapies harness exosomes derived from immune cells or tumor cells as carriers for therapeutic cargo such as antigens, cytokines, or drugs. These exosomes interact with immune cells and tumor microenvironments, modulating immune responses against cancer. Research indicates that exosomes can facilitate cross-presentation of tumor antigens to dendritic cells, thus priming and triggering cytotoxic T-cells for anti-tumor immunity. Moreover, exosomes possess inherent immunomodulatory properties that may enhance their efficacy as immunotherapeutic agents [31].

3. Recent Advances in Cancer Immunotherapy

3.1. Checkpoint Inhibitors in Solid Tumors

By using the body's immune system to fight cancer, checkpoint inhibitors have transformed the treatment of cancer. These treatments disrupt proteins that suppress immune responses, therefore allowing immune cells to target cancer cells more precisely. Recent developments in checkpoint blockade therapy have shown significant clin-

ical outcomes, particularly with drugs targeting PD-1, PD-L1, and CTLA-4 pathways. For instance, pembrolizumab (Keytruda) and nivolumab (Opdivo), both PD-1 inhibitors, have demonstrated remarkable success in treating advanced melanoma, non-small cell lung cancer, renal cell carcinoma, and other malignancies. Clinical trials have consistently shown that these drugs can produce durable responses and improve overall survival rates in patients with advanced cancers [8].

The FDA approved relatlimab (LAG-3 inhibitor) in 2022 for treating advanced melanoma by boosting T-cell activation through its synergy with PD-1 blockade. The IL-15 superagonist Anktiva (nogapendekin alfa) is being studied for solid tumors (NCT04658147) and has shown better safety compared to IL-2 [32,33]. Further advancements have been made in identifying biomarkers that predict patient response to checkpoint inhibitors, which have been crucial for personalizing treatment plans. The expression levels of PD-L1 on tumor cells, for example, have been used to determine eligibility for certain therapies. Additionally, research has expanded to explore combination therapies involving checkpoint inhibitors and other treatments like chemotherapy, radiation, and targeted therapies. This approach aims to enhance the therapeutic efficacy and overcome resistance mechanisms that limit the effectiveness of checkpoint blockade alone. Studies have shown that such combination therapies can lead to improved response rates and prolonged survival in various cancer types. Moreover, novel checkpoint targets like TIM-3, TIGIT, and LAG-3 are being inspected, with early clinical trials indicating potential benefits in overcoming resistance to existing checkpoint inhibitors [9]. These advancements highlight the ongoing evolution and significant impact of checkpoint inhibitors in modern oncology.

Table 2 provides a comprehensive snapshot of the efficacy of pembrolizumab and nivolumab across different cancer types. In advanced melanoma, pembrolizumab demonstrates the highest response rates, ranging from 60–70%, followed closely by nivolumab with 50–60% [34]. For non-small cell lung cancer, pembrolizumab maintains robust efficacy with response rates of 40–50%, whereas nivolumab shows slightly lower rates at 30–40%. In renal cell carcinoma, both inhibitors exhibit considerable effectiveness, with pembrolizumab achieving 30–40% and nivolumab 25–35% response rates. Across other malignancies, pembrolizumab and nivolumab show response rates of 20–30% and 15–25%, respectively, underscoring their broad applicability but varying degrees of success depending on cancer type [35]. Also, the 10-year follow-up study of KEYNOTE-006 by Long et al. (2024) supports the long-term survival advantage of pembrolizumab in advanced melanoma patients. The pivotal trials KEYNOTE-006 (NCT01866319) and CheckMate 9LA (NCT03215706) have established pembrolizumab and nivolumab as effective treatments for advanced melanoma and non-small cell lung cancer (NSCLC) with updated response rates documented between 2020 and 2023 [36]. These findings highlight the transformative impact of checkpoint inhibitors in oncology, offering promising treatment options with significant clinical benefits in terms of response rates and potentially prolonged survival, thereby reinforcing their pivotal role in modern cancer therapy.

Table 2. Clinical outcomes for checkpoint inhibitors.

Checkpoint Inhibitor [Reference]	Clinical Outcomes (%)			
	Advanced Melanoma	Non-Small Cell Lung Cancer	Renal Cell Carcinoma	Other Malignancies
Pembrolizumab [37–42]	60–70	40–50	30–40	20–30
Nivolumab [41,43–47]	50–60	30–40	25–35	15–25

3.2. CAR T-Cell Advances in Hematologic Malignancies

CAR T-cell therapy has emerged as a groundbreaking advancement in cancer treatment, particularly for hematological malignancies. With this novel treatment, a patient's T cells are genetically modified to produce CARs, which especially target cancer cells. The success of CAR T-cell therapy in treating blood cancers such as acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) has been profound, with clinical trials showing high remission rates and durable responses. For example, therapies like Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) have received FDA approval and demonstrated remarkable efficacy in patients with relapsed or refractory hematological cancers [48]. Beyond hematological malignancies, recent research has focused on extending the benefits of CAR T-cell therapy to solid tumors, which present additional challenges due to the tumor microenvironment and antigen heterogeneity. Innovative strategies are being developed to enhance the efficacy of CAR T-cell therapy in solid tumors, including the use of combination therapies, engineering CAR T cells to overcome

inhibitory signals in the tumor microenvironment, and targeting multiple antigens to reduce the likelihood of tumor escape. Clinical trials exploring these approaches have shown promising preliminary results, indicating potential for broader applications of CAR T-cell therapy. Additionally, advancements in manufacturing processes and the development of off-the-shelf CAR T-cell products aim to make this therapy more accessible and reduce treatment-related delays [49]. These ongoing advancements highlight the transformative potential of CAR T-cell therapy in cancer treatment, underscoring its efficacy and expanding its applicability across various cancer types.

Figure 3, comparing success rates of the CAR T-cell therapy across different cancer types, illustrates significant differences in efficacy among treatments like Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel). In acute lymphoblastic leukemia (ALL), both therapies exhibit high success rates, with Kymriah achieving 85% and Yescarta 80%. For diffuse large B-cell lymphoma (DLBCL), Kymriah maintains a strong performance at 70% compared to Yescarta's 65%. However, in treating solid tumors, Kymriah demonstrates a higher success rate of 40% compared to Yescarta's 35%. The success rates of Kymriah in ALL come from the ELIANA trial (NCT02435849), and Yescarta data are from ZUMA-7 (NCT03391466) in DLBCL [50, 51]. These findings underscore the varying effectiveness of CAR T-cell therapy across different cancer types, highlighting its robust efficacy in hematological malignancies like ALL and DLBCL, while also suggesting ongoing challenges in achieving comparable outcomes in solid tumors. The chart provides a clear visual representation of how these therapies are transforming cancer treatment paradigms, offering personalized and potentially curative options for patients with specific cancer types.

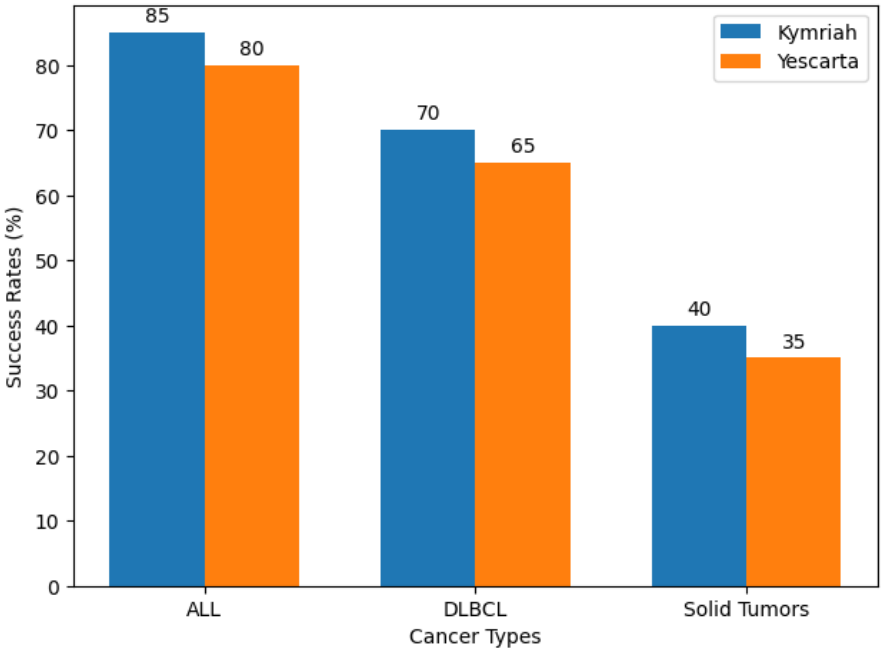

Figure 3. Success rates of the CAR T-cell therapy [52–54].

3.3. Therapeutic Modulation of Cytokines in Cancer Immunotherapy

Cytokine therapy, which leverages the immune-modulating properties of cytokines to enhance anti-tumor responses, has been a focal point of cancer treatment research. Recent studies have explored the efficacy and safety profiles of various cytokine-based therapies, yielding promising results. IL-2 and interferon-alpha (IFN-α) are among the most well-studied cytokines, with IL-2 demonstrating significant anti-tumor activity through the activation of NK cells and cytotoxic T lymphocytes. Clinical trials have shown that high-dose IL-2 therapy can induce durable remissions in patients with metastatic melanoma and renal cell carcinoma. However, its use is limited by severe toxicity and adverse effects [55,56]. To mitigate these challenges, researchers have developed modified cytokines and combination therapies that enhance efficacy while reducing toxicity. Pegylated forms of IFN-α, for instance, have been shown to prolong drug activity and improve patient tolerability. Additionally, combining cytokine therapy with immune checkpoint inhibitors has demonstrated synergistic effects, improving overall response rates

and survival outcomes in various cancers. Studies have also focused on the use of other cytokines like interleukin-15 (IL-15) and interleukin-21 (IL-21), which exhibit potent anti-tumor properties with potentially lower toxicity profiles. These advancements in cytokine therapy are expanding the arsenal of cancer immunotherapeutics, providing new hope for effective and safer treatment options for patients [57].

3.4. Synergistic Strategies in Oncolytic Immunotherapy

Oncolytic immunotherapy, which employs genetically modified viruses to selectively infect and destroy cancer cells, has made significant strides in recent years. Oncolytic viruses not only prompt direct oncolysis but additionally stimulate systemic anti-tumor immune responses by releasing tumor-associated antigens and creating an inflammatory tumor microenvironment. Recent advancements have led to the development and approval of several oncolytic viruses for clinical use, including talimogene laherparepvec (T-VEC), a modified herpes simplex virus type 1, which has shown efficacy in treating advanced melanoma [58]. Research has focused on enhancing the therapeutic efficacy of oncolytic viruses through genetic modifications that improve their selectivity, replication, and immunogenicity. The genetically modified oncolytic adenovirus LOAd703 contains immune-stimulatory transgenes CD40L and 4-1BBL to enhance antigen presentation and T-cell co-stimulation in tumor environments. The early-phase clinical trial NCT04123470 shows promising results for pancreatic cancer treatment through localized tumor destruction and strong tumor-specific immune response activation, which leads to increased cytotoxic T lymphocyte infiltration and elevated pro-inflammatory cytokine levels. The Phase I/II studies indicate that combining LOAd703 with standard chemotherapy or immune checkpoint inhibitors produces potential synergistic effects [59]. For instance, viruses can be engineered to express cytokines such as GM-CSF, which further boost the immune response against tumors. Combination therapies that pair oncolytic viruses with other immunotherapies, such as checkpoint inhibitors, are also being explored to overcome resistance and improve treatment outcomes. Clinical trials have demonstrated that these combination approaches can lead to improved survival rates and more robust anti-tumor responses, highlighting the potential of oncolytic immunotherapy as an influential tool to fight against the deadly cancer [60,61].

3.5. Harnessing Exosomes for Targeted Immune Modulation

Exosome-based immunotherapy represents a promising frontier in cancer treatment, leveraging the natural properties of exosomes—small extracellular vesicles—to modulate immune responses and deliver therapeutic molecules. Exosomes derived from tumor cells and immune cells exhibit unique composition profiles that can directly influence anticancer immunity. These vesicles can carry proteins, nucleic acids, and lipids, allowing them to transfer functional molecules between cells and modulate the immune system's response to cancer [62]. Recent research has highlighted the potential of exosomes as both therapeutic agents and delivery vehicles in cancer immunotherapy. For instance, exosomes can be engineered to carry specific antigens or immune-modulating molecules, enhancing their ability to stimulate an anti-tumor immune response. The exoSTING trial (NCT04592484) assesses exosome-delivered STING agonists in solid tumors and shows early-phase efficacy in enhancing dendritic cell priming [63]. Clinical applications of exosome-based therapies are being explored, with some studies demonstrating their ability to improve the efficacy and reduce the toxicity of conventional cancer treatments. Despite these promising advances, issues such as the standardization of isolation of exosomes and characterization techniques, as well as large-scale manufacturing, must be resolved before exosome-based treatments may become generally accessible in healthcare settings [64].

4. Clinical Applications and Challenges of Immunotherapy

4.1. Clinical Successes

Immunotherapy has heralded a paradigm shift in cancer treatment, demonstrating significant successes across various malignancies. Key among these are checkpoint inhibitors, which have transformed the approach of solid tumor therapy. Clinical trials underscore their efficacy in enhancing overall survival and disease control rates, particularly in advanced melanoma and lung cancer patients [3,4]. By blocking immune checkpoints like CTLA-4 and PD-1, these therapies allow the body's immune system to focus and destroy cancer cells effectively. Integration of checkpoint inhibitors into standard treatment protocols has led to prolonged remissions and improved quality of

life [2]. Another groundbreaking advancement is CAR T-cell therapy, which is notably effective in hematological malignancies. Studies showcase its transformative impact, achieving unprecedented responses in patients with refractory B-cell lymphomas and acute leukemias. By genetically modifying patients' T-cells to recognize and attack cancer cells bearing specific antigens, CAR T-cell therapies have achieved durable remissions and even potential cures. Such successes highlight the personalized and precise nature of immunotherapy in treating otherwise resistant cancers [65].

4.2. Challenges

Despite its remarkable achievements, immunotherapy faces formidable challenges that limit its widespread applicability and efficacy. One critical issue is the emergence of resistance mechanisms, discussed in detail [66]. Tumors can adapt to evade immune detection or suppress immune responses over time, necessitating innovative strategies to overcome resistance and sustain treatment efficacy. From mild skin rashes to severe autoimmune responses impacting many organ systems, immune-related adverse events (irAEs) often pose major therapeutic problems. Balancing therapeutic benefits with potential toxicities remains a crucial consideration in clinical practice. Furthermore, the high cost of immunotherapy and accessibility barriers present significant hurdles. The complex logistics and substantial financial burden associated with therapies like CAR T-cell treatments limit their availability, especially in resource-limited settings. Addressing these disparities requires collaborative efforts among healthcare providers, policymakers, and pharmaceutical companies to ensure equitable access and affordability of these life-saving treatments.

4.3. Future Directions

Looking forward, ongoing research endeavors aim to address current challenges and expand the therapeutic potential of immunotherapy. Advances in biomarker discovery offer promise in identifying predictive markers of treatment response, enabling more precise patient selection and personalized therapy approaches [67]. Combination therapies that synergize different immunotherapeutic modalities or integrate immunotherapy with standard therapeutic approaches, such as radiotherapy or chemotherapy, aim to enhance efficacy and overcome resistance mechanisms. Exploration of novel targets and immune pathways, as discussed in, presents opportunities to broaden the scope of immunotherapy beyond current indications. Innovations such as exosome-based therapies and engineered immune cells hold potential to refine treatment strategies further, improve outcomes, and minimize adverse effects. Progress in these areas hinges on sustained investment in basic and translational research, rigorous clinical trials, and collaborative efforts across disciplines. In conclusion, while immunotherapy has achieved remarkable clinical successes, navigating its challenges and exploring new frontiers are imperative for maximizing its impact in cancer care. By advancing personalized medicine, refining treatment protocols, and fostering interdisciplinary collaborations, the field of immunotherapy stands poised to redefine oncology practices, providing optimism for improved results and quality of life for cancer patients globally.

5. Technological Advances and Innovations

5.1. Drug Delivery Systems in Immunotherapy

Advancements in drug delivery techniques have significantly bolstered the efficacy of immunotherapy by enhancing the precision and efficiency of therapeutic agent delivery to tumor sites. These technologies are designed to optimize the bioavailability of immunotherapeutic drugs while minimizing systemic toxicity, thus enhancing their overall therapeutic potential. One of the most promising approaches involves nanotechnology-based delivery systems, such as liposomes, nanoparticles, and micelles. These nanoscale carriers can encapsulate immunotherapeutic drugs, protecting them from degradation in the bloodstream and ensuring their stable and controlled release at the tumor site. The ability to functionalize the surface of these nanocarriers with targeting ligands allows for the specific targeting of tumor cells, thereby enhancing the precision of immunotherapy and reducing off-target effects. For instance, studies have demonstrated the successful use of nanoparticles in delivering checkpoint inhibitors and cytokines directly to tumor cells, resulting in improved anti-tumor responses and reduced systemic side effects [68]. In addition to nanoparticles, biomaterial-based scaffolds, and injectable hydrogels have emerged as innovative delivery systems for immunotherapy. These platforms can deliver immunotherapeutic agents directly to the tumor

microenvironment, providing a sustained release of therapeutic molecules such as cytokines, antibodies, or cellular therapies. This localized delivery approach helps maintain a therapeutic concentration of the agents at the tumor site for extended periods, enhancing their efficacy. Hydrogels may be designed to release immune-stimulating cytokines in a regulated manner, enhancing the localized immune response against the tumor. Furthermore, advances in microfluidic technologies have led to the development of sophisticated delivery devices that can administer multiple immunotherapeutic agents in a precise and controlled manner, enabling synergistic treatment strategies. Such devices can be programmed to release different drugs at specific intervals, optimizing the timing and combination of therapies to maximize their anti-tumor effects [69].

Recent research has also focused on integrating these advanced delivery systems with novel therapeutic modalities such as oncolytic viruses and exosome-based therapies. Oncolytic viruses, engineered to selectively infect and lyse cancer cells, can be combined with nanoparticle carriers to enhance their delivery and efficacy. Similarly, exosome-based therapies, which utilize naturally occurring vesicles for intercellular communication, can benefit from targeted delivery systems to improve their distribution and therapeutic impact. The combination of these innovative delivery technologies with cutting-edge immunotherapeutic agents holds great promise for the future of cancer treatment, offering the potential for more effective and less toxic therapeutic options for patients. Overall, these advancements in drug delivery systems are poised to transform the field of oncology immunotherapy by refining the precision, efficacy, and safety of therapeutic interventions [68,70].

Table 3, summarizing nanotechnology-based delivery systems in immunotherapy, highlights several key points crucial to understanding their impact and applications. Liposomes, nanoparticles, and micelles serve as versatile carriers for delivering checkpoint inhibitors, cytokines, and small-molecule drugs, respectively, to targeted tumor sites. Their ability to encapsulate therapeutic agents ensures precise delivery, reducing off-target effects and enhancing bioavailability. Liposomes excel in delivering large molecules like checkpoint inhibitors and cytokines, offering targeted therapy that minimizes systemic toxicity. Nanoparticles, on the other hand, provide sustained release mechanisms, prolonging drug circulation and improving treatment efficacy. Micelles enhance the solubility and circulation time of small-molecule drugs, optimizing their therapeutic potential. Overall, these nanocarriers represent pivotal advancements in immunotherapy, facilitating tailored treatment strategies that maximize therapeutic benefits while minimizing adverse effects, thereby exemplifying the convergence of nanotechnology and oncological innovation in modern medicine.

Table 3. Nanotechnology-based delivery systems.

Nanocarrier [Reference]	Applications	Benefits
Liposomes [71]	Delivery of checkpoint inhibitors, cytokines	Targeted delivery to tumor cells, enhanced bioavailability
Nanoparticles [72]	Encapsulation of therapeutic agents	Precise delivery, sustained release, reduced off-target effects
Micelles [73]	Delivery of small-molecule drugs	Improved solubility, prolonged circulation time

5.2. Biotechnological Innovations in Immunotherapy

Recent biotechnological innovations are at the forefront of shaping the future of immunotherapy, offering new avenues for enhancing the efficacy and precision of cancer treatment. These advancements include the development of more sophisticated diagnostic tools, novel therapeutic agents, and cutting-edge delivery systems, all of which contribute to the refinement of immunotherapy strategies. One of the key areas of innovation is the use of next-generation sequencing (NGS) technologies, which have significantly advanced our understanding of the genetic and molecular landscape of tumors. By providing detailed insights into the mutational profiles of individual cancers, NGS enables the identification of novel targets for immunotherapy and facilitates the development of personalized treatment plans. This precision medicine strategy guarantees that patients have the most suitable and efficacious treatments tailored to the distinct attributes of their cancer [2]. In addition to genomic innovations, the use of exosome-based therapies represents a promising biotechnological advancement in immunotherapy. Exosomes, which are small extracellular vesicles involved in intercellular communication, can be engineered

to deliver therapeutic molecules directly to tumor cells. These vesicles may transport many contents, including nucleic acids, proteins, and tiny compounds, making them excellent tools for personalized therapy. Research has shown that exosomes derived from immune cells can enhance anti-tumor immune responses by delivering immune-stimulating molecules to the tumor microenvironment. Furthermore, exosome-based therapies offer a high degree of biocompatibility and low toxicity, making them attractive candidates for clinical application.

Table 4 summarizes biomaterial-based delivery systems utilized in immunotherapy, highlighting their characteristics, applications, and benefits in enhancing treatment efficacy. Biomaterial-based scaffolds are noted for their structural support, biocompatibility, and ability to deliver a variety of therapeutic agents such as cytokines, antibodies, and CAR T-cells. These scaffolds enable localized delivery and sustained release of drugs, facilitating immune activation within the tumor microenvironment. Injectable hydrogels, on the other hand, are viscoelastic materials capable of gelating in situ after injection. They offer advantages such as prolonged drug release, spatial control over drug distribution, and the ability to minimize systemic toxicity by targeting therapeutic agents directly to the tumor site. Together, these biomaterial-based delivery systems represent innovative approaches in immunotherapy, aiming to improve treatment outcomes through enhanced precision and efficacy. Another significant biotechnological innovation is the integration of advanced bioinformatics and artificial intelligence (AI) in immunotherapy research and development. AI-driven algorithms can analyze vast amounts of data from clinical trials, genomic studies, and patient records to identify patterns and predict responses to immunotherapy. This data-centric methodology may expedite the identification of novel biomarkers for treatment response and resistance, facilitating the development of more efficacious and individualized immunotherapeutic techniques. Additionally, AI can optimize the design and conduct of clinical trials by identifying the most promising therapeutic combinations and patient populations, thereby improving the efficiency and success rates of these studies [74].

Table 4. Biomaterial-based scaffolds versus injectable hydrogels delivery systems.

Delivery System [Reference]	Characteristics	Applications	Enhanced Efficacy
Biomaterial-based scaffolds [75]	Provide structural support; biocompatible; tunable degradation rates	Deliver cytokines, antibodies, CAR T-cells	Localized delivery; sustained release; immune activation in tumor microenvironment
Injectable hydrogels [76]	Viscoelastic; injectable; gelation in situ; biodegradable	Release cytokines, antibodies, small molecules	Prolonged drug release; spatial control; minimize systemic toxicity

Table 5 illustrates how advanced delivery systems, specifically oncolytic viruses and exosome-based therapies, can benefit from integration with advanced delivery technologies in immunotherapy. Oncolytic viruses, designed to selectively infect and destroy cancer cells, can be combined with nanoparticle carriers to enhance their delivery to tumor cells while stimulating immune responses against cancer. This integration improves tumor targeting, boosts immune activation, and reduces systemic toxicity, thereby enhancing therapeutic outcomes. Similarly, exosome-based therapies utilize naturally occurring vesicles to deliver therapeutic molecules directly to tumors. When integrated with biomaterial-based scaffolds, exosome delivery can be further optimized for localized drug release, prolonging therapeutic effects and minimizing off-target effects. These examples highlight the potential of combining advanced delivery systems with immunotherapies to improve treatment efficacy and patient outcomes in both preclinical and clinical settings.

Table 5. Integration of advanced delivery systems with immunotherapies.

Delivery System [Reference]	Integration Benefits	Examples	Therapeutic Outcomes
Oncolytic viruses [77]	Enhanced delivery to tumor cells; stimulation of immune response	Combination with nanoparticle carriers	Improved tumor targeting; enhanced immune activation; reduced toxicity
Exosome-based therapies [78]	Precise delivery of therapeutic payloads; modulation of tumor microenvironment	Integration with biomaterial-based scaffolds	Localized drug release; prolonged therapeutic effect; minimized off-target effects

Moreover, advances in biotechnology have led to the creation of novel immune-modulating agents, such as bispecific antibodies and engineered cytokines, which can enhance the specificity and potency of immune responses against cancer. Bispecific antibodies are designed to bind to two different antigens simultaneously, bringing immune cells into proximity with tumor cells and facilitating their destruction. Engineered cytokines, on the other hand, are modified to improve their stability and reduce toxicity, allowing for more effective stimulation of the immune system. These innovations, combined with improved delivery technologies, are poised to transform the landscape of cancer immunotherapy, offering new hope for patients with refractory or advanced cancers. As biotechnological advancements continue to evolve, they will undoubtedly play a critical role in the ongoing effort to harness the full potential of the immune system in the fight against cancer [2].

5.3. Integrating AI: From Neoantigen Discovery to Clinical Application

The immunotherapy pipeline benefits from artificial intelligence (AI), which plays an essential role in both neoantigen discovery and mRNA vaccine formulation. Machine learning algorithms speed up the process of identifying tumor-specific neoantigens through genomic and transcriptomic data analysis, which results in more accurate targeting for personalized cancer vaccines. The tool NeoaPred uses deep learning to predict immunogenic neoepitopes with high accuracy, and Tumor AgDB 1.0 functions as a database that collects tumor-associated antigens from different cancer types to help develop vaccines and choose antigens [79]. AI systems help detect biomarkers through the analysis of multi-omics and imaging data to identify patients who would benefit from immune checkpoint inhibitors or CAR T-cell therapies [80]. AI models with advanced capabilities optimize mRNA vaccine delivery vectors and codon usage to improve both translational efficiency and immunogenicity. AI continues to expand its function in developing next-generation cancer immunotherapies through design prediction and refinement processes [81].

6. Discussion

Using the body's immune system to fight malignancies aggressively, immunotherapy has become a transforming method of cancer treatment. This review has highlighted significant advancements and challenges across several key modalities within immunotherapy, including CAR T-cell therapy, checkpoint inhibitors, oncolytic immunotherapy, cytokine therapy, and exosome-based immunotherapy. Each modality offers distinct mechanisms to enhance anti-tumor immune responses, yet they also present unique challenges that must be addressed to maximize their clinical impact. CAR T-cell therapies show outstanding results in hematologic malignancies, achieving remission rates above 80% in ALL, but their effectiveness against solid tumors is restricted. The main reason for this difference lies in the complex, hostile tumor microenvironment (TME) of solid cancers, which contains immunosuppressive factors, including regulatory T cells and myeloid-derived suppressor cells, and inhibitory cytokines such as TGF-β [82]. The antigen heterogeneity within solid tumors creates a challenge for consistent targeting because tumor cells can reduce or eliminate the expression of the selected CAR antigen, thus enabling immune evasion. Researchers have developed innovative approaches to tackle these challenges by creating armored CAR T-cells, which receive genetic modifications to produce pro-inflammatory cytokines, including interleukin-12 (IL-12). The modified cells can transform the TME structure, which enhances T-cell function and cytotoxic activity. Researchers are developing three main approaches to enhance CAR T-cell therapy in solid tumors: dual-targeting CARs and checkpoint-resistant CAR designs, and TME-modulating agents for improved cell infiltration and persistence [83].

CAR T-cell therapies achieve clinical success, yet their high production costs and limited accessibility prevent their widespread use. The current autologous CAR T-cell manufacturing process requires complex procedures that take time and cost between $475,000 and more than $500,000 per treatment before adding hospitalization and supportive care expenses. The combination of high production expenses, specialized treatment requirements, and individual cell processing methods makes these therapies inaccessible to patients who lack access to major academic hospitals or low-resource settings [84]. Researchers, together with biotech companies, work on developing allogeneic CAR T-cell therapies, which use healthy donor cells to produce bulk quantities. The new therapies work to decrease production duration and create standardized dosing protocols while making their manufacturing more cost-effective through large-scale production methods. The initial clinical trials of allogeneic CAR T-cells (e.g., ALLO-501, UCART19) have shown promising results regarding both safety and efficacy. The implementation

of centralized cell processing hubs together with payer-based reimbursement models and public-private partnerships represents current efforts to enhance affordability and equitable access. The life-extending benefits of CAR T-cell therapy need to overcome existing barriers to ensure wider availability among diverse patient groups [85].

7. Comparison of Findings

The great importance of checkpoint inhibitors, including nivolumab and pembrolizumab, in treating different tumors emphasizes their efficiency in contemporary oncology [8,9]. Clinical outcomes, as summarized in **Table 2**, reveal notable response rates in non-small cell lung cancer, advanced melanoma, and renal cell carcinoma, although responses vary across different malignancies [8]. These agents have significantly improved overall survival and quality of life for many patients by unleashing immune responses against cancer cells [2]. In contrast, CAR T-cell therapy has shown remarkable success primarily in hematological malignancies like acute lymphoblastic leukemia and diffuse large B-cell lymphoma [11, 48]. The high remission rates and potential for durable responses with therapies like Kymriah and Yescarta demonstrate the precision and potency of genetically engineered T-cells in targeting specific cancer antigens [86].

Cytokine therapy, particularly interleukin-2 and interferon-alpha, has demonstrated significant anti-tumor activity but is limited by severe toxicity profiles [87, 88]. Strategies to enhance their efficacy while minimizing adverse effects are critical for broader clinical application. Oncolytic immunotherapy, utilizing modified viruses to selectively infect and target cancer cells, has shown promising results in treating advanced melanoma and is being explored in combination with other immunotherapies to overcome resistance mechanisms [89]. Exosome-based immunotherapy represents a nascent field with potential applications in modulating immune responses and delivering therapeutic payloads. Despite promising results in preclinical studies, challenges such as standardization of production methods and large-scale clinical validation remain significant barriers to clinical translation [90].

8. Strengths and Limitations

Each immunotherapy modality offers unique strengths and limitations that influence its clinical applicability. Checkpoint inhibitors excel in treating a wide range of solid tumors but may be less effective in tumors lacking sufficient immune cell infiltration or displaying resistance mechanisms [9]. CAR T-cell therapy achieves remarkable responses in hematological cancers but faces challenges in treating solid tumors due to antigen heterogeneity and hostile tumor microenvironments. Cytokine therapy's robust anti-tumor effects are tempered by severe toxicity, necessitating precise dosing and combination strategies to maximize therapeutic benefits while minimizing adverse events. Oncolytic viruses show promise in inducing direct tumor cell lysis and enhancing immune responses, but require optimization in delivery and combination therapies to achieve consistent clinical outcomes. Exosome-based therapies offer the potential for targeted delivery of therapeutic agents and modulation of immune responses, but require further research to address technical and regulatory challenges before widespread clinical adoption.

9. Recommendations and Future Directions

To advance immunotherapy and maximize its clinical impact, several key strategies should be pursued:

1. **Enhanced Biomarker Discovery:** Continued research into predictive biomarkers, like mutational burden and PD-L1 expression, will facilitate more precise patient selection and personalized treatment strategies.
2. **Combination Therapies:** Synergistic combinations of immunotherapies with conventional treatments, targeted therapies, and other immunomodulatory hold promise for overcoming resistance mechanisms and improving treatment outcomes.
3. **Advanced Delivery Systems:** Further development of nanotechnology-based delivery systems and biomaterial scaffolds can optimize the delivery of immunotherapeutic agents, enhancing their efficacy and reducing systemic toxicity.
4. **Regulatory Innovation:** Streamlined regulatory pathways and standardized manufacturing processes for novel immunotherapies, including exosome-based therapies and oncolytic viruses, are essential to accelerate clinical translation and ensure patient access.
5. **Integration of AI and Bioinformatics:** Utilization of AI-driven algorithms and genomic analyses will aid in labelling novel therapeutic targets, optimizing clinical trial design, and predicting treatment responses, thereby

accelerating the development of next-generation immunotherapies.

10. Conclusion

In conclusion, immunotherapy has revolutionized cancer treatment by harnessing the immune system's potent capabilities to combat tumors effectively. Though with different strengths and constraints, important modalities include checkpoint inhibitors, CAR T-cell treatment, cytokine therapy, oncolytic immunotherapy, and exosome-based methods, which have shown notable clinical breakthroughs. Checkpoint inhibitors have shown significant efficacy in several solid tumors, but CAR T-cell therapy has attained unparalleled results in hematological cancers. Despite challenges such as resistance mechanisms, immune-related adverse events, and high treatment costs, ongoing advancements in biomarker discovery, combination therapies, and advanced delivery systems hold promise for enhancing treatment outcomes and expanding the scope of immunotherapy. Future research should focus on optimizing therapeutic strategies, integrating AI-driven approaches for personalized medicine, and addressing regulatory and logistical barriers to ensure equitable access to these transformative therapies. By continuing to innovate and collaborate across disciplines, immunotherapy stands poised to redefine cancer care, giving patients across new optimism for better survival and quality of life.

Author Contributions

Conceptualization, A.Z.A., M.F.S., A.A.S., M.E.K., S.S.A.-M. and J.M.B.; validation, A.A.S. and M.E.K.; formal analysis, A.Z.A. and M.F.S.; data curation, A.Z.A. and M.F.S.; writing—original draft preparation, A.Z.A. and M.F.S.; writing—review and editing, A.A.S. and M.E.K. All authors have read and agreed to the published version of the manuscript.

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The article is comprehensive in its consideration of ethical concepts. The research's goals and methodology were explained to the participants. Participants were also told that their information would be kept private, that they would be allowed to withdraw from the study at any time, and that they would be given access to the study's findings if they so choose. The ethics committee gave the study the all-clear with reference number: OSHSU2125-1765-1801.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data presented in the manuscript.

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Conflicts of Interest

The authors declared no conflict of interest.

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