Review

Discovery Medicine 2025; 37(194): 411–432
https://doi.org/10.24976/Discov.Med.202537194.35

Unlocking the Potential of Immunomodulators as Synergistic Immune-Based Therapies in Cancer

Shivani Tomar[1,†], Saleha Siddiqui[2,†], Rajiv Pathak[3], Vivek Srivastava[1,*]

[1]Department of Chemistry & Biochemistry, Sharda School of Engineering & Science, Sharda University, Greater Noida, UP 201310, India
[2]Department of Pediatric Surgery, All India Institute of Medical Sciences, 110029 New Delhi, India
[3]Department of Genetics, Albert Einstein College of Medicine, Bronx, New York, NY 10461, USA
*Correspondence: vivek.srivastava1@sharda.ac.in (Vivek Srivastava)
[†]These authors contributed equally.
Published: 20 March 2025

Over the recent years, immunomodulators have opened a new avenue in cancer treatment by virtue of their ability to boost the immune system for neoplastic cell elimination. Improving treatment outcomes by leveraging the interaction of these agents with traditional cancer treatments is the main emphasis of this review. Checkpoint inhibitors, chemokine receptors, and pattern recognition receptors are the immunological targets of their interactive mechanisms. Immunomodulators are generally categorized as inhibitors of checkpoint, cytokines, agonists, or adjuvants. Despite their high efficacy and specificity, modern-day antibody-based therapies face several key limitations such as immunogenicity, insufficient tissue penetration, and restricted oral bioavailability. To address these shortcomings, researchers are crafting small molecules with the potential for oral administration and improved pharmacokinetic properties. These agents can augment antibody therapies for synergistic effects to enhance therapeutic efficacy for different types of cancers. This review explores the synergy between immunomodulators and traditional cancer treatments (chemotherapy, radiation, and targeted therapies) as well as newer strategies like adoptive cell therapies (chimeric antigen receptor therapies such as chimeric antigen receptor-T (CAR-T) cell therapy and chimeric antigen receptor-natural killer (CAR-NK)). These combinations improve treatment effectiveness in a number of ways: radiotherapy increases tumor antigen presentation and T-cell infiltration, chemotherapy-induced immunogenic cell death boosts immune responses and targeted therapies lessen immunosuppression in the tumor microenvironment. Despite the potential appeal as adjuvants, immunomodulators also pose challenges in maximizing their efficacy and minimizing adverse effects. In this paper, clinical trials proving the effectiveness of these combined techniques are reviewed, and innovative approaches including next-generation checkpoint inhibitors and delivery systems based on nanoparticles are also highlighted. Overall, this review evaluates the existing impact of immunomodulatory adjuvants and their prospective trends in cancer care. Further development of immunomodulators will pave the way for more accessible and effective therapies, marking a significant step towards personalized oncological interventions.

Keywords: immunomodulators; cancer; therapeutics; drugs; inhibitors; cytokines

Introduction

Cancer therapies have evolved tremendously over the past few decades, shifting from traditional approaches like radiation and chemotherapy to more targeted and precise alternatives. Historically, cancer treatment primarily relied on surgery, chemotherapy, and radiation therapy, which aimed to physically destroy cancerous cells [1]. These approaches often lack specificity, which causes extensive harm to healthy cells and serious adverse effects. The primary mode of medication often involves surgical procedures for solid tumors, focusing on the removal of cancerous growths, especially polyps and adenomas during the initial stages.

Chemotherapy employs various drugs that inhibit cancer cell growth and replication, such as alkylating agents like cyclophosphamide creates covalent bonds with DNA, while methotrexate mimics folic acid to disrupt metabolic pathways [2]. Paclitaxel, also known as Taxol, is a crucial cancer treatment that targets microtubules, preventing cell proliferation and apoptosis by binding to β-tubulin subunits [3]. Upon the induction of radiation therapy, the release of neoantigens and the enhanced expression of antigen presentation molecules on neoplastic cells are two distinctive signs of tumor cell death, a biological process that aids in enhancing cancer immune response [4–6]. Particle beam therapy is an advanced radiation treatment that uses charge particles to target the tumor with precision, capable of minimizing radiation exposure to nearby healthy tissues [7–9]. Immunotherapy surpasses traditional approaches, offering a precise and sustained anticancer response. Immunomodulation is a broad category of oncology therapy that uses a host defense mechanism to counter tumor growth. Cancer immunotherapy encompasses various strategies, includ-

ing tumor vaccines (i.e., immunization against known tumor antigens), monoclonal antibodies, oncolytic virus therapy, cytokine-based therapies, T-cell transfer therapies, and pathogen recognition receptor agonists, which are being actively explored in combination immunotherapy contexts [10]. A recent review by Mitra *et al.* [11] has highlighted advancements in cancer immune evasion mechanisms and evaluated immunotherapeutic approaches such as cancer vaccines, adoptive cell therapy, and antibody-based treatments, providing a comprehensive overview of established and emerging strategies, which is particularly insightful to the development of effective anticancer immunotherapies. One innovative approach involves the use of immune checkpoint inhibitors, such as blockers of the programmed cell death protein 1 (PD-1) pathway. Such agents function by reactivating exhausted T cells, thereby enhancing the immune system's ability to target and destroy tumor cells. Additionally, oncogenic vaccine therapies are engineered to activate the host defense system to attack cancer by presenting neoplastic epitopes [1,10]. With the emergence of cutting-edge molecular biology approaches, targeted therapies have appeared as a fundamental aspect of modern oncology. These therapies are designed to specifically target the molecular alterations that are unique to cancer cells. For example, small-molecule inhibitors and monoclonal antibodies are engineered to bind to oncogenic proteins that support tumor growth, allowing for a more focused treatment approach [1].

Proteolysis-targeting chimeras (PROTACs) are the molecules that harness the cell ubiquitin-proteasome system to selectively tag target protein (e.g., androgen receptor) for degradation by recruiting E3 ubiquitin ligase [12]. Bavedegalutamide Androgen Receptor Variant-110 (ARV-110) targets steroid hormone receptors in prostate carcinoma and ARV-471 targets estrogen receptors in breast cancer [13,14]. Monoclonal antibody comprises five distinct immunoglobulin subclasses, namely Immunoglobulin M (IgM), Immunoglobulin D (IgD), Immunoglobulin G (IgG), Immunoglobulin A (IgA), and Immunoglobulin E (IgE). Among these, IgG1 (pro-inflammatory) and IgG4 (anti-inflammatory) subtypes are commonly used in the production of targeted antibodies due to their long half-life and strong binding affinity [1]. New therapies incorporate toxins or radiolabeled compounds like iodine-131 or yttrium-90 into the monoclonal antibodies [15]. These isotope markers can form cytotoxic compounds and enable targeted chemotherapy, significantly improving their efficacy in cancer treatment.

Laser-induced thermal therapy and photosensitized therapies aligned with nano-engineered medicine in cancer therapy [1,16]. Nanoparticles absorb near-infrared light and generate free radicals to kill malignant cells. Nanoparticles can be specifically designed to trigger apoptosis, or programmed cell death, by delivering tumor suppressor drugs or genes directly to cancer cells. For example, nano-conjugates with targeting moieties are found on the malignant cells, thereby activating the cascade pathway [17]. Similarly, nanoparticles can be engineered to induce cytochrome c efflux within the cells that activate the intrinsic mitochondrial pathway and lead to apoptosis. This tailored therapeutic approach enhances the effectiveness of cancer therapies by ensuring that the pro-apoptotic signals are delivered precisely where they are needed [18]. This review bridges the knowledge gap by examining the intricate relationship between immunomodulators and conventional therapies, highlighting the molecular mechanisms underlying adoptive cell therapies, checkpoint inhibition, Toll-like receptor (TLR) agonism, and cytokine-driven immune activation.

Through a systematic evaluation of recent studies, we highlight and provide insights supporting the synergistic potential of immunomodulators with conventional therapies and other emerging agents including bispecific antibodies and nanoparticle-based delivery systems. Our analysis draws upon pivotal clinical studies to highlight the optimal combination regimes. Conclusively, we discuss the evolving landscape of immunomodulatory therapies including existing challenges like toxicity and immune-related adverse effects. We also explore the future directions for enhancing their efficacy through innovative trial designs and precision oncology.

Immune System's Role in Cancer Progression and Therapy

The body's defense mechanism uses a range of mechanisms to fight against cancer cells. Normal cells express a higher density of histocompatibility antigens that enable the host defense to recognize them as "self" cells. In contrast, cancer cells display downregulation of human leukocyte antigen (HLA) molecules, which makes them more recognizable to T lymphocytes. However, stress signals such as major histocompatibility complex class I chain-related A/B (MICA/B), expressed on tumor cells, bind to natural killer group 2D (NKG2D) receptors on natural killer (NK) cells, triggering their activation [19]. CD16 receptors on NK cells bind to IgG antibodies, which recognize tumor-associated antigens and trigger antibody-dependent cellular cytotoxicity (ADCC), to destroy tumor cells. Dendritic cells help in processing and presenting antigens to cytotoxic T cells via HLA class 2. CD8+ T lymphocytes are directly involved in targeting tumor cells through perforin-mediated membrane pore formation and granzyme-induced cell death, and CD4+ helper cells enhance these responses by supporting the activation of cytotoxic T cells, as shown in Fig. 1 (Ref. [20–23]). In addition to this, lipid asymmetry on the cell membrane serves as another important mechanism for the host defense system to detect cancerous cells. Abnormalities in lipid distribution would be interpreted by immune cells that a cell is potentially malignant, further aiding in the identification and eradication of foreign cells [24].

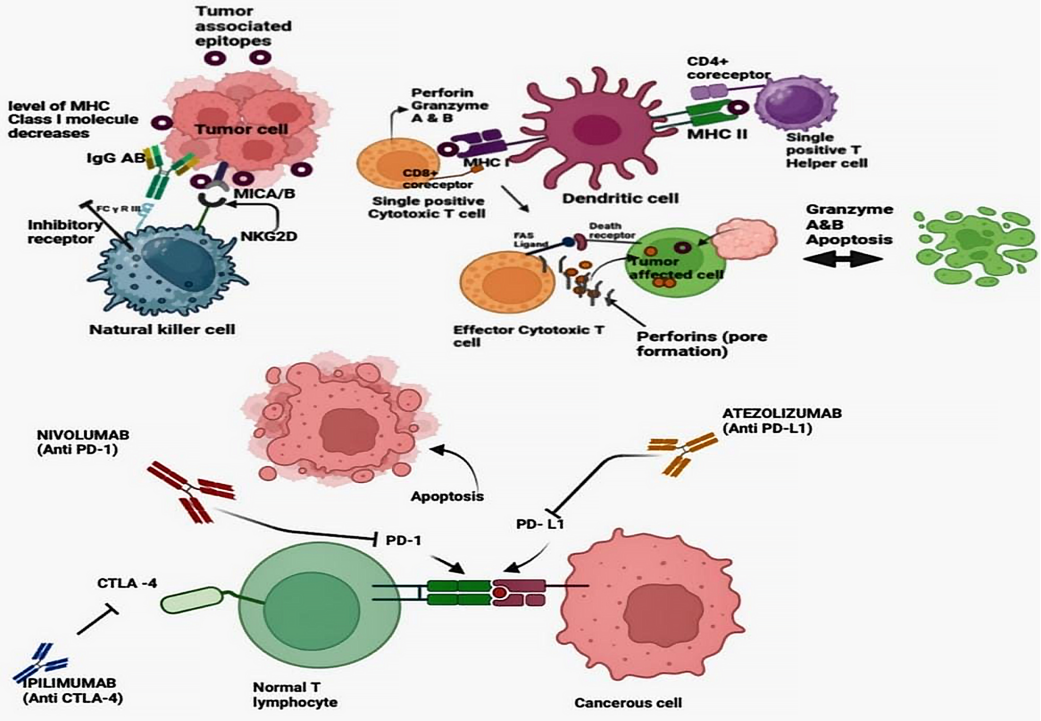

Fig. 1. The interactions between the immune system and tumor cells, and the roles of various immune cells and checkpoint inhibitors in targeting cancer. Tumor cells express tumor-associated epitopes and reduced levels of major histocompatibility complex (MHC) class 1 molecule. This reduced expression makes it vulnerable to natural killer (NK) cells. Dendritic cells process and present tumor epitopes via MHC class I and MHC class II to cytotoxic T lymphocytes and helper T cells. Immunotherapy drugs or checkpoint inhibitors block checkpoint molecules present on effector T cells and on tumor cells. MICA/B, major histocompatibility complex class I chain-related A/B; IgG, Immunoglobulin G; NKG2D, natural killer group 2D; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; CTLA-4, Cytotoxic T lymphocyte-associated protein 4. This image is created using Biorender (https://biorender.com/) [20–23].

Immunotherapy can also be classified on the basis of the type of immunological reaction. TLRs are a group of peptides that play an essential role in the first line of defense system, particularly in reaction to infections. They trigger the release of cytokines that promote inflammation and help to stimulate the acquired immune response in CD4+ or CD8+ cells [20,25]. Polyinosinic-polycytidylic acid with Poly-L-Lysine and Carboxymethylcellulose (Poly-ICLC) and lipopolysaccharide (LPS) are TLR3 activators used in vaccine-based therapies and tumor prophylaxis, respectively, and are safe and effective in interacting with TLR4 and LPS [26–28]. Peptide vaccines, which can be either therapeutic or preventive, are developed to stimulate or revive anti-tumor immunity. Therapeutic vaccines focus on training the host defense system to bind and neutralize targeted foreign antigens, thereby activating T cells that target cancer cells. On the other hand, cancer vaccines directly prompt the immune system to attack cancer cells. To boost the therapeutic response of these vaccines, they are frequently coupled with adjuvants, including dendritic cells, which are considered a natural type of adjuvant [21,29,30].

Cellular therapy in cancer treatment harnesses living cells to help fight cancer. This strategy aims to precisely target and eradicate cancer cells by altering or leveraging the recipient's own effector cells or other cell types. Chimeric antigen receptor-T (CAR-T) cell therapy is among the leading forms of cellular therapy where T lymphocytes are genetically recombinant to express a receptor that specifically targets oncolytic cells [31]. When these cells bind to their target, they become activated and release cytotoxic molecules like perforin and granzyme B, inducing apoptosis in the tumor cells. Additionally, these cells can attract macrophages to the tumor region by secreting cytokines. This concerted collaboration among the immune cells enhances the attack on tumor cells, thereby causing their elimination [32]. A notable aspect of CAR-T cell therapy is its ability to formulate long-lived T cells, which can provide long-term immunity against cancer. In passive immunotherapy, cytotoxic T cells or NK cells are isolated from the recipient and then cultivated *in vitro* where they are multiplied and programmed to discriminate between one's own cells and foreign cells [33]. In the predominant form of this therapy, killer T cells are treated with cytokines to enhance their ability to destroy tumor cells, while other

therapy variants entail the collection of T cells that have already invaded the tumor, expansion of their population, and re-administration to the recipient [34]. By leveraging the body's natural defenses, this approach enhances the immune system's reaction to cancer.

Immunomodulators

Immunomodulators, including immunostimulants, immunosuppressants, and immunoadjuvants, are therapeutic medications intended to modify and enhance immune function. These immunomodulators have two modes of action: non-specific and specific [35]. The specific ones only work in the presence of a particular foreign antigen, triggering an immune response to the foreign antigen, which is similar to that induced by a therapeutic vaccine or adjuvant [36]. On the other hand, non-specific immunomodulators can either boost or suppress the immune response; instead of targeting a specific antigen, they exert a more general effect on the immune system. Immunomodulators are categorized into three main classes: type I immunomodulators, which are applied in individuals with a healthy immune system to ensure proper function; type II immunomodulators, which are designed for individuals with impaired immune function such as those with immunodeficiency diseases; and type III immunomodulators, which are more superior to the other types, effectively acting on both normal and weakened immune systems [37]. In short, immunomodulators influence immune responses by interacting with various molecules and signaling pathways. For instance, they target cytokines, which are crucial messengers in the immune system.

Classification of Immunomodulators

Immunomodulators are classified into two primary types: immunosuppressants and immunostimulants. Immunosuppressants are further divided into glucocorticoids, which help mitigate inflammation and suppress immune response, and non-steroid agents such as calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and antimetabolite, which target specific pathways in immune cell activation. These agents are commonly used in patients receiving organ transplants and those with autoimmune disorders. In contrast, immunostimulant agents such as interferon and interleukins enhance immune function, promoting a stronger response against infection and cancer, as shown in Fig. 2 (Ref. [38]).

Immunosuppressant Drugs

Glucocorticoids. Interleukin (IL)-2 is identified as a critical growth factor for T lymphocytes. Upon binding to its specific T cell receptor, IL-2 activates a signaling cascade that promotes the proliferation of these immune cells. Immunosuppressant drugs target lymphocytes to manage and control immune response effectively. Glucocorticoids represent a class of steroid hormones produced by the adrenal gland that suppress the initial inflammatory response and the activity of immune cells like macrophages and T lymphocytes [33]. Dexamethasone (synthetic corticosteroid) is a powerful immunosuppressant that induces apoptosis in T lymphocytes, resulting in the decline of the immune response critical for the resolution of multiple myeloma. It is also used to treat allergic responses, nausea, and vomiting, which are the adverse effects of chemotherapy [39].

Alkylating Agents. Cyclophosphamide is an alkylating agent, which exhibits both antineoplastic and immunoregulatory effects. While immunosuppressants are more targeted in their action, the cytostatic agent is used for treating not only various solid tumors but also autoimmune diseases such as anemia due to immune dysfunction, granulomatosis with polyangiitis, and systemic lupus erythematous [40]. Cytostatic drugs inhibit cell division, posing a significant effect on the immune system. They are often combined with other immunosuppressive medications like calcineurin inhibitors, corticosteroids, and antibodies to enhance their effectiveness. Calcineurin inhibitors are known to decrease IL-2 synthesis. Anti-metabolites such as azathioprine and methotrexate inhibit T-cell proliferation. Methotrexate is a folic acid analog that hinders the synthesis of tetrahydrofolate synthesis. Methotrexate is a folic acid analog that hinders the synthesis of tetrahydrofolate synthesis. It reduces the proliferation of immune cells by inhibiting the synthesis of DNA and RNA, thereby reducing inflammation and modulating the immune response. This mechanism of action enables methotrexate to effectively manage autoimmune diseases and prevent transplant rejection [2,34].

Immunostimulatory Drugs

Bacterial Metabolites. Bacterial metabolites, particularly those derived from the bacterium Bacillus Calmette-Guérin (BCG), play an important role in boosting the natural defense system. These metabolites stimulate a robust immune response, which is crucial for combating infections and diseases. They enhance the activity of two vital types of immune cells: B cells, which produce immunoglobulins, and T lymphocytes, which are essential for directly attacking infected or cancerous cells. Importantly, it has been proven that BCG possesses the ability to prevent and treat certain types of cancer, specifically carcinoma; by capitalizing on the enhanced immune activity, it triggers to effectively target and eliminate cancer cells, as shown in Fig. 2. Such ability makes BCG and its metabolites valuable tools in immunotherapy and cancer treatment [38].

Recombinant Cytokines. Cytokines, such as interferons and interleukins, exert a profound effect on the modulation of immune responses. Recent advances in this regard are marked by clinical trials of recombinant cytokine produced

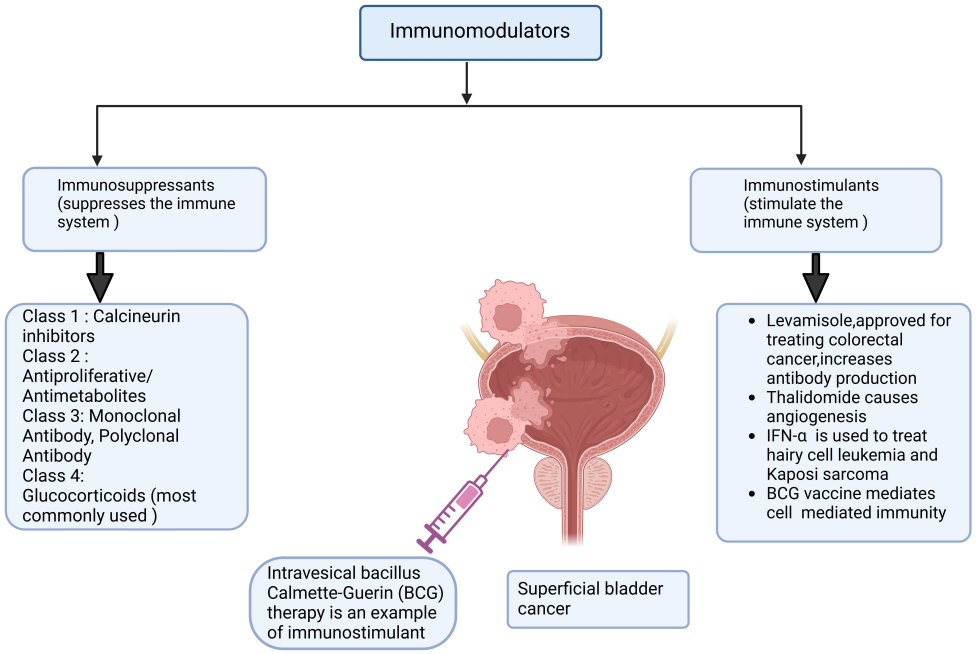

Fig. 2. The roles and mechanisms of different classes of immunomodulators in modulating immune response. Different classes of immunosuppressants and drugs are used to stimulate immune response. One classic example discussed is the Bacillus Calmette-Guérin (BCG) vaccine, which is a live attenuated vaccine used primarily against tuberculosis and is used as an immunotherapy treatment for superficial bladder cancer. The BCG works by stimulating the immune system to recognize and fight off *Mycobacterium tuberculosis* and cancer cells, enhancing the natural body defenses. This image is created using Biorender (https://biorender.com/) [38].

using plant-based expression systems to treat cancer and immune disorders [41]. IL-12 has shown notable efficacy in stimulating anti-tumor immunity. It promotes the differentiation of naïve T cells into T helper 1 (Th1) cells. These Th1 cells subsequently produce interferon-gamma (IFN-γ), a cytokine that inhibits angiogenesis and induces apoptosis. Researchers are now focusing on the development of combination therapies that integrate cytokines with complementary approaches, including immune checkpoint inhibition, targeted antibodies, and novel vaccine strategies, to enhance immune-mediated cancer elimination and restore immune function [42].

Plant-Based Immunomodulators. Certain plants and compounds, such as Tulsi (*Ocimum sanctum*) and azadirachtin (extracted from the *A. indica* plant), have been found to possess immunomodulatory properties that stimulate the immune system. Tulsi, also known as holy basil, is known to enhance the activity of neutrophils, thereby augmenting specific as well as non-specific immune reactions and fortifying the body's defense against pathogens [43]. Azadirachtin can increase leukocyte count and boost the antigen-specific and antibody responses in certain organisms [44]. Curcuma longa, commonly referred to as turmeric, possesses a potent bioactive compound known as curcumin, which helps in the reduction of inflammation by inhibiting the production of molecules that cause inflammation in immune cells. It has been shown to inhibit cyclooxygenase 2 (COX-2), an enzyme involved in inflammation and cancer. The development of new blood vessels, which is necessary for tumor growth and metastasis, can be inhibited by curcumin [45].

Categories of Immunomodulators in Cancer Therapy. T lymphocyte invasion of the neoplastic niche is essential for the body's defense against malignancies. This tumor niche can also promote the expansion of immunosuppressive cells like regulatory T cells (Tregs). This creates a challenging environment for the immune system to effectively target oncolytic cells [46]. Aluminum adjuvants, such as aluminum phosphate and aluminum hydroxide, have been used for over a century to enhance the immune response triggered by vaccines. They are recognized as some of the safest and most extensively used adjuvants in the world. These adjuvants were among the first to receive U.S. Food and Drug Administration (FDA) approval for use in human vaccines [22].

Agents and Approaches for Cancer Immunomodulation

Immune Checkpoint Inhibitors (ICIs)

Malignant cells can destroy immune checkpoint-related mechanisms for immune evasion by using negative feedback mechanisms that help them escape immune responses. A protein called programmed death ligand 1 (PD-

L1) interacts with PD-1 to signal T lymphocytes not to attack cancer cells. The clinical application of antibodies that interfere with immunological checkpoints has been a major turning point in cancer immunotherapy, by blocking this pathway with inhibitors like nivolumab, pembrolizumab, and cemiplimab [11,23,47–49]. Pembrolizumab is widely used for metastatic cervical cancer while combination therapy involving atezolizumab or durvalumab coupled with chemotherapy has shown efficacy in extensive small-cell lung cancer and urothelial cancer. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) is another critical molecule in this domain, serving as an immune checkpoint that engages with the B7 ligand family to dampen immune reactions. Ipilimumab, which is a monoclonal antibody against CTLA-4, was approved by the FDA in 2011. It functions by blocking the interaction between B7 and CTLA-4, thus reactivating the cytotoxic activity of T lymphocytes, as shown in Fig. 1. Ipilimumab is used in combination with nivolumab (anti-PD-1) for the treatment of advanced renal cell carcinoma and malignant pleural mesothelioma. T cell immunoglobulin and mucin-domain containing protein (TIM-3), an integral membrane protein, forms part of the host defense mechanism against cytopathogenic agents and recognizes pathogen-associated molecular patterns (PAMP), subsequently triggering an immune response by suppressing T cell activity to prevent over-activation [49]. This suppression causes T cell exhaustion, impairing their ability to attack and destroy tumor cells, particularly in the treatment of advanced solid tumors. LY3321367 is an anti-TIM-3 monoclonal antibody (mAbs) developed by Eli Lilly to block the interaction of TIM-3 with its ligand. Lymphocyte-activation gene 3 (LAG-3), which is upregulated in Tregs, aids cancer cells in evading the immune system. Relatlimab combined with nivolumab has been shown to treat unresectable or metastatic melanoma, a particularly aggressive form of skin cancer that often metastasizes to other parts of the body. By inhibiting LAG-3, relatlimab enhances T-cell activation [50] as depicted in Table 1 (Ref. [23,47–50]).

Cytokine and Growth Factor

Preclinical studies have demonstrated the anticancer effects of several cytokines, like myeloid growth factor, type 1 interferons (IFN-1s), IFN-γ, IL-2, IL-12 and IL-15. IFN-1s have historically been viewed as having anticancer properties by virtue of their ability to boost cellular quiescence, arrest cellular proliferation, and encourage programmed cell death in cancerous cells, as well as to strengthen the oncolytic response [51–58]. Interferon is essential for the maintenance of killer T lymphocytes. It has been reported that high-dose interferon-alpha (IFN-α) was utilized as adjuvant therapy following surgical removal of the tumor to lower the risk of relapse. It potentiates the antitumor activity of antibodies targeting growth factor receptors, such as human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR) [59]. Upon stimulation by IFN-1, TLR4 and TLR3 recognize cytosolic DNA and start a chain reaction of pro-inflammatory cytokines, enhancing the immune response against tumors and infections. They can also boost the maturation of dendritic cells and NK cells. Growth of cancer cells can be effectively hindered by IFN-γ, triggering the phosphorylation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. The IFN-γ also helps in limiting angiogenesis, initiating apoptosis in Tregs, improving dendritic cell maturation, augmenting M1-like macrophage activity, and weakening TH2 and TH17 (a subset of T helper cells) responses and autoimmune reactions. The clinical response to immune checkpoint inhibitors may be predicted by the observed IFN-γ signature. Patients with urothelial and non-small cell lung cancer (NSCLC) who may benefit from durvalumab, an anti-PD-L1 antibody, may be identified by a four-gene IFN-γ signature [60]. Recombinant human IL-15 (rhIL-15) has been thoroughly investigated for its potential as an immunomodulator against cancer. Out of the participants, four patients completed at least two cycles of therapy, while a total of 19 patients managed to finish at least two cycles. A moderately toxic rhIL-15 injection significantly increased the number of circulating NK, and major histocompatibility complex (MHC) class 1 restricted T cells in individuals with melanoma and renal cell carcinoma. The treatment increased circulating NK cells, especially the CD56 bright subset and moderately increased CD8+ T cells [61].

Another kind of cytokine that is particularly involved in influencing proliferation and differentiation is the mitogenic or proliferation factors. Mitogenic factors such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) are essential for the advancement of cancer because they stimulate angiogenesis (restoring blood flow to ischemic tissue), tumorigenesis, and metastasis. In ischemic conditions, VEGF expression is upregulated, leading to the accumulation of immunosuppressive cells such as Tregs and myeloid-derived suppressor cells, which inhibit T cell activity and promote tumor growth. Activation of TGF-β signaling occurs when TGF-β ligand binds to type II receptors results in activation and phosphorylation of type I receptors (TGF-β-RI), which in turn leads to the phosphorylation of small mothers against decapentaplegic homolog 2 & 3 (SMAD2 & SMAD3) proteins. TGF-β in cancer prevents tumor growth by arresting the cell cycle, but afterward, it promotes cancer expansion through epithelial-mesenchymal transition, metastasis, chemotherapy resistance, angiogenesis, and immune system evasion. A phase II clinical trial (NCT00431561) showed promising results in treating glioblastoma carcinoma with AP12009, a unique oligodeoxynucleotide that targets TGF-β. The treatment demonstrated significant efficacy in one-third of the patients. Additionally, research on gastric stump carcinoma (GSC) found that us-

Table 1. Immune checkpoint inhibitors and their roles in cancer.

Immunosuppressors	Mechanism	Immune checkpoint inhibitors	Therapeutic approaches	References
PD-1	PD-1, a protein on T cells, serves as a "brake" that acts to prevent the immune response from being over-activated.	Nivolumab Pembrolizumab Cemiplimab	Nivolumab has been approved for treating bronchogenic carcinoma. Pembrolizumab is used for treating metastatic cervical cancer.	[23,48]
PD-L1	Tumor cells exhibit PD-L1, which binds to PD-1, allowing them to manipulate the defense system and evade detection.	Atezolizumab Durvalumab	Atezolizumab and durvalumab are used for treating advanced urothelial carcinoma.	[47,48]
CTLA-4	CTLA-4 is a protein that recruits two key proteins found on APC—HLA-B7-1 and HLA-B7-2.	Ipilimumab	For treating renal adenocarcinoma and malignant pleural mesothelioma.	[23,48]
TIM-3	TIM-3 can cause T cells to become less effective over time, reducing their ability to attack cancer cells.	Eli Lilly and Company (Indianapolis, IN, USA) created the medication LY3321367, which is an anti-TIM-3 antibody or, when associated with an anti-PD-L1 antibody, an anti-TIM-3 antibody.	Used for curing advanced solid tumors.	[49]
LAG-3	On APCs, LAG-3 attaches to MHC class II molecules and sends inhibitory signals that reduce T cell activity.	Relatlimab	Relatlimab is mainly applied in combination with nivolumab to treat metastatic or incurable melanoma.	[23,50]

Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; CTLA-4, Cytotoxic T lymphocyte-associated protein 4; APC, antigen-presenting cell; HLA, human leukocyte antigen; TIM-3, T cell immunoglobulin and mucin-domain containing protein; LAG-3, Lymphocyte-activation gene 3.

ing RGFP966 and a histone deacetylase (HDAC3) inhibitor helped control SMAD7 acetylation, which can aid in cancer treatment [62,63]. The FDA-approved combination of lenvatinib and pembrolizumab (KEYNOTE-775/Study 309, NCT03517449, Phase 3) demonstrated superior clinical outcomes in advanced endometrial cancer patients with mismatch repair-proficient tumors [64], as mentioned in Table 2 (Ref. [59–64]).

Toll-Like Receptor Agonist

Pathogen-conserved molecular patterns are recognized and bound by pattern recognition receptors on cell types that present antigens, including dendritic cells and monocytes. This recognition initiates signaling cascades within immune cells, ultimately triggering a coordinated immune response. Among pattern recognition receptors, TLRs are key components of innate immunity and have emerged as promising therapeutic targets for innovative cancer treatments, including those for cervical cancer [65]. Pro-inflammatory cytokines are released to fight off infections. Pro-inflammatory cytokines, like interferons and inflammatory mediators, are released to fight off infections. These cytokines also activate the adaptive immune system, stimulating T cells to target and remember pathogens, preparing the body for future infections. Poly-ICLC and LPS are used as adjuvants in cancer vaccines to enhance the immune response. Similarly, interferons and inflammatory mediators are produced when imiquimod, a drug used to treat epidermal carcinomas, binds to TLR7. Upon binding to TLR9, CpG oligodeoxynucleotides resemble bacterial DNA and activate T cells and dendritic cells. Cancer vaccines leverage these chemicals to strengthen the immune system. Monophosphoryl lipid A (MPL), an LPS derivative, binds to TLR4 and initiates the nuclear factor kappa B (NF-κB) pathway, enhancing the host defense system's capacity to identify and eliminate oncolytic cells [26–28].

Monoclonal Antibodies

Monoclonal antibodies bind to distinct receptors on cancer cells, such as EGFR, which plays a critical role in tumor cell proliferation and metastasis. By blocking these receptors, mAbs effectively inhibit the signaling pathway that drives tumor growth and division, thereby halting cancer progression. Furthermore, mAbs also utilize ADCC in a process involving the Fc regions of the mAbs that engage with Fc receptors on NK cells, which leads to the recruitment of NK cells to the tumor site. Upon activation, NK cells release cytotoxic substances that selectively eliminate cancer cells, as shown in Fig. 3 (Ref. [33]). This method is commonly used to treat B-cell lymphoma. This therapeutic approach involves targeted immunoglobulin that selectively binds to the CD20 molecule found in the cancerous

Table 2. Clinical anticancer outcomes and other details of cytokines.

Cytokine	Source	Mechanism	Key biological processes used in cancer treatment	Clinical outcomes	References
IFN-1s	Immune cells, tumor cells, endothelial cells, PDCs, and CAFs	TLR4 and TLR3 activate cytosolic DNA, triggering pro-inflammatory cytokines and enhancing the immune response against tumors and infections.	IFN-1s stimulate tumor cell apoptosis, promote dendritic cell maturation and antigen presentation, and enhance natural killer cell activation, thereby reducing tumor size and preventing cancer spread, thus enhancing the immune response against cancer.	Lowers relapse risk after surgical resection of tumor; Boosts the effectiveness of targeted cancer therapies, including HER2 inhibitors and EGFR inhibitors.	[59]
IFN-γ	CTLs	When IFN-γ binds to its receptor, it phosphorylates Janus kinases and activates STAT1, which in turn stimulates the JAK/STAT signaling cascade.	IFN-γ suppresses Treg activities, reduces Th2 and Th17 responses, activates T and NK cells, and improves antigen presentation.	Predicts response to immune checkpoint inhibitors; Identifies patients who may benefit from durvalumab; Specific to urothelial and NSCLC patients. Uses four-gene IFN-γ signature for identification.	[60]
IL-15	Macrophages	IL-15Rα ligand presents interferon regulatory factor elements to NK and T cells and nuclear factor kappa-light-chain-enhancer of activated B cells.	The function of engineered IL-15 proteins is to activate and promote the growth of these immune cells, which increases their capacity to recognize and eliminate cancer cells.	Increased circulating NK cells; Enhanced CD56 bright subset; Moderately increased CD8+ T cells; Increased MHC class 1, restricted T cells; Moderately toxic treatment.	[61]
TGF-β	Epithelial cells, immune cells, platelets	TGF-β ligand binds to type II receptors, activates the phosphorylation of type I receptors (TGF-β-RI), and phosphorylates SMAD2 and SMAD3 proteins.	Initially, TGF-β arrests the cell cycle and prevents tumor growth. Later, it promotes cancer expansion through epithelial-mesenchymal transition, metastasis, chemotherapy resistance, angiogenesis, and immune system evasion.	Promising results in glioblastoma carcinoma; Significant efficacy in one-third of patients; Controlled SMAD7 acetylation; Potential aid in cancer treatment; Targeted TGF-β expression.	[62,63]
VEGF	Immune cells and non-immune cells	Ischemia	VEGF supports cancer growth and increases the accumulation of Treg and MDSCs, which aid in neoplastic evasion.	Lenvatinib + pembrolizumab for treatment of advanced endometrial cancer (KEYNOTE-775/Study 309, NCT03517449, Phase 3) shows a higher objective response rate and exerts a beneficial effect on tumors without mismatch repair deficiency.	[64]

Abbreviations: IFN-1s, type 1 interferons; PDCs, Plasmacytoid dendritic cells; CAF, Cancer-associated fibroblasts; TLR, Toll-like receptor; CTLs, cytotoxic T lymphocytes; STAT1, signal transducer and activator of transcription 1; JAK, Janus kinase; NK, natural killer; Th, Helper T cell; VEGF, vascular endothelial growth factor; Treg, regulatory T cell; MDSCs, Myeloid-derived suppressor cells; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; TGF-β, transforming growth factor beta; NSCLC, non-small cell lung cancer; SMAD2, small mothers against decapentaplegic homolog 2.

B lymphocytes. When the antibody binds to CD20, it triggers several processes that destroy the tumor cells. This approach triggers an immune activation to combat malignancy [33]. Herceptin and Erbitux are monoclonal antibodies primarily used in combating ductal carcinoma and specific epithelial cancer affecting the cervical and cranial regions, respectively. Herceptin targets the HER2 receptors and blocks the signals that promote cancer cell growth and division. Targeted therapies like Erbitux inhibit the receptor tyrosine kinase, which is often overexpressed in cancer cells [1]. Monoclonal antibodies may strengthen future cancer treatments by augmenting tumor-targeting selectivity, thereby bridging the gap toward achieving therapeutic goals.

Cancer Vaccines and Oncolytic Viruses

The goal of utilizing cancer vaccines is to fortify the body's defenses against cancerous antigens. Cancer vaccines are classified into four types, each type leveraging a distinct mechanism to combat cancerous cells. These include cellular vaccines like dendritic cell-based vaccines that utilize cellular components to stimulate immunity and oncolytic viruses-based vaccines that harness modified viruses to deliver oncogenic proteins. Additionally, peptide-based vaccines coupled with immunoadjuvants employ specific protein fragments to trigger an immune response. The limited ability of this type of vaccine is due to the variability of HLA and the small size of the antigenic determinant. The low-molecular-weight antigen can boost their antigenicity by conjugating with molecular chaperons, whereas nucleic acid-based vaccine uses genetic material to instruct cells to neoplastic antigens and facilitate macrophages and dendritic cells to process and present epitopes [66].

Oncolytic viruses could directly or indirectly destroy tumor cells. Herpes simplex viruses are the most common vector, showing abnormally overexpressed surface markers on cancer cells and possessing the ability to invade targeted cells [67–69]. Proliferation of the oncolytic viruses leads to cellular disruption and expulsion of newly produced bacteriophage, which penetrates surrounding tissues [70]. The tumor microenvironment releases microbial signature molecules, cellular distress signals, and cancer-specific markers, which can be detected by macrophages and dendritic cells. These cells activate anticancer immune defense by stimulating T cells to elicit tumor-targeted cytotoxicity and adaptive immunity, as shown in Fig. 4 (Ref. [67–70]). While oncolytic viruses-based vaccines offer several advantages, such as increased exposure to tumor antigens, selective replication, and immune system activation, some of their shortcomings should not be overlooked, including weak immune response, low tumor-targeting selectivity, the need to determine the optimal viral dosage, and the need to manage viral growth inside target cells [71–73].

Combination Strategies: Immunomodulators with Conventional Cancer Therapies

A deeper dissection of the complex molecular mechanisms has rapidly transformed our understanding of diseases. This fresh insight is paving the way for the development and testing of innovative therapeutic approaches. Numerous combination therapies have been proposed and are now being used in the battle against different types of cancer throughout the past several years. Despite relative obscurity a few years ago, targeted medication therapy, immunotherapy, and customized medicine are now commonly used as therapeutic approaches [74].

Combination therapy combines the enduring advantages of immunotherapy with the rapid eradication of tumors observed with targeted therapies, providing potential clinical benefits. Immunotherapy, in particular, could promote the potent tumor responses induced by targeted therapy, resulting in extended remissions where robust host responses against several antigens may reduce the likelihood of the emergence of drug-resistant cancer cells [74,75].

Immunomodulators and Chemotherapy

Chemotherapy has been an integral component of cancer treatment for many years. However, immune checkpoint inhibitors (ICIs) have been a breakthrough in the last decade and are now the first-line treatment for numerous malignancies. Although substantial progress has been made, primary and acquired resistance remains a perennial challenge in treatment, yielding a response rate of about 20% across solid malignancies treated with ICI monotherapy [76].

The inability of conventional chemotherapy to specifically target malignant cells is one of its primary drawbacks. The efficiency of treatment is limited by this nonspecificity, which reduces the capacity to deliver medications directly to tumor tissues. As a result, over the past ten years, novel strategies that harness and train a patient's immune system to identify and target altered cells by identifying a variety of cell surface markers have been created [77]. Treatment success has been greatly increased by combining immunotherapy and chemotherapy, especially for tumors that are challenging to treat, such as triple-negative breast cancer [78–80].

Chemoimmunotherapy is a new approach that combines immunotherapy with chemotherapy to improve clinical results. Drugs used in immunotherapy can be used either alone or in combination with chemotherapy to directly target cancer cells and strengthen the immune system's defenses against the disease. The FDA-approved medication tisagenlecleucel, which treats B-cell lymphoblastic leukemia by modifying the patient's CAR-T cells, is a prime example of this approach [81].

Another group of G protein-coupled receptors (GPCRs) that are involved in controlling the growth of

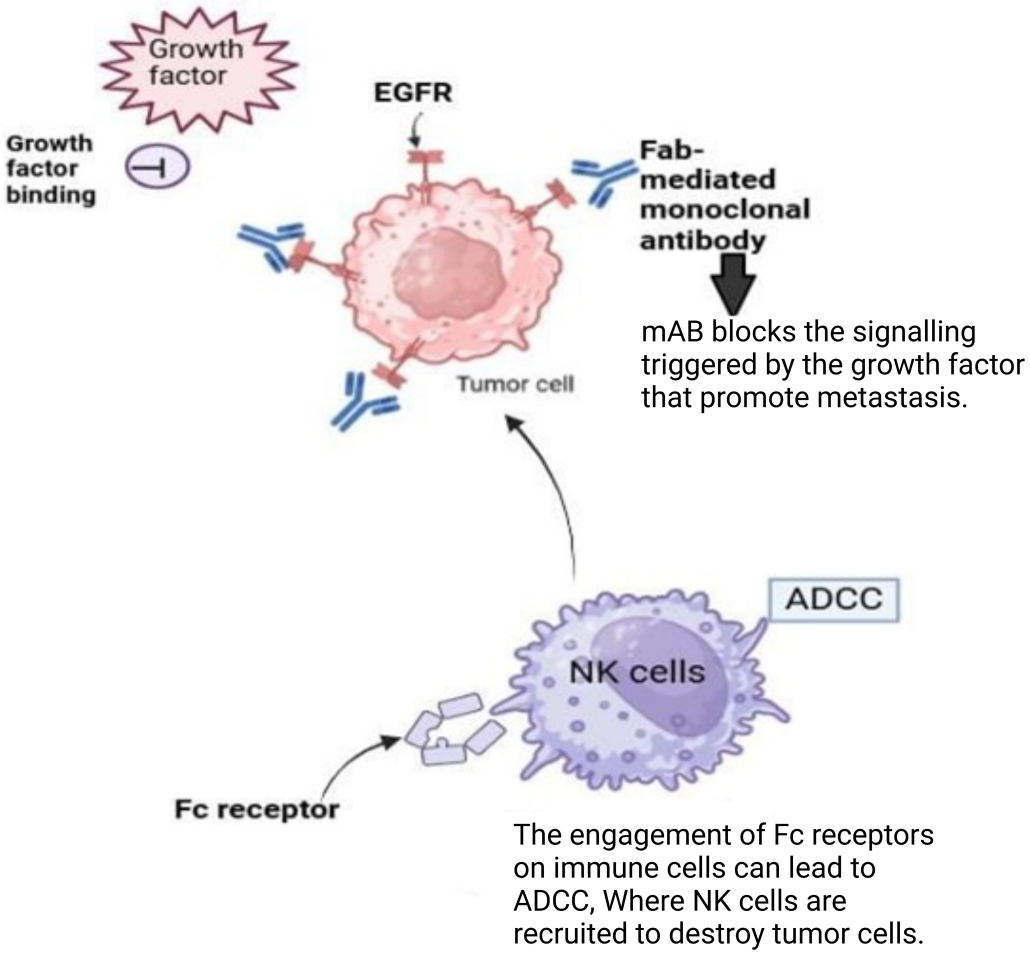

Fig. 3. Monoclonal antibodies (mAb) as targeted therapies in cancer treatment. The mAbs specifically bind to cancer cell receptors like epidermal growth factor receptor (EGFR), blocking signals that promote cell growth and division, thereby inhibiting tumor growth. The Fc receptors on natural killer (NK) cells promote the destruction of tumor cells through an antibody-dependent cellular cytotoxicity (ADCC) mechanism. When the encodes bind to the antibody on the cancer cells, the NK cells release cytotoxic substances to target and kill the cancer cells. This image is created using Biorender (https://biorender.com/) [33].

tumors are adenosine receptors (ARs) [82]. Among the four known ARs (A1, A2A, A2B, and A3) [83], the adenosine A2B receptor (A2BR) exhibits potential as a target for chemotherapeutic strategies [84], whereas the adenosine A2A receptor (A2AR) is the primary target for immunotherapy [85,86]. Now being investigated for their potential in combined chemotherapeutic and immunotherapeutic interventions, dual-target drugs that act on both A2AR and A2BR receptors present a potentially new treatment alternative for cancer [87,88].

Immunomodulators and Radiotherapy

Radiation therapy stands as an essential method for managing unresectable malignancies. This treatment causes cellular damage and death by directly delivering carbon-ion radiation or X-rays that damage DNA to tumor cells [89]. Free radicals created by ionizing radiation damage vital cellular constituents, resulting in chromosomal abnormalities and double-stranded DNA breaks. The delayed onset of negative effects can be explained by the possibility that these severely damaged cells will divide a few more times before undergoing cell death. Additionally, radiation triggers cellular signaling pathways that initiate lung fibrosis and inflammatory processes, which can lead to adverse effects including elevated intracranial pressure, skin redness, and swelling [90].

When used in conjunction with immunotherapy, radiation therapy enhances immune responses by exposing tumor-specific antigens to immune cells. Research on the effectiveness, benefits, and potential of combined radiation and immunotherapy in treating metastatic tumors is crucial because of the synergistic effect attained in reducing tumor size and treating metastases. The “abscopal effect”, in which targeted radiation on a tumor may trigger the immune system to identify and target metastatic tumors outside the radiation field, is a notable consequence of this combination therapy [91]. Antigen-presenting cells can identify antigens released by irradiated tumors at the initial phase of

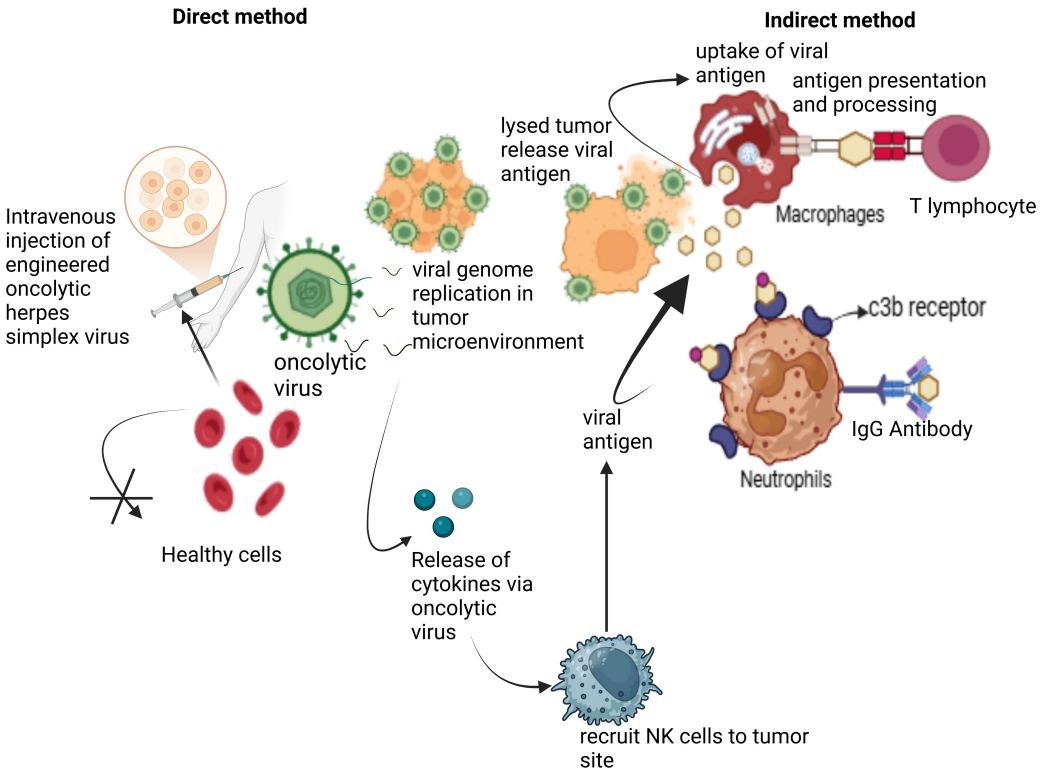

Fig. 4. Dual Mechanisms of Action: Direct and Indirect Anti-tumor Effects of Oncolytic Viruses. Direct method: The oncolytic viruses are injected into the bloodstream. They selectively infect tumor cells without harming normal cells. Once the viruses reach the tumor, they replicate inside tumor cells. The replication of the viruses within the oncolytic cell causes the cell to rupture, releasing the viruses to infect nearby tumor cells. The lysed tumor cells release pro-inflammatory cytokines that attract other immune cells such as natural killer (NK) cells to the tumor microenvironment, thereby extending the immune-mediated tumor destruction at a greater scale. Indirect method: Virus-mediated lysis of tumor cells causes the release of viral antigen into the tumor microenvironment. Macrophages process the viral antigen and present it to T lymphocytes, which can target and kill the tumor cells. This image is created using Biorender (https://biorender.com/) [67–70].

the process, triggering T cell activation and proliferation by presenting the tumor antigens to T cells in lymph nodes. Tumor-specific T cells that are produced then travel to distant, non-irradiated tumors to aid in their identification and elimination [92]. It has been demonstrated that combining immunotherapy with radiation results in a more robust and long-lasting T-cell response [93].

Immune checkpoint inhibitors have been the most extensively researched immunotherapies used in conjunction with radiation therapy, and the results have revealed favorable clinical outcomes. Combining ICIs with radiation therapy improves the systemic effects of immunotherapy and the local effects of radiation in preclinical models. The immunogenic effects of radiation, including antigen presentation, T cell activation and trafficking, and stimulator of interferon genes (STING) pathway activation, augment the immunological pathways targeted by CTLA-4 and PD-1 inhibitors [91]. Additionally, radiation promotes an adaptive immune response by increasing the absorption of foreign DNA into the cytoplasm, which in turn triggers the production of interferon via the cyclic GMP–AMP synthase (cGAS)-STING pathway [94]. The potential of this combined strategy to augment the palliative advantages of radiation monotherapy, overcome primary and acquired resistance to ICIs, and improve local tumor management is being investigated in ongoing research.

Immunomodulators and Targeted Therapies

Immunotherapy and targeted therapy, which each addresses a separate aspect of tumor management, have emerged as viable treatments for cancer patients. Despite the fact that both have demonstrated efficacy against a variety of malignancies, sometimes they are often limited by low or transient response rates when used alone. While targeted medicines block important biochemical pathways necessary for tumor development and survival, immunotherapy triggers a long-lasting immune response that can maintain long-term tumor control. Targeted treatments and cytotoxic drugs can also alter immune responses, implying that combining them with immunotherapy could greatly enhance clinical results.

A particularly promising approach that targets the immune system as well as the molecular dynamics of cancer is the combination of immunotherapy and epigenetic treatment. This strategy increases the immune system's capacity to identify and eliminate tumor cells while reversing cancer-related epigenetic alterations with medications like azacitidine and entinostat [95]. In cancer models, research has demonstrated several advantages of this combination, including triggering cancer cell death, improving immune recognition of tumors, decreasing immunosuppressive cells in tumor environment, and boosting efficacy of immunotherapies like adoptive cell transfer and checkpoint inhibitors. Specifically, research in melanoma, renal, and lung cancer models has shown encouraging results, with some cases showing complete tumor eradication [96,97] the possibility of this approach in treating metastatic melanoma and lung cancer is being investigated in clinical trials [98].

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations, accounting for approximately 86% of rat sarcoma (RAS)-driven cancers worldwide, are predominantly associated with lung, pancreatic, and colon cancers, and are linked to poor prognosis and reduced overall survival. Recent advancements in immunomodulatory approaches, such as combining *KRAS* mutant-targeted therapies with immune checkpoint inhibitors and T-cell-based strategies, show significant promise in enhancing anti-tumor responses and improving outcomes in patients with *KRAS*-driven malignancies [99]. Similarly, mitogen-activated protein kinase kinase (MEK) inhibitors, targeting the Mitogen-activated protein kinase (MAPK) signaling pathway, play a crucial role in enhancing immunotherapy efficacy by increasing tumor antigen expression, promoting T-cell infiltration, and mitigating immunosuppression within the tumor microenvironment. Preclinical models of colorectal and melanoma cancers have demonstrated encouraging anti-tumor responses with this approach. In metastatic colorectal cancer, the MEK inhibitor cobimetinib has been shown to enhance the efficacy of the anti-PD-L1 antibody atezolizumab. A deeper understanding of the mechanisms by which targeted therapies foster anti-tumor immunity will enable the development of rational combination therapies that achieve rapid tumor eradication while promoting durable immune responses, ultimately leading to more effective cancer treatments.

Emerging Immunomodulatory Agents and Novel Approaches

In order to fully utilize the immune system's therapeutic potential, cellular immunotherapy has advanced past conventional techniques and into an exciting transformational phase. Advanced bispecific antibodies that connect immune cells to cancer cells; precisely engineered adoptive cell therapies, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-edited CAR-T cells, that target tumor-specific antigens; improved checkpoint inhibitors that revitalize exhausted T cells within the tumor microenvironment; and advanced nanoparticle delivery systems that maximize the distribution of immunomodulators are some of the innovative approaches that have revolutionized cancer treatment. These methods give new prospects for better results across a variety of tumors by combining the advantages of cellular engineering, molecular precision, and creative delivery mechanisms.

Next-Generation Checkpoint Inhibitors

A number of inhibitory immune receptors, such as PD-1, CTLA-4, LAG-3, TIM-3, T-cell Ig and ITIM domain (TIGIT), and B- and T-lymphocyte attenuator (BTLA), have been identified as "immune checkpoints" in cancer. These receptors are important regulators that keep the immune system in balance by limiting excessive responses. By preventing immune cells from inadvertently attacking healthy tissue, these checkpoints are essential for self-tolerance. Immune checkpoint receptors on immune cells like T cells bind to homologous receptors on aberrant cells, such as cancer cells, and send a "switch off" signal that stops the immune system from attacking the tumor. By interfering with this signal, ICIs enable T cells to locate and destroy tumor cells [11,100].

Tremelimumab (NCT01008358) and other anti-CTLA-4 antibodies function by obstructing the CTLA-4 pathway. This keeps T cells from being suppressed and encourages the release of important cytokines that strengthen the immune system, like IFN-γ and IL-2. In conditions such as lung cancer, melanoma, and kidney cancer, this enhances the body's anti-cancer immune response. The FDA has approved ipilimumab (NCT01658878), another anti-CTLA-4 antibody, for the treatment of melanoma. Additionally, it is occasionally used in conjunction with nivolumab to treat hepatocellular carcinoma [101].

In phase II clinical studies, nivolumab, a humanized antibody that targets PD-1 on activated T cells, has strong anti-tumor effectiveness [102]. However, the necessity for next-generation ICIs is highlighted by the resistance mechanisms that tumors develop against anti-CTLA-4 and anti-PD-1/PD-L1 treatments. To enhance the effectiveness and results of cancer treatment, treatments that target TIGIT, LAG-3, and TIM-3 are being developed [100].

Bispecific Antibodies and Immune Cell Engagers

Today, one of the main problems with mAb treatments is that they can cause an unintended immunological reaction, which can result in the development of antibodies against the medication. This may lessen the clinical efficacy of the treatment.

Nonetheless, the creation of bispecific mAbs and improvements in mAb production techniques, which would also influence endogenous B cell action, offer prospects for improved therapeutic efficacy [103]. The capacity of bis-

pecific antibodies (bsAbs) to carry out tasks that are merely achievable when two antibodies with distinct binding specificities are combined into a single molecule is one of its unique advantages [104].

Multispecific antibodies termed bispecific killer engagers (BiKEs) and trispecific killer engagers (TriKEs) are generated by combining two or three separate single-chain variable segments. When treating complicated disorders involving a variety of receptors, ligands, and signaling pathways, this multi-targeting strategy is beneficial. BiKEs and TriKEs facilitate the attachment of NK cells to tumor cells, increasing NK cell activation and encouraging NK cell-mediated cancer cell killing [105,106].

Bispecific T cell engager (BiTE) antibodies, which are produced from T cells, have been approved by the FDA for a number of cancer types due to their remarkable efficacy against both large tumors and minimal residual disease [107]. Research by Kufer *et al*. [108] has demonstrated the great potency of bispecific antibodies linked to CD3/target antigens, which attract CD8+ and CD4+ T cells to target cancer cells directly at particular effector-to-target ratios [108]. ABBV-428 is a potential bispecific antibody that is presently undergoing phase I clinical trials. It targets both CD40 and the tumor protein mesothelin [109]. With significant therapeutic promise, more bispecific immunomodulatory antibodies are also currently being evaluated in clinical settings.

Adoptive Cell Therapies

Adoptive cell therapy, sometimes referred to as cellular immunotherapy, is a cancer treatment that targets and eliminates tumors using the patient's own immune cells. To strengthen the immune system's reaction to malignancy, this strategy includes isolating the patient's immune cells, growing them to a large quantity, and then rendering them. Engineered natural killer cell therapy, tumor-infiltrating lymphocyte (TIL) therapy, CAR-T cell therapy, and engineered T cell receptor (TCR) therapy are important cancer immunotherapy techniques [11,110]. Even in HLA-matched ovarian cancer cell lines that are resistant to chemotherapy, studies have demonstrated that TILs can have encouraging anti-cancer effects [111,112]. By interacting with MHC class I and MHC class II molecules, engineered TCRs are able to identify tumor antigens. This enables the cells to efficiently target the antigens, combat the immunosuppressive environment of the tumor, stop antigen escape, and lessen adverse consequences [113,114]. In order to improve the patient's NK cells' capacity to combat tumor cells, NK cell treatment involves genetically altering the cells to introduce antigen specificity. Structurally similar to CAR-T cells, chimeric antigen receptor-natural killer (CAR-NK) cells need co-stimulatory molecules such as CD28, 4-1BB, and CD134 to boost their ability to proliferate and destroy cancer, particularly solid tumors. Compared to CAR T-cell therapy, which takes longer to take effect, CAR-NK cell therapy provides a faster option [115]. CAR-T therapies, like tisagenlecleucel, are FDA-approved for B-cell acute lymphoblastic leukemia, while CAR-NK cells are under investigation for solid tumors like glioblastoma (GBM) [116]. Genetically modified multifunctional human NK cells (CD73.mCAR-pNK) have substantial anti-GBM activity, which effectively addresses tumor heterogeneity and immunosuppressive tumor microenvironment, according to research by Wang *et al*. [117]. For solid tumors, CAR-NK cell therapy is safer than CAR-T therapy due to the brief half-life of CAR-NK cells, which minimizes adverse effects on healthy tissues and lowers the likelihood of graft-versus-host disease [118]. The prostate stem cell antigen CAR_s15 NK cells engineered by Teng *et al*. [119] have shown anti-pancreatic effects, highlighting their notable potential in tumor suppression. In experimental models, the combination of cabozantinib with NK-92 cells that have been altered to target EGFR has shown increased efficacy, pointing to a new therapeutic strategy for renal cancers [118]. Unprocessed antigens and tumor cell surface components including glycolipids and carbohydrates are the target of CAR T-cell therapy. Without the need for MHC class I and MHC class II expression, this strategy leverages the patient's CD4+ and CD8+ T lymphocytes to identify and eliminate the cancer cells using stable, effective, and secure gene transfer techniques. Then, these altered T cells destroy tumor cells mainly by cytolyzing them through granzyme and perforin release, and occasionally by triggering apoptosis via the Fas receptor (Fas)/Fas-ligand or tumor necrosis factor (TNF)/TNF-receptor pathways [114,120].

Nanoparticle-Based Delivery of Immunomodulators

A variety of immunological reactions and pathways can be triggered by the inherent immune-stimulating properties of nanoparticles (NPs). Depending on their chemical and physical characteristics, different kinds of NPs have distinct impacts on the immune system. For instance, silver-based NPs decrease inflammation by blocking TLR signaling, but gold-based NPs cause inflammation by activating NF-κB pathways. The production of reactive oxygen species (ROS) is the primary mechanism through which multiple types of NPs influence immune responses. The effects of various materials vary: carbon nanotubes lower immune responses generally, iron oxide nanoparticles (NPs) lessen specific antigen responses, and CeO2 NPs suppress inflammatory signals. The immunological effects of NPs are also significantly influenced by their stability and breakdown patterns. The physical and chemical characteristics of NPs influence their usage in immunological applications, as evident by the increased toxicity of more readily degradable materials like ZnO in comparison to stable compounds like TiO_2 [121].

There has been a report that special "amphiphilic" vaccines were manufactured by combining an antigen with a

lipophilic albumin-binding tail. The lipid head binds to DNA segments containing CpG sequences that interact with TLR9. By targeting lymph nodes, this combination delivery approach efficiently transports both peptide antigens and CpG DNAs via a nanocarrier, increasing T cell responses and anti-tumor efficacy [122].

To reverse low oxygen levels in tumors, other researchers developed a liposome-based delivery system for catalase and hydrogen peroxide (H_2O_2). This enhancement improves the efficacy of anti-CTLA-4 treatment and radiation therapy in combination with immunotherapy [123]. There have been relentless investigations on NP vaccines owing to their superiority to traditional vaccination formulations in a number of ways, including greater localization, improved lymphatic circulation, increased uptake by antigen-presenting cells (APCs), and stronger B cell activation through receptor crosslinking. Therefore, it is critical to deepen our understanding of how the NPs interact with and penetrate through lymphoid tissue, and specifically what cell types they interact with, in order to provide more insights into developing more effective NP vaccines.

Key Clinical Trials on Immunomodulators as Adjuvant Cancer Therapies: Efficacy and Safety Profiles

Ipilimumab was authorized by the FDA in 2011 as an immunomodulatory cancer therapy for the treatment of skin cancer. Clinical trials (NCT02559829) demonstrated notable improvements in patients treated with ipilimumab. A study of 1861 patients using the therapy showed that 10% achieved objective responses, while 20% survived for around 10 years [124]. Some patients experienced prolonged disease stabilization or unconventional immune responses. Ipilimumab has shown limited effectiveness in non-melanoma cancers, prompting further research on its potential in kidney, lung, and prostate cancer. A study found that 10% of patients with advanced kidney cancer responded positively to ipilimumab (NCT00364723) treatment [125]. In lung cancer, combining ipilimumab with chemotherapy phase III trials (NCT00084812) extended progression-free survival by one month, but overall survival did not improve significantly [126]. Ipilimumab's efficacy in prostate cancer has been investigated in several studies. In one study involving 110 individuals, ipilimumab reduced prostate-specific antigen (PSA) levels by 50% in a few patients [127]. A large trial of 799 patients found that ipilimumab (NCT02020029) extended progression-free survival by one month and might prolong survival in patients with favorable prognostic features [128]. Two ongoing phase III trials are currently underway to further investigate ipilimumab's efficacy and potential so as to provide valuable insights into its role in cancer treatment, particularly in the form of combination therapy [128].

A study has reported that nivolumab induced durable tumor regressions in patients with advanced cancer, with a therapeutic rate of response of 17% in lung cancer, 27% in kidney cancer, and 31% in melanoma, and extended survival (9.9–22.4 months) [128]. The FDA has approved nivolumab for chemotherapy-refractory squamous lung cancer, and multiple pharmaceutical companies are developing PD-1 pathway-blocking drugs [129]. Ongoing clinical trials are exploring the full potential of these treatments in various cancer types. This breakthrough offers new hope for patients with advanced cancer, revolutionizing the landscape of cancer care. Studies have shown that the combined blockade of LAG-3 and PD-1 holds promise in cancer treatment and the establishment of autoimmunity models [130]. Double-knockout mice lacking both LAG-3 and PD-1 exhibit severe autoimmune reactions, while dual blockade of LAG-3 and PD-1 leads to elimination of cancerous cells in some models without causing significant autoimmune side effects. Currently, an anti-LAG-3 blocking antibody (clinical trial NCT02968109) is in phase I clinical trials for cancer treatment, with cohorts receiving either anti-LAG-3 monotherapy or combination therapy with anti-PD-1. This innovative approach offers potential breakthroughs in cancer treatment and immune regulation [131]. Eftilagimod alfa (IMP321), an immunotherapy, was tested in a 2006 phase I trial (NCT00369718) for advanced renal cell carcinoma. Results showed no significant response, but diagnostic confirmation was evaluated in 7 out of 8 patients receiving higher doses. Subsequent trials combining IMP321 with chemotherapy/immunotherapy showed promise in melanoma, breast cancer, and pancreatic neoplasms, with a favorable safety profile [132]. The study investigated the dual blockade of TIM-3 and PD-1 has shown remarkable potential in cancer treatment. By targeting both molecules, tumor growth can be controlled more effectively than blocking either alone. TIM-3 has emerged as a promising target for cancer immunotherapy to achieve combined immune checkpoint blockade, which potentially improves treatment outcomes. Currently, anti-human TIM-3 blocking antibodies are still under development. The importance of TIM-3 in regulating immune cell function and preventing excessive responses has been highlighted. The potential advantages of combined blockage in the therapy of cancer are realized through the integration of TIM-3 and PD-1, which suggests a more worn-out immune state. Sym023 has been evaluated in a 2018 phase I trial for advanced solid tumors/lymphomas, showing promise in patients with stable disease. This led to combination trials of Sym021/Sym022. Sabatolimab, an anti-TIM-3 antibody from Novartis, was found to trigger manageable side effects and demonstrate potential benefits in a phase I trial for advanced malignancies [133]. Other TIM-3 inhibitors (INCAGN2390, LY3321367, BMS-986258, SHR1702) are currently being tested in phase I trials, alone or with anti-PD-1/PD-L1 therapies, for advanced cancer [133].

Tumors can evade the surveillance of the immune system with the aid of an essential enzyme called indoleamine 2,3-dioxygenase (IDO). IDO weakens T cells and reduces their ability to fight tumors by preventing the breakdown of kynurenine necessary for T cell activity. Additionally, IDO promotes the formation of Tregs, which inhibits the natural defense system [134]. The use of pembrolizumab combined with epacadostat, an IDO inhibitor, in treating advanced melanoma and urothelial carcinoma has been investigated. Phase I/II trials showed promising results, but a phase III study found no superiority of this combination over pembrolizumab alone. However, a subsequent phase III study (KEYNOTE-672/ECHO-307) in urothelial cancer patients showed improved overall response rates (31.8% vs 24.5%) following the implementation of the combination therapy. New studies are investigating epacadostat's efficacy in glioblastoma, pancreatic adenocarcinoma, and breast cancer, in combination with other treatments [135]. Other IDO-targeting therapies, like BMS-986205, are also showing promise, despite some (PF-06840003 and LY3381916) being terminated or abandoned. These ongoing trials aim to enhance IDO inhibition's potential in treating solid tumors, offering hope for improved cancer treatments [135], as described in Table 3 (Ref. [124–126,128,131–136]).

Challenges and Limitations of Immunotherapy

The field of cancer immunotherapy faces several significant challenges that require innovative solutions and comprehensive research. At the outset, initiating preliminary studies that accurately depict human protection against infection is essential to comprehending the intricate relationships between functioning of the immune system and malignancies. Humanized mouse models, which incorporate human immune cells and tumors, are increasingly used to study these interactions, but they come with limitations such as the lack of tumor heterogeneity and the difficulty in distinguishing between anti-tumor and alloantigen responses [137]. Identifying the dominant drivers of cancer immunity involves understanding the role of tumor-driving mutations, which can either promote cancer growth or expose tumors to the immune system. Immune-based treatments can target the neoantigens resulting from these mutations, but it can be difficult to control their frequency and uniformity across various cancer types [137]. The quantity of mutations within a tumor is referred to as mutational load or tumor genetic heterogeneity. High mutational load correlates with an increased amount of abnormal protein, making them visible to the immune system. Loss of heterozygosity (LOH) in *HLA* genes is a phenomenon where a tumor loses genetic diversity in its HLA genes, potentially impairing immune recognition. When a tumor loses genetic diversity in its HLA genes, it can evade immune recognition, making it challenging for the immune system to target the tumor. Tumor mutational Burden (TMB) refers to the number of mutations within a tumor's genome [138]. However, the TMB thresholds might differ for inflammatory tumors with immune cell infiltration. The optimal cutoff for TMB in inflammatory tumors is currently unknown, and researchers and clinicians are still trying to determine the specific TMB threshold that would predict a favorable response to immunotherapy in inflammatory tumors. Understanding the optimal TMB cutoff for inflammatory tumors could have significant implications for personalized cancer treatment, enabling clinicians to better predict which patients with inflammatory tumors would benefit from immunotherapy [138].

A key challenge in immunotherapy is the precise regulation of immune cell migration and adhesion within the tumor microenvironment. Effective immune responses are enabled by the interactions between immune cells, extracellular matrix, and stromal structures, highlighting the need for strategies that enhance these processes to improve immunotherapy outcomes [139]. Different organs have unique immune environments, influencing how tumors interact with the immune system. Understanding these organ-specific differences is important for designing tailored immunotherapies that are effective in various tumor locations. The effectiveness of cancer treatments is influenced by the specific organs affected by metastasis. Organ-specific immunity plays a crucial role in determining treatment outcomes. For example, patients with liver metastases have poor prognosis due to the liver's unique immune environment, while those experiencing lymph node metastases have better survival rates. The bone microenvironment poses challenges for anti-cancer treatments due to its specialized stromal interactions and immune-suppressive cytokines [140]. In contrast, organs with high immune cell presence offer more favorable conditions for anti-cancer immunity. To improve treatment outcomes, clinicians should consider organ-specific approaches, taking into account the distinct immune characteristics of different metastasis sites. Tumors can evade the immune system through primary mechanisms (initial evasion) or secondary mechanisms (evasion after immune activation). A more in-depth dissection of these mechanisms will pave the way for developing strategies to prevent immune escape and improve the durability of immunotherapy responses [141–144].

Resistance to Immunotherapy

Unresponsive to cancer treatments in certain patients could be caused by various factors suppressing the immune response. Immunomodulatory therapy can be hindered by three distinct immune evasion mechanisms, including inherent, adaptive, and acquired evasion. Inherent evasion occurs when cancer cells are naturally resistant to treatment, often due to genetic changes that inhibit immune response [145]. As treatment progresses, adaptive resistance can develop as cancer cells attempt to evade the immune system. This type of resistance results from the ongoing interactions

Table 3. Clinical trial outcomes for immunomodulatory cancer therapies.

Immunomodulators	Clinical trial ID	Cancer type	Treatment outcome	Clinical trial phase	References
Ipilimumab	NCT02559829	Skin cancer	10% of patients achieved objective responses, 20% survived for ~10 years, and some patients showed prolonged disease stabilization or experienced unconventional immune responses.	Phase-III	[124]
	NCT00364723	Kidney cancer	10% of patients with advanced kidney cancer responded positively to treatment.	Phase-II	[125]
	NCT00084812	Lung cancer	Combination with chemotherapy extended progression-free survival by 1 month, but overall survival did not significantly improve.	Phase-III	[125,126]
	NCT02020029	Prostate cancer	Ipilimumab reduced PSA levels by 50% in a few patients and extended progression-free survival by 1 month in a large trial of 799 patients.	Phase-III	[128]
Nivolumab	NCT01642004	Lung cancer	Patients achieved a 17% therapeutic response rate and long-term survival (9.9–22.4 months). Nivolumab was FDA-approved for chemotherapy in the treatment of refractory squamous lung cancer.	Phase-III	[136]
	NCT02017717	Kidney cancer	Patients achieved a 27% therapeutic response rate.	Phase-III	[136]
	NCT01585987	Melanoma	Patients achieved a 31% therapeutic response rate.	Phase-III	[136]
Anti-LAG-3 & Anti-PD-1	NCT02968109	Various cancers and autoimmune diseases	Dual blockade of LAG-3 and PD-1 showed promise in cancer treatment. This combination caused severe autoimmune reactions in knockout mice but was effective in eliminating cancerous cells in some models.	Phase-I	[131]
IMP321	NCT00369718	Renal cell carcinoma	IMP321 caused no significant response in most patients, but diagnostic confirmation was evaluated in 7 out of 8 patients receiving higher doses.	Phase-I	[132]
	NCT01497828	Melanoma, breast cancer, pancreatic cancer	IMP321 showed therapeutic promise when combined with chemotherapy/immunotherapy, with a favorable safety profile.	Phase-II	[132]
Sym023 (TIM-3 inhibitor)	2018, not specified	Solid tumors, lymphomas	Stable disease observed in several patients, leading to combination trials with other therapies.	Phase-I	[133]
Sabatolimab (TIM-3 inhibitor)	Not specified	Advanced malignancies	Patients with advanced malignancies receiving sabatolimab demonstrated manageable side effects, indicating its potential benefits based on phase I trial's results.	Phase-I	[133]
Pembrolizumab + epacadostat (IDO inhibitor)	KEYNOTE-672/ECHO-307	Urothelial cancer	Combination therapy improved the overall response rates (31.8% vs. 24.5%) compared to pembrolizumab monotherapy.	Phase-III	[134]
BMS-986205 (IDO Inhibitor)	Not specified	Various solid tumors	Early trials of IDO inhibition showed promise for treating solid tumors.	Ongoing	[135]

Abbreviations: PSA, prostate-specific antigen; IDO, indoleamine 2,3-dioxygenase; FDA, Food and Drug Administration.

between the immune system and tumor. On the other hand, acquired resistance occurs after initial treatment success, where cancer cells develop resistance mechanisms, leading to relapse. This is often driven by genetic changes over time [146].

Resistance factors can be intrinsic, such as genetic mutations and protein expression changes within cancer cells that hinder immune recognition. Extrinsic factors also play a role, involving surrounding stromal and immune cells, abnormal blood vessels, and host factors like age, sex, overall health, and lifestyle [147].

To improve treatment outcomes, researchers are working tirelessly to understand and overcome these resistance mechanisms. By addressing intrinsic and extrinsic factors, scientists aim to enhance immunotherapy efficacy and achieve better patient outcomes. Unraveling the intricacies of drug resistance by disentangling the complex interplay between cancer cells, tumor microenvironment, and host factors is essential for the development of more effective, innovative anticancer strategies, which hold promise to improve success rates post-treatment and transform lives of cancer patients.

Immunotherapy-Related Adverse Events

Immunotherapy may result in a number of adverse events or treatment-related side effects. These incidents may differ in intensity and influence multiple body systems, usually as a result of the immune system being triggered to attack both healthy tissues and cancer cells. Some of the most commonly reported adverse effects include skin reactions, gastrointestinal issues, and hormonal imbalances [148]. In recent studies, it has been observed that several combinations of immunotherapy and radiotherapy tend to lead to higher rates of adverse reactions, with a notable proportion of patients experiencing grade 3 or higher side effects. For instance, data shows that up to 47.3% of patients may suffer from severe adverse events when treated with certain immunotherapy regimens. Additionally, when combining immunotherapy with radiotherapy, about 89.4% of patients have reported experiencing adverse reactions of varying severity [148]. Overall, 94.5% of cases have documented some form of adverse effect, highlighting the importance of ongoing monitoring and management during treatment to mitigate these risks [149].

Patient Selection and Biomarker Development

When testing new immunomodulatory therapies, closely monitoring patients is crucial to ensuring safety and efficacy. These treatments can be highly effective, but only for some patients. To improve success rates, biomarkers that can identify treatment responders should be explored. Monitoring the immune response during clinical trials is vital, including measuring cytokine levels to comprehend how the natural defence system responds to therapy. Additionally, analyzing drug-specific antibodies throughout clinical trials is essential [150,151]. Drug-specific antibodies generated by the immune system in response to biologic drugs can neutralize treatment effects. Thus, managing the neutralizing effect by these antibodies is critical to ensure optimal treatment effects. Studies on currently underway to develop screening and identification methods for these antibodies, predict their formation, and minimize their neutralizing effect. For instance, Bharadwaj *et al.* [152] developed a large-scale test to quantify reactions to narcotics, optimizing it with five different antibodies. Another group developed a machine learning prediction model to analyze serum metabolites and lipids in multiple sclerosis patients treated with interferon-beta (IFN-β), which accurately predicts the anti-drug antibody status. These efforts aim to provide early prediction tools for biologics success, reducing therapeutic drug loss when antibody responses to drugs arise, in order to enhance patient outcomes. This prediction model developed using patient data at baseline or the third month for estimating treatment effectiveness has demonstrated remarkable accuracy, with an F1 score of 0.735 (a measure of overall accuracy) and specificity of 0.83 (a measure of true negative predictions), offering a potential non-invasive tool for predicting treatment success in various diseases, thereby constituting a strong impetus for revolutionizing personalized medicine [152,153].

Conclusion

The advancements in cancer research has significantly transformed the role of immunotherapy in combating cancer, highlighting the need for more sophisticated delivery systems and a better understanding of the association between malignancies and the immune system. The success of these treatments relies on identifying precise therapeutic targets and bridging the gap between laboratory findings and patient care. Targeted treatments show considerable promise as they increase the vulnerability of cancer cells to immune attacks. These methods provide immediate benefits and prevent cancer recurrence in the long run. On a separate note, with the advancements in immunotherapy, therapies can be tailored to a patient's immune system and tumor features, moving toward realizing the adoption of precision medicine approaches. In addition to ensuring that these novel techniques are safe and do not elicit substantial adverse effects, well-designed clinical studies are warranted to determine the optimal treatment combination and sequence. The use of immunotherapy combined with other therapeutic modalities proves to be the most feasible and effective mode of cancer treatment in future for improving prognosis of cancer patients worldwide.

Availability of Data and Materials

Not applicable.

Author Contributions

ST: Conceptualization, visualization, creation of models, supervision, formal analysis and addressed revision. SS: Conceptualization, visualization, supervision, and addressed revision. RP: Conceptualization, formal analysis, investigation, analyzed the written part and advised SS, ST and VS on further improvement. VS: Conceptualization, visualization, supervision, addressed revision, and approved the final manuscript. All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The support of Advanced Molecular Biology Research Lab of the Department of Chemistry & Biochemistry, Sharda School of Engineering & Science, Sharda University, Greater Noida, has been highly acknowledged. The authors thank Ankush Yadav, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland, for correcting grammatical errors.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Liu B, Zhou H, Tan L, Siu KTH, Guan XY. Exploring treatment options in cancer: Tumor treatment strategies. Signal Transduction and Targeted Therapy. 2024; 9: 175.

[2] Raimondi MV, Randazzo O, La Franca M, Barone G, Vignoni E, Rossi D, *et al*. DHFR Inhibitors: Reading the Past for Discovering Novel Anticancer Agents. Molecules. 2019; 24: 1140.

[3] Fanale D, Bronte G, Passiglia F, Calò V, Castiglia M, Di Piazza F, *et al*. Stabilizing versus destabilizing the microtubules: a double-edge sword for an effective cancer treatment option? Analytical Cellular Pathology (Amsterdam). 2015; 2015: 690916.

[4] Germano G, Lamba S, Rospo G, Barault L, Magrì A, Maione F, *et al*. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature. 2017; 552: 116–120.

[5] Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, *et al*. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. The Journal of Experimental Medicine. 2006; 203: 1259–1271.

[6] Kwilas AR, Donahue RN, Bernstein MB, Hodge JW. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. Frontiers in Oncology. 2012; 2: 104.

[7] Lomax AJ, Bortfeld T, Goitein G, Debus J, Dykstra C, Tercier PA, *et al*. A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy. Radiotherapy and Oncology. 1999; 51: 257–271.

[8] Slater JM, Archambeau JO, Miller DW, Notarus MI, Preston W, Slater JD. The proton treatment center at Loma Linda University Medical Center: rationale for and description of its development. International Journal of Radiation Oncology, Biology, Physics. 1992; 22: 383–389.

[9] Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. Journal of Clinical Oncology. 2007; 25: 953–964.

[10] Hoteit M, Oneissi Z, Reda R, Wakim F, Zaidan A, Farran M, *et al*. Cancer immunotherapy: A comprehensive appraisal of its modes of application. Oncology Letters. 2021; 22: 655.

[11] Mitra A, Kumar A, Amdare NP, Pathak R. Current Landscape of Cancer Immunotherapy: Harnessing the Immune Arsenal to Overcome Immune Evasion. Biology. 2024; 13: 307.

[12] Neklesa T, Snyder LB, Willard RR, Vitale N, Pizzano J, Gordon DA, *et al*. ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. Journal of Clinical Oncology. 2019; 37: 10.1200.

[13] Gough SM, Flanagan JJ, Teh J, Andreoli M, Rousseau E, Pannone M, *et al*. Oral Estrogen Receptor PROTAC Vepdegestrant (ARV-471) Is Highly Efficacious as Monotherapy and in Combination with CDK4/6 or PI3K/mTOR Pathway Inhibitors in Preclinical ER+ Breast Cancer Models. Clinical Cancer Research. 2024; 30: 3549–3563.

[14] Karlitepe A, Ozalp O, Avci CB. New approaches for cancer immunotherapy. Tumour Biology. 2015; 36: 4075–4078.

[15] Sathyanarayanan V, Neelapu SS. Cancer immunotherapy: Strategies for personalization and combinatorial approaches. Molecular Oncology. 2015; 9: 2043–2053.

[16] Boyacıoğlu Ö, Bilgiç E, Varan C, Bilensoy E, Nemutlu E, Sevim D, *et al*. ACPA decreases non-small cell lung cancer line growth through Akt/PI3K and JNK pathways in vitro. Cell Death & Disease. 2021; 12: 56.

[17] Winifred Nompumelelo Simelane N, Abrahamse H. Nanoparticle-Mediated Delivery Systems in Photodynamic Therapy of Colorectal Cancer. International Journal of Molecular Sciences. 2021; 22: 12405.

[18] Pessoa J. Cytochrome c in cancer therapy and prognosis. Bioscience Reports. 2022; 42: BSR20222171.

[19] Guerra N, Tan YX, Joncker NT, Choy A, Gallardo F, Xiong N, *et al*. NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. Immunity. 2008; 28: 571–580.

[20] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity. 2011; 34: 637–650.

[21] Le Gall CM, Weiden J, Eggermont LJ, Figdor CG. Dendritic cells in cancer immunotherapy. Nature Materials. 2018; 17: 474–475.

[22] Zhong X, Zhang Y, Tan L, Zheng T, Hou Y, Hong X, *et al*. An aluminum adjuvant-integrated nano-MOF as antigen delivery system to induce strong humoral and cellular immune responses. Journal of Controlled Release. 2019; 300: 81–92.

[23] Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, *et al*. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. The New England Journal of Medicine. 2022; 386: 24–34.

[24] Butler LM, Perone Y, Dehairs J, Lupien LE, de Laat V, Talebi A, *et al*. Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention. Advanced Drug Delivery Reviews. 2020; 159: 245–293.

[25] Kircheis R, Planz O. The Role of Toll-like Receptors (TLRs) and Their Related Signaling Pathways in Viral Infection and Inflammation. International Journal of Molecular Sciences. 2023; 24: 6701.
[26] Sultan H, Salazar AM, Celis E. Poly-ICLC, a multi-functional immune modulator for treating cancer. Seminars in Immunology. 2020; 49: 101414.
[27] Melssen MM, Petroni GR, Chianese-Bullock KA, Wages NA, Grosh WW, Varhegyi N, *et al*. A multipeptide vaccine plus toll-like receptor agonists LPS or polyICLC in combination with incomplete Freund's adjuvant in melanoma patients. Journal for Immunotherapy of Cancer. 2019; 7: 163.
[28] Yeh DW, Lai CY, Liu YL, Lu CH, Tseng PH, Yuh CH, *et al*. CpG-oligodeoxynucleotides developed for grouper toll-like receptor (TLR) 21s effectively activate mouse and human TLR9s mediated immune responses. Scientific Reports. 2017; 7: 17297.
[29] Kaufmann SHE, Weiner J, von Reyn CF. Novel approaches to tuberculosis vaccine development. International Journal of Infectious Diseases. 2017; 56: 263–267.
[30] Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal Transduction and Targeted Therapy. 2023; 8: 450.
[31] Tokarew N, Ogonek J, Endres S, von Bergwelt-Baildon M, Kobold S. Teaching an old dog new tricks: next-generation CAR T cells. British Journal of Cancer. 2019; 120: 26–37.
[32] Watanabe N, McKenna MK, Rosewell Shaw A, Suzuki M. Clinical CAR-T Cell and Oncolytic Virotherapy for Cancer Treatment. Molecular Therapy. 2021; 29: 505–520.
[33] Chen L, Xie T, Wei B, Di DL. Current progress in CAR-T cell therapy for tumor treatment. Oncology Letters. 2022; 24: 358.
[34] Sharma Y, Arora M, Bala K. The potential of immunomodulators in shaping the future of healthcare. Discover Medicine. 2024; 1: 37.
[35] Lee SJ, Chinen J, Kavanaugh A. Immunomodulator therapy: monoclonal antibodies, fusion proteins, cytokines, and immunoglobulins. The Journal of Allergy and Clinical Immunology. 2010; 125: S314–S323.
[36] Keystone EC. Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: a review of longterm data. The Journal of Rheumatology. 2011; 38: 1552–1562.
[37] Shouse AN, LaPorte KM, Malek TR. Interleukin-2 signaling in the regulation of T cell biology in autoimmunity and cancer. Immunity. 2024; 57: 414–428.
[38] Fritschi N, Curtis N, Ritz N. Bacille Calmette Guérin (BCG) and new TB vaccines: Specific, cross-mycobacterial and off-target effects. Paediatric Respiratory Reviews. 2020; 36: 57–64.
[39] Rosenberg AS. From mechanism to resistance - changes in the use of dexamethasone in the treatment of multiple myeloma. Leukemia & Lymphoma. 2023; 64: 283–291.
[40] Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nature Reviews. Immunology. 2008; 8: 59–73.
[41] Sirko A, Vaněk T, Góra-Sochacka A, Redkiewicz P. Recombinant cytokines from plants. International Journal of Molecular Sciences. 2011; 12: 3536–3552.
[42] García-Martínez E, Smith M, Buqué A, Aranda F, de la Peña FA, Ivars A, *et al*. Trial Watch: Immunostimulation with recombinant cytokines for cancer therapy. Oncoimmunology. 2018; 7: e1433982.
[43] Divekar PA, Narayana S, Divekar BA, Kumar R, Gadratagi BG, Ray A, *et al*. Plant Secondary Metabolites as Defense Tools against Herbivores for Sustainable Crop Protection. International Journal of Molecular Sciences. 2022; 23: 2690.
[44] Dave N, Iqbal A, Patel M, Kant T, Yadav VK, Sahoo DK, *et al*. Deciphering the key pathway for triterpenoid biosynthesis in *Azadirachta indica* A. Juss.: a comprehensive review of omics studies in nature's pharmacy. Frontiers in Plant Science. 2023; 14: 1256091.
[45] Bhaumik S, Jyothi MD, Khar A. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. FEBS Letters. 2000; 483: 78–82.
[46] Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacology & Therapeutics. 2021; 221: 107753.
[47] Mathieu L, Shah S, Pai-Scherf L, Larkins E, Vallejo J, Li X, *et al*. FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer. The Oncologist. 2021; 26: 433–438.
[48] Herzberg B, Campo MJ, Gainor JF. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer. The Oncologist. 2017; 22: 81–88.
[49] He Y, Cao J, Zhao C, Li X, Zhou C, Hirsch FR. TIM-3, a promising target for cancer immunotherapy. OncoTargets and Therapy. 2018; 11: 7005–7009.
[50] Ibrahim R, Saleh K, Chahine C, Khoury R, Khalife N, Cesne AL. LAG-3 Inhibitors: Novel Immune Checkpoint Inhibitors Changing the Landscape of Immunotherapy. Biomedicines. 2023; 11: 1878.
[51] Goldstein D, Laszlo J. The role of interferon in cancer therapy: a current perspective. CA: a Cancer Journal for Clinicians. 1988; 38: 258–277.
[52] Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nature Reviews. Cancer. 2004; 4: 11–22.
[53] Lee S, Margolin K. Cytokines in cancer immunotherapy. Cancers. 2011; 3: 3856–3893.
[54] Nicholas C, Lesinski GB. Immunomodulatory cytokines as therapeutic agents for melanoma. Immunotherapy. 2011; 3: 673–690.
[55] Sim GC, Radvanyi L. The IL-2 cytokine family in cancer immunotherapy. Cytokine & Growth Factor Reviews. 2014; 25: 377–390.
[56] Ardolino M, Hsu J, Raulet DH. Cytokine treatment in cancer immunotherapy. Oncotarget. 2015; 6: 19346–19347.
[57] Floros T, Tarhini AA. Anticancer Cytokines: Biology and Clinical Effects of Interferon-α2, Interleukin (IL)-2, IL-15, IL-21, and IL-12. Seminars in Oncology. 2015; 42: 539–548.
[58] Waldmann TA, Chen J. Disorders of the JAK/STAT Pathway in T Cell Lymphoma Pathogenesis: Implications for Immunotherapy. Annual Review of Immunology. 2017; 35: 533–550.
[59] Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G. Type I interferons in anticancer immunity. Nature Reviews. Immunology. 2015; 15: 405–414.
[60] Jorgovanovic D, Song M, Wang L, Zhang Y. Roles of IFN-γ in tumor progression and regression: a review. Biomarker Research. 2020; 8: 49.
[61] Miller JS, Morishima C, McNeel DG, Patel MR, Kohrt HEK, Thompson JA, *et al*. A First-in-Human Phase I Study of Subcutaneous Outpatient Recombinant Human IL15 (rhIL15) in Adults with Advanced Solid Tumors. Clinical Cancer Research. 2018; 24: 1525–1535.
[62] Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-β signal transduction for fibrosis and cancer therapy. Molecular Cancer. 2022; 21: 104.
[63] Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature. 2003; 425: 577–584.
[64] Ghalehbandi S, Yuzugulen J, Pranjol MZI, Pourgholami MH. The role of VEGF in cancer-induced angiogenesis and research progress of drugs targeting VEGF. European Journal of Pharmacology. 2023; 949: 175586.
[65] Agarwal M, Kumar M, Pathak R, Bala K, Kumar A. Exploring

TLR signaling pathways as promising targets in cervical cancer: The road less traveled. International Review of Cell and Molecular Biology. 2024; 385: 227–261.

[66] Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. Journal of Hematology & Oncology. 2022; 15: 28.

[67] Gopinath SCB, Hayashi K, Lee JB, Kamori A, Dong CX, Hayashi T, *et al*. Analysis of compounds that interfere with herpes simplex virus-host receptor interactions using surface plasmon resonance. Analytical Chemistry. 2013; 85: 10455–10462.

[68] Yu Z, Chan MK, O-charoenrat P, Eisenberg DP, Shah JP, Singh B, *et al*. Enhanced nectin-1 expression and herpes oncolytic sensitivity in highly migratory and invasive carcinoma. Clinical Cancer Research. 2005; 11: 4889–4897.

[69] Flores EB, Aksoy BA, Bartee E. Initial dose of oncolytic myxoma virus programs durable antitumor immunity independent of in vivo viral replication. Journal for Immunotherapy of Cancer. 2020; 8: e000804.

[70] Curti BD, Richards J, Hyngstrom JR, Daniels GA, Faries M, Feun L, *et al*. Intratumoral oncolytic virus V937 plus ipilimumab in patients with advanced melanoma: the phase 1b MITCI study. Journal for Immunotherapy of Cancer. 2022; 10: e005224.

[71] Mahalingam D, Wilkinson GA, Eng KH, Fields P, Raber P, Moseley JL, *et al*. Pembrolizumab in Combination with the Oncolytic Virus Pelareorep and Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma: A Phase Ib Study. Clinical Cancer Research. 2020; 26: 71–81.

[72] Monge C, Xie C, Myojin Y, Coffman K, Hrones DM, Wang S, *et al*. Phase I/II study of PexaVec in combination with immune checkpoint inhibition in refractory metastatic colorectal cancer. Journal for Immunotherapy of Cancer. 2023; 11: e005640.

[73] Chesney JA, Puzanov I, Collichio FA, Singh P, Milhem MM, Glaspy J, *et al*. Talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone for advanced melanoma: 5-year final analysis of a multicenter, randomized, open-label, phase II trial. Journal for Immunotherapy of Cancer. 2023; 11: e006270.

[74] Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, *et al*. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. Genes & Diseases. 2022; 10: 1367–1401.

[75] Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nature Reviews. Cancer. 2012; 12: 237–251.

[76] Jenkins RW, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. British Journal of Cancer. 2018; 118: 9–16.

[77] Vigneron N. Human Tumor Antigens and Cancer Immunotherapy. BioMed Research International. 2015; 2015: 948501.

[78] Kim I, Sanchez K, McArthur HL, Page D. Immunotherapy in triple-negative breast cancer: present and future. Current Breast Cancer Reports. 2019; 11: 259–271.

[79] Marra A, Viale G, Curigliano G. Recent advances in triple negative breast cancer: the immunotherapy era. BMC Medicine. 2019; 17: 90.

[80] Sambi M, Bagheri L, Szewczuk MR. Current Challenges in Cancer Immunotherapy: Multimodal Approaches to Improve Efficacy and Patient Response Rates. Journal of Oncology. 2019; 2019: 4508794.

[81] Ledford H. Engineered cell therapy for cancer gets thumbs up from FDA advisers. Nature. 2017; 547: 270.

[82] Allard B, Allard D, Buisseret L, Stagg J. The adenosine pathway in immuno-oncology. Nature Reviews. Clinical Oncology. 2020; 17: 611–629.

[83] Pasquini S, Contri C, Borea PA, Vincenzi F, Varani K. Adenosine and Inflammation: Here, There and Everywhere. International Journal of Molecular Sciences. 2021; 22: 7685.

[84] Franco R, Rivas-Santisteban R, Navarro G, Reyes-Resina I. Adenosine Receptor Antagonists to Combat Cancer and to Boost Anti-Cancer Chemotherapy and Immunotherapy. Cells. 2021; 10: 2831.

[85] Helms RS, Powell JD. Rethinking the adenosine-A_{2A}R checkpoint: implications for enhancing anti-tumor immunotherapy. Current Opinion in Pharmacology. 2020; 53: 77–83.

[86] Yu F, Zhu C, Xie Q, Wang Y. Adenosine A_{2A} Receptor Antagonists for Cancer Immunotherapy. Journal of Medicinal Chemistry. 2020; 63: 12196–12212.

[87] Yan W, Ling L, Wu Y, Yang K, Liu R, Zhang J, *et al*. Structure-Based Design of Dual-Acting Compounds Targeting Adenosine A_{2A} Receptor and Histone Deacetylase as Novel Tumor Immunotherapeutic Agents. Journal of Medicinal Chemistry. 2021; 64: 16573–16597.

[88] Churov A, Zhulai G. Targeting adenosine and regulatory T cells in cancer immunotherapy. Human Immunology. 2021; 82: 270–278.

[89] Wang Y, Deng W, Li N, Neri S, Sharma A, Jiang W, *et al*. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Frontiers in Pharmacology. 2018; 9: 185.

[90] Chen Y, Williams J, Ding I, Hernady E, Liu W, Smudzin T, *et al*. Radiation pneumonitis and early circulatory cytokine markers. Seminars in Radiation Oncology. 2002; 12: 26–33.

[91] Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nature Reviews. Cancer. 2018; 18: 313–322.

[92] Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Current Problems in Cancer. 2016; 40: 10–24.

[93] Bang A, Schoenfeld JD. Immunotherapy and radiotherapy for metastatic cancers. Annals of Palliative Medicine. 2019; 8: 312–325.

[94] Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, *et al*. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity. 2014; 41: 843–852.

[95] Ribas A, Wolchok JD. Combining cancer immunotherapy and targeted therapy. Current Opinion in Immunology. 2013; 25: 291–296.

[96] Walsh RJ, Sundar R, Lim JSJ. Immune checkpoint inhibitor combinations-current and emerging strategies. British Journal of Cancer. 2023; 128: 1415–1417.

[97] Tang T, Huang X, Zhang G, Hong Z, Bai X, Liang T. Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy. Signal Transduction and Targeted Therapy. 2021; 6: 72.

[98] Guo CX, Huang X, Xu J, Zhang XZ, Shen YN, Liang TB, *et al*. Combined targeted therapy and immunotherapy for cancer treatment. World Journal of Clinical Cases. 2021; 9: 7643–7652.

[99] Ebert PJR, Cheung J, Yang Y, McNamara E, Hong R, Moskalenko M, *et al*. MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade. Immunity. 2016; 44: 609–621.

[100] Dhasmana A, Dhasmana S, Haque S, Cobos E, Yallapu MM, Chauhan SC. Next-generation immune checkpoint inhibitors as promising functional molecules in cancer therapeutics. Cancer Metastasis Reviews. 2023; 42: 597–600.

[101] He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Research. 2020; 30: 660–669.

[102] Gaikwad S, Agrawal MY, Kaushik I, Ramachandran S, Srivastava SK. Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy. Seminars in Cancer Biology. 2022; 86: 137–150.

[103] Shi F, Xue R, Zhou X, Shen P, Wang S, Yang Y. Telitacicept as a BLyS/APRIL dual inhibitor for autoimmune disease. Immunopharmacology and Immunotoxicology. 2021; 43: 666–673.

[104] Zhang T, Lin Y, Gao Q. Bispecific antibodies targeting immunomodulatory checkpoints for cancer therapy. Cancer Biology & Medicine. 2023; 20: 181–195.

[105] Felices M, Lenvik TR, Davis ZB, Miller JS, Vallera DA. Generation of BiKEs and TriKEs to Improve NK Cell-Mediated Targeting of Tumor Cells. Methods in Molecular Biology. 2016; 1441: 333–346.

[106] Shi Y, Tomczak K, Li J, Ochieng JK, Lee Y, Haymaker C. Next-Generation Immunotherapies to Improve Anticancer Immunity. Frontiers in Pharmacology. 2021; 11: 566401.

[107] Dreier T, Lorenczewski G, Brandl C, Hoffmann P, Syring U, Hanakam F, *et al*. Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. International Journal of Cancer. 2002; 100: 690–697.

[108] Kufer P, Mack M, Gruber R, Lutterbüse R, Zettl F, Riethmüller G. Construction and biological activity of a recombinant bispecific single-chain antibody designed for therapy of minimal residual colorectal cancer. Cancer Immunology, Immunotherapy. 1997; 45: 193–197.

[109] Luke JJ, Barlesi F, Chung K, Tolcher AW, Kelly K, Hollebecque A, *et al*. Phase I study of ABBV-428, a mesothelin-CD40 bispecific, in patients with advanced solid tumors. Journal for Immunotherapy of Cancer. 2021; 9: e002015.

[110] Al Saber M, Biswas P, Dey D, Kaium MA, Islam MA, Tripty MIA, *et al*. A comprehensive review of recent advancements in cancer immunotherapy and generation of CAR T cell by CRISPR-Cas9. Processes. 2021; 10: 16.

[111] Sakellariou-Thompson D, Forget MA, Hinchcliff E, Celestino J, Hwu P, Jazaeri AA, *et al*. Potential clinical application of tumor-infiltrating lymphocyte therapy for ovarian epithelial cancer prior or post-resistance to chemotherapy. Cancer Immunology, Immunotherapy. 2019; 68: 1747–1757.

[112] Verdegaal EME, Santegoets SJ, Welters MJP, de Bruin L, Visser M, van der Minne CE, *et al*. Timed adoptive T cell transfer during chemotherapy in patients with recurrent platinum-sensitive epithelial ovarian cancer. Journal for Immunotherapy of Cancer. 2023; 11: e007697.

[113] Fesnak AD, June CH, Levine BL. Engineered T cells: the promise and challenges of cancer immunotherapy. Nature Reviews. Cancer. 2016; 16: 566–581.

[114] Vonderheide RH, June CH. Engineering T cells for cancer: our synthetic future. Immunological Reviews. 2014; 257: 7–13.

[115] Rezvani K. Adoptive cell therapy using engineered natural killer cells. Bone Marrow Transplantation. 2019; 54: 785–788.

[116] Herrera L, Santos S, Vesga MA, Carrascosa T, Garcia-Ruiz JC, Pérez-Martínez A, *et al*. The Race of CAR Therapies: CAR-NK Cells for Fighting B-Cell Hematological Cancers. Cancers. 2021; 13: 5418.

[117] Wang J, Toregrosa-Allen S, Elzey BD, Utturkar S, Lanman NA, Bernal-Crespo V, *et al*. Multispecific targeting of glioblastoma with tumor microenvironment-responsive multifunctional engineered NK cells. Proceedings of the National Academy of Sciences of the United States of America. 2021; 118: e2107507118.

[118] Wang W, Liu Y, He Z, Li L, Liu S, Jiang M, *et al*. Breakthrough of solid tumor treatment: CAR-NK immunotherapy. Cell Death Discovery. 2024; 10: 40.

[119] Teng KY, Mansour AG, Zhu Z, Li Z, Tian L, Ma S, *et al*. Off-the-Shelf Prostate Stem Cell Antigen-Directed Chimeric Antigen Receptor Natural Killer Cell Therapy to Treat Pancreatic Cancer. Gastroenterology. 2022; 162: 1319–1333.

[120] Feins S, Kong W, Williams EF, Milone MC, Fraietta JA. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. American Journal of Hematology. 2019; 94: S3–S9.

[121] Perez-Potti A, Rodríguez-Pérez M, Polo E, Pelaz B, Del Pino P. Nanoparticle-based immunotherapeutics: From the properties of nanocores to the differential effects of administration routes. Advanced Drug Delivery Reviews. 2023; 197: 114829.

[122] Liu H, Moynihan KD, Zheng Y, Szeto GL, Li AV, Huang B, *et al*. Structure-based programming of lymph-node targeting in molecular vaccines. Nature. 2014; 507: 519–522.

[123] Song X, Xu J, Liang C, Chao Y, Jin Q, Wang C, *et al*. Self-Supplied Tumor Oxygenation through Separated Liposomal Delivery of H_2O_2 and Catalase for Enhanced Radio-Immunotherapy of Cancer. Nano Letters. 2018; 18: 6360–6368.

[124] Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, *et al*. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. Journal of Clinical Oncology. 2015; 33: 1889–1894.

[125] Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, *et al*. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. Journal of Immunotherapy. 2007; 30: 825–830.

[126] Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, *et al*. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. Journal of Clinical Oncology. 2023; 41: 1200–1212.

[127] Fong L, Kwek SS, O'Brien S, Kavanagh B, McNeel DG, Weinberg V, *et al*. Potentiating endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA4 blockade and GM-CSF. Cancer Research. 2009; 69: 609–615.

[128] Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, *et al*. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. The Lancet. Oncology. 2014; 15: 700–712.

[129] Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, *et al*. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014; 515: 558–562.

[130] Kreidieh FY, Tawbi HA. The introduction of LAG-3 checkpoint blockade in melanoma: immunotherapy landscape beyond PD-1 and CTLA-4 inhibition. Therapeutic Advances in Medical Oncology. 2023; 15: 17588359231186027.

[131] Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, *et al*. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Research. 2012; 72: 917–927.

[132] Brignone C, Escudier B, Grygar C, Marcu M, Triebel F. A phase I pharmacokinetic and biological correlative study of IMP321, a novel MHC class II agonist, in patients with advanced renal cell carcinoma. Clinical Cancer Research. 2009; 15: 6225–6231.

[133] Cao E, Zang X, Ramagopal UA, Mukhopadhaya A, Fedorov A, Fedorov E, *et al*. T cell immunoglobulin mucin-3 crystal structure reveals a galectin-9-independent ligand-binding surface. Immunity. 2007; 26: 311–321.

[134] Hosseinalizadeh H, Mahmoodpour M, Samadani AA, Roudkenar MH. The immunosuppressive role of indoleamine 2, 3-dioxygenase in glioblastoma: mechanism of action and immunotherapeutic strategies. Medical Oncology. 2022; 39: 130.

[135] Mitchell TC, Hamid O, Smith DC, Bauer TM, Wasser JS, Olszanski AJ, *et al*. Epacadostat Plus Pembrolizumab in Patients

With Advanced Solid Tumors: Phase I Results From a Multicenter, Open-Label Phase I/II Trial (ECHO-202/KEYNOTE-037). Journal of Clinical Oncology. 2018; 36: 3223–3230.

[136] Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, *et al*. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. Journal of Clinical Oncology. 2014; 32: 1020–1030.

[137] Zitvogel L, Pitt JM, Daillère R, Smyth MJ, Kroemer G. Mouse models in oncoimmunology. Nature Reviews. Cancer. 2016; 16: 759–773.

[138] Ahmed J, Das B, Shin S, Chen A. Challenges and Future Directions in the Management of Tumor Mutational Burden-High (TMB-H) Advanced Solid Malignancies. Cancers. 2023; 15: 5841.

[139] Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, *et al*. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nature Genetics. 2019; 51: 202–206.

[140] Mastrogiovanni M, Donnadieu E, Pathak R, Di Bartolo V. Subverting *Attachment* to Prevent *Attacking*: Alteration of Effector Immune Cell Migration and Adhesion as a Key Mechanism of Tumor Immune Evasion. Biology. 2024; 13: 860.

[141] Landi L, D'Incà F, Gelibter A, Chiari R, Grossi F, Delmonte A, *et al*. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. Journal for Immunotherapy of Cancer. 2019; 7: 316.

[142] Lavin Y, Kobayashi S, Leader A, Amir EAD, Elefant N, Bigenwald C, *et al*. Innate Immune Landscape in Early Lung Adenocarcinoma by Paired Single-Cell Analyses. Cell. 2017; 169: 750–765.e17.

[143] Azizi E, Carr AJ, Plitas G, Cornish AE, Konopacki C, Prabhakaran S, *et al*. Single-Cell Map of Diverse Immune Phenotypes in the Breast Tumor Microenvironment. Cell. 2018; 174: 1293–1308.e36.

[144] Guo X, Zhang Y, Zheng L, Zheng C, Song J, Zhang Q, *et al*. Global characterization of T cells in non-small-cell lung cancer by single-cell sequencing. Nature Medicine. 2018; 24: 978–985.

[145] Sade-Feldman M, Yizhak K, Bjorgaard SL, Ray JP, de Boer CG, Jenkins RW, *et al*. Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. Cell. 2018; 175: 998–1013.e20.

[146] Bai R, Chen N, Li L, Du N, Bai L, Lv Z, *et al*. Mechanisms of Cancer Resistance to Immunotherapy. Frontiers in Oncology. 2020; 10: 1290.

[147] Said SS, Ibrahim WN. Cancer Resistance to Immunotherapy: Comprehensive Insights with Future Perspectives. Pharmaceutics. 2023; 15: 1143.

[148] Yu S, Wang Y, He P, Shao B, Liu F, Xiang Z, *et al*. Effective Combinations of Immunotherapy and Radiotherapy for Cancer Treatment. Frontiers in Oncology. 2022; 12: 809304.

[149] Staudt RE, Carlson RD, Snook AE. Targeting gastrointestinal cancers with chimeric antigen receptor (CAR)-T cell therapy. Cancer Biology & Therapy. 2022; 23: 127–133.

[150] Zhou X, Yao Z, Bai H, Duan J, Wang Z, Wang X, *et al*. Treatment-related adverse events of PD-1 and PD-L1 inhibitor-based combination therapies in clinical trials: a systematic review and meta-analysis. The Lancet. Oncology. 2021; 22: 1265–1274.

[151] Siebert JC, Walker EB. Monitoring cytokine profiles during immunotherapy. Immunotherapy. 2010; 2: 799–816.

[152] Bharadwaj P, Riekofski C, Lin S, Seaman MS, Garber DA, Montefiori D, *et al*. Implementation of a three-tiered approach to identify and characterize anti-drug antibodies raised against HIV-specific broadly neutralizing antibodies. Journal of Immunological Methods. 2020; 479: 112764.

[153] Waddington KE, Papadaki A, Coelewij L, Adriani M, Nytrova P, Kubala Havrdova E, *et al*. Using Serum Metabolomics to Predict Development of Anti-drug Antibodies in Multiple Sclerosis Patients Treated With IFNβ. Frontiers in Immunology. 2020; 11: 1527.