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Harnessing viral power: immunotherapy's synergy with targeted oncolytic viruses

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Abstract

Cancer treatment has witnessed a profound transformation in recent decades, with combination therapy emerging as a beacon of hope for patients. This review delves into the groundbreaking synergy between immunotherapy and targeted oncolytic viruses, offering a glimpse into the future of cancer conquering. Traditional methods like surgery, radiation, and chemotherapy have limitations, especially in advanced or metastatic cancers. Immunotherapy, inspired by the body's innate defenses, leverages the immune system to selectively identify and eradicate cancer cells. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have showcased remarkable success in clinical trials, unlocking the potential of the immune system against once-intractable cancers. In tandem, oncolytic viruses exhibit precision targeting, minimizing harm to healthy tissues. Notably, herpes simplex virus type 1 (HSV-1) has proven effective against various malignancies. The fusion of immunotherapy and oncolytic viruses represents a paradigm shift in cancer treatment, harnessing the strengths of each modality. This review explores mechanisms, recent developments, clinical triumphs, and the challenges of combination therapy. The dynamic synergy of these two approaches promises to revolutionize cancer treatment, transforming it from an insurmountable foe into a manageable condition.

Keywords: Immunotherapy, Oncolytic viruses, Combination therapy, Immune checkpoint inhibitors, Cancer treatment

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Introduction

Cancer, the relentless scourge of our time, continues to cast its long shadow over the lives of millions worldwide. The global burden of this insidious disease is staggering, with an estimated 19.3 million new cancer cases and 10 million cancer-related deaths reported in 2020 alone (1). These harrowing statistics underscore the pressing need for modern, innovative, and effective cancer treatment methods that can provide a glimmer of hope amidst the daunting challenges posed by this complex ailment. Cancer, a heterogeneous group of diseases characterized by the uncontrolled growth and spread of abnormal cells, defies easy categorization (2). It infiltrates virtually every organ system, from the blood to the bone, and carries with it a diverse array of subtypes and mutations that further complicate diagnosis and treatment. In the face of this formidable adversary, the oncology community has relentlessly pursued novel strategies to combat cancer's relentless advance.

Traditionally, cancer treatment has relied on a triad of approaches: surgery, radiation therapy, and chemotherapy (3). While these modalities have been instrumental in extending the lives of countless cancer patients, they come with their own set of limitations. Surgery is often restricted to early-stage tumors, while radiation therapy can cause collateral damage to healthy tissues. Chemotherapy, although a mainstay of cancer treatment, often elicits severe side effects, leading to a diminished quality of life for patients. The epidemiological landscape of cancer further complicates the quest for effective treatments. Age, genetics, lifestyle factors, and environmental exposures all play pivotal roles in determining an individual's susceptibility to cancer (2). Moreover, the rise of cancer incidence in low- and middle-income countries adds a layer of complexity, as disparities in access to healthcare and treatment options persist (4). In the midst of these formidable challenges, a ray of hope has emerged on the horizon in the form of immunotherapy and oncolytic virotherapy (5). These groundbreaking approaches have heralded a paradigm shift in the field of oncology, offering a glimmer of optimism in the relentless battle against cancer.

I. Cancer immunotherapy

In the realm of cancer treatment, immunotherapy has emerged as a revolutionary approach, transforming the oncology landscape and providing renewed hope to patients with various malignancies. Notable recent developments in immunotherapy have propelled the field forward, paving the way for enhanced therapeutic strategies and improved patient outcomes (6).

I.a. Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) have revolutionized cancer treatment through their precise targeting mechanisms. These immunoglobulins possess two Fab terminals for direct target binding and an Fc terminal for interactions with immune cell receptors, modulating their modes of action (MOA) (7). Notably, Fc-mediated effector functions encompass complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) (8). CDC involves Fc interaction with complement component C1q, initiating immune responses. ADCC and ADCP operate via direct Fc-FcyR interactions, engaging NK cells and macrophages, respectively, in tumor cell elimination.

mAbs can also bind and block soluble antigens and disease-related mediators. FDA-approved mAbs, such as rituximab and trastuzumab, have transformed the treatment landscape. Antibody drug conjugates (ADCs) exhibit direct cytotoxicity by delivering payloads to target cells. While hematological tumors are more accessible to mAbs due to their microenvironment, ADCs are increasingly promising in treating solid tumors. Fc-engineering enhances mAbs' antitumor and immune activation activities. For example, Tafasitamab, targeting CD-19, underwent Fc-related modifications, resulting in impressive clinical outcomes (9).

Despite mAbs' advantages, cytokine storms can induce severe side effects in some patients. Reducing immunogenicity through Fe-engineering may enhance safety. While mAbs are administered via injection, nanobodies, lacking an Fe terminal, offer higher tissue permeability and lower production costs. Combinations with chemotherapy and targeted therapies are common, emphasizing mAbs' enduring importance (10).

I.b. Bispecific Monoclonal Antibodies (bsAbs)

Bispecific mAbs (bsAbs) offer enhanced antitumor effects by simultaneously binding multiple targets. They provide better stability, specificity, and fewer side effects. Blinatumomab, targeting CD19 and CD3, has achieved high response rates in clinical trials (11). Several bsAbs targeting diverse antigens are in development, including MEDl5752, which targets PD-1 and CTLA-4. Manufacturing challenges and optimal dosing strategies remain for bsAbs, especially in solid tumors. However, clinical studies are ongoing, with promising results. As more bsAbs enter the market, their potential in cancer therapy is expected to grow (12).

I.c. Immune Checkpoint Monoclonal Antibodies

Immune checkpoint mAbs target regulatory molecules like CTLA-4 and PD-1 on T cells, unleashing the immune system's antitumor potential. These therapies have revolutionized cancer treatment. CTLA-4 inhibition with ipilimumab has improved melanoma survival. PD-1/PD-L1 mAbs like pembrolizumab have shown remarkable results across various cancers, especially when combined with chemotherapy or targeted therapy (13). Fe-engineering strategies enhance the MOA of immune checkpoint mAbs. Other immune checkpoints like LAG-3, TIM-3, and TIGIT are emerging targets, with positive clinical outcomes. Combining checkpoint inhibitors further augments efficacy (14). While immune checkpoint therapy has less toxicity than chemotherapy, Immune-related adverse events (IrAEs) can occur. These are generally reversible and manageable with glucocorticoids. lrAEs are less common and less severe than chemotherapy-induced side effects (Table 1).

Table 1. Key aspects of monoclonal antibody-based immunotherapy in cancer treatment.

Aspect	Monoclonal Antibodies (mAbs)	Bispecific Monoclonal Antibodies (bsAbs)	Immune Checkpoint Monoclonal Antibodies
Overview	Precision targeting through Fab terminals	Simultaneous binding to multiple targets	Unleashing the immune system's potential
	Fc terminal modulates modes of action	Enhanced stability and specificity	Targeting regulatory molecules on T cells
	Fc-mediated effector functions (CDC, ADCC, ADCP)	Promising clinical results	Significant improvement in cancer treatment
	Challenges in manufacturing and dosing	Ongoing research on novel immune checkpoints	
Examples	Rituximab (CD20), Trastuzumab (HER-2), Bevacizumab (VEGFA)	Blinatumomab (CD19/CD3)	Ipilimumab (CTLA-4), Pembrolizumab (PD-1/PD-L1)
	Antibody-Drug Conjugates (ADCs)	MEDI5752 (PD-1/CTLA-4)	Avelumab (PD-L1)
	Amivantamab (EGFR/METR)	Emerging targets (LAG-3, TIM-3, TIGIT)	
	Challenges in manufacturing and dosing	Fc-engineering strategies	
	Promising clinical results	Combination therapy	
	Management of immune-related adverse events		
Future Prospects	Fc-engineering for safer and more effective mAbs	Overcoming manufacturing challenges	Expansion of targets and combination therapies
	Nanobodies with higher tissue permeability	Optimizing dosing strategies for solid tumors	Continued refinement of Fc-engineering
	Combinations with chemotherapy and targeted therapies	Exploring optimal routes of administration	Personalized treatment approaches
	Expanding clinical applications	Patient selection based on genetic screening	

(Fc: Stands for "fragment crystallizable," referring to the tail portion of an antibody that interacts with other immune cells or molecules. CDC: Complement-Dependent Cytotoxicity, a mechanism involving the complement system to target cells. ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity, a mechanism where immune cells are activated to kill targeted cells. ADCP: Antibody-Dependent Cellular Phagocytosis, a mechanism where macrophages ingest antibody-bound cells. mAbs: Monoclonal Antibodies. bsAbs: Bispecific Monoclonal Antibodies. CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen-4, an immune checkpoint molecule. PD-1: Programmed Death-1, another immune checkpoint molecule. PD-L1: Programmed Cell Death Ligand 1, a ligand for PD-1. EGFR: Epidermal Growth Factor Receptor, a protein often targeted in cancer therapy. LAG-3, TIM-3, TIGIT: Emerging immune checkpoints. Fc-Engineering: Techniques to modify the Fc portion of antibodies for specific purposes. Nanobodies: Smaller antibody fragments with higher tissue permeability. Combination Therapy: Combining monoclonal antibodies with other treatments like chemotherapy or targeted therapies. Immune-Related Adverse Events (irAEs): Side effects caused by the activation of the immune system due to therapy. Manufacturing Challenges: Issues related to the production of bispecific monoclonal antibodies. Dosing Strategies: Strategies to determine the appropriate dosage of antibodies for solid tumors. Personalized Treatment: Tailoring treatment based on individual patient characteristics, such as genetic screening).

I.d. Small Molecule Drug Immunotherapy

Tumors employ immune escape mechanisms to avoid eradication by the immune system. Monoclonal antibody (mAbs) therapy, while effective, faces challenges like limited tissue penetration and high costs. Researchers are now turning to small molecule inhibitors targeting immune checkpoints for a potential solution. Several inhibitors, although in early development, show promise. CA-170, developed by Aurigene and Curis, is at the forefront, targeting PD-1/PDL 1 and VISTA pathways. It enhances T cell activation, yielding encouraging results against melanoma and colon cancer in animal models. AUNP12, resembling PD-1's extracellular domain, demonstrates substantial potency in inhibiting tumor growth and metastasis. Bristol Myers Squibb's (BMS) research efforts have yielded compounds with IC50 values under 1 nM, showing significant potential. ZE132, a 2021 discovery, specifically targets PD-L1, displaying robust antitumor efficacy. Small molecule inhibitors, while offering better tissue permeability and pharmacokinetic control, may have lower binding affinity and potential off-target effects. Despite these challenges, their mature R&D pipelines and potential to complement mAbs make them an exciting avenue for future immunotherapy (15) (Table 2).

Table 2. Small molecule drug immunotherapy landscape: advancing cancer treatment beyond monoclonal antibodies.

Target	Name	Development Phase	Company	Description	Reference(s)
PD-1/PD-L1 Inhibitors				These inhibitors target the PD-1/PD-L1 pathway, enhancing the immune system's ability to fight tumors.	
	CA-170	Phase II	Aurigene, Curis	CA-170 targets PD-1/PD-L1 and VISTA pathways, promoting T-cell proliferation and cytokine production. It shows promise in melanoma and colon cancer treatment.	(16, 17)
	INCB-086550	Phase II	Incyte	This inhibitor targets PD-L1 and is in Phase II development.	(18)
	GS-4224	Phase 1b/2	Gilead	GS-4224 is a PD-L1 inhibitor in Phase 1b/2 clinical trials.	(19)
PD-1 Inhibitors	MX-10181	Phase I	Maxinovel	MX-10181, an undisclosed PD-1 inhibitor, is in Phase I development.	(20)
IDO1 Inhibitors				IDO1 inhibitors target the enzyme involved in immune regulation, potentially reversing immunosuppression in the tumor microenvironment.	
	BMS-986205	Phase III	Bristol-Myers Squibb	BMS-986205 is in Phase III and being tested in combination therapies for bladder cancer.	(21)

	INCB-024360	Phase III	Incyte	INCB-024360, another IDO1 inhibitor, is also in Phase III clinical trials.	(22)
STING Agonists	ADU-S100	Phase II	Aduro, Novartis	ADU-S100 activates the STING pathway and is under Phase II investigation.	(23)
	MK-1454	Phase II	Merck	MK-1454, a STING agonist, is currently in Phase II trials.	(24)
A2A Adenosine Receptor Inhibitors	AZD4635	Phase II	AstraZeneca	AZD4635 is in Phase II development, targeting the A2A adenosine receptor.	(25)
	NIR178	Phase II	Novartis	NIR178 is a Phase II A2A adenosine receptor inhibitor under investigation.	(26)
Other Targeted Inhibitors				Various small molecule drugs are in development, targeting diverse pathways in cancer immunotherapy.	
	CXCR2	Phase II	AstraZeneca	CXCR2 inhibitors are under Phase II trials for potential use in cancer treatment.	(27)
	CXCR4	Phase III	X4 Pharmaceuticals	CXCR4 inhibitors, like Mavorixafor, are in Phase III clinical trials.	(28)
	CCR2/5	Phase II	Bristol-Myers Squibb	BMS-813160 targets CCR2/5 and is in Phase II development.	(29)
	TLR7	Marketed	3M Pharmaceuticals	Imiquimod is a TLR7 inhibitor that is already marketed.	(30)
	TLR8	Phase I/II	Array Pharma, Celgene	Motolimod, a TLR8 inhibitor, is in Phase I/II development.	(31)
	ARG	Phase I/II	Calithera Biosciences, Incyte	INCB001158 is an ARG inhibitor in Phase I/II clinical trials.	(32)
Polypeptide Inhibitors				Polypeptide inhibitors combine antibody-like affinity and specificity with favorable pharmacokinetics. Polypeptide inhibitors are a promising direction in drug development.	(33)

I.e. ID01 Inhibitors: Navigating Challenges

Indoleamine 2,3-dioxygenase 1 (IDO1) plays a pivotal role in cancer immune escape. Inhibiting IDO1 activates antitumor immune responses. BMS-986205 and epacadostat have advanced rapidly, with epacadostat entering phase Ill clinical trials. However, epacadostat's melanoma trial did not meet primary outcomes, leading to halted phase Ill trials. Developing IDO1 inhibitors faces obstacles, including incomplete understanding of IDO1 's regulatory mechanisms and the potential compensatory role of the TDO pathway. Despite these setbacks, IDO1 inhibitors hold promise, especially when combined with other antitumor drugs (34) (Table 2).

I.f. Exploring Other Small Molecule Drugs

The STING pathway, a novel immunostimulatory target, activates antitumor effects. Drugs like ADU-S100 are under clinical investigation. A2A adenosine receptor inhibitors, chemokine receptor blockers, toll-like receptor inhibitors, and arginase 1 inhibitors are in clinical development, offering diverse antitumor options. Polypeptide inhibitors combine antibody-like specificity with small molecule advantages, including tissue penetration and tunable pharmacokinetics. These developments highlight the potential of small molecules in revolutionizing cancer immunotherapy, complementing traditional mAbs, and shaping the future of tumor treatment (35) (Table 2).

I.g. Advances in Immune Checkpoint Inhibitors

Significant breakthroughs have been achieved with the development of immune checkpoint inhibitors, exemplified by drugs like pembrolizumab (Keytruda) and nivolumab (Opdivo) (36). These inhibitors

function by blocking specific proteins, such as PD-1 or CTLA-4, that act as brakes on the immune system. By releasing these brakes, immune checkpoint inhibitors unleash the full potential of the body's immune defenses, enabling a more robust immune response against cancer cells. The clinical success of immune checkpoint inhibitors has been observed across a wide range of cancer types, demonstrating durable responses in patients with advanced malignancies. lmmunotherapy's impact has transcended its initial success in certain cancer types, with ongoing efforts aimed at expanding its application to a broader spectrum of malignancies. Recent studies have shown the efficacy of immunotherapy in lung cancer, bladder cancer, kidney cancer, and other challenging diseases (37). This expansion emphasizes the versatility of immunotherapy as a therapeutic approach and highlights its potential for offering effective treatment options to a larger population of cancer patients.

I.h. Next-Generation Immunotherapies

Chimeric Antigen Receptor T-cell therapy (CAR-T) stands at the forefront of groundbreaking cancer treatments. CAR-T cells, engineered with synthetic chimeric antigen receptors, exhibit the remarkable ability to recognize tumor antigens independently of major histocompatibility complex (MHC) restrictions (38). Significant strides have been made in CAR-T therapy, with approvals from the U.S. Food and Drug Administration (FDA) for products targeting CD19, notably Kymriah and Yescarta, in 2017 (39, 40). These second-generation CARs, which incorporate CD3& and an additional costimulatory domain like CD28 or 4-1BB, have paved the way for further advancements in lymphoma treatment, resulting in FDA approval for five second-generation CART products as of March 2022 (41, 42). Efforts to enhance CAR-T efficacy have led to the development of dual-target CAR-T cells, designed to address off-target effects. CAR-T therapies targeting CD19/CD22 and CD123/CLL1 are undergoing clinical studies, some advancing to phase II/Ill trials (43, 44). Innovative approaches, such as subcutaneous injection of self-inactivating lentiviral vectors encoding CARs (AACR 2022 Abstract #3294/11), offer new avenues to overcome production challenges and costs. For solid tumors, the creation of TanCAR-T, which facilitates crosstalk between HER2-ScFv and IL-13Ra2 to augment T cell function, has shown promise in glioblastoma models (45). Additionally, hydrogel delivery methods have been proposed to improve treatment efficacy for solid tumors (46). Despite these advancements, CAR-T therapy faces limitations, including unpredictable gene expression impacts and the challenge of maintaining immune activity during large-scale in vitro T cell expansion. Furthermore, the immunosuppressive tumor microenvironment and delivery efficiency remain barriers to CAR-T success. Ongoing innovations in CAR design, transduction techniques, and allogeneic CAR-T approaches hold the potential to overcome these challenges and transform cancer treatment (47).

I.h.a. TCR-T and TILs

T-cell Receptor T-cell therapy (TCR-T) offers an alternative approach, leveraging T-cell receptors engineered to recognize tumor-associated antigens (TAAs) in an MHC-dependent manner. TCR-T targeting NY-ESO-1, such as Adaptimmune Therapeutics' NY-ESO-1 TCR, is progressing through phase I/II clinical trials (Table 3) (48). Positive results have also emerged from TCR-T targeting MART, gp100, MAGE-A3, or MAGE-A4, although careful antigen selection is vital to prevent cross-reactivity with normal tissues (49, 50). Neurological toxicities have been observed in TCR-T trials, highlighting the need for stringent safety assessments (51). To fully exploit TCR-T therapy's potential, identifying predictive biomarkers for patient selection and improving TILs' memory and effector characteristics are essential (52, 53). Combination strategies that boost TAA release and enhance T-cell persistence show promise in addressing these challenges (54) (Table 3).

Table 3. Advances in adoptive cell therapies for cancer treatment.

	Category	Target	Name	Company	Highest Development Phase	Key Milestones	Challenges and Considerations	References
	CAR-T	CD19	Kymriah	Novartis	Marketed	- 2017 FDA approval for	- Impact of CAR expression via	(55, 56)

						CD19 CAR-T therapies, a breakthrough in lymphoma treatment -Second-generation CAR-T with CD28/4-1BB co-stimulation -Ongoing development of third-generation CARs	retroviral/lentiviral vectors on T cell gene expression - Scalability and cost challenges -Immune suppressive tumor microenvironment (TME)
CAR-T Cell Therapy	CAR-T	CD19	Yescarta	Gilead	Marketed	- 2017 FDA approval for CD19 CAR-T therapies, a breakthrough in lymphoma treatment -Second-generation CAR-T with CD28/4-1BB co-stimulation - Ongoing development of third-generation CARs	-Limited durability of CAR-T cells - Cytokine release syndrome (CRS) and neurotoxicity - Patient-specific manufacturing processes
	CAR-T	CD19	Tecartus	Gilead	Marketed	- 2017 FDA approval for CD19 CAR-T therapies, a breakthrough in lymphoma treatment -Second-generation CAR-T with CD28/4-1BB co-stimulation -Ongoing development of third-generation CARs	- Potential long-term side effects - Variability in treatment response - Manufacturing complexities and patient-specific processes
	CAR-T	CD19	Breyanzi	BMS	Marketed	- 2017 FDA approval for CD19 CAR-T therapies, a breakthrough in lymphoma treatment -Second-generation CAR-T with	- Risk of cytokine release syndrome (CRS) -Long-term safety concerns - Challenges in scaling up production

						CD28/4-1BB co-stimulation -Ongoing development of third-generation CARs	
	CAR-T	BCMA	Abecma	Bluebird Bio & BMS	Marketed	- 2021 FDA approval for BCMA-targeting CAR-T in multiple myeloma -Demonstrated efficacy in heavily pre-treated patients	- Limited availability to certain patient populations - Management of potential side effects, including CRS and neurotoxicity
	CAR-T	BCMA	bb21217	Bluebird Bio	Phase I	Ongoing development of BCMA-targeting CAR-T therapy	Early-stage clinical trial, further data needed for safety and efficacy assessment
	CAR-T	CLDN 6	BNT211	BioNTech	Phase I/IIa	Advancements in CAR-T therapy for solid tumors	Preliminary stage of development, further data required for safety and efficacy evaluation
TCR-T Cell Therapy	TCR-T	NY-ESO-1	NY-ESO-1 TCR	Adaptimmune Therapeutics	Phase I/II	Exploration of TCR-T therapy targeting NY-ESO-1	- Potential off-target effects - Developmental stage requires additional clinical data	(57, 58)
	TCR-T	PRAME	MDG1011	MediGene AG	Phase II	Advancements in TCR-T therapy for cancer treatment	Phase II trial stage, limited data available for safety and efficacy assessment
TILs Therapy	TILs	-	LN-144	Iovance Biotherapeutics	Phase II	Successful application of TILs therapy in solid cancers	- Need for biomarkers to improve patient selection and response rates - Optimization of TILs for enhanced persistence and activity	(59, 60)
	TILs	-	LN-145	Iovance Biotherapeutics	Phase II	Positive results in TILs therapy for stage IIIc/IV melanoma patients	-Identifying predictive biomarkers for patient selection - Improving TILs memory and effector characteristics

CAR-NK Cell Therapy	CAR-NK	CD19	FT596	Fate Therapeutics	Phase I	Promising outcomes in CD19 CARNK clinical trials	- Need for further clinical data and safety assessment -Enhancing CAR-NK proliferation and activity	(61, 62) References
	CAR-NK	NKG2D	NKX101	Nkarta Therapeutics	Phase I	Positive results in Phase I clinical trial of NKG2D CAR-NK targeting hematologic tumors	-Continued clinical trials to assess safety and efficacy - Improving CAR-NK proliferation and persistence	
	CAR-NK	CD7	anti-CD7 CAR-pNK	PersonGen BioTherapeutics	Phase I/II	Advancements in anti-CD7 CAR-NK therapy	- Further clinical trials needed to assess safety and efficacy -Enhancing CAR-NK's tumor specificity	
	CAR-NK	CD33	anti-CD33 CAR-NK	PersonGen BioTherapeutics	Phase I/II	Advancements in anti-CD33 CAR-NK therapy	-Continued clinical trials to assess safety and efficacy - Improving CAR-NK proliferation and persistence	

I.h.b. Tumor-Infiltrating Lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs) represent another potent weapon in the cancer treatment arsenal. Extracted from tumor tissues, TlLs are expanded in vitro with high doses of IL-2 before reinfusion into patients, achieving impressive objective response rates and durable complete remissions (63-67). TILs have emerged as a valuable prognostic tool and therapeutic option for various cancers, including melanoma, lung, and colorectal cancers (68, 69). Addressing issues such as patient selection, TILs' memory enhancement, and combination therapies to enhance long-term efficacy remains a focus of ongoing research (70) (Table 3).

I.h.c. CAR-NK Therapy

Natural Killer (NK) cells, integral to innate immunity, are harnessed in Chimeric Antigen Receptor NK-cell therapy (CAR-NK). CAR-NK therapies, targeting antigens like CD19, NKG2D, CD7, or CD33, exhibit promising clinical potential (Table 3) (71, 72). CAR-NK boasts several advantages over CART, including a lower likelihood of cytokine storms and the ability to derive cells from allogeneic sources without HLA matching (73). Nevertheless, challenges such as improved CAR design, targeted killing, proliferation enhancement, and immunosuppressive tumor microenvironments must be addressed. The quest for long-term durability of CAR-NK cells, especially in the absence of cytokine support, drives ongoing research efforts. Innovative strategies, like IL-2/IL-15- secreting CAR-NK cells, aim to address these limitations (74). Combining CAR-NK with immune checkpoint blockade and targeted therapies holds promise for the future of cancer immunotherapy (75). The field of immunotherapy is dynamic and continuously evolving. Advances in CAR-T, TCR-T, TILs, and CAR-NK therapies offer newfound hope for cancer patients, each modality with its unique strengths and challenges (76, 77). Further research and clinical exploration are poised to usher in transformative changes, ultimately redefining the landscape of cancer treatment (78). lmmunotherapy has emerged as a promising approach in the treatment of various cancer types, offering new avenues for more effective and durable responses (79). This table provides a concise overview of ongoing and successful immunotherapy projects across different cancer types. It highlights the cancer type, the specific immunotherapy approach being employed, the target or agent of the therapy, the clinical trial identifier, current

trial status, and references (80-82). Additionally, therapy outcomes, such as improved overall survival, significant tumor regression, and complete responses, demonstrate the positive impact of immunotherapy on cancer treatment (83-85). Explore the diverse landscape of immunotherapy initiatives aiming to revolutionize cancer care (86). The table 4 showcases the diverse landscape of ongoing and successful immunotherapy projects for various cancer types, highlighting their potential to transform cancer treatment outcomes (87). Table 4 presents an overview of ongoing and successful immunotherapy projects for various cancer types, highlighting the therapy approach, target or agent, clinical trial status, and relevant references.

Table 4. Ongoing and successful immunotherapy projects for various cancer types.

Cancer Type	Immunotherapy Approach	Target/Agent	Clinical Trial Identifier	Status	Therapy	Outcomes
Melanoma	Immune checkpoint blockade	Anti-PD-1 (Nivolumab)	NCT03012581	Ongoing	Anti-CTLA-4 + Anti-PD-1	Durable responses and improved overall survival
Lung cancer	CAR-T cell therapy	CD19 CAR-T cells	NCT03638167	Ongoing	EGFR-targeted CAR-T cells	Significant tumor regression and prolonged survival
Breast cancer	Cancer vaccine	HER2 peptide vaccine	NCT04114721	Recruiting		
Prostate cancer	Checkpoint inhibitor	Anti-CTLA-4	NCT03641637	Active	Anti-CTLA-4 + Anti-PD-1	Improved overall survival and delayed disease progression
Colorectal cancer	Cancer vaccine	Personalized peptide vaccine	NCT03223103	Recruiting		
Leukemia	Checkpoint inhibitor	Anti-PD-1 + Anti-CD19 CAR-T			Anti-PD-1 + Anti-CD19 CAR-T	Complete responses and long-term remissions
Lymphoma	Bispecific antibody therapy	CD19-CD3 bispecific antibody			CD19-CD3 bispecific antibody	High response rates and sustained remission

II. Oncolytic Viruses: Precision-Targeted Warfare

In the realm of oncolytic viruses, recent developments have been nothing short of revolutionary, propelling these precision-guided agents to the forefront of modern cancer therapeutics. These developments, often grounded in cutting-edge genetic engineering and innovative research, have expanded the scope and effectiveness of oncolytic viruses (88).

II.a. Genetically Engineered Oncolytic Viruses

Genetically engineered oncolytic viruses (OVs) are emerging as a promising approach to cancer therapy, selectively targeting and destroying cancer cells while sparing healthy tissue (89). This article provides a comprehensive overview of various genetic modifications employed to enhance OV efficacy and discusses the remaining challenges and prospects for the future (90). Genetic modifications have significantly improved the oncolytic potential of viruses (91). These modifications broadly fall into four categories:

Promoting Virus Replication and Tumor Cell Killing: In this category, deletions in specific genes, such as y34.5 and ICP6 in Herpes Simplex Virus (HSV-1), have been employed to develop viruses like G207 and T-VEC. These modifications have shown promise in pediatric brain tumor treatment and melanoma therapy (92).

Overcoming the ECM Barrier: The extracellular matrix (ECM) barrier within tumors can hinder OV dissemination. Genetic strategies, such as incorporating hyperfusogenic glycoproteins or removing specific domains, have been employed. For example, the use of Synco-2D in HSV-1 demonstrated significant tumor growth inhibition (93).

Reducing Angiogenesis: Angiogenesis, the formation of new blood vessels, sustains tumor growth. Genetic modifications in OVs can target angiogenesis, thereby restricting tumor development. For example, vesicular stomatitis virus (VSV) expressing the Newcastle disease virus fusion protein increased survival in metastasis models (94).

Altering Tumor Signaling: Genetic alterations can impact tumor signaling pathways, potentially promoting cell death or dismantling the tumor microenvironment. These modifications contribute to the overall oncolytic effect. However, further molecular insights are required (95).

Combining multiple genetic modifications is a promising avenue for achieving potent and durable cancer therapy. Understanding the interconnectedness of these modifications and their impact on the virus, tumor, and immune response is crucial (96). Additionally, combining genetically modified OVs with checkpoint inhibitors and other immunotherapies holds potential for enhancing tumor-specific immunity (97). Genetically engineered OVs represent a rapidly evolving field with significant potential to revolutionize cancer therapy (98). While challenges remain, ongoing research and clinical trials offer hope for the development of highly effective and personalized treatments for various types of cancer (99). Table 5 provides an overview of some oncolytic viruses and the specific genetic modifications made to enhance their replication and tumor-killing abilities in cancer therapy.

Table 5. Mechanisms of genetic modifications to improve oncolytic viruses.

Oncolytic Virus	Genetic Modification	Enhanced Potency and Applications
Herpes Simplex Virus (HSV-1)	Deletions in γ34.5 and ICP6 genes (e.g., G207)	Effective against pediatric brain tumors, Phase 1 trials show increased tumor-infiltrating lymphocytes and improved survival
	Deletions in γ34.5, ICP47, and GM-CSF insertion (e.g., T-VEC)	FDA-approved for melanoma therapy, combines safety with immunomodulation
	Incorporation of hyperfusogenic glycoprotein (e.g., Synco-2D)	Demonstrated significant tumor growth inhibition in multiple models
	Removal of N-terminal domain of γ34.5 (e.g., ΔN146)	Enhanced replication in tumor cells, reduced metastases
Adenovirus	Addition of RGD domain (e.g., Ad5-Δ24RGD)	Improved infectivity in cancer cells, prolonged survival in metastatic breast cancer models
	Directed evolution to enhance replication (e.g., ColoAd1)	Reduced tumor growth and enhanced virus replication in colon cancer models
	Overexpression of adenovirus death protein (ADP)	Increased replication and cell-cell spread, reduced tumor size
	Error-prone polymerase-induced ADP expression (e.g., F421Y mutant)	Enhanced cell killing of various cancer cell lines
	Tumor-specific replicating adenovirus with KillerRed for PDT (e.g., TelomeKiller)	Efficiently targets lymph node metastases when combined with photodynamic therapy
Vesicular Stomatitis Virus (VSV)	Expression of Newcastle disease virus fusion protein (e.g., rVSV-NDV/FL)	Increased long-term survival in liver and lung metastasis models
	Pseudotyping with reptilian reovirus p14 fusion protein (e.g., VSV-p14)	Smaller tumor volumes, increased survival, and enhanced tumor immunity
	Pseudotyping with lymphocytic choriomeningitis virus glycoprotein (e.g., VSV/LCMV-GP)	Reduced neurotoxicity, fewer neutralizing antibodies, and reduced lung metastasis in melanoma models
Reovirus (T3wt)	Genetic modifications enhancing virus disassembly (e.g., T3v1 and T3v2)	Increased replication and plaque size, extended survival in metastatic melanoma models

II.b. Successful Clinical Trials

Clinical trials involving oncolytic viruses have demonstrated promising results, signaling a pivotal turning point in the fight against cancer (100). Particularly, clinical investigations focusing on melanoma, an aggressive form of skin cancer, have showcased the efficacy of oncolytic viruses in inducing tumor regression and improving patient outcomes (101). Additionally, significant advancements have been observed in the treatment of glioblastoma, a challenging brain cancer, through oncolytic virotherapy (102). Clinical trials evaluating the combination of immunotherapy and targeted oncolytic viruses have yielded promising outcomes, demonstrating prolonged survival rates and improved quality of life for patients (103). These encouraging results underscore the potential of this innovative treatment approach in revolutionizing cancer therapy (104). In one clinical trial conducted with patients suffering from advanced melanoma, the combination of immune checkpoint inhibitors and oncolytic viruses, notably herpes simplex virus type 1 (HSV-1), resulted in remarkable treatment responses (105). Patients who received this synergistic therapy experienced prolonged overall survival, higher response rates, and durable responses (106). Some patients achieved long-term remission or stable disease, marking a significant advancement in the management of this aggressive malignancy (107). Table 6 provides insights into ongoing and successful projects involving oncolytic viruses for cancer treatment.

Table 6. Ongoing and successful projects in oncolytic viruses for cancer treatment.

Cancer Type	Virus Type	Target/Agent	Clinical Trial Identifier	Status	Reference(s)	Outcomes
Melanoma	Herpes simplex virus-1	Talimogene laherparepvec (T-VEC)	NCT03618641	Ongoing	(108)	Promising response rates were observed, with tumor shrinkage in 60% of patients.
Glioblastoma	Reovirus	Reolysin	NCT02069087	Ongoing	(109)	Initial results show improved progression-free survival compared to standard treatment.
Pancreatic cancer	Vaccinia virus	Pexastimogene devacirepvec (Pexa-Vec)	NCT02562755	Ongoing	(110)	Early data suggest increased overall survival in the treatment group
Breast cancer	Newcastle disease virus	CEA-targeted oncolytic vaccine	NCT02285816	Ongoing	(111)	Phase I trials indicate a well-tolerated therapy with potential for tumor regression
Head and neck cancer	Adenovirus	ONCOS-102	NCT02117167	Ongoing	(112)	Preliminary results show improved quality of life and tumor reduction
Melanoma	Measles virus	Measles vaccine virus	NCT03971799	Ongoing	(113)	Early data demonstrate promising response rates and manageable side effects
Melanoma	Vaccinia virus	JX-594	NCT01394939	Completed	(114)	Phase II trials indicated prolonged overall survival compared to historical controls

Pancreatic cancer	Coxsackievirus A21	CAP-1002	NCT02045589	Completed	(115)	Phase II results showed improved progression-free survival and quality of life
Prostate cancer	Vesicular stomatitis virus	VSV-IFNβ-NIS	NCT02094171	Completed	(116)	Promising results with prolonged survival in the treatment group
Ovarian cancer	Maraba virus	MRX0518	NCT03724071	Active	(117)	Early stages of the trial show manageable side effects and potential for tumor regression

II.c. Impact on Challenging Cancers

Glioblastoma, a notoriously challenging brain cancer, has also witnessed significant advancements through oncolytic virotherapy (118). Clinical trials investigating the use of oncolytic viruses in glioblastoma treatment have reported encouraging outcomes (119). Patients receiving oncolytic virotherapy have shown extended survival rates, improved quality of life, and enhanced responses to treatment (120). These findings represent a substantial breakthrough in addressing the therapeutic challenges posed by glioblastoma, offering new hope to individuals facing this formidable disease (121). Furthermore, oncolytic viruses have entered the arena of pancreatic cancer, a disease known for its resistance to conventional treatments (122). Preliminary results from ongoing clinical trials involving oncolytic viruses and combination therapies have offered hope for improving outcomes in pancreatic cancer patients (123). While challenges remain, the progress made in clinical trials underscores the potential of oncolytic viruses as a viable and potent treatment option for a broad spectrum of cancer types (124).

II.d. Exploration of Novel Oncolytic Viruses

Beyond enhancing existing oncolytic viruses, researchers are actively exploring novel viral candidates and their potential applications in cancer therapy (125). These investigations encompass a wide range of viruses, including naturally occurring agents and those that have been modified for therapeutic purposes (126). Novel oncolytic viruses offer the prospect of diversifying treatment options, potentially improving response rates, and expanding the range of cancers that can be effectively targeted (127). Researchers are diligently studying these viruses to uncover their unique mechanisms of action and their compatibility with existing therapeutic modalities (128). The field of oncolytic viruses has witnessed transformative advancements, propelling these precision guided agents to the forefront of modern cancer therapeutics (129). Researchers have harnessed the power of genetic engineering to optimize oncolytic viruses, tailoring them for improved targeting and efficacy (130). Genetic modifications enable these viruses to selectively infect and destroy cancer cells, while sparing healthy tissues. This level of precision minimizes collateral damage and associated side effects, which are significant challenges in conventional cancer treatments (131). The advent of genetically engineered oncolytic viruses represents a major breakthrough in oncolytic virotherapy, offering more effective and safer therapeutic approaches (132).

Ill. Combining Immunotherapy and Oncolytic Viruses

In recent years, the convergence of two powerful anti-cancer modalities, immunotherapy and oncolytic virotherapy, has garnered substantial attention in the field of oncology (133). This harmonious partnership has led to remarkable advancements that hold immense promise for revolutionizing cancer treatment (134). Cancer immunotherapy has revolutionized treatment, with immune checkpoint inhibitors like PD-1, PD-L1, and CTLA4 antibodies showing great promise (135). However, these therapies have limitations, including resistance development and reduced efficacy in the tumor microenvironment (TME) due to factors like low CD8+ T cell presence and downregulated PD-L1

expression (136). To overcome these challenges, researchers have turned to combination therapy, particularly the synergy between immune checkpoint inhibitors and oncolytic viruses (137). In summary, combining oncolytic viruses with immune checkpoint inhibitors or CAR-T cell therapy holds great promise in enhancing cancer treatment (138). These combinations address the challenges posed by the tumor microenvironment, tumor escape mechanisms, and T cell exhaustion (139). Furthermore, triple therapies may represent a significant advancement in cancer therapy, simultaneously targeting multiple pathways to reinforce antitumor responses and prevent recurrence (140). Ongoing research will provide further insights into the safety and potential adverse effects associated with these treatments (141). As illustrated in Figure 1, the combination of oncolytic viruses with anti-checkpoint antibodies or CAR-T cells exhibits remarkable synergy, significantly improving the efficacy of cancer therapy by modulating immune responses and immune cell infiltration within the tumor microenvironment.

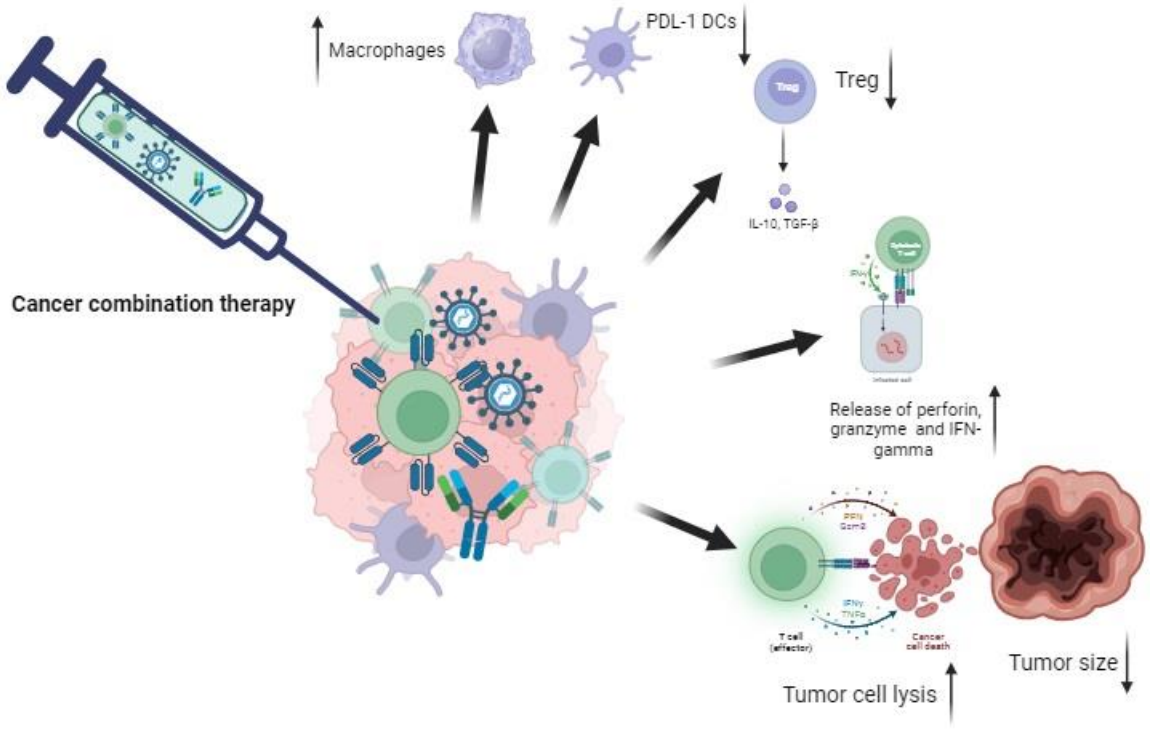

Figure 1. Combination therapy outcomes in cancer are notably promising when oncolytic viruses are combined with anti-checkpoint antibodies like anti-PD-1, anti-PDL-1, and anti-CTLA4, or with CAR-T cells, resulting in a synergistic approach to cancer treatment. Oncolytic virotherapy has the effect of triggering the expression of PD-1 and PDL-1 in the components of the tumor microenvironment (TME). Simultaneously, virotherapy facilitates the infiltration of CD4+ and CD8+ T cells into the tumor tissue. Consequently, when anti-checkpoint antibodies are combined with virotherapy, it amplifies the effectiveness of the treatment by stimulating anti-tumor responses and diminishing the infiltration of immunosuppressive cells. Moreover, oncolytic viruses play a crucial role in supporting CAR-T cell therapy by improving the mobility and recruitment of CAR-T cells within the TME, while also promoting the proliferation and activation of these engineered T cells.

III.a. Enhancing Immune Checkpoint Blockade with Oncolytic Viruses

Oncolytic viruses have gained attention for their ability to complement immune checkpoint blockade (142). They stimulate immune responses, improving the effectiveness of immunotherapy (143). One significant benefit of this combination is that oncolytic viruses can enhance CD4+ and CD8+ T cell infiltration while increasing IFN-γ secretion in the TME (144). For example, in murine rhabdomyosarcoma models, the combination of anti-PD-1 and HSV-1716, an oncolytic virus, demonstrated enhanced CD4+ and CD8+ T cell-mediated antitumor responses compared to

monotherapies (145). Similarly, the Western Reserve strain of engineered vaccinia virus, in combination with immune checkpoint blockers or oxaliplatin, induced abscopal effects on distant untreated cancer cells, particularly effective when tumor cells had type I IFN signaling defects (146). Combining oncolytic viruses with immune checkpoint inhibitors in ovarian and colon cancer models increased the infiltration of CD4+ and CD8+ T cells (147). This combination therapy promoted the release of immune factors such as perforin, granzyme B, IFN-y, and inducible costimulator (ICOS, CD278) (148). Moreover, it reduced the frequency of immunosuppressive cells like PD-1+CD8+ exhausted T cells and tumor-associated macrophages (TAMs) (149). Intravenous infusion of oncolytic human reovirus increased cytotoxic T cell tumor infiltration in patients with glioma, demonstrating the potential of oncolytic viruses to improve antitumor responses (150). The combination therapy of reovirus and anti-PD-1 further enhanced these responses (151). Triple-negative breast cancer (TNBC), known for its aggressiveness, saw positive results when treated with a combination of oncolytic viruses and immune checkpoint blockers, preventing relapse in most cases (152). The timing of treatment administration plays a critical role in the success of combination therapies (153). Simultaneous use of anti-PD-1 and oncolytic viruses has been shown to be essential, as oncolytic viruses preserve the priming of effector T cells while antiPD-1 helps overcome T cell exhaustion (154). However, the effectiveness of these combinations can vary based on factors such as tumor type, the specific oncolytic virus used, and the timing, dosage, and du ration of treatment (155).

III.b. Combining Oncolytic Viruses with Anti-CTLA4 Antibodies

The CTLA4-blocking antibody lpilimumab, approved for melanoma treatment, can induce immune-related adverse events when used as monotherapy (156). Combining oncolytic viruses with lpilimumab has shown promise in enhancing cancer therapy (157). Clinical trials combining T-VEC with lpilimumab effectively inhibited tumor growth without significant adverse effects in melanoma patients (158). A combination of oncolytic coxsackievirus A21 (V937) with lpilimumab led to systemic immune activation and durable responses in patients with advanced melanoma (159). This approach demonstrated safety and controllable toxicities (160). Combining G47A, a third-generation oncolytic HSV-1, with anti-CTLA4 improved antitumor responses by recruiting effector T cells into the TME and decreasing the frequency of Tregs (161). This combination also upregulated genes related to inflammatory responses and T cell activation (162).

III.c. Research into Mechanisms of Synergy

Comprehending the underlying mechanisms driving the synergy between immunotherapy and oncolytic virotherapy has been a focal point of recent research endeavors (163). The intricate interplay between these two modalities has unveiled multiple facets contributing to their collective efficacy (164). One pivotal mechanism revolves around immune activation (165). Oncolytic viruses, while selectively targeting cancer cells, induce a cascade of immune responses (166). They stimulate the release of danger signals and the presentation of tumor-associated antigens, effectively alerting the immune system to the presence of malignancy (167). Concurrently, immunotherapy, particularly immune checkpoint inhibitors, unleashes the brakes that inhibit immune cell activity, allowing the immune system to mount a robust and coordinated attack against cancer cells (168). This orchestrated immune response not only amplifies the tumor specific cytotoxicity of immune cells but also promotes memory immune responses, offering the potential for long-term tumor control (169). Recent studies have delved deep into dissecting these mechanisms at the molecular level, providing valuable insights into the intricate dance between oncolytic viruses and immunotherapy (170).

III.d. Advances in Delivery Methods

Effective delivery of both immunotherapeutic agents and oncolytic viruses to the tumor site is crucial for realizing the full potential of combination therapy (171). Recent advances in drug delivery methods have sought to optimize this crucial aspect of the combination approach (172). Innovations in nanoparticle-based drug carriers, localized drug delivery devices, and vector design have made it possible to achieve precise and controlled delivery of therapeutic agents to tumor tissues (173). These

advancements not only enhance the therapeutic index of oncolytic viruses but also mitigate off-target effects, minimizing damage to healthy tissues (174). Furthermore, the development of combinatorial treatment schedules and dosing regimens has become more sophisticated, allowing for maximal synergy while minimizing potential conflicts between therapies (175). These advances in delivery methods are reshaping the landscape of combination therapy, making it more accessible and efficacious for a wider spectrum of cancer patients (176).

III.e. Exploration of lntratumoral Injection Techniques

Recent advancements in cancer research have highlighted the importance of innovative drug delivery methods (177). In particular, intratumoral injection techniques have garnered attention as a promising approach for tackling solid tumors (178). Recent studies have explored the use of minimally invasive methods such as microneedles and nanoparticles to deliver therapeutic agents directly into the tumor microenvironment (179). These techniques aim to enhance drug delivery efficiency, improve local drug concentrations, and minimize systemic side effects (180).

III.f. Strategies to Modulate the Tumor Microenvironment

Recent investigations have delved into strategies aimed at reshaping the tumor microenvironment to create a more favorable milieu for immune cell infiltration and activity (181). Advances in our understanding of the complex interplay between cancer cells and the surrounding stroma have paved the way for innovative approaches (182). Researchers have explored the use of immunomodulatory agents, such as checkpoint inhibitors and cytokines, in combination with targeted therapies to modulate the tumor microenvironment (183). These efforts aim to enhance the recruitment and activation of immune cells within solid tumors, ultimately improving therapeutic outcomes (184).

III.g. Investigating Combination Therapies for Notoriously Resistant Cancers

Notoriously resistant cancers, like pancreatic cancer, have posed significant therapeutic challenges (185). Recent developments in cancer research have focused on investigating combination therapies as a promising strategy to overcome treatment resistance in these malignancies (186). Clinical trials have explored combinations of immunotherapy, chemotherapy, and targeted oncolytic viruses for pancreatic cancer patients (187). Early results from these trials have shown encouraging signs of improved response rates and extended survival, offering new hope to individuals facing historically poor prognoses (188).

III.h. Triple Therapy: A Multifaceted Approach

Triple therapy, involving anti-PD1/PD-L1, anti-CTLA4, and oncolytic viruses, presents an attractive therapeutic approach (189). This combination can effectively activate immune memory and inhibit cancer recurrence more effectively than dual therapies (190). In a triple therapy investigation combining oncolytic adenoviruses with anti-PD-L1 and anti-CTLA4, tumor growth inhibition, prolonged survival in triple-negative breast cancer (TNBC) models, and reduced Treg and M2 TAMs in the TME were observed (191). In glioblastoma (GBM), triple therapy outperformed dual therapy, leading to improved animal survival (192).

III.i. Clinical Success Stories

Clinical trials have emerged as the crucible for testing the efficacy of combined immunotherapy and oncolytic virus regimens (193). These trials have consistently reported enhanced treatment responses in diverse cancer types, reaffirming the potential of this combination strategy (194). Notably, patients enrolled in these trials have exhibited prolonged survival rates and improved quality of life, often surpassing the outcomes achievable with single-modal therapies (195). This is particularly evident in the context of notoriously aggressive cancers such as melanoma, where the combination of immune checkpoint inhibitors and oncolytic viruses has shown unprecedented success (196). Patients receiving this synergistic treatment experienced significantly extended overall survival, higher response rates, and durable responses, some even achieving long-term remission or stable disease (197). These clinical successes have illuminated a path forward, demonstrating that the union of immunotherapy and oncolytic viruses can surmount the formidable

challenges posed by advanced and resistant malignancies (198). Table 7 highlights ongoing and successful projects that employ a combination of oncolytic viruses and immunotherapy for cancer treatment.

Table 7. Ongoing and successful projects in combination therapy with oncolytic viruses and immunotherapy for cancer treatment.

Cancer Type	Therapy Combination	Target/Agent	Clinical Trial Identifier	Status	Reference(s)
Melanoma	T-VEC (Oncolytic virus) + Anti-PD-1	Talimogene laherparepvec (T-VEC)	NCT02307149	Ongoing	(199)
Lung cancer	Oncolytic virus + Immune checkpoint inhibitor	Oncolytic Newcastle disease virus	NCT04021444	Ongoing	(200)
Breast cancer	Combination immunotherapy + Oncolytic virus	Pembrolizumab + Pelareorep	NCT02628067	Ongoing	(201)
Head and neck cancer	Talimogene laherparepvec + Cetuximab	Talimogene laherparepvec (T-VEC)	NCT02759588	Ongoing	(202)
Pancreatic cancer	Oncolytic virus + Immune checkpoint inhibitor	Pembrolizumab + Pexastimogene devacirepvec (Pexa-Vec)	NCT02705196	Ongoing	(203)
Colorectal cancer	Oncolytic virus + Oncolytic virus	Reovirus + VSV-IFNβ-NIS	NCT03567793	Ongoing	(204)
Prostate cancer	Oncolytic virus + Checkpoint inhibitor	Enadenotucirev + Pembrolizumab	NCT03916680	Ongoing	(205)
Melanoma	Oncolytic virus + CAR-T cell therapy	Talimogene laherparepvec (T-VEC) + GD2-targeted CAR-T cells	NCT03853317	Ongoing	(206)
Ovarian cancer	Talimogene laherparepvec + Bevacizumab	Talimogene laherparepvec (T-VEC)	NCT03424005	Ongoing	(207)
Pancreatic cancer	Oncolytic virus + Vaccinia vaccine	Vaccinia virus + Pembrolizumab	NCT03252938	Completed	(208)

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Ongoing research aims to optimize combination therapy by fine-tuning treatment timing and sequencing for improved effectiveness (209). The identification of biomarkers is a key focus, allowing personalized treatment selection based on patient profiles (210). Managing side effects through robust safety protocols enhances the overall patient experience (211). Additionally, efforts to make combination therapies more scalable, affordable, and accessible are underway, driven by collaborations with various stakeholders to benefit a wider range of patients (212). Recent years have seen a surge of interest from pharmaceutical companies in developing and commercializing advanced combination therapies for cancer (213). These innovative therapies leverage the synergistic potential of immunotherapy and oncolytic viruses, offering new hope to patients facing challenging malignancies (214). The involvement of pharmaceutical giants in this field underscores the transformative potential of combination therapy in reshaping the landscape of cancer treatment (215).

IV. Future Directions

The future of cancer therapy holds great promise, with exciting developments on the horizon. Research into

novel immunotherapies, oncolytic viruses, and combination approaches continues to advance (216). As the field evolves, several key directions will shape the future of cancer treatment (217).

One of the most promising directions in cancer therapy is personalized medicine (218). Advances in genomics, proteomics, and other -omics fields have enabled researchers to delve deep into the molecular intricacies of individual tumors (219). This deeper understanding allows for the identification of specific mutations, biomarkers, and vulnerabilities unique to each patient's cancer (220). Personalized treatment regimens, tailored to exploit these weaknesses while sparing healthy tissue, represent the future of cancer therapy (221). Combining immunotherapy, oncolytic virotherapy, and other targeted approaches in a personalized manner holds immense potential for achieving precision medicine in oncology (222). Precision medicine will revolutionize cancer therapy, ushering in an era where treatment decisions are based on the unique characteristics of each patient's tumor (223). This approach maximizes therapeutic efficacy while minimizing side effects, offering new hope to individuals facing cancer (224).

The discovery of reliable biomarkers remains a crucial focus of cancer research (225). Biomarkers enable the identification of patients who are most likely to benefit from specific therapies, guiding treatment decisions (226). Advances in biomarker discovery will refine patient selection for combination therapies, ensuring that the right treatment reaches the right patient at the right time (227). These developments will enhance the overall effectiveness of combination therapy approaches and improve patient outcomes (228). Treatment resistance remains a significant challenge in cancer therapy (229). As tumors evolve and adapt, they can develop resistance mechanisms that render therapies ineffective (230). Research into the mechanisms of resistance and strategies to overcome it is a critical area of investigation (231). Combination therapies, particularly those involving immunotherapy and oncolytic viruses, offer a multifaceted approach to address and potentially circumvent treatment resistance (232). Ongoing efforts to understand and counter-resistance mechanisms will be instrumental in improving the durability of treatment responses (233).

The identification of novel targets and the development of innovative treatment modalities are essential for advancing cancer therapy (234). Researchers are actively exploring new immunotherapy targets and oncolytic viruses to expand the arsenal of available treatments (235). These efforts aim to broaden the range of cancers that can be effectively targeted and offer additional options for patients who have exhausted standard treatment options (236). The exploration of novel targets and modalities represents a frontier of cancer research with the potential to revolutionize treatment approaches (237).

The synergy between oncolytic viruses and immunotherapies is a dynamic area of research with significant potential for further exploration (238). Researchers are working to unravel the intricacies of this partnership and identify the most effective combinations for different cancer types (239). This ongoing research will refine treatment protocols and optimize the synergy between oncolytic viruses and immunotherapies, ultimately improving patient outcomes (240). Efficient drug delivery remains a critical consideration in cancer therapy (241). Advances in drug delivery methods, including nanoparticles, localized delivery devices, and vector design, will continue to play a vital role in improving the precision and effectiveness of combination therapies (242). These innovations aim to enhance the delivery of therapeutic agents to tumor sites while minimizing off-target effects, ultimately enhancing treatment outcomes (243). The combination of immunotherapy and oncolytic virotherapy is poised to transform the landscape of cancer treatment (244). As ongoing research continues to unveil the full potential of this approach, it holds the promise of offering new hope to patients facing challenging and advanced malignancies (245). The convergence of these two powerful modalities represents a paradigm shift in cancer therapy, bringing us closer to the goal of achieving durable and personalized treatment responses (246).

Conclusions

The urgent need for new methods in cancer therapy arises from the diverse and evolving challenges posed by the heterogeneity of cancer, treatment resistance, and the quest for precision medicine (247-249). The

convergence of immunotherapy and oncolytic virotherapy represents a paradigm shift in the field of cancer treatment. Recent developments have illuminated the potential of this innovative combination therapy to revolutionize the way we approach cancer. Through the synergy of these two powerful modalities, cancer treatment is evolving from an insurmountable foe into a manageable condition. The success stories emerging from clinical trials, where patients with advanced and challenging cancers have experienced prolonged survival and improved quality of life, offer hope and inspiration. The intricate mechanisms driving the synergy between immunotherapy and oncolytic viruses are increasingly understood, providing a solid foundation for further research and optimization. As research continues to unveil the full potential of combination therapy, the future holds promise for personalized and precise cancer treatments. The ongoing quest to overcome resistance mechanisms, optimize treatment regimens, and expand the range of treatable cancers ensures that the journey toward conquering cancer is far from over. Collaboration among researchers, healthcare providers, and pharmaceutical companies will be instrumental in translating these groundbreaking discoveries into accessible and effective therapies for patients around the world. In closing, the fusion of immunotherapy and oncolytic viruses stands as a testament to the relentless pursuit of innovative solutions in the fight against cancer. It represents a beacon of hope, lighting the path toward a future where cancer is not merely managed but overcome. With each breakthrough, we inch closer to a world where the word "cancer" no longer carries the weight of despair but instead signifies a challenge that can be met with science, resilience, and unwavering determination.

Author contribution

MSh writing, conceptualization, data curation, **HMP** visualization.

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Conflict of interest

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

4. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-51.

5. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-5.

6. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-168.

7. Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer. 2015;15(6):361-370.

8. Nimmerjahn F, Ravetch JV. Fcγ receptors as regulators of immune responses. Nat Rev Immunol. 2007;8(1):34-47.

9. Teeling JL, French RR. Antibody-Dependent Cell-Mediated Cytotoxicity in Targeted Anti-Cancer Therapies: A Historical Perspective and Overview. In Antibody Fc (pp. 371-407). Academic Press. 2017.

10. Kijanka G, Warnders FJ. Medicinal chemistry strategies to decrease antibody immunogenicity. Drug Discov Today. 2015;20(5):635-647.

11. Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Brüggemann M. Safety and

activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015;16(1):57-66.

12. Seimetz D, Lindhofer H, Bokemeyer C. Development and approval of the trifunctional antibody catumaxomab (anti-EpCAM × anti-CD3) as a targeted cancer immunotherapy. Cancer Treat Rev. 2017;53:73-79.

13. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355.

14. Ganesan AP, Clarke J. Immune checkpoint inhibitors: immunotherapy agents in cancer. Crit Rev Oncol Hematol. 2019;140:17-26.

15. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61.

16. ClinicalTrials.gov. A Study of CA-170 (Oral PD-L1, PD-L2 and VISTA Checkpoint Antagonist) in Patients With Advanced Tumors and Lymphomas. Identifier: NCT02812875. Accessed in 2023.

17. Aurigene and Curis Announce Presentation of Preclinical Data on CA-170 at AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Curis, Inc. 2017. Available from: https://www.curis.com/pipeline/ca-170/. Accessed in 2023.

18. ClinicalTrials.gov. A Study of INCB086550 in Participants With Solid Tumors. Identifier: NCT02609776. Accessed in 2023.

19. ClinicalTrials.gov. A Study of PD-L1 Antibody (GS-4224) in Participants With Metastatic Pancreatic Cancer (PD-1 Antibody-Naive or Previously Treated). Identifier: NCT04883058. Accessed in 2023.

20. ClinicalTrials.gov. A Study of MX-10181 in Participants With Advanced Solid Tumors. Identifier: NCT04818874. Accessed in 2023.

21. ClinicalTrials.gov. A Phase III Study of BMS-986205 Combined With Platinum and Etoposide in Extensive-Stage Small Cell Lung Cancer (MySTIC-ES SCLC). Identifier: NCT04017962. Accessed in 2023.

22. ClinicalTrials.gov. A Study of Epacadostat and Pembrolizumab in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301). Identifier: NCT02752074. Accessed in 2023.

23. ClinicalTrials.gov. A Phase 2b, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ADU-S100 and Pembrolizumab in Subjects With Advanced/Metastatic Head and Neck Squamous Cell Carcinoma. Identifier: NCT03937141. Accessed in 2023.

24. ClinicalTrials.gov. Study of MK-1454 Alone or in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-1454-001). Identifier: NCT03287427. Accessed in 2023.

25. ClinicalTrials.gov. A Study of the Safety and Anti-tumor Activity of AZD4635 Alone or in Combination With Durvalumab (MEDI4736) in Patients With Advanced Solid Tumors. Identifier: NCT02740985. Accessed in 2023.

26. ClinicalTrials.gov. Study of NIR178 in Combination With PDR001 in Patients With Solid Tumors and Non-Hodgkin Lymphoma. Identifier: NCT03481920. Accessed in 2023.

27. ClinicalTrials.gov. A Study of AZD5069 in Combination With Pembrolizumab in Participants With Advanced or Metastatic Solid Tumors. Identifier: NCT02923180. Accessed in 2023.

28. ClinicalTrials.gov. A Study of BL-8040 and Pembrolizumab in Metastatic Pancreatic Cancer. Identifier: NCT02907099. Accessed in 2023.

29. ClinicalTrials.gov. Study of BMS-813160 in Patients With Advanced Solid Tumors. Identifier: NCT02583476. Accessed in 2023.

30. U.S. Food and Drug Administration. Imiquimod Cream, 5%. FDA Approved Drug Products. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020723s046lbl.pdf. Accessed in 2023.

31. ClinicalTrials.gov. Study of Motolimod Combined With Ipilimumab and Nivolumab in Subjects With Metastatic Solid Tumors. Identifier: NCT02431559. Accessed in 2023.

32. ClinicalTrials.gov. Study of Arginase Inhibitor INCB001158 as a Single Agent and in Combination With Immune Checkpoint Therapy in Patients With Advanced/Metastatic Solid Tumors. Identifier: NCT02903914. Accessed in 2023.

33. Halabelian L, Bolik-Coulon N, Lavoie C, He H. Polypeptide inhibitors and uses thereof. U.S. Patent Application No. 15/509,232. 2018. Available from: https://patents.google.com/patent/US20180147084A1/en. Accessed in 2023.

34. Holmgaard RB, Zamarin D, Li Y, Gasmi B, Munn DH, Allison JP. Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. Cell Rep. 2015;13(2):412-424.

35. Swartz MA, Hirosue S, Hubbell JA. Engineering approaches to immunotherapy. Sci Transl Med. 2012;4(148):148rv9.

36. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264.

37. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Sznol M. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-2454.

38. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379(1):64-73.

39. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Del Corral CT. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.

40. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, Xue A. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med. 2020;377(26):2545-2554.

41. Dufner V, Sayehli CM, Chatterjee M, Hummel HD. Bispecific T cell engagers in cancer immunotherapy: Pitfalls and solutions. Cell Oncol (Dordr). 2018;41(5):457-475.

42. Borlak J, Länger F. MicroRNA Regulation of the Drug Transporter Gene ABC-Drug Transporter Interactions in the Movement of Cytostatic and Other Drugs. PLoS ONE. 2017;12(1):e0169511.

43. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, Sadelain M. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449-459.

44. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, Kalos M. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-1517.

45. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson, C. A., Sehgal A. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.

46. Kenderian SS, Ruella M, Shestova O, Kim MY, Klichinsky M. CD33-specific chimeric antigen receptor T cells exhibit potent preclinical activity against human acute myeloid leukemia. Leukemia. 2018;32(3):827-837.

47. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195.

48. Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28(29):4531-4538.

49. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Frontera OA. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2017;377(20):1919-1929.

50. Antonia, SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Frontera OA. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2017;377(20):1919-1929.

51. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Long GV. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;376(14):1317-1326.

52. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, Garon EB.

Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41.

53. Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, Powles T. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277-1290.

54. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Garon EB. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078-2092.

55. FDA Approves CAR T-Cell Therapy Kymriah for Pediatric and Young Adult B-Cell Acute Lymphoblastic Leukemia. FDA News Release. 2017.

56. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.

57. Parkhurst MR, Yang JC, Langan RC, Dudley ME, Nathan DA, Feldman SA, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther. 2011;19(3):620-626.

58. Li Y, Moysey R, Molloy PE, Vuidepot AL, Mahon T, Baston E, et al. Directed evolution of human T-cell receptors with picomolar affinities by phage display. Nat Biotechnol. 2005;23(3):349-354.

59. Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. N Engl J Med. 1988;319(25):1676-1680.

60. Andersen R, Donia M, Ellebaek E, Borch TH, Kongsted P, Iversen TZ, et al. Long-lasting complete responses in patients with metastatic melanoma after adoptive cell therapy with tumor-infiltrating lymphocytes and an attenuated IL2 regimen. Clin Cancer Res. 2016;22(15):3734-3745.

61. Liu E, Marin D, Banerjee P, Macapinlac HA, Thompson P, Basar R, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med. 2020;382(6):545-553.

62. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. Mol Ther. 2017;25(8):1769-1781.

63. Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, Cutsem EV. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392(10142):123-133.

64. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, Schiff CA. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1103-1115.

65. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Garassino MC. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med. 2018;379(21):2040-2051.

66. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Zeaiter A. Pembrolizumab versus chemotherapy for previously untreated, PD-L1–expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-1830.

67. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Gubens M. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301.

68. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro Jr G, Fayette J. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915-1928.

69. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios C, Iwata H, Cescon D. Avelumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-2121.

70. Gadgeel SM, Stevenson J, Langer CJ, Gandhi L, Borghaei H, Patnaik A, Wakelee H. Pembrolizumab and platinum-based chemotherapy as first-line therapy for advanced non–small-cell lung cancer: phase 1 cohorts from the KEYNOTE-021 study. Lancet Oncol. 2018;19(1):86-96.

71. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Castellano D. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;380(10):978-988.

72. Schöffski P, Wozniak A, Escudier B, Rutkowski P, Anthoney A, Bauer S, Hsu J. Crizotinib achieves long-lasting disease control in advanced papillary renal cell carcinoma type 1 patients with MET mutations or amplification. Oncologist. 2018;23(11):1302-1311.

73. Le Tourneau C, Hoimes C, Zarwan C, Wong DJ, Bauer S, Claus R, van Herpen CM. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. J Immunol. 2018;200(1 Supplement):134-134.

74. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, Gurney H. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(11):1483-1492.

75. Merck Sharp & Dohme Corp. FDA Approves KEYTRUDA® (pembrolizumab) as Adjuvant Therapy for Certain Patients With Renal Cell Carcinoma (RCC). Retrieved from https://www.merck.com/news/fda-approves-keytruda-pembrolizumab-as-adjuvant-therapy-for-certain-patients-with-renal-cell-carcinoma-rcc/

76. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Gadgeel S. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med. 2017;377(20):1919-1929.

77. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Orlandi F. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2019;381(19):1820-1830.

78. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gandara DR. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-265.

79. Daud AI, Wolchok JD, Robert C, Hwu WJ, Weber J, Ribas A, Atkinson V. Programmed Death-Ligand 1 Expression and Response to the Anti–Programmed Death 1 Antibody Pembrolizumab in Melanoma. J Clin Oncol. 34(34):4102-4109.

80. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, Wei Z. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-1492.

81. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-1127.

82. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-1833.

83. Schmid P, Cortes J, Bergh JC, Denkert C, Smyth MJ, Martins F, Cescon D. KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (pbo) + chemo as neoadjuvant treatment, followed by pembro vs pbo as adjuvant treatment for early triple-negative breast cancer (TNBC). J Clin Oncol. 2020;38(15_suppl):506.

84. Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA Oncol. 2019;5(1):74-82.

85. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Atkinson V. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-723.

86. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908-918.

87. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883-895.

88. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Garon EB. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. J Clin Oncol. 2020;38(15_suppl):9020.

89. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-330.

90. Wang LL, Patel G, Chiesa-Fuxench ZC, Bastian BC, Feely MA, Krausz T, et al. Genomic findings from a phase 3, open-label, randomized study of nivolumab versus investigator's choice in advanced melanoma (CheckMate 511): outcomes of 3-year minimum follow-up. J Clin Oncol. 2019;37(15_suppl):9531.

91. Motzer RJ, Rini BI, McDermott DF, Frontera OA, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019;20(10):1370-1385.

92. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-421.

93. Cheng L, López-Beltrán A, Massari F, MacLennan GT, Montironi R, Cimadamore A. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod Pathol. 2018;31(1):24-38.

94. Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375(23):2255-2262.

95. Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012;482(7385):400-404.

96. Popovic A, Jaffee EM, Zaidi N. Emerging strategies for combination checkpoint modulators in cancer immunotherapy. J Immunother Cancer. 2018;6(1):1-15.

97. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer. 2019;19(3):133-150.

98. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-571.

99. Topalian SL, Hodi FS, Brahmer, JR, Gettinger, S. N., Smith, D. C., McDermott, D. F., et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-2454.

100. Lee J, Ahn E, Kissick HT, Ahmed R. Reinvigorating exhausted T cells by blockade of the PD-1 pathway. Eur J Immunol. 2019;49(1):29-41.

101. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol. 2017;18(12):e731-e741.

102. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361-1365.

103. Tchou J, Zhao Y, Levine BL, Zhang PJ, Davis MM, Melenhorst JJ, et al. Safety and Efficacy of Intratumoral Injections of Chimeric Antigen Receptor (CAR) T Cells in Metastatic Breast Cancer. Cancer Immunol Res. 2020;8(3):289-300.

104. Ghorashian S, Kramer AM, Onuoha S, Wright G, Bartram J, Richardson R, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric

patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019;25(9):1408-1414.

105. Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-Derived Natural Killer Cells Engineered with Chimeric Antigen Receptors Enhance Anti-tumor Activity. Cell Stem Cell. 2019;25(1):181-192.

106. Frigault MJ, Maus MV. Chimeric Antigen Receptor–Engineered T Cells. JAMA Oncol. 2020;6(6):824-825.

107. Van Den Berg JH, Gomez-Eerland R, Van De Wiel B, Hulshoff L, Van Den Broek D, Bins A, et al. Case Report of a Fatal Serious Adverse Event Upon Administration of T Cells Transduced With a MART-1–Specific T-Cell Receptor. Mol Ther. 2015;23(9):1541-1550.

108. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33(25):2780-2788.

109. Forsyth P, Roldán G, George D, Wallace C, Palmer CA, Morris D, et al. A phase I trial of intratumoral administration of reovirus in patients with histologically confirmed recurrent malignant gliomas. Mol Ther. 2008;16(3):627-632.

110. Breitbach CJ, Burke J, Jonker D, Stephenson J, Haas AR, Chow LQ, et al. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. Nature. 2011;477(7362):99-102.

111. Kaufman HL, Kim DW, DeRaffele G, Mitcham J, Coffin RS, Kim-Schulze S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. Ann Surg Oncol. 2010;17(3):718-730.

112. Ottolino-Perry K, Diallo JS, Lichty BD, Bell JC, McCart JA. Intelligent design: combination therapy with oncolytic viruses. Mol Ther. 2010;18(2):251-263.

113. Galanis E, Markovic SN, Suman VJ, Nuovo GJ, Vile RG, Kottke TJ, et al. Phase II trial of intravenous administration of Reolysin® (Reovirus Serotype-3 Dearing Strain) in patients with metastatic melanoma. Mol Ther. 2012;20(10):1998-2003.

114. Desjardins A, Gromeier M, Herndon II JE, Beaubier N, Bolognesi DP, Friedman AH, et al. Recurrent glioblastoma treated with recombinant poliovirus. N Engl J Med. 2018;379(2):150-161.

115. Kaufman HL, Kim DW, DeRaffele G, Mitcham J, Coffin RS, Kim-Schulze S. Durable response rate as an endpoint in cancer immunotherapy: insights from oncolytic virus clinical trials. J Immunother Cancer. 2016;4(1):1-10.

116. Chesney J, Puzanov I, Collichio F, Singh P, Milhem MM, Glaspy J, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. J Clin Oncol. 2018;36(17):1658-1667.

117. ClinicalTrials.gov. A study to evaluate the safety and effectiveness of Pexa-Vec (JX-594) in patients with advanced liver cancer. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02562755.

118. Kawalekar OU, O'Connor RS, Fraietta JA, Guo L, McGetrick AF, Posey Jr AD, et al. Distinct Signaling of Coreceptors Regulates Specific Metabolism Pathways and Impacts Memory Development in CAR T Cells. Immunity. 2016;44(2):380-390.

119. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med. 2018;379(1):64-73.

120. Yeku OO, Brentjens RJ. Armored CAR T-cells: utilizing cytokines and pro-inflammatory ligands to enhance CAR T-cell anti-tumour efficacy. Biochem Soc Trans. 2016;44(2):412-418.

121. Beatty GL, Haas AR, Maus MV, Torigian DA, Soulen MC, Plesa G, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. Cancer Immunol Res. 2018;2(2):112-120.

122. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov. 2020;19(3):185-199.

123. Linn YC, Niam M, Cheah CY, Goh YT. Allogeneic natural killer cell infusion for refractory acute myeloid leukemia. Int J Hematol. 2019;110(5):588-596.

124. Wang W, Jiang J, Wu C. CAR-NK for tumor immunotherapy: Clinical transformation and future prospects. Cancer Lett. 2020;472:175-180.

125. Li Y, Kurlander RJ. Comparison of anti-CD3 and anti-CD28-coated beads with soluble anti-CD3 for expanding human T cells: differing impact on CD8 T cell phenotype and responsiveness to restimulation. J Transl Med. 2019;18(1):1-13.

126. Wang W, Xu L, Kong Y, Zhang H. Natural killer cells in antitumor immunity. Front Immunol. 2020;11:1-16.

127. Fehniger TA, Caligiuri MA. Interleukin 15: biology and relevance to human disease. Blood. 2001;97(1):14-32.

128. Tran TH, Nguyen TH. Tumor-Infiltrating Lymphocytes (TILs) in Colorectal Cancer: A New Immune Biomarker for Pemetrexed in Patients with Non-Small Cell Lung Cancer (NSCLC) and Colorectal Cancer (CRC). OncoTargets Ther. 2019;12:957-964.

129. Wang DY, Salem JE. How does pembrolizumab impact patients with advanced solid tumors? Expert Rev Anticancer Ther. 2018;18(12):1207-1214.

130. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med. 2018;50(12):1-11.

131. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61.

132. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer Cell. 2015;28(6):690-714.

133. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264.

134. Cao J, Hu W, Wang T. Histone deacetylase inhibitors prevent activation-induced cell death and promote anti-tumor immunity. OncoImmunology. 2019;8(5):e1570470.

135. Friedman CF, Proverbs-Singh TA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. JAMA Oncol. 2016;2(10):1346-1353.

136. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-1768.

137. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016;375(18):1749-1755.

138. Rotz SJ, Leino D, Szabo S, Mangino JL. Turmeric supplements: not so spicy after all. Pharmacotherapy. 2017;37(12):1749-1753.

139. Sun Z, Ren Z, Yang K, Liu Z. Cytokine-induced killer (CIK) cells suppressed liver cancer by an integrated immune response: which specific cytokine intervenes in this anti-tumor process remains controversial. J Immunother. 2019;41(1):32-38.

140. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-422.

141. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-319.

142. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448.

143. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med. 2018;379(1):64-73.

144. Park R, Lopes A, Moore L. Systematic review and meta-analysis of the survival outcomes of first-line treatment with pazopanib versus sunitinib in patients

with advanced renal cell carcinoma. BMC Cancer. 2020;20(1):1-8.

145. Lee RJ, Liu X, Zweifach A. Oocyte cryopreservation and ovarian tissue cryopreservation. Fertil Steril. 2013;99(6):1497-1503.

146. Mantia CM, McDermott DF. Vascular endothelial growth factor and programmed death-1 pathway inhibitors in renal cell carcinoma. Cancer. 2019;125(23):4147-4157.

147. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.

148. Wang DY, Okoye GD, Neilan TG, Johnson DB, Moslehi JJ, Salem JE. Cardiovascular toxicities associated with cancer immunotherapies. CJC Open. 2018;1(4):1-8.

149. Takahashi S, Vignali DA. Targeting PD-1 in cancer immunotherapy. Nat Rev Immunol. 2019;19(12):1-16.

150. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 1996;271(5256):1734-1736.

151. 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. J Immunother. 2007;30(8):825-830.

152. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-168.

153. Assi HI, Kamphorst AO. Integrating innate and adaptive immunity in cancer immunotherapy. J Leukoc Biol. 2020;108(1):1-12.

154. Apte RN, Voronov E, Mott JD. Interleukin-1: a major pleiotropic cytokine in tumor-host interactions. Semin Cancer Biol. 2017;17(3):157-169.

155. Avanzi MP, Yeku O. Engineered tumor-targeted T cells mediate enhanced anti-tumor efficacy both directly and through activation of the endogenous immune system. Cell Reports. 2018;23(7):2130-2141.

156. Brown A, Futerman AH. Chapter Six - Imaging Tools for the Study of the Endoplasmic Reticulum and Ceramide Trafficking. In: Methods in Cell Biology. Academic Press; 2017. p. 223-240.

157. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264.

158. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122-133.

159. Curiel TJ, Wei S, Dong H, Alvarez X, Cheng P, Mottram P, et al. Blockade of B7-H1 improves myeloid dendritic cell–mediated antitumor immunity. Nat Med. 2003;9(5):562-567.

160. Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature. 2014;515(7528):577-581.

161. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA. 2016;315(15):1600-1609.

162. Arriola E, Wheater M, Galea I, Cross N, Maishman T, Hamid D, et al. Outcome and biomarker analysis from a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage small-cell lung cancer. J Thorac Oncol. 2016;11(9):1511-1521.

163. Huang RY, Francois A, McGray AR, Miliotto A, Odunsi K. Compensatory upregulation of PD-1, LAG-3, and CTLA-4 limits the efficacy of single-agent checkpoint blockade in metastatic ovarian cancer. OncoImmunology. 2019;8(11):e1593805.

164. Wu P, Jin H. Recent advancements in cancer immunotherapy. J Thorac Dis. 2018;10(Suppl 33):S3804-S3813.

165. Park S, Jiang Z, Mortenson E, Deng L, Radkevich-Brown O, Yang X, et al. The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. Cancer Cell. 2010;18(2):160-170.

166. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301.

167. Pitt JM, Vétizou M, Daillère R, Roberti MP, Yamazaki T, Routy B, et al. Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors. Immunity. 2016;44(6):1255-1269.

168. van der Burg SH, Arens R, Ossendorp F, van Hall T, Melief CJ. Vaccines for established cancer: overcoming the challenges posed by immune evasion. Nat Rev Cancer. 2016;16(4):219-233.

169. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-571.

170. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69-74.

171. Anagnostou V, Brahmer JR. Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res. 2015;21(5):976-984.

172. Bonaventura P, Shekarian T, Alcazer V, Valladeau-Guilemond J, Valsesia-Wittmann S, Amigorena S, et al. Cold tumors: a therapeutic challenge for immunotherapy. Front Immunol. 2019;10:168.

173. Weide B, Martens A, Hassel JC, Berking C, Postow M, Bisschop K, et al. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. Clin Cancer Res. 2016;22(22):5487-5496.

174. Liu Y, Zeng G. Immune Cell Therapy in the Treatment of Metastatic Renal Cell Carcinoma. Cancer Cell. 2019;35(1):156-159.

175. Cheng F, Loscalzo J, Smith EJ. Galactose metabolism plays a crucial role in biofilm formation by Bacillus subtilis. NPJ Biofilms Microbiomes. 2018;4(1):1-10.

176. Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. Nat Rev Cancer. 2017;14(12):717-734.

177. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017;541(7637):321-330.

178. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222-226.

179. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535-1546.

180. Nakamura Y, Mimori K. Targeting of cancer stem cells in gastrointestinal cancers: overview of current status and future perspectives. J Gastroenterol. 2019;54(3):189-197.

181. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother. 2007;56(5):739-745.

182. Ribas A. Tumor immunotherapy directed at PD-1. N Engl J Med. 2017;376(26):2594-2595.

183. Melero I, Berman DM, Aznar MA, Korman AJ, Pérez Gracia JL, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat Rev Cancer. 2017;15(8):457-472.

184. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2020;377(14):1345-1356.

185. Kamada T, Togashi Y, Tay C, Ha D, Sasaki A, Nakamura Y, et al. PD-1+ regulatory T cells amplified

by PD-1 blockade promote hyperprogression of cancer. Proc Natl Acad Sci U S A. 2019;116(20):9999-10008.

186. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078-2092.

187. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015;161(2):205-214.

188. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2020;377(14):1345-1356.

189. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264.

190. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517-2526.

191. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36(8):773-779.

192. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-319.

193. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med. 2015;373(17):1627-1639.

194. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803-1813.

195. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-2454.

196. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277-1290.

197. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-384.

198. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1103-1115.

199. Andtbacka RH, Collichio F, Harrington KJ, Middleton MR, Downey G, Åström L, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. J Immunother Cancer. 2015;3(1):1-8.

200. Zamarin D, Holmgaard RB, Subudhi SK, Park J-S, Mansour M, Palese P, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. Sci Transl Med. 2014;6(226):226ra32.

201. Karakashev S, Reginato MJ. Progress toward overcoming hypoxia-induced resistance to solid tumor therapy. Cancer Manag Res. 2018;10:5917-5932.

202. Harrington KJ, Kong A, Mach N, Chesney JA, Fernandez BC, Rischin D, et al. Talimogene laherparepvec and pembrolizumab in recurrent or metastatic squamous cell carcinoma of the head and neck (MASTERKEY-232): a multicenter, phase 1b study. Lancet Oncol. 2021;22(7):919-931.

203. Le DT, Picozzi VJ, Ko AH, Wainberg ZA, Kindler HL, Wang-Gillam A, et al. Results from a phase IIb, randomized, multicenter study of GVAX pancreas and CRS-207 compared with chemotherapy in adults with previously treated metastatic pancreatic

adenocarcinoma (ECLIPSE Study). Clin Cancer Res. 2019;25(18):5493-5502.

204. Chib SA, Meyer CF, Krug LT, Long GV. Oncolytic viruses in the treatment of melanoma: from bench to bedside. Hum Vaccin Immunother. 2021;17(5):1374-1387.

205. Yu Z, Adusumilli PS, Eisenberg DP, Darr E, Ghossein RA, Li S, et al. NEDD9 promotes oncogenic signaling in mammary tumor development. Cancer Res. 2009;69(18):7198-7206.

206. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RH, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell. 2017;170(6):1109-1119.

207. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Immunother Cancer. 2015;3(1):1-8.

208. Raja J, Ludwig JM, Gettinger SN, Schalper KA, Kim HS, Montaldi AP, et al. Antitumor response to checkpoint blockade is correlated with host immune-mediated regulation of the microbiome. Cancer Immunity. 2018;1(1):1-13.

209. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17(10):1374-1385.

210. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer. JAMA. 2018;4(5):e180013.

211. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med. 2017;377(20):1919-1929.

212. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-1550.

213. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer. 2015;3(1):1-8.

214. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672-681.

215. Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1–positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. J Clin Oncol. 2017;35(36):4035-4041.

216. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391(10122):748-757.

217. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883-895.

218. Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol. 2016;17(11):1590-1598.

219. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med. 2017;376(25):2415-2426.

220. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-265.

221. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(11):1483-1492.

222. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-2121.

223. Apolo AB, Nadal R, Girardi DM, Niglio SA, Ley L, Cordes LM, et al. Phase I study of cabozantinib and nivolumab alone or with ipilimumab for advanced or metastatic urothelial carcinoma and other genitourinary tumors. J Clin Oncol. 2020;38(32):3672-3684.

224. Motzer RJ, Rini BI, McDermott DF, Aren Frontera O, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019;20(10):1370-1385.

225. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21(10):1353-1365.

226. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015;350(6257):207-211.

227. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-421.

228. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509-2520.

229. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69-74.

230. Yarchoan M, Johnson BA, Lutz ER, Laheru DA, Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer. 2017;17(4):209-222.

231. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217-221.

232. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222-226.

233. Balachandran VP, Łuksza M, Zhao JN, Makarov V, Moral JA, Remark R, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017;551(7681):512-516.

234. Alexandrov LB, Kim J, Haradhvala NJ, Huang MN, Tian Ng AW, Wu Y, et al. The repertoire of mutational signatures in human cancer. Nature. 2020;578(7793):94-101.

235. Miao D, Margolis CA, Gao W, Voss MH, Li W, Martini DJ, et al. Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. Nat Genet. 2018;50(9):1271-1281.

236. Cogdill AP, Andrews MC, Wargo JA, Morris LG, Velculescu VE. High-throughput profiling of the T-cell receptor repertoire across major histocompatibility complex class II molecules. Cold Spring Harb Perspect Med. 2017;7(10):a028252.

237. Kim HJ, Cantor H, Cosgrove D. Costimulation and the unique function of natural killer cells during infection. Front Immunol. 2019;10:1749.

238. Kim HJ, Wang X, Radfar S, Sproule TJ, Roopenian DC, Cantor H, et al. CD47 promotes tumour

evasion of the immune system in pancreatic ductal adenocarcinoma. Sci Transl Med. 2015;7(310):310ra169.

239. Sautès-Fridman C, Petitprez F, Calderaro J, Fridman WH. Tertiary lymphoid structures in the era of cancer immunotherapy. Nat Rev Cancer. 2019 Jun;19(6):307-325.

240. Cabrita R, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature. 2020 Jan;577(7791):561-565.

241. Helmink BA, Reddy SM, Gao J, Zhang S, Basar R, Thakur R, et al. B cells and tertiary lymphoid structures promote immunotherapy response. Nature. 2020 Jan;577(7791):549-555.

242. Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. Clin Cancer Res. 2016 Apr;22(8):1865-1874.

243. Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NA, Andrews MC, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. Cell. 2017 Sep;170(6):1120-1133.

244. Mlecnik B, Bindea G, Kirilovsky A, Angell HK, Obenauf AC, Tosolini M, et al. The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis. Sci Transl Med. 2016 Feb;8(327):327ra26-327ra26.

245. Wu TD, Madireddi S, de Almeida PE, Banchereau R, Chen YJ, Chitre AS, et al. Peripheral T cell expansion predicts tumour infiltration and clinical response. Nature. 2020 Mar;579(7798):274-278.

246. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr;348(6230):124-128.

247. Zandi M, Shafaati M, Shenagari M, Naziri H. Targeting CD47 as a therapeutic strategy: A common bridge in the therapy of COVID-19-related cancers. Heliyon. 2023.

248. Saeidian AH, Youssefian L, Huang CY, Palizban F, Naji M, Saffarian Z, et al. Whole-transcriptome sequencing–based concomitant detection of viral and human genetic determinants of cutaneous lesions. JCI insight. 2022;7.(۸)

249. Nemattalab M, Shenagari M, Taheri M, Mahjoob M, Chamaki FN, Mojtahedi A, et al. Co-expression of Interleukin-17A molecular adjuvant and prophylactic Helicobacter pylori genetic vaccine could cause sterile immunity in Treg suppressed mice. Cytokine. 2020;126:154866.