HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2469416
https://doi.org/10.1080/21645515.2025.2469416

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Harnessing live vectors for cancer vaccines: Advancing therapeutic immunotherapy

Chinmay T. Jani[a], Aysswarya Manoharan[a], Peter J. DeMaria[b], and Marijo Bilusic[a]

[a]Sylvester Comprehensive Cancer Center, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA; [b]NEXT Oncology, San Antonio, TX, USA

ABSTRACT

Cancer vaccines represent a promising approach within immunotherapies. These vaccines are tailored to target tumor-specific antigens, thereby offering a precision approach to cancer treatment. The key principles in developing therapeutic cancer vaccines include identifying appropriate vaccine targets and selecting effective vaccine delivery platforms. These delivery platforms are diverse and have evolved to enhance the immune response. This review explores live cancer vaccines and the biological entities involved. Live cancer vaccines leverage the use of various biological entities to stimulate an immune response. These biological entities including bacterial, yeast-based and viral vectors, have unique properties that can be harnessed to target and destroy cancer cells while eliciting a robust immune response. Clinical trials of cancer vaccines are investigating standalone and combination treatment strategies in the prophylactic, adjuvant, and palliative settings. This review offers insights into the current oncologic vaccine landscape and potential future development.

ARTICLE HISTORY
Received 23 October 2024
Revised 3 February 2025
Accepted 16 February 2025

KEYWORDS
Cancer immunotherapy; cancer vaccine; immuno-oncology; live vector; therapeutic cancer vaccine; therapeutic vaccine; vaccine; antigen cascade

Introduction

Cancer vaccines represent a promising therapeutic branch within immuno-oncology.[1,2] Unlike traditional prophylactic vaccines designed to prevent diseases, therapeutic cancer vaccines treat existing cancers by stimulating the immune system to recognize and kill tumor cells.[1,3] These vaccines are generally precision therapies that target tumor-specific antigens (TSAs). The integration of cancer vaccines with other immunotherapies underscores their potential to complement existing treatments (i.e., immune checkpoint inhibitors (ICI), adoptive cell therapies, and monoclonal antibodies) to enhance efficacy and improve patient outcomes.[3]

Key in the development of therapeutic cancer vaccines is the selection of appropriate vaccine target and vaccine platform (delivery system). Ideal vaccine targets include tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are proteins overexpressed in tumor cells but also in normal cells at lower levels,[4] while TSAs are unique proteins expressed exclusively by tumor cells. Neoantigens, a subset of TSAs, are newly formed antigens specifically generated from tumor-specific mutations, providing highly distinct and personalized targets for vaccine-induced immune responses.[5] Along with TAAs and TSAs, human endogenous retroviral elements (HERVs) have been used to develop cancer vaccines and chimeric antigen receptor (CAR)-expressing T cells.[5,6] Activation of the HERVs can lead to a state of viral mimicry, inducing an innate immune response and production of cytokines.[6,7] By mimicking viral infections, HERVs function as an intrinsic adjuvant sensitizing cancer cells for immune recognition.[5]

The platforms used to deliver cancer vaccines are diverse and have evolved to enhance the immune response. Cancer vaccines can be characterized by these platforms and include vector-based vaccines, recombinant vectors, peptide-based vaccines, deoxyribonucleic acid (DNA)-based vaccines, messenger ribonucleic acid (mRNA) vaccines, whole-cell vaccines, gangliosides, genes and dendritic cell (DC) vaccines.[1,8] Vector-based vaccines use viral, yeast or bacterial vectors to deliver genetic material encoding tumor antigens, leveraging the vectors' natural ability to infect cells and induce immunity. Whole-cell vaccines employ whole tumor cells, often attenuated via genetic modification or irradiation, to stimulate a broad immune response against multiple antigens. Tumor antigen-loaded DC vaccines utilize DCs loaded with tumor antigens to activate T cells, the primary effectors of the immune response.[1,8]

Live cancer vaccines leverage various biological entities, including live or recombinant vectors to stimulate an immune response. Each of these biological entities has unique properties that can be harnessed to target and destroy cancer cells while eliciting a robust immune response.[1,9] The delivery methods for live cancer vaccines are crucial as they influence the vaccine's ability to reach and stimulate the immune system.[10,11] The strategy of using the immune system to treat cancer dates back to the 1800s, when physicians observed significant tumor shrinkage in patients following acute infections. Dr. William Coley pioneered an early vaccine product (known as Coley's Toxins) developed from inactivated Streptococcus and Serratia species.[12] In the early 1900s, patients with tuberculosis were noted to develop cancers less frequently than patients without tuberculosis.[13] This observation spurred interest in exploring Bacillus Calmette-Guérin (BCG) as a potential cancer treatment, with initial experiments

CONTACT Marijo Bilusic mxb2305@med.miami.edu Sylvester Comprehensive Cancer Center, University of Miami Leonard M. Miller School of Medicine, 1475 Northwest 12th Avenue, Suite 3039, Miami, FL 33136, USA.

beginning in the 1930s.[14] By the 1970s, BCG vaccine had been established as the standard of care for non-muscle invasive bladder cancer (NMIBC) and later received FDA approval in the 1990s.[15] During this time, vaccine development expanded bacterial vectors to include other pathogens (i.e., viruses, yeast, and fungi), which were also found to exhibit anti-tumor. This broadened the scope of interest in pathogen-based immunotherapy, laying the groundwork for further advancements in cancer vaccines.

This review provides an in-depth exploration of various live cancer vaccines, examining the biological entities used as vectors involved with a focus on the most extensively researched bacteria, yeast, and viruses, including oncolytic viruses. This comprehensive analysis offers valuable insights into the current landscape of live cancer vaccines and potential future directions in the field. To ensure a focused scope, this review will concentrate on the most extensively studied vector platforms and highlight ongoing clinical trials as of September 15, 2024.

Bacterial vectors

Listeria monocytogenes

Listeria monocytogenes (Lm) as a vector for cancer vaccines marks a pivotal development in immunotherapy. Leveraging the unique properties of this intracellular bacterial pathogen, researchers have enhanced the delivery and presentation of TAAs, thereby eliciting robust immune responses.[16–18] Lm possesses an inherent ability to infect both phagosomal and cytosolic compartments of Antigen Presenting Cells (APC).[19] This dual access facilitates the presentation of antigens via both major histocompatibility complex (MHC) class I and class II pathways, thereby stimulating both CD8+ cytotoxic T lymphocytes and CD4+ helper T cells.[18–20] The innate response is initially mediated by the activation of toll-like receptors (TLR), which results in downstream signaling and the production of pro-inflammatory cytokines.[21] Once phagocytized, Lm may be processed in the phagolysosomal compartment and peptides presented on MHC Class II to activate Lm-specific CD4+ T cell responses. Alternatively, Lm can escape the phagosome and enter the cytosol, leading to CD8+ T cell activation.[19,22] This combination of responses is crucial for a sustained anti-tumor immune response and makes Lm a powerful vaccine vector.[18–20]

Aduro Biotech, now Chinook Therapeutics, developed two Lm platforms: LADD (Live Attenuated Double Deleted) and pLADD (personalized LADD). LADD utilizes genetically modified bacteria to express TAAs. The pLADD platform builds upon LADD by formulating vaccines incorporating predicted neoantigen epitopes for a more targeted immune response. One such vaccine, CRS-207, expresses mesothelin, a TAA overexpressed in pancreatic, ovarian, and lung cancers.[19,23] Initial clinical trials demonstrated its safety and ability to induce mesothelin-specific T-cell responses.[24] However, the Food and Drug Administration (FDA) placed these studies on clinical hold in 2016 for safety after a patient treated with CRS-207 developed listeria bacteremia.[25,26] The hold was lifted after modifying the protocol and excluding patients with certain prostheses. Later, a pLADD platform-based clinical trial on colorectal cancer (CRC) was terminated due to business realignment.[27] Currently, the sole active study of CRS-207 is a Phase 2 study of epacadostat, pembrolizumab, and CRS-207, with or without cyclophosphamide and GVAX, which is a granulocyte-macrophage colony-stimulating factor (GM-CSF) – transduced autologous tumor-cell vaccine in patients with metastatic pancreas cancer. The study has recruited 41 patients with no active recruiting and pending results.[28] While patients who developed listeria infection as a consequence of treatment generally responded to antibiotics, the ongoing development of listeria-based products must consider strategies to minimize infectious toxicity (i.e., attenuated bacterial strains, incorporation of stronger antimicrobial prophylaxis into the study treatment).[25] This approach could enhance the risk/benefit profile and expand the potential approvability of these products.

A key innovation in Listeria-based vaccines is the fusion of the antigen with Listeriolysin O (LLO), a virulence factor of Listeria.[29] This fusion enhances the immunogenicity of the antigen and promotes stability and effective presentation to the immune system.[29] In vaccines targeting prostate cancer, prostate-specific antigen (PSA) is fused with LLO, resulting in a potent and targeted immune response against PSA-expressing tumor cells.[29] Advaxis Inc., now Ayala Pharmaceutics, had focused on developing Lm vaccines based on the XFL-7 and LmddA strains. These LLO-based vaccine strains typically express TAAs episomally, promoting robust antigen presentation and activation of the immune response. Among the vaccine strains, three specifically targeted the E7 protein from HPV-16, PSA, and Her2.[30–32] Similar to the LADD platform, one patient who received this vaccine in 2013 died in 2015 with trace amounts of bacteria in the blood leading to a brief hold by FDA.[26] However, as of date 15th September 2024, all studies of this product have been terminated. Johnson & Johnson (JNJ) also evaluated vaccines targeting epidermal growth factor receptor variant III (EGFRvIII) and mesothelin (JNJ-61757) and multiple prostate cancer antigens (JNJ-61809). The Phase I trial evaluated the safety of JNJ-61809, targeting four relevant prostate cancer antigens with no reported dose-limiting toxicities (DLT).[33]

Despite compelling pre-clinical and early clinical data, safety and efficacy concerns led to the termination of all clinical trials of this vaccine product except one ongoing trial of RT201 (Tumor Antigen-specific Macrophage Tumor Vaccine) in the Treatment of Advanced Cervical Cancer.[25–26,34–36] Lm vaccine products have been studied in combination with other agents to a limited extend.[34,37] Two promising platforms under research in pre-clinical studies, Lm-RIID (Lm recombinase-induced intracellular death) and KBMA (Killed but metabolically active) strains, achieve this goal primarily by deleting virulence factors. The anti-tumor KBMA Lm stimulates effective CD4+ and CD8 + T cell responses and an increase in the number of mature Dendritic Cells in colon cancer model without significantly side effects while Lm-RIID commits suicide intracellulary by inducing Cre recombinase in host cell cytosol to delete essential genes for bacterial viability.[38,39] As a result, Lm-RIID can elicit potent anti-tumor effects without normal tissue injury. Besides, Lm-RIID exhibits a higher clearance rate than double-deleted Lm strains.[37,40]

Salmonella

Salmonella typhimurium (ST) strains have also been engineered to exert anticancer effects.[41,42] These strains colonize tumor tissues at a rate 1000 times higher than normal tissues, with preclinical murine studies demonstrating activity in multiple tumor models.[42] ST achieves tumor lysis by promoting apoptosis in tumor cells through nutritional deficiency and bacterial toxin release. Additionally, ST can induce autophagy, which downregulates the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways, inhibits the expression of hypoxia-inducible factor 1-alpha (HIF-alpha) and vascular endothelial growth factor (VEGF), and eventually slows tumor growth.[41–44] ST also downregulates certain oncoproteins involved in drug resistance and tumor metastasis.[45,46]

Several strains of ST have been engineered to enhance their safety and efficacy, the most prominent being VNP0009 and CHI4550. VNP0009 is a genetically modified strain designed to minimize virulence while retaining its ability to target and kill cancer cells.[42] This strain has been tested in multiple clinical trials, demonstrating a tolerable safety profile, though no objective tumor regression was reported.[47,48] Subsequent development explored the oral route with ST Ty21a expressing VEGF Receptor-2, leading to the first-in-kind oral V×M01vaccine against advanced pancreatic cancer, which showed safety, immunogenicity, and increased vaccine-specific T cell responses compared to placebo.[49] Another Phase I, dose-escalation, single-dose trial of oral, attenuated ST-containing human interleukin (IL)-2 demonstrated a statistically significant increase in circulating natural killer (NK) and NK-T cells, indicating an immunologic effect despite no observed survival benefit.[50] The current active study, NCT9234, is a Phase II trial with the primary objective to assess the efficacy of multiple-dose oral administration of Saltikva, an attenuated strain of ST expressing IL-2, in patients with metastatic pancreatic cancer on a standard of care (SOC) (either FOLFIRINOX or Gemcitabine/Abraxane, in combination with Saltikva).[51]

A new modified strain of VNP0009, SGN1, is being investigated in an ongoing clinical trial, NCT3345. This strain overexpresses L-methionine, allowing it to target and preferentially replicate in tumors, depriving them of methionine.[52] Pre-clinical data in combination with PD-L1 (programmed death ligand-1) in murine melanoma models have shown that combination therapy with systemic anti-PD-L1 therapy results in better antitumor activity than individual monotherapies.[52] Currently, SGN1 studies are actively recruiting.[53,54] Another active trial for patients with multiple myeloma: NCT2291 is a Phase I dose escalation study of TXSVN, a weakened form of a live vaccine strain of Salmonella (also known as the CVD908ssb strain) that has been genetically modified to produce the protein survivin, a tumor antigen. Survivin, a member of the inhibitor of apoptosis protein family, serves a dual function by promoting cellular proliferation and inhibiting apoptosis. Its elevated expression in tumor cells represents an adaptation that enables the evasion of apoptosis. However, the overexpression of survivin in tumors compared to normal tissues presents an attractive target for immunotherapy, aiming to disrupt this tolerance mechanism. Widely recognized as a TAA, it has emerged as a significant target for investigation both in vitro and in clinical trials for cancer diagnosis and treatment.[55,56]

A modified version of VNP0009 was engineered to express single-chain antibody fragments specific to carcinoembryonic antigen (CEA), a marker commonly found on human gastrointestinal tract carcinomas, pancreatic cancer, NSCLC, and breast cancer. Additionally, to boost antitumor activity, an extra copy of the sipB gene, which encodes the proapoptotic Salmonella invasion protein B, was inserted into the VNP0009 chromosome. While Salmonella naturally targets tumor tissues, these modifications enable recombinant vaccines to be specifically guided and concentrated within tumors, effectively delivering apoptotic proteins to eliminate cancer cells.[57]

BCG

BCG, a live-attenuated form of *Mycobacterium bovis*, was first used successfully to treat NMIBC in 1976.[58] Since FDA approval in 1990, BCG has become SOC for intermediate- and high-risk NMIBC following transurethral bladder tumor resection.[59,60] Although the precise mechanisms of BCG's antitumor effects remain unclear, several theories have emerged. It is believed to stimulate innate and adaptive immune responses through local inflammatory reactions.[61] Some studies suggest BCG activates TLR-7, inducing cytotoxic effects on tumor cells.[62,63] Preclinical evidence also indicates that BCG recruits macrophages and pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, into the tumor microenvironment (TME), potentially promoting tumor apoptosis and clearance.[64] Beyond bladder cancer, BCG has been evaluated in combination with other therapies for malignancies, though such studies have been limited. For example, a 2008 study explored using the New York esophageal squamous cell carcinoma 1 (NY-ESO-1) recombinant peptide vaccine with BCG and GM-CSF in urothelial carcinoma. This combination elicited antibody and T-cell responses, with BCG serving as an adjuvant.[65] These findings suggest that BCG may enhance immunological responses when used in combination therapies; however, its role in such settings remains largely exploratory. There are two ongoing trials Phase III trials evaluating the use of BCG in bladder cancer (Table 1). The S1602 trial investigates different strains of BCG with or without a BCG vaccine in high-grade NMIBC. One of its primary objectives is to determine whether intradermal Tokyo-172 BCG vaccination before intravesical Tokyo-172 BCR strain instillation improves the time to high-grade recurrence for patients with BCG-naïve NMIBC.[66] Another trial is a multicenter study assessing the efficacy and safety of tislelizumab combined with BCG bladder instillation in preventing postoperative recurrence in intermediate- and high-risk NMIBC.[67]

Clostridium

One of the key challenges in cancer treatment is that many tumors thrive in hypoxic, poorly vascularized environments, which hinders effective therapy delivery. Due to their growing

Table 1. Active clinical trials of bacterial vector-based cancer vaccines.

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title	Start Date	Results Posted	NCT Number
				Listeria					
1	RT201	Tumor Antigen-specific	Cervical	Vaccine Monotherapy	I	Clinical Research on the Safety and Effectiveness of RT201 (Tumor Antigen-specific Macrophage Tumor Vaccine) in the Treatment of Advanced Cervical Cancer.	10/1/2021	No	NCT0301
				Salmonella					
1	Modified Salmonella Typhimurium SGN1	No TSA	Various cancers	Vaccine Monotherapy	I/IIa	Phase I/IIa, Open-label Study to Evaluate Safety, Tolerability and Preliminary Efficacy of Modified Salmonella Typhimurium SGN1 in Patients With Advanced Solid Tumor	1/16/2023	No	NCT8150
2			Various cancers	Vaccine Monotherapy	I	A Phase I/IIa, Open-label, Dose Escalation and Dose-Expansion Study to Evaluate the Safety and Tolerability of Modified Salmonella Typhimurium SGN1 Administered Via Intratumoral Injection in Patients With Advanced Solid Tumors	4/19/2023	No	NCT3345
3	Saltikva (Attenuated Salmonella Typhimurium Containing the Human Gene for Interleukin-2)	IL-2	Pancreatic cancer	Vaccine Monotherapy FOLFIRINOX + Vaccine Gemcitabine/Abraxane + Vaccine	II	A Phase 2 Study of Saltikva (Attenuated Salmonella Typhimurium Containing the Human Gene for Interleukin-2) in Patients With Metastatic Pancreatic Cancer	10/20/2020	No	NCT9234
4	Salmonella CVD908ssb strain (TXSVN Vaccine)	Survivin	Multiple myeloma	Vaccine Monotherapy	I	Multiple Myeloma Trial of Orally Administered Salmonella Based Survivin Vaccine.	8/6/2921	No	NCT2291
				BCG					
1	BCG Vaccine	No TSA	Bladder cancer	Tislelizumab + Vaccine	III	Multicenter Clinical Trial on the Effectiveness and Safety of Instillation of BCG and Alternative BCG Protocols for Intermediate and High-risk Non-muscle Invasive Bladder Cancer	6/1/2023	No	NCT1110[67]
2	BCG Tokyo-172 Strain Vaccine	No TSA	Bladder cancer	Vaccine Monotherapy	III	S1602, A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming With Intradermal BCG Before Intravesical Therapy for BCG-Naive High-Grade Non-muscle Invasive Bladder Cancer	2/24/2017	No	NCT1660

BCG: Bacillus Calmette-Guérin. TSA: Tumor-Specific Antigen. Sr. No: Serial Number.

ability in oxygen-poor conditions, *Clostridium* species can lyse tumor cells by colonizing and metabolizing within hypoxic TMEs.[68] Clostridial-directed enzyme prodrug therapy (CDEPT) is an innovative approach that utilizes clostridium's preference for hypoxic environments. In CDEPT, Clostridium is genetically engineered to activate nontoxic prodrugs into active chemotherapeutic agents.[68,69] Although no ongoing clinical trials use CDEPT, preclinical studies have generated promising results.[69] Another area of interest involves using C. butyricum MIYAIRI 588 (CBM588) in combination with BCG in bladder cancer. A preclinical study found that CBM588 was as effective as BCG in enhancing the release of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from neutrophils, promoting apoptosis of cancer cells.[70] C. novyi-NT, a modified strain of C. novyi, has also shown potential. Preclinical single-dose administration of C. novyi generated tumor regression in small murine tumors, although responses in larger murine tumors were less impressive. A high percentage of animals treated with C. novyi experienced fatal toxicity, highlighting the need for additional safety development.[71,72] Attempts were made to reduce toxicity by removing a bacterial gene shown to correlate with toxicity, but safety concerns persisted.[73,74] In a Phase 1 trial completed in 2001, a melanoma vaccine incorporating epitopes from tetanus toxoid successfully induced CD4+ T-helper cell responses.[75] Recent studies on C. tetani-based products primarily focus on combination therapies, where the accompanying product also serves as an immune stimulant. One study evaluating the combination of the Human Papillomavirus (HPV) vaccine GARDASIL with REPEVAX (diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine) demonstrated favorable tolerability and evidence of immunological response.[76] Another trial evaluated the combination of the ALVAC-CEA/CD80 (B7.1) vaccine with chemotherapy and tetanus vaccine, finding an acceptable safety profile, although no significant clinical or T-cell response was observed.[77] Although Clostridium-based therapies demonstrated potential for targeting malignant cells, the discontinuation of earlier studies highlights significant challenges in translating this approach to clinical practice. Furthermore, there are no ongoing studies utilizing Clostridium as a vector for cancer vaccines, underscoring the need for renewed research efforts and innovations to overcome these limitations.

Yeast

Yeast-based cancer vaccines represent a cost effective, versatile and promising approach leveraging innate and adaptive immune responses.[78–80] Yeast is an effective platform for delivering TAAs due to its proven ability to generate robust immune activation. The immune system recognizes engineered yeast cells expressing TAAs as foreign, prompting DCs to phagocytose them. The TAAs are processed and presented on MHC molecules, activating CD4+ and CD8+ T-cells. Additionally, yeast cells contain pathogen-associated molecular patterns (PAMP), such as β-glucans, which bind to pattern recognition receptors (PRR) on immune cells. This interaction enhances immune activation and fosters a pro-inflammatory environment, leading to an effective anti-tumor response.[78,80,81] Also, heat-killed yeast, which is extremely stable and easy to transport and store, offers practical advantages over other vaccine platforms.

Preclinical studies have demonstrated the efficacy of yeast-based vaccines across multiple cancer models, including melanoma, breast cancer, and prostate cancer.[82–85] In one study using human CEA-transgenic mice, a recombinant S. cerevisiae expressing human CEA (yeast-CEA) was evaluated for its ability to elicit CEA-specific T-cell responses and antitumor activity. The results demonstrated that yeast-CEA vaccination could break immune tolerance and elicit both CEA-specific CD4+ and CD8+ T-cell responses.[85,86] In tumor-bearing mice, repeated administration of yeast-CEA significantly reduced tumor burden and increased overall survival, particularly in models of pulmonary metastasis and subcutaneous pancreatic tumors.[85]

While there is no FDA-approved yeast-based therapeutic cancer vaccine, there are currently multiple investigational products under study (Table 2). GI-6207 is a yeast-CEA vaccine, genetically modified to express the recombinant CEA protein using heat-killed *Saccharomyces cerevisiae* as a vector. In clinical trials, patients with metastatic CEA-expressing carcinomas received subcutaneous vaccine with minimal toxicity while inducing antigen-specific immune responses and stabilizing CEA levels.[87] GI-4000 is a yeast-based vaccine that targets mutations in the RAS oncogene. RAS plays a crucial role in many solid tumors, including pancreatic and NSCLC. A Phase-II trial showed that GI-4000 was well tolerated and immunogenic when used as consolidation therapy in patients with stage I-III KRAS-mutant lung cancer.[88] Immune responses were measured by interferon-γ (IFNγ) ELISpot assay and by regulatory T cell (Treg) frequencies on treatment. In pancreatic cancer, a phase II trial (NCT6406) combined GI-4000 with gemcitabine for patients with resected RAS-mutated tumors, showing trends toward improved survival in certain patient subgroups identified by proteomic signatures predictive of GI-4000 responsiveness.[89] However, despite the promising immune responses, many GI-4000 trials have failed (either terminated or withdrawn) secondary to poor accrual or lack of efficacy.[90] GI-6301 is a yeast-based vaccine that targets brachyury, a transcription factor overexpressed in various advanced cancers as well as universally in chordoma. A Phase I clinical trial[91] demonstrated the vaccine's ability to induce brachyury-specific immune responses with minimal adverse effects. Early signs of clinical activity were observed.[92] However, a Phase II trial combining GI-6301 with radiation therapy for patients with unresectable chordoma was terminated early due to a lack of synergistic antitumor efficacy.[93] For the brachyury vaccine, recent efforts have shifted toward non-yeast-based platforms, such as the BN-Brachyury vaccine, which employs a heterologous prime-boost strategy using Modified Vaccinia Ankara (MVA) for priming and Fowlpox Virus (FPV) for boosting. The prime-boost strategy is used to enhance and sustain the immune response against a target, particularly when the body may quickly neutralize the initial vaccine. The prime dose introduces the immune system to the target antigen, while subsequent booster doses use a different vaccine platform to bypass immune neutralization and strengthen the response. Early trials of this vaccine in patients

Table 2. Active clinical trials of yeast vector-based cancer vaccines.

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title	Start Date	Results Posted	NCT Number
1	OPT-821	GD2L and GD3L	Neuroblastoma	Oral dietary supplement (Beta glucan) + Vaccine	I/II	Phase I/II Trial of a Bivalent Vaccine With Escalating Doses of the Immunological Adjuvant OPT-821, in Combination With Oral β-glucan for High-Risk Neuroblastoma	5/27/2009	No	NCT1560
2	GI-4000 (Pancreatic Cancer Vaccine)	KRAS	Pancreatic Cancer	ALT-803 ETBX-011 ETBX-021 ETBX-051 ETBX-061 GI-4000 GI-6207 GI-6301 haNK for infusion Avelumab Bevacizumab Capecitabine Cyclophosphamide Fluorouracil Leucovorin nab-Paclitaxel Oxaliplatin SBRT	I/II	QUILT-3.080: Phase 1B/2 Trial Of The NANT Pancreatic Cancer Vaccine As Treatment For Subjects With Pancreatic Cancer Who Have Progressed on or After Standard-Of-Care Therapy.	7/17/2018	Yes	NCT6869
3	GI-4000 (NANT Pancreatic Cancer Vaccine)	KRAS	Pancreatic Cancer	ALT-803 ETBX-011 GI-4000 haNK for infusion Avelumab Bevacizumab Capecitabine Cyclophosphamide Fluorouracil Leucovorin nab-paclitaxel Omega-3 acid Oxalipatin SBRT	I/II	Molecularly Informed Integrated Immunotherapy Combining Innate haNK Cell Therapy With Adaptive T-cell Therapy (Adenovirus, Yeast, Fusion Protein Vaccine) in Subjects With Pancreatic Cancer Who Have Progressed on or After Standard-of-care Therapy.	11/6/2017	Yes	NCT9248

(*Continued*)

Table 2. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title	Start Date	Results Posted	NCT Number
4	GI-4000 (NANT CRC Vaccine)	KRAS	CRC	ETBX-011 ETBX-021 ETBX-051 ETBX-061 GI-4000 GI-6207 GI-6301 haNK for infusion Avelumab Cetuximab Capecitabine Cyclophosphamide Fluorouracil Leucovorin nab-paclitaxel Omega-3 acid Oxaliplatin SBRT	I/II	A Phase 1b/2 Trial of the NANT CRC Vaccine vs Regorafenib in Subjects With Metastatic CRC Who Have Been Previously Treated With Standard-of-Care Therapy	9/28/2018	Yes	NCT3157
5	GI-4000 (NANT TNBC Vaccine)	KRAS	Breast Cancer	*N*-803 ETBX-011 ETBX-051 ETBX-061 GI-4000 GI-6207 GI-6301 haNK for infusion Avelumab Bevacizumab Capecitabine Cyclophosphamide Fluorouracil Leucovorin nab-paclitaxel Cisplatin SBRT	I/II	Molecularly Informed Integrated Immunotherapy Combining Innate haNK Cell Therapy With Adenoviral and Yeast-based Vaccines to Induce T-cell Responses in Subjects With TNBC Who Have Progressed on or After Standard-of-care Therapy.	3/19/2018	Yes	NCT7085
6	TLPO vaccine	The patient's TL	Solid Tumor	Vaccine monotherapy	II	A Prospective, Open-Label, All-Comers Phase IIa Trial of The TLPO Cancer Vaccine in Solid Tumor Malignancies	11/29/2023	No	NCT5221
7	YE-NEO-001	Personalized targets	Various Cancers	Vaccine monotherapy	I	QUILT-2.025 NANT Neoepitope Yeast Vaccine (YE-NEO-001): Adjuvant Immunotherapy Using a Personalized Neoepitope Yeast-Based Vaccine To Induce T-Cell Responses In Subjects W/ Previously Treated Cancers.	8/10/2018	No	NCT2718

CRC: Colorectal Cancer, haNK: High-affinity Natural Killer Cells, YE-NEO-001: Neoepitope Yeast Vaccine, SBRT: Stereotactic body radiation therapy, Sr. No: Serial Number. TL: Tumor Lysate, TLPO: Tumor Lysate Particle Only, TNBC: Triple Negative Breast Cancer.

with metastatic solid tumors have shown a good safety profile and the induction of brachyury-specific T-cell responses.[94]

Efforts to develop yeast-based personalized cancer vaccines, such as neoepitope yeast vaccine YE-NEO-001, have also been underway. They have been explored for use in metronomic combination therapies for pancreatic cancer,[95,96] and CRC.[97] One of the Phase I trials of NANT vaccine for Triple Negative Breast Cancer (TNBC) showed safety and efficacy in combination with chemo-radiation.[98] However, it was prematurely terminated before the completion for Phase II.[99] These personalized neoepitope vaccines, which target cancer-specific mutations, represent a new frontier in cancer immunotherapy.

Viral vectors (including oncolytic viruses)

Over a century ago, tumor regression was observed in cancer patients infected with certain viruses.[100] Since then, multiple trials have evaluated the role of various viruses as vectors for cancer vaccines. The use of viruses in vaccines can be divided into two groups: oncolytic viruses (OV) and genetically engineered viruses. While viral-based therapeutic cancer vaccines are engineered to express tumor antigens via transgenes, OV do not target a specific tumor antigen.[101] Rather, OVs exert direct cytotoxic effects on cancer cells. Tumor cells lyse and spill their contents, offering a host of TSAs to the immune system to ultimately effect an antitumor response.[100,102] The FDA and European Medicines Agency (EMA) approved the first OV, Imlygic (talimogene laherparepvec, or T-VEC), in 2015.[103,104] Multiple OV products are now under investigation both as monotherapy and in combination.[103] As of September 2024, 114 active clinical trials are ongoing.[105]

Amongst various virus platforms, adenovirus and poxvirus have been extensively studied historically and possess well-characterized genomes. Adenovirus was among the earliest viruses used as a vector for gene therapy.[106] Advances in genetic engineering have further enhanced the safety and efficacy of adenoviral vectors, increasing their use in experimental therapies.[107] Poxvirus, on the other hand, gained prominence due to its large genome, which allows for easy genetic manipulation.[108] Similarly, herpes simplex virus (HSV) is recognized for its ability to infect both dividing and non-dividing cells and its favorable safety profile, making it a suitable vector for cancer vaccine delivery systems.[109] At the same time retrovirus vectors, such as lenti- and gammaretroviruses, are the most common choice for the transformation of isolated patient cells ex vivo.[110] Lentiviral vectors, in particular, are extensively utilized in the manufacturing of CAR-T cells[110] An alphavirus vector, AVX701 (CEA(6D)-VRP), has also been evaluated in phase I/II clinical trial patients with metastatic cancer expressing CEA with vaccine successfully elicited CEA-specific T-cell and antibody responses in most patients.[111] Other platforms, utilizing measles virus, alphavirus, and retroviruses, have also been studied and described.[101,106,110] However, given that the majority of currently active clinical trials focus on adenovirus, poxvirus, and HSV, and considering the unique attributes of these vectors, this review will primarily focus on adenovirus, poxvirus, and HSV as leading candidates in ongoing clinical trials.

Pox virus

Pox viruses, including vaccinia, offer several characteristics that make them attractive vectors. A large viral genome facilitates the insertion of multiple therapeutic genes.[108] Vaccinia vaccines elicit robust immune responses by inducing interferon (IFN) production and activating both cellular and humoral immunity.[112,113] Studies have demonstrated that pox virus strains, including particularly MVA, are safe and well tolerated in humans.[114,115] While the anti-tumor efficacy of pox virus-based therapeutic cancer vaccines has not reached the threshold for regulatory approval, ongoing studies seek to enhance efficacy (Table 3). One promising strategy involves a pox virus vaccine modified to express three costimulatory molecules or TRICOM: B7.1, ICAM-1 (Intracellular adhesion molecule-1), and LFA-3 (Lymphocyte function-associated antigen 3). These molecules enhance the immune response by promoting T-cell proliferation and cytokine production.[116] MVA-Bavarian Nordic (MVA-BN)-brachyury-TRICOM vaccine has been developed to target brachyury, the previously noted transcription factor associated with increased cytokine release, angiogenic factor production, and IL-8 signaling.[117] Elevated IL-8 levels drive epithelial-to-mesenchymal transition in malignant cells, which increases tumor cell motility and invasiveness.[117] A Phase 1 clinical trial with escalating doses of this vaccine in patients with solid tumors demonstrated no DLTs, with most patients showing a brachyury-specific T-cell response.[118] Another Phase 1 trial evaluating the PROSTVAC-V/F vaccine incorporating PSA and TRICOM demonstrated a favorable toxicity profile as well as evidence of vaccinia-specific immune response.[119] However, no studies of this product have met their primary endpoint for efficacy as of this publication.

Pexa-Vec is one of the most extensively studied oncolytic Vaccinia Virus (oVV). JX-594 (Pexa-Vec) is an engineered vaccinia virus, used initially as a vaccine for smallpox, now repurposed for cancer therapy. It selectively infects and lyses tumor cells due to their defective antiviral responses. Pexa-Vec also expresses GM-CSF, promoting immune cell recruitment. Strong immune-stimulating properties make it suitable for combination with immunotherapies, especially in advanced liver cancer.[103,120] However, phase III trials in combination with sorafenib have failed to improve outcomes as compared to SOC.[103,121] A Phase I/II clinical trial of Pexa-Vec in combination with cemiplimab in RCC is ongoing.[122]

Several other oVVs are also being investigated. Double deleted vaccinia virus (vvDD), derived from the most potent strain of vaccinia virus (Western Reserve Strain), has shown promising outcomes.[123] vvDD was engineered to co-express somatostatin receptor and cytosine deaminase, generating a vvDD-CDSR strain, also known as JX-929, which has demonstrated tolerable safety as well as tumor specificity.[103,123,124] Various oVVs currently undergoing phase I clinical study include hV01 (recombinant human IL-21 oVV), IDOV-SAFE, GC001, and TG6050.[125–128] Based on previous trials showing a lower effect on eliciting an immune response by systemic administration, most of these trials are now evaluating intra-tumoral drug route. One exception is IDOV-SAFE, which remains a systemically-administered product.[103,126]

Table 3. Active clinical trials of viral vector-based cancer vaccines.

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
				Adenovirus					
1	Autologous dendritic cell adenovirus CCL21 vaccine	CCL21	NSCLC	Vaccine Pembrolizumab	I	A Phase I Trial of Intratumoral Administration of CCL21-Gene Modified Dendritic Cell (Ad-CCL21-DC) Combined With Intravenous Pembrolizumab for Advanced NSCLC	7/8/2019	No	NCT6361
2	Nous-209 vaccine	GAd20-209-FSP and MVA-209-FSP	CRC, gastric or GEJ tumors	Vaccine Pembrolizumab	I/II	A Phase I/II, Multicenter, Open-Label Study of Nous-209 Genetic Vaccine for the Treatment of Microsatellite Unstable Solid Tumors.	10/21/2019	No	NCT1310
3			Lynch Syndrome	Vaccine monotherapy	I/II	A Phase Ib/II Clinical Trial of Nous-209 for Recurrent Neoantigen Immunogenicity and Cancer Immune Interception in Lynch Syndrome		No	NCT8866
4	PRGN-2009	HPV 16/18 E6 and E7	Cervical Cancer	Vaccine Pembrolizumab	II	A Randomized, Open-label, Two-arm, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of PRGN-2009 in Combination With Pembrolizumab Versus Pembrolizumab Monotherapy in Patients With Recurrent or Metastatic Cervical Cancer.	11/2024	No	NCT7151
5	DCs vaccine combined with CIK	MUC1 and Survivin	AML	Adenovirus-transfected DC + CIK	I/II	Safety and Therapeutic Efficacy of DCs Vaccine Combined With Cytokine-induced Killer Cells in Patients With AML: a Phase I/II Study	11/2024	No	NCT8663
6	Combination of trivalent adenovirus-5 (Tri-Ad5) vaccines and IL-15 superagonist nogapendekin alfa inbakicept (N-803) vaccines	MUC1, CEA and brachyury	Lynch Syndrome	Vaccine monotherapy	II	A Phase IIB Clinical Trial of the Multitargeted Recombinant Adenovirus 5 (CEA/MUC1/Brachyury) Vaccine (TRI-AD5) and IL-15 Superagonist N-803 in Lynch Syndrome	5/8/2023	No	NCT9011
7	NANT Pancreatic Cancer Vaccine:	multiple neoantigens	Pancreatic Cancer	ALT-803 ETBX-011 GI-4000 haNK for infusion avelumab bevacizumab Capecitabine Cyclophosphamide Fluorouracil Leucovorin nab-Paclitaxel lovaza Oxaliplatin SBRT	I/II	NANT Pancreatic Cancer Vaccine: Molecularly Informed Integrated Immunotherapy Combining Innate High-affinity Natural Killer (haNK) Cell Therapy With Adaptive T-cell Therapy (Adenovirus, Yeast, Fusion Protein Vaccine) in Subjects With Pancreatic Cancer Who Have Progressed on or After Standard-of-care Therapy	11/6/2017	Yes	NCT9248

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
				Oncolytic Adenovirus					
1	LOAd703	No TSA	Pancreatic Cancer	LOAd703 Gemcitabine Nab-paclitaxel atezolizumab	I/II	Phase I/IIa Trial Evaluating Safety of LOAd703, an Armed Oncolytic Adenovirus for Pancreatic Cancer	11/2016	No	NCT5196
2			Pancreatic Adenocarcinoma Ovarian Cancer Biliary Carcinoma CRC	LOAd703 monotherapy	I/II	Phase I/II Trial Investigating an Immunostimulatory Oncolytic Adenovirus for Cancer	3/1/2018	Yes	NCT5989
3	Recombinant Human Adenovirus Type 5	No TSA	Uterine Cervical Neoplasms	Recombinant human adenovirus Camrelizumab	II	Oncolytic Virus(H101) Combined With Camrelizumab for Recurrent Cervical Cancer: a Prospective, Multicenter Study	03/2022	No	NCT4905
4			Cholangiocarcinoma	Recombinant Human Adenovirus Type 5 HAIC of FOLFOX	IV	Recombinant Human Adenovirus Type 5 Combined With Hepatic Artery Infusion Chemotherapy of FOLFOX in Patients With Intrahepatic Mass-forming Cholangiocarcinoma: a Single-site, Single-arm, Prospective Study	8/1/2022	No	NCT4002
5	H101	No TSA	Malignant Pleural Mesothelioma	Oncolytic Adenovirus H101 pdL1- inhibitor	Observational	Observation of the Efficacy and Safety of Oncolytic Adenovirus Injection Combined With Programmed Death Receptor Inhibitors in Treatment of Advanced Malignant Pleural Mesothelioma: a Single Center, Prospective, Case Registration Study	7/20/2023	No	NCT1636
6	KD01(recombinant oncolytic adenovirus)	No TSA	Cervical Cancer	KD01 monotherapy	I	The Safety, Tolerability, and Efficacy of Intratumoral Administration of the Recombinant Oncolytic Adenovirus Injection (KD01) in Patients With Cervical Malignancies	4/1/2024	No	NCT2598
7			Bladder Cancer	KD01 Camrelizumab	II	Phase II Single Center Open-Label Single-Arm Study of the Safety and Efficacy of Oncolytic Adenovirus H101 Combined With PD-1 Inhibitor in Patients With Non-muscle-invasive Bladder Cancer Who Failed BCG Therapy	8/26/2022	No	NCT4897
8	GM103	No TSA	Head and Neck Cancer Malignant Melanoma CRC RCCCervical Cancer Breast Cancer	GM103 vs GM103 Pembrolizumab	I/II	A Phase I/II, Open-label, Dose-escalation With Expansion Study of GM103 Via Intratumoral Injection, Alone and in Combination With Pembrolizumab in Adult Patients With Locally Advanced, Unresectable, Refractory and/or Metastatic Solid Tumors	2/20/2024	No	NCT5025
9	Recombinant Human Adenovirus Type 5	No TSA	Cervical Cancer	AK104 Recombinant Human Adenovirus 5 Injection	II	Efficacy and Safety of AK104 Combined With Pemetrexed, Carboplatin and Recombinant Human Adenovirus 5 Injection in Advanced Recurrent Cervical Cancer: a Multicenter, Single-arm, Prospective Phase II Clinical Study	2/20/2024	No	NCT5046

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
10	TILT-123	No TSA	Melanoma Head and Neck SCC	TILT-123 Avelumab	I	A Phase I Open-Label, Dose-escalation Clinical Trial of Tumor Necrosis Factor Alpha and IL-2 Coding Oncolytic Adenovirus TILT-123 and Avelumab in Solid Tumor Patients (Melanoma and SCCHN) Refractory to or Progressing After Anti-PD(L)1	3/8/2023	No	NCT2932
11			Ovarian and Fallopian tube tumor	TILT-123 pembrolizumab pegylated liposomal doxorubicin	I	A Two-part, Phase I/Ib, Open-Label, Dose-escalation Trial of Tumor Necrosis Factor Alpha and Interleukin-2 Coding Oncolytic Adenovirus (TILT-123) in Combination With Pembrolizumab (Phase I Part) and Pembrolizumab and Pegylated Liposomal Doxorubicin (Phase Ib Part) in Patients With Platinum Resistant or Refractory Ovarian Cancer.	5/17/2022	No	NCT1318
12			Advanced Solid Tumors	TILT-123 monotherapy	I	A Phase 1, Open-Label, Dose-escalation Clinical Trial of Tumor Necrosis Factor Alpha and Interleukin-2 Coding Oncolytic Adenovirus (TILT-123) in Patients With Injectable Solid Tumors	1/11/2021	No	NCT5327
13			Metastatic Melanoma	TILT-123 monotherapy	I	A Phase 1, Open-Label, Dose-Escalation Clinical Trial of Tumor Necrosis Factor Alpha and Interleukin 2 Coding Oncolytic Adenovirus TILT-123 in Melanoma Patients Receiving Adoptive Cell Therapy With Tumor Infiltrating Lymphocytes	2/26/2020	No	NCT7473
14	ORCA-010	No TSA	Adenocarcinoma of the Prostate	ORCA-010 monotherapy	I	A Phase I/IIa Study Evaluating the Safety and Tolerability of Intratumoral Administration of ORCA-010 in Treatment-Naïve Patients With Localized Prostate Cancer.	11/12/2019	No	NCT7002
15	DNX-2401	No TSA	IDH1 wt (Wild Type) Allele Recurrent Anaplastic Astrocytoma GBM Gliosarcoma Glioma	Oncolytic Adenovirus Ad5-DNX-2401 Therapeutic Conventional Surgery	I	Phase I Clinical Trial of Allogeneic Bone Marrow Human Mesenchymal Stem Cells Loaded With A Tumor Selective Oncolytic Adenovirus, DNX-2401, Administered Via Intra-Arterial Injection in Patients With Recurrent High-Grade Glioma	2/12/2019	No	NCT6568
16	AdMA3	No TSA	NSCLC Cutaneous SCC Merkel Cell Carcinoma Melanoma Pancreatic Cancer TNBC Head and Neck Cancer	MG1MA3 AdMA3	I/II	A Phase I/II Study of MG1 Maraba/MAGE-A3 (MG1MA3), With and Without Adenovirus Vaccine, With Transgenic MAGE-A3 Insertion (AdMA3) in Patients With Incurable Advanced/ Metastatic MAGE-A3-Expressing Solid Tumours	1/22/2015	No	NCT5816

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
17	CAdVEC	No TSA	Bladder Cancer Head and Neck SCC Salivary Gland Cancer Lung Cancer Breast Cancer Gastric Cancer Esophageal Cancer CRC Pancreatic Adenocarcinoma	CAdVEC monotherapy	I	A First in Human Phase I Trial of Binary Oncolytic Adenovirus in Combination With HER2-Specific Autologous CAR T Cells in Patients With Advanced HER2 Positive Solid Tumors	12/14/2020	No	NCT0256
18	BioTTT001	No TSA	Gastric Cancer	BioTTT001 intraperitoneal infusion SOX regimen Toripalimab	II	A Clinical Study to Evaluate the Safety and Efficacy of Recombinant Human nsIL12 Oncolytic Adenovirus Injection (BioTTT001) in Combination With SOX and Toripalimab in Patients With Peritoneal Metastases From Gastric Cancer	4/2/2024	No	NCT3121
19			Advanced Solid Tumors	BioTTT001 injection	I	Phase I Clinical Study on the Safety, Tolerability, and Pharmacokinetics of Recombinant Human nsIL12 Oncolytic Adenovirus Injection (BioTTT001) in Patients With Malignant Solid Tumors	5/7/2024	No	NCT5846
20			CRC	BioTTT001 hepatic artery infusion Toripalimab Regorafenib	I	A Clinical Study to Evaluate the Safety and Efficacy of Recombinant Human nsIL12 Oncolytic Adenovirus Injection (BioTTT001) in Combination With Toripalimab and Regorafenib in Patients With Liver Metastases From Colorectal Cancer	4/2/2024	No	NCT3134
21	AloCELY	No TSA	Diffuse Intrinsic Pontine Glioma Medulloblastoma	AloCELYVIR monotherapy	I/II	Phase IB Clinical Trial to Assess the Safety, Tolerability, and Preliminary Efficacy of AloCELYVIR (Mesenchymal Allogenic Cells + ICOVIR-5) in Children, Adolescent and Young Adults With Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG) in Combination With Radiotherapy or Medulloblastoma in Relapse/ Progression in Monotherapy	4/19/2021	No	NCT8533
22	Ad-TD-nsIL12	No TSA	Diffuse Intrinsic Pontine Glioma	Ad-TD-nsIL12 monotherapy	I	Oncolytic Virus Ad-TD-nsIL12 for Primary Pediatric Diffuse Intrinsic Pontine Glioma	1/4/2023	No	NCT7712
23			Diffuse Intrinsic Pontine Glioma	Ad-TD-nsIL12 monotherapy	I	Oncolytic Virus Ad-TD-nsIL12 for Progressive Pediatric Diffuse Intrinsic Pontine Glioma	1/4/2023	No	NCT7699
24	AdAPT-001	No TSA	Advanced Solid Tumors Sarcoma, Chondrosarcoma	AdAPT-001 + ICI	II	An Adapted Phase 2a/2b, Study to Evaluate the Safety, Tolerability, and Efficacy of AdAPT-001 in Subjects With Refractory Solid Tumors	3/29/2021	No	NCT3942
25	TS-2021	No TSA	GBM	TS-2021 monotherapy	I	Clinical Study on the Safety and Efficacy of the Third-Generation Oncolytic Virus TS-2021 in the Treatment of Recurrent Malignant Glioma	8/29/2024	No	NCT5527
26	JNJ-84916	No TSA	Advanced Solid Tumors	JNJ-84916 + Cetrelimab	I	Phase 1 Study of Intratumoral Administration of JNJ-84916, an Oncolytic Virus, as Monotherapy and in Combination for Advanced Solid Tumors	4/10/2024	No	NCT1578
27	CG0070	No TSA	Bladder cancer	CG0070 + Nivolumab	I	A Phase 1 Study of CG0070 Combined With Nivolumab in Cisplatin Ineligible Patients With Muscle Invasive Bladder Cancer (MIBC)	10/26/2020	No	NCT0671

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
				Poxvirus (Including Vaccinia)					
1	MVA-BN-Brachyury	Brachyury	Advanced Solid Tumors	Vaccine, M7824, N-803 and Epacadostat	I/II	A Phase I/II Study of Immunotherapy Combination BN-Brachyury Vaccine, M7824, N-803 and Epacadostat (QuEST1)	5/1/2018	No	NCT3945
2	CV301 vaccine	CEA and MUC-1 and B7-1, ICAM-1 and LFA-3	Small Bowel and CRC	Vaccine MSB1359C N-803 NHS-IL12	II	Phase II Trial of Combination Immunotherapy in Subjects With Advanced Small Bowel and Colorectal Cancers	9/22/2020	Yes	NCT1955
3	PANVAC-V, PANVAC-F	CEA and MUC-1 and B7-1, ICAM-1 and LFA-3	Pancreatic Cancer	Vaccine monotherapy + Sargramostim	I	Immunotherapy for Unresectable Pancreas Cancer: A Phase 1 Study of Intratumoral Recombinant Fowlpox PANVAC (PANVAC-F) Plus Subcutaneous Recombinant Vaccinia PANVAC (PANVAC-V), PANVAC-F and Recombinant Granulocyte-Macrophage Colony Stimulating Factor (rH-GM-CSF)	2/1/2010	No	NCT9734
4	Multi-peptide CMV-MVAVaccine.	CMV tumor-associated TAAs, including UL83 (pp65), UL123 (IE1) and UL122 (IE2)	Hematologic malignancies	Vaccine monotherapy +/- Letermovir	II	A Phase II Randomized, Placebo-Controlled, Multicenter Trial to Evaluate the Protective Function of CMV-MVA Triplex Vaccine in Adult Recipients of Haploidentical Hematopoietic Stem Cell Transplant	11/27/2019	Yes	NCT0277
5			Hematologic malignancies	Vaccine monotherapy		A Phase II Randomized, Placebo-Controlled, Multicenter Trial to Evaluate the Protective Function of a CMV-MVA Triplex Vaccine in Recipients of an Allogeneic Hematopoietic Stem Cell Transplant	5/11/2025	Yes	NCT6933
6			Hematologic malignancies	Anti-CD19-CAR CMV-specific T-lymphocytes Leukapheresis Lymphodepletion Therapy Multi-peptide CMV-MVA Vaccine	I	A Pilot / Feasibility Study of Autologous CMV-Specific CD19-CAR T Cells Plus CMV-MVA Triplex Vaccine in Patients With Intermediate or High Grade B-Lineage Non-Hodgkin Lymphoma	9/29/2023	No	NCT1913
7			Hematologic malignancies	Anti-CD19-CAR CMV-specific T-lymphocytes Autologous Hematopoietic Stem Cell Transplantation Multi-peptide CMV-Modified Vaccinia Ankara Vaccine Myeloablative Conditioning	I	Pilot/Feasibility Study of CMV-Specific CD19-CAR T Cells Plus CMV-MVA Triplex Following Autologous Hematopoietic Stem Cell Transplantation for Patients With Intermediate or High Grade B-Lineage Non-Hodgkin Lymphoma (B-NHL)	8/1/2023	No	NCT2635
8	Nous-209	GAd20-209-FSP and MVA-209-FSP	CRC	Vaccine Pembrolizumab	I/II	A Phase I/II, Multicenter, Open-Label Study of Nous-209 Genetic Vaccine for the Treatment of Microsatellite Unstable Solid Tumors	10/21/2019	No	NCT1310
9		GAd20-209-FSP and MVA-209-FSP	Lynch Syndrome	Vaccine monotherapy	I/II	A Phase Ib/II Clinical Trial of Nous-209 for Recurrent Neoantigen Immunogenicity and Cancer Immune Interception in Lynch Syndrome	11/10/2022	No	NCT8866
10	MVA Expressing p53	p53	p53 expressing solid tumors	Vaccine Pembrolizumab	I	A Phase I Study of a p53MVA Vaccine in Combination With Pembrolizumab	6/14/2016	No	NCT2963

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
11	PROSTVAC-V and PROSTVAC-F	PSA and the three co-stimulatory molecule transgenes (TRICOM), B7.1, ICAM-1), and LFA-3.	Prostate Cancer	Vaccine CV301 +/- MSB1359C (M7824)	II	Phase II Trial of Combination Immunotherapy in Biochemically Recurrent Prostate Cancer	3/20/2018	No	NCT5871
				Oncolytic Vaccinia					
1	hV01	No TSA	Advanced Solid Tumors	hV01 monotherapy	I	A Phase I Dose Escalation Study to Evaluate the Safety, Tolerance, Pharmacokinetics, and Biological Properties of Recombinant Human IL-21 Oncolytic Vaccinia Virus Injection (hV01) in Patients With Advanced Malignant Solid Tumors	7/5/2023	No	NCT4376
2	GC001	No TSA	Cervical Cancer CRC Lung Cancer Ovarian CancerPancreatic Cancer HCC Breast Cancer Gastric Cancer	GC001 monotherapy	I	A Phase I Study Evaluating the Safety, Tolerability, Biodistribution and Shedding of the Virus, Pharmacodynamics, Immunogenicity, and Antitumor Activity of GC001 Oncolytic Vaccinia Virus Injection in Patient With Advanced Solid Tumors.	4/26/2023	No	NCT8307
3	RGV004	No TSA	Relapsed or Refractory B-cell Lymphoma	RGV004 monotherapy	I	Exploratory Study of a Novel Oncolytic Vaccinia Virus Expressing Bispecific Antibody in the Treatment of Refractory/Relapsed B-cell Lymphoma	2/8/2022	No	NCT7025
4	IDOV-SAFE	No TSA	Advanced Malignant Solid Tumor of Digestive System	IDOV-SAFE monotherapy	I	An Open Label, Dose-escalation and Extension, Phase I Clinical Study on Evaluating Safety, Tolerability and Pharmacodynamics of Intravenous Administration of IDOV-SAFE in Patients With Advanced Malignant Solid Tumors Who Have Failed in Standard Treatment.	5/6/2024	No	NCT0309
5	Pexa-Vec	No TSA	RCC	Pexa-Vec Cemipilimab	I/II	A Phase 1b/2a Dose-escalation and Safety/Efficacy Evaluation Study of Pexa-Vec (Thymidine Kinase-Deactivated Vaccinia Virus Plus GM-CSF) in Combination With Cemiplimab (REGN2810; Anti-PD-1) in Patients With Metastatic or Unresectable Renal Cell Carcinoma (RCC)	6/7/2018	Yes	NCT4083
6	KM1	No TSA	Ovarian Cancer	KM1 + Chemotherapy	I	A Single-Arm, Open-Label Clinical Study to Evaluate the Safety, Tolerance and Preliminary Efficacy of KM1 Oncolytic Vaccinia Virus Injection Combined With Chemotherapy in Subjects With Recurrent or Refractory Ovarian Cancer	2/1/2023	No	NCT4731

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
7	Olvimulogene nanivacirepvec	No TSA	NSCLC	Olvimulogene nanivacirepvec Platinum chemotherapy: carboplatin or cisplatin Non-platinum chemotherapy: paclitaxel or nab-paclitaxel for squamous cell NSCLC or pemetrexed for Nonsquamous cell NSCLC ICI: pembrolizumab, nivolumab, cemiplimab, atezolizumab, durvalumab Docetaxel	II	A Randomized Phase 2 Study Assessing the Efficacy and Safety of Olvimulogene Nanivacirepvec Followed by Platinum-doublet Chemotherapy + Physician's Choice of Immune Checkpoint Inhibitor Compared With Docetaxel in Patients With NSCL Cancer After First Progression While on Front-line Immune Checkpoint Inhibitor-based Maintenance	9/26/2024	No	NCT3665
8	TG6050	No TSA	NSCLC	TG6050 monotherapy	I	A Phase I Dose-escalation Trial of TG6050 Administered by Intravenous Infusion in Patients With Advanced Non-small Cell Lung Cancer (NSCLC)	4/5/2023	No	NCT8926
9	VET3-TGI	No TSA	CRCHead and Neck SCC Cervical CancerRCC Melanoma Merkel Cell Carcinoma of SkinMesothelioma NSCLC	VET3-TGI Pembrolizumab	I	A Phase 1/1b Study of VET3-TGI Administered Alone and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors	9/16/2024	No	NCT4815
10	Olvi-Vec	No TSA	Ovarian Cancer Fallopian Tube Cancer Primary Peritoneal Cancer	Olvi-Vec Platinum chemotherapy: carboplatin (preferred) or cisplatin. Non-platinum chemotherapy: Physician's Choice of gemcitabine, Taxane (paclitaxel, docetaxel or nab-paclitaxel) or pegylated liposomal doxorubicin. Bevacizumab (or biosimilar)	III	A Randomized Phase 3 Study Assessing the Efficacy and Safety of Olvi-Vec Followed by Platinum-doublet Chemotherapy and Bevacizumab Compared With Physician's Choice of Chemotherapy and Bevacizumab in Women With Platinum-Resistant/Refractory Ovarian Cancer (PRROC) (OnPrime, GOG-3076)	8/31/2022	No	NCT1471
11	BT-001	No TSA	Soft Tissue Sarcoma Merkel Cell Carcinoma MelanomaTNBC NSCLC	BT-001 Pembrolizumab	I/II	A Phase I/IIa Study of Intra-tumoral BT-001 (TG6030) Administered Alone and in Combination With Pembrolizumab in Patients With Cutaneous or, Subcutaneous Lesions or Easily Injectable Lymph Nodes of Metastatic/ Advanced Solid Tumors.	2/25/2021	No	NCT5331

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
				Oncolytic HSV					
1	BS-006	No TSA	Uterine Cervical Neoplasms	BS-006 monotherapy	I	A First-in-human Phase I Two-stage Clinical Trial for Intratumoral Injection of Recombinant Oncolytic Type II Herpes Simplex Virus (BS-006) in Patients With Recurrent Cervical Cancer	9/16/2022	No	NCT3440
2	C134	No TSA	GBM of Brain Anaplastic Astrocytoma of Brain Gliosarcoma of Brain	C134 monotherapy	I	A Phase I Trial of IRS-1 HSV C134 Administered Intratumorally in Patients With Recurrent Malignant Glioma	9/23/2019	No	NCT7576
3	HSV G207	No TSA	Primary CNS malignancy	G207 monotherapy	II	Phase II Clinical Trial of HSV G207 with a Single 5 Gy Radiation Dose in Children with Recurrent High-Grade Glioma	12/2024	No	NCT2933
4			GBM	G207 monotherapy	I	Phase 1 Trial of Engineered HSV G207 in Children With Recurrent or Refractory Cerebellar Brain Tumors	9/12/2019	No	NCT1388
5	M032	No TSA	GBMAnaplastic Astrocytoma Gliosarcoma	M032 monotherapy	I	A Phase 1 Study of M032 (NSC 73972), a Genetically Engineered HSV-1 Expressing IL-12, in Patients With Recurrent/Progressive Glioblastoma Multiforme, Anaplastic Astrocytoma, or Gliosarcoma	11/25/2013	Yes	NCT2827
6			GBM Anaplastic Astrocytoma Gliosarcoma	M032 Pembrolizumab	I/II	A Phase I/II Study of Pembrolizumab and M032 (NSC 73972), a Genetically Engineered HSV-1 Expressing IL-12, in Patients With Recurrent/ Progressive and Newly Diagnosed Glioblastoma Multiforme, Anaplastic Astrocytoma, or Gliosarcoma	2/25/2022	No	NCT4430
7	MVR-C5252	No TSA	High-Grade Glioma	MVR-C5252 monotherapy	I	The PuMP Trial: "A Multistage Phase 1 Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of the Oncolytic HSV1 MVR-C5252 in Patients With Recurrent High-Grade Glioma"	6/11/2024	No	NCT6744

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
8	OH2	No TSA	Solid Tumor Gastrointestinal Cancer	OH2 injection, with or without irinotecan or HX008	I/II	Phase I/II Study of OH2 Injection, an Oncolytic Type 2 Herpes Simplex Virus Expressing Granulocyte Macrophage Colony-Stimulating Factor, in Malignant Solid Tumors	4/2/2019	No	NCT6525
9			Bladder Carcinoma	Monotherapy OH2 injection	II	Efficacy and Safety Study of Oncolytic Virus (OH2) Intratumoral Injection in Locally Advanced or Metastatic Bladder Cancer a Phase II Clinical Trial	5/25/2022	No	NCT8789
10			Non-muscle-invasive Bladder Cancer	Monotherapy OH2 injection	I/II	Oncolytic Virus (OH2) Adjuvant Therapy After Transurethral Resection of Bladder Tumor in Non-Muscle-Invasive Bladder Cancer Who Have Failed First-line Prophylactic Intravesical Instillation Therapy: a Phase Ib/II Clinical Trial	7/11/2022	No	NCT2136
11			CNS Tumors	Monotherapy OH2 injection	I/II	A Clinical Study of Oncolytic Virus (OH2) Injection in the Treatment of Patients Undergoing Surgery After Recurrence of Central Nervous System Tumors	11/16/2021	No	NCT5074
12			Melanoma	OH2 HX008 injection	I/II	Phase Ib Study of the Combination Use of Recombinant Human GM-CSF Type II Herpes Simplex Virus (OH2) Injection (Vero Cells) and HX008 Injection in the Treatment of Melanoma	12/1/2020	No	NCT6443
13			Melanoma	OH2 Pembrolizumab	I/II	Open and Incremental Phase I Clinical Trial of Recombinant Human GM-CSF Type II Herpes Simplex Virus (OH2) Injection (Vero Cells) in the Treatment of Advanced Solid Tumors	11/22/2018	No	NCT6967
14			Melanoma	OH2 Salvage chemotherapy or best supportive care	III	To Evaluate a Phase III Study of OH2 Versus Investigator-selected Salvage Chemotherapy or Best Supportive Care in Melanoma Patients Who Had Failed Standard Therapy	3/8/2023	No	NCT8707

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
15	R130	No TSA	Sarcoma Carcinoma Breast Cancer Pancreatic Cancer CRCGastric Cancer Liver Cancer Lung Cancer Gynecologic Cancer	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Advanced Solid Tumors	3/2/2023	No	NCT0374
16			Digestive Cancer Breast Cancer Lung Cancer Brain CancerMelanoma Gynecologic Cancer Head and Neck Cancer Kidney Cancer	R130 Monotherapy	I	An Open, Single-armed, Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130 OV) for the Treatment of Advanced Solid Tumors	6/24/2023	No	NCT1111
17			Head and Neck Cancer Esophageal Cancer Otorhinolaryngologic Neoplasms Pharyngeal Cancer	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Relapsed/Refractory Head and Neck Cancer	3/27/2023	No	NCT0240
18			Lung Cancer (NSCLC. SCLC) Bronchial Cancer Sarcoma CRC Gastric Cancer Liver Cancer Breast Cancer Pancreatic Cancer Head and Neck Cancer Ovarian Cancer	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Relapsed/Refractory Advanced Solid Tumors	3/30/2023	No	NCT6075
19			Cervical Cancer Endometrial Cancer	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Relapsed/Refractory Cervical and Endometrial Cancer	2/6/2023	No	NCT2677
20			Osteosarcoma Sarcoma,Soft Tissue	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Advanced Bone and Soft Tissue Tumors	7/12/2023	No	NCT1282
21			Osteosarcoma Sarcoma,Soft Tissue	R130 Monotherapy	I	A Clinical Study on Oncolytic Virus Injection (R130) for the Treatment of Relapsed/Refractory Bone and Soft Tissue Tumors	4/10/2023	No	NCT1456
22			Ovarian Cancer Peritoneal Carcinomatosis Fallopian Tube Cancer	R130 Monotherapy	I	A Clinical Safety and Efficacy Study on Oncolytic Virus Injection (R130) for the Treatment of Relapsed/Refractory Ovarian Cancer	12/2/2022	No	NCT1783

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
23	RP1	No TSA	Cutaneous SCC Merkel Cell Carcinoma BCC Melanoma	RP1 (intra-tumoral injection)	I/II	An Open-Label, Multicenter, Phase 1B/2 Study of RP1 in Solid Organ and Hematopoietic Cell Transplant Recipients With Advanced Cutaneous Malignancies	5/15/2020	No	NCT9436
24			Cutaneous SCC	RP1 Cemipilimab	II	A Randomized, Controlled, Open-Label, Phase 2 Study of Cemiplimab as a Single Agent and in Combination With RP1 in Patients With Advanced Cutaneous Squamous Cell Carcinoma	10/8/2019	No	NCT0436
25			Melanoma	RP1 monotherapy	I	Phase I Pilot Study of RP1 in Primary Melanoma to Reduce the Risk of Sentinel Lymph Node Metastasis	2/2/2024	No	NCT6938
26			MelanomaNon-melanoma Skin Cancer NSCLC	RP1 Nivolumab	II	An Open-Label, Multicenter, Phase 1/2 Study of RP1 as a Single Agent and in Combination With PD1 Blockade in Patients With Solid Tumors	9/20/2017	No	NCT7348
27	RP2	No TSA	Metastatic Uveal Melanoma	RP2 Ipilimumab / Nivolumab	II / III	A Randomized, Phase 2/3, Open-Label Study to Investigate the Efficacy and Safety of RP2 in Combination With Nivolumab Versus Ipilimumab in Combination With Nivolumab in Immune Checkpoint Inhibitor-Naïve Adult Patients With Metastatic Uveal Melanoma	1/27/2025	No	NCT1406
28	RP2/RP3	No TSA	mCRC	RP2 RP3 Atezolizumab Bevacizumab	II	A Phase 2 Clinical Trial Investigating Oncolytic Immunotherapy in Combination With Atezolizumab and Bevacizumab for the Treatment of Patients With Advanced Microsatellite Stable and Mismatch Repair Proficient Colorectal Carcinoma	6/29/2023	No	NCT3611
29	RP3	No TSA	Advanced Solid Tumor	RP3 Nivolumab	I	An Open-Label, Multicenter, Phase 1 Study of RP3 as a Single Agent and in Combination With PD-1 Blockade in Patients With Solid Tumors	12/29/2020	No	NCT5978
30			HCC	RP3 Atezolizumab Bevacizumab	II	A Phase 2, Open-label, Multicenter Study Investigating RP2 Oncolytic Immunotherapy in Combination With Second-line Therapy in Patients With Locally Advanced Unresectable, Recurrent and/or Metastatic Hepatocellular Carcinoma	8/1/2024	No	NCT3598
31	T3011	No TSA	mCRC	T3011 hepatic artery infusion Toripalimab Regorafenib	I	A Clinical Study to Evaluate the Safety and Efficacy of Herpes Virus T3011 Injection in Combination With Toripalimab and Regorafenib in Patients With Liver Metastases From Colorectal Cancer	4/2/2024	No	NCT3303
32			Advanced Solid Tumor	T3011 Monotherapy	I/II	A Phase I/IIa Study to Assess the Safety, Tolerability, Biodistribution and Pharmacodynamic of T3011 Herpes Virus Administered Via Intravenously in Patients With Advanced Solid Tumors	3/1/2022	No	NCT8268
33			Advanced Solid Tumor	T3011 Monotherapy	I/II	A Phase I/IIa Study to Assess the Safety, Tolerability, Biodistribution and Pharmacodynamic of T3011 Herpes Virus Administered Via Intratumoral Injection in Patients With Advanced Solid Tumors	4/21/2020	No	NCT2792

(*Continued*)

Table 3. (Continued).

Sr No.	Vaccine	Antigen	Cancer Indication	Drug Combination	Phase	Study Title			NCT Number
34	T-VEC	No TSA	TNBC	T-VEC Paclitaxel	I/II	A Phase 1/2 Study of Talimogene Laherparepvec in Combination With Neoadjuvant Chemotherapy in Triple Negative Breast Cancer	5/2/2017	Yes	NCT9855
35	VG161	No TSA	Gastric Cancer	oHSV-1 (Vero Cell) Nivolumab	I/II	A Dose Ascending, Open Phase Ib/IIa Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetic Characteristics and Preliminary Efficacy of VG161 Combined With Nivolumab Injection in Subjects With Metastatic Gastric Cancer	11/17/2022	No	NCT8925
36			HCC	oHSV-1 (Vero Cell) Camrelizumab	I/II	An Open-label Phase Ib/IIa Clinical Trial of VG161 Combined With Camrelizumab in the Treatment of Advanced Primary Hepatocellular Carcinoma	11/30/2023	No	NCT4001
37	VG2025	No TSA	Advanced Solid Tumor	VG2025 Monotherapy	I	A Dose Escalation, Open-label Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Biologic Effect of VG2025 in the Treatment of Patients With Advanced Malignant Solid Tumors	8/23/2022	No	NCT7849

AML: Acute Myeloid Leukemia, B7.1: CD80, BCC: Basal Cell Carcinoma, CAR: chimeric antigen receptor, CCL21: C-C motif chemokine ligand 21, CEA: carcinoembryonic antigen, CRC: Colorectal Cancer, CIK: cytokine-induced killer, CMV: Cytomegalovirus, CNS: central nervous system, DIPG: Diagnosed Diffuse Intrinsic Pontine Glioma, dMMR: deficient mismatch repair, DCs: Dendritic Cells, Hank: High-affinity Natural Killer, HCC: Hepatocellular Carcinoma, HER-2: human epidermal growth factor receptor 2, HPV: human papillomavirus, HSV: herpes simplex virus, GBM: Glio-Blastoma Multiforme, GEJ: Gastro Esophageal Junction, ICAM-1: intercellular adhesion molecule-1, IL: interleukin, LFA-3: lymphocyte function-associated antigen-3, mCRC: metastatic colorectal cancer, MSI-H: microsatellite instability-high, MUC-1: mucin 1, MVA: Modified Vaccine Ankara, NSCLC: Non-Small Cell Lung Cancer, oAV: Oncolytic Adenovirus, oHSV: Oncolytic HSV virus, OV: Oncolytic Virus, oVV: Oncolytic Vaccinia Virus, Pd-1: Programmed Cell Death Protein 1, pMMR: proficient mismatch repair, MSS: microsatellite stability, PRROC: Platinum-Resistant/Refractory Ovarian Cancer, PSA: Prostate Specific Antigen, RCC: Renal Cell Carcinoma, rH-GM-CSF: Recombinant Granulocyte-Macrophage Colony Stimulating Factor, RP1: Vusolimogene oderparepvec, SCC: Squamous Cell Carcinoma, SCCHN: Squamous Cell Carcinoma of head and neck, SCLC: Small Cell Lung Cancer, Sr. No: Serial Number. TAA: Tumor-Associated Antigen, TNBC: Triple Negative Breast Cancer, TRICOM: TRIad of COstimulatory Molecules, TSA: Tumor-Specific Antigen, T-VEC: Talimogene Laherparepvec, WT: Wild Type.

While the majority of development is occurring in advanced solid tumors, RGV004 is also being investigated in B-cell lymphoma.[129]

Among chemotherapy combination trials, KM1 and Olvi-Vec (Olvimulogene nanivacirepvec) are currently being evaluated. KM1 is a genetically modified recombinant vaccinia virus that has demonstrated therapeutic efficacy in various solid tumors, including ovarian cancer. In the ongoing phase 1 study, KM1 is administered via intraperitoneal infusion in combination with chemotherapy. The physician's choice of agents includes carboplatin or cisplatin, gemcitabine, taxanes, or pegylated liposomal doxorubicin, with or without bevacizumab.[130] Olvimulogene nanivacirepvec (Olvi-Vec), currently in phase 2 testing, has shown broad infectivity and therapeutic potential across a variety of tumor types, including NSCLC and platinum-resistant/refractory ovarian cancer (PRROC). In the ongoing phase 2 trial (VIRO-25), Olvi-Vec is being evaluated in combination with platinum-doublet chemotherapy and ICI.[131] Building on the efficacy and safety results from the phase 2 VIRO-15 trial, a phase 3 trial (OnPrime GOG-3076) is now assessing its role in combination with chemotherapy – including carboplatin, cisplatin, gemcitabine, taxanes, or pegylated liposomal doxorubicin – in conjunction with bevacizumab for PRROC.[132] Another vaccine, VET3-TGI, is oncolytic immunotherapy currently in phase 1 evaluation (STEALTH-001 trial) to treat advanced cancers. Although it has not yet been administered to human patients, it has been designed to selectively infect and kill cancer cells while sparing healthy tissue. The phase 1 study consists of dose escalation and expansion groups. Group A evaluates the highest tolerated dose (HTD) of VET3-TGI administered intratumorally, while Group C determines the HTD when administered intravenously. Groups B and D assess the combination of VET3-TGI with pembrolizumab, starting at the HTD identified in Groups A and C, respectively.[133] Additionally, BT-001, an oncolytic vaccinia virus containing genes encoding the 4-E03 human recombinant anti-hCTLA4 antibody and human GM-CSF, is under investigation in a phase 1/2 trial. This trial is evaluating its combination with pembrolizumab for metastatic melanoma, TNBC, and Merkel cell carcinoma.[134]

Adenovirus

Adenovirus, a non-enveloped virus with a double-stranded DNA genome, has more than 50 known serotypes that can cause human illness.[135] They are highly efficient in transducing both dividing and non-dividing cells, making them a promising tool in cancer vaccine development.[106,136] Key advantages include their well-characterized genome, ease of genetic manipulation, and broad tropism.[135] Advances in genetic engineering have further improved their safety and efficacy.[107] This has paved the way for various vaccine platforms targeting specific TAAs, including CEA, Mucin 1 (MUC1), and PSA.

One notable example is ETBX-011, an engineered adenoviral vaccine that encodes a modified CEA (Table 3). This vaccine includes the highly immunogenic epitope CAP1-6D, which has been shown to induce CEA-specific, cell-mediated immune responses with potent antitumor activity.[137] Initial Phase 1/2 trials in patients with metastatic CRC (mCRC) demonstrated favorable safety and immunogenicity profiles.[138,139] However, the Phase II trial evaluating (Adenovirus type 5) Ad5-CEA combination with avelumab vs SOC (FOLFOX + bevacizumab) in mCRC did not show sufficient improvement in progression-free survival, although it did generate multifunctional CD4+/CD8+ T cells specific to MUC1 and brachyury.[140] An ongoing trial now compares the vaccine with regorafenib in mCRC.[97]

To address the challenge of tumor heterogeneity, recombinant adenoviral vaccines targeting a broader range of TAAs have shown promise in preclinical models.[137,141] An ongoing Phase 2 trial[142] is further evaluating the Tri-Ad5 vaccine regimen in combination with the IL-15 superagonist nogapendekin alfa inbakicept (*N*-803) in Lynch Syndrome. The goal is to assess its effectiveness in preventing cancer in this high-risk population. Ad5-PSA, an adenoviral vaccine encoding PSA and prostate stem cell antigen, has also demonstrated strong preclinical efficacy.[143] This was followed by a Phase 1 trial, which confirmed the vaccine's safety.[137,144] Future studies will likely evaluate the vaccine's clinical benefits when combined with other immunotherapy agents or palliative radiation therapy.[145]

A related trial[146] investigates Maraba's product, MG1-MAGEA3, both as monotherapy and with a prime/boost strategy incorporating an adenovirus vaccine also targeting MAGEA3 (Melanoma-associated antigen). Early results suggest that the Ad-MAGEA3 prime followed by the MG1-MAGEA3 boost is tolerable and determined a recommended Phase 2 dose.[147] Trial NCT9760 is evaluating the combination of MG1-MAGEA3 with Ad-MAGEA3 with pembrolizumab in NSCLC; accrual is complete, and results are pending.[148] In addition, novel platforms are being developed to further enhance immune responses in hard-to-treat cancers. One such platform is the PRGN-2009 therapeutic gorilla adenovirus-based vaccine, which targets HPV-associated malignancies. PRGN-2009 contains multiple cytotoxic T cell epitopes targeting the viral oncoproteins HPV 16/18 E6 and E7, including T cell enhancer agonist epitopes. Preclinical studies have shown a significant reduction in tumor volume in humanized mouse models.[149] A Phase I study demonstrated that PRGN-2009, both as monotherapy and in combination with bintrafusp alfa (BA) – a bifunctional Tumor Growth Factor (TGF)-β trap/anti-PD-L1 fusion protein – was safe, well-tolerated, and induced HPV-specific T-cell immune responses in patients with recurrent/metastatic HPV-associated cancers. The combination of PRGN-2009 and BA exhibited clinical activity, in both patients naïve or resistant to ICI.[150] A Phase II study is currently evaluating the combination of PRGN-2009 with pembrolizumab, with biological correlative assays underway.[151]

Another innovative approach is the development of Nous-209, a cancer vaccine aimed at targeting multiple neoantigens shared across both sporadic and hereditary microsatellite instability (MSI)-high tumors.[152] Nous-209 uses a heterologous prime/boost strategy, combining two multivalent viral vector platforms: GAd-209, which consists of four great ape

adenovirus (GAd) vectors, and MVA-209, which contains four MVA vectors. Each vector encodes a synthetic polypeptide, allowing for broad neoantigen coverage.[153] Currently, Nous-209 is being tested in a Phase 1/2 trial[154] in patients with metastatic mismatch repair-deficient (dMMR) gastric, CRC, and gastroesophageal junction (GEJ) tumors, in combination with pembrolizumab. Interim results have demonstrated that the vaccine, when combined with pembrolizumab, is safe, immunogenic, and shows early signs of clinical efficacy.[155] Moreover, Nous-209 is also being explored as a preventive vaccine for Lynch syndrome carriers without any existing malignancies.[156]

Adenoviral vectors have also been widely utilized in gene therapy applications, particularly in DC vaccines. These vectors are highly effective at transducing DCs, which are crucial in initiating adaptive immune responses. Several trials have explored autologous DC adenovirus CCL21 vaccines in NSCLC. While one trial[157] was terminated, another[158] demonstrated promising immune responses in advanced NSCLC, although detailed results are yet to be reported. An active but non-recruiting trial[159] evaluates the combination of the CCL21 adenovirus vaccine with pembrolizumab in Stage IV NSCLC. Ongoing trials, such as NCT8663, are investigating adenoviral-transfected DC vaccines combined with cytokine-induced killer (CIK) cells in patients with acute myeloid leukemia (AML), targeting antigens like MUC1 and survivin.[160]

In addition, adenoviruses have emerged as powerful tools in developing OVs. One of the earliest OVs, Oncorine, was approved for clinical use in China in 2005[103]. However, as monotherapy, it failed to demonstrate sufficient therapeutic efficacy in patients with refractory solid tumors.[103] ONYX-015, one of the first attenuated adenoviruses, was designed to selectively replicate in p53-deficient tumor cells, a common mutation in many cancers, while leaving normal tissue unaffected. Since then, newer oncolytic adenoviruses (oAV) have been developed, including ONCOS-102, LoAd703, TILT-123, ORCA-010, and CG0070 (Cretostimogene grenadenorepvec). These viruses incorporate the intact E1B 55 kDa gene, which enhances viral replication and has been engineered to replicate in cancer cells preferentially.[103] Additionally, many of these oAVs feature modified fibers on their capsids, improving their ability to infect cancer cells independently of the coxsackie and adenovirus receptors, further enhancing their therapeutic potential.[161,162]

Several oAVs are undergoing clinical trials (Table 3). LOAd703 is an immunostimulatory gene therapy utilizing a selectively replicating adenovirus as a gene vehicle. The virus expresses the transgenes trimerized membrane-bound isoleucine zipper (TMZ)-CD40L and 41BBL under the control of a cytomegalovirus (CMV) promoter. The LOKON002 trial, a Phase I/II study, evaluated LOAd703 in patients with pancreatic, biliary, ovarian, and CRC cancers.[163] Results from LOKON002 showed that combining LOAd703 with nab-paclitaxel plus gemcitabine in patients with advanced pancreatic ductal adenocarcinoma was feasible and safe.[164] It also showed that LOAd703 has the ability to generate an inflamed tumor microenvironment in immunologically "cold" tumors, thereby priming them for ICIs or other immunotherapies, such as adoptive T or NK cell transfer.[165] Additionally, the LOKON001 trial is assessing LOAd703 administered via intratumoral injections for pancreatic cancer, combined with SOC treatment, including gemcitabine and nab-paclitaxel, with or without the anti-PD-L1 antibody atezolizumab.[166] Another oncolytic adenovirus, H101—a recombinant human Ad5—is being evaluated in various trials. In unresectable intrahepatic cholangiocarcinoma, H101 is combined with FOLFOX chemotherapy, while in advanced mesothelioma, it is being studied in combination with PD-1 inhibitors to reverse immune resistance.[167,168] In recurrent cervical cancer, it is being investigated along the anti-PD-1 antibody camrelizumab via intratumoral injections.[169]

TILT-123, another oncolytic Ad5 engineered to express TNF-α and IL-2, has emerged as a key therapeutic agent, with trials in melanoma, ovarian carcinoma, and head and neck cancers, where it is being tested in combination with ICIs.[170–173] The TUNIMO trial demonstrated that TILT-123 was safe and capable of inducing antitumor effects in both local and distant lesions in heavily pre-treated patients.[174] Across three trials – TUNIMO, TUNINTIL, and PROTA – TILT-123 was well-tolerated, with no DLTs reported, and it showed significant intratumoral immunomodulation following a single intravenous administration.[175] Similarly, CG0070, another oAV has shown encouraging results. This conditionally replicating dsDNA-based Ad5 is genetically engineered with the essential E1a gene under the control of the human E2F1 promoter. A Phase 1 trial combining CG0070 with nivolumab for cisplatin-ineligible muscle-invasive bladder cancer (MIBC) reported no dose-limiting toxicities, achieving a 42.1% pathologic complete response rate and a 70.4% 1-year recurrence-free survival, highlighting the potential of this combination regimen to enhance therapeutic efficacy in cisplatin-ineligible patients with muscle-invasive bladder cancer.[176]

Another notable viral vector is Seneca Valley Virus (SVV-001), a replication-competent oncolytic picornavirus initially discovered as a contaminant in laboratory adenovirus preparation.[177] SVV-001 was evaluated in a Phase 1 clinical trial, where a single IV dose was well tolerated in patients with advanced solid tumors exhibiting neuroendocrine features. The study reported a clinical benefit rate of 85% of neuroendocrine neoplasms.[178] Future trials are planned in combination with ICI, focusing on solid tumors with enhanced patient selection guided by biomarker-driven approaches. Other promising trials include ORCA-010, a novel oAV being evaluated for intratumoral administration in treatment-naïve patients with localized prostate cancer[179] and DNX-2401,[180] designed to be delivered intra-arterially for recurrent glioblastoma. Newer OVs, such as MEM-288[181]and Ixovex-1,[182] are currently under investigation for use in NSCLC and head and neck cancers, often in combination with ICI. Additional trials are exploring the efficacy of oAV such as CAdVEC[183] and BioTTT001[184–186] in HER2-positive solid tumors. Further details of ongoing trials are available in Table 3.

Herpes viruses

HSV is a promising vector for the delivery of TAAs due to its ability to infect a broad range of dividing and non-dividing host cells, accept large DNA inserts and a good safety profile.[109] Deleting the glycoprotein H gene from HSV results in a "disabled" virus that is only capable of one

round of infection.[109,187,188] HSV has also been utilized as a vector for oncolysis. Like adenovirus, oncolytic HSV (oHSV) can promote antitumor immune response.[103,189,190] Derived from HSV-1, T-VEC is the first FDA-approved OV for melanoma.[191] T-VEC has been modified to preferentially replicate in tumor cells and produce GM-CSF. T-VEC's ability to generate tumor-specific immune responses and induce systemic immunity has made it a promising candidate for combination with ICI.[191] Imlygic (T-VEC oHSV) remains the only oHSV to be approved by the US FDA and EMA to date.[103] T-VEC is also under investigation in new indications (i.e., in combination with paclitaxel for TNBC.[192]

Multiple trials are currently underway to evaluate the efficacy and safety of oHSV across various malignancies (Table 3). CAN-3110,a replication-competent HSV-1, is being developed for adult patients with recurrent high-grade glioma.[193] A Phase I trial in recurrent GBM demonstrated that CAN-3110 preferentially replicates in tumor cells due to its association with nestin, a protein overexpressed in GBM but absent in healthy brain cells.[194] Similarly, C134, a second-generation chimeric Human CMV/HSV-1 oncolytic virus, has been engineered for late viral protein synthesis and enhanced intra-tumor replication. It has shown a favorable safety profile in preclinical models and has advanced to a Phase I trial for primary CNS malignancies.[195,196] HSV-1 G207 is another genetically engineered oHSV lacking genes essential for replication in normal brain tissue. Phase I trial showed acceptable safety and responses in patients with recurrent or progressive pediatric high-grade gliomas.[196,197] M032 is also being evaluated in recurrent glioblastoma and anaplastic astrocytoma, both as a standalone therapy and in combination with ICIs.[198,199] Beyond its oncolytic activity, M032 functions as a gene therapy vector, delivering IL-12 directly into tumor cells, thereby enhancing the anti-tumor immune response.[200]

Multiple recombinant oHSVs have also been developed.[201] These recombinant oHSVs are mutated or multimutated conditionally replicating recombinants, restricting the viral replication and final cell lysis to actively replicating cancer cells.[202] Amongst ongoing trials, RP1 is being tested for cutaneous squamous cell carcinoma, Merkel cell carcinoma, and melanoma in combination with ICI,[203,204] while RP2 and RP3 are in trials for uveal melanoma and mCRC, paired with ICI.[205,206] The recombinant OV R130 is under early-phase investigation for a range of advanced solid tumors.[207–209]

Amongst other oHSV with ongoing trials, BS-006 is under investigation in the Phase I trial for intratumoral injection in cervical cancer.[210] OH2, is being explored across several cancers, including bladder cancer, CNS tumors, and melanoma, with combination approaches involving pembrolizumab in certain cases.[211–214] OH2, a genetically engineered oHSV type 2, was designed to selectively amplify tumor cells and express GM CSF to enhance antitumor immune responses.[215] T3011 is another promising candidate being tested for advanced solid tumors such as CRC and lung cancer, administered either intratumorally or via hepatic artery infusion[216,217] T3011 is a replication-competent, genetically modified, next-generation oHSV. Deletion of one ICP34.5 copy and retention of ICP47 maximizes its replication activity and virulence attenuation. Moreover, T3011 was inserted with biologically active IL-12 and anti-PD-1 antibody genes. Therefore, while lysing tumor cells, T3011 can significantly improve the TME and elicit the body's specific anti-tumor immunity.[218]

Conclusion

Cancer vaccines represent a rapidly evolving frontier in immunotherapy, stimulating the immune system to recognize and attack TAAs or TSAs. Each bacterial, viral, or yeast-based vector platform has unique advantages and limitations, and at present, there is no clear superior platform. Bacterial platforms such as LM and Clostridium excel in targeting hypoxic tumor environments. Viral vectors like adenovirus and HSV are highly effective in generating strong immune responses and direct oncolytic effects. Yeast-based vaccines offer stability, scalability, and the ability to present multiple tumor antigens to the immune system. Studies to date show that while cancer vaccines are active products, monotherapy administration is insufficient to generate adequate efficacy data necessary for regulatory approval. As such, sponsors of investigational therapeutic vaccines routinely incorporate other immune-stimulating products (whether approved or investigational) into their development programs. Beyond synergistic strategies and immunogenic intensification, there is the potential to enhance efficacy by targeting tumor neoantigens (i.e., personalized vaccines). While therapeutic vaccines as a class have been shown to be generally well tolerated and often have a more favorable safety profile relative to that of cytotoxics or other immuno-oncology products, further efficacy data will support making broad claims about the future role of therapeutic vaccines in the treatment of cancer.

Acknowledgments

The authors acknowledge Sylvester Comprehensive Cancer Center and Adam Weiss for their support in producing this article.

Disclosure statement

CJ: None; AM: None; PD: Pyxis Oncology - Consultant; MB: Hookipa Pharma, Inc. Research funding – institutional.

Funding

CJ: None.AM: None.PD: Pyxis Oncology - Consultant.MB: Hookipa Pharma, Inc. Research funding – institutional.

Notes on contributor

Marijo Bilusic's current research interests focus on tumor immunology and the development of novel immunotherapy approaches for prostate cancer and other genitourinary tumors using therapeutic cancer vaccines, antibodies, immune modulators or immune checkpoint inhibitors, not only as monotherapies but in combination with other therapies as part of an immuno-oncology programmatic effort. He received his M.D. from the University of Zagreb School of Medicine and completed his Ph.D. training at the University of Split School of Medicine. In addition, he completed postdoctoral research fellowship in physiological genomics at the Medical College of Wisconsin's Human and Molecular Genetics Center. He completed a clinical fellowship in medical oncology and hematology at the National Cancer Institute (NCI) and the National

Heart, Lung, and Blood Institute. He served as an assistant professor at the Fox Chase Cancer Center and then joined the NCI Genitourinary Malignancy Branch as an Associate Research Physician. At the NCI, he also served as fellowship Program Director from July 2018 – July 2021. His passion for teaching and mentoring has earned multiple awards at NIH, including the National Institutes of Health (NIH) Director's Award. In 2021, Dr. Bilusic joined Sylvester Comprehensive Cancer Center/ University of Miami as Professor of Medicine and GU Medical Oncology Team Lead.

Author contributions

CJ, PD, AM and MB wrote the manuscript jointly and contributed equally to this work. All authors were involved in the conception, design, analysis, and interpretation of data, drafting the paper, and revising the paper for critical content. All authors have read and approved the final version of the manuscript.

Ethical approval

Ethical approval was not required for this study, as it is a review article.

Abbreviations

Ad5	Adenovirus 5
AE	Adverse event
AKT/mTOR	Protein kinase B/mammalian target of rapamycin
AML	Acute myeloid leukemia
APC	Antigen-presenting cell
B7.1	CD80
BA	Bintrafusp alfa
BC	Breast cancer
BCG	Bacillus Calmette-Guérin
CAR	Chimeric antigen receptor
CBM588	C. butyricum MIYAIRI 588
CDEPT	Clostridial-directed enzyme prodrug therapy
CEA	Carcinoembryonic antigen
CG0070	Cretostimogene grenadenorepvec
CIK	Cytokine-induced killer
CMV	Cytomegalovirus
CRC	Colorectal cancer
DC	Dendritic cell
DLT	Dose-limiting toxicities
dMMR	Mismatch repair-deficient
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
GAd	Great ape adenovirus
GBM	Glioblastoma multiforme
GEJ	Gastro-esophageal junction
GI-6207	Yeast-CEA vaccine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVAX	GM-CSF – transduced autologous tumor-cell vaccine
HERV	Human endogenous retroviral element
HIF	Hypoxia-inducible factor
HPV	Human papillomavirus
HSV	Herpes simplex virus
HTD	Highest Tolerated Dose
ICAM-1	Intercellular adhesion molecule 1
ICI	Immune checkpoint inhibitor
IFN	Interferon
IL	Interleukin
JNJ	Johnson & Johnson
KBMA	Killed but metabolically active
LADD	Live attenuated double deleted
LFA-3	Lymphocyte function-associated antigen 3
Lm	Listeria monocytogenes
Lm-RIID	Lm recombinase-induced intracellular death
MAGE	Melanoma-associated antigen
mCRC	Metastatic CRC
MHC	Major histocompatibility complex
MIBC	Muscle Invasive Bladder Cancer
MSI	Microsatellite instabillity
MUC1	Mucin 1
MVA	Modified Vaccinia ankara
MVA-BN	MVA-Bavarian Nordic
NK	Natural killer
NMIBC	Non-muscle-invasive bladder cancer
NY-ESO-1	New York esophageal carcinoma antigen1
NSCLC	Non-small cell lung cancer
oAV	Oncolytic adenovirus
oHSV	Oncolytic HSV virus
Olvi-Vec	Olvimulogene nanivacirepvec
OV	Oncolytic virus
oVV	Oncolytic vaccinia virus
PAMP	Pathogen-associated molecular pattern
PD-L1	Programmed death ligand 1
PK	Pharmaco-kinetics
pLADD	Personalized live attenuated double deleted
PRR	pattern recognition receptor
PSA	Prostate-specific antigen
RCC	Renal cell carcinoma
RNA	Ribonucleic acid
SOC	Standard of care
ST	Salmonella typhimurium
TAA	Tumor-associated antigen
TGF	Transforming growth factor
TLR	Toll-like receptor
TNF- α	Tumor-necrosis factor-alpha
TME	Tumor microenvironment
TNBC	Triple negative breast cancer
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
T-VEC	Talimogene laherparepvec
TSA	Tumor-specific antigen
TURBT	Transurethral bladder tumor resection
VEGF	Vascular endothelial growth factor
VLP	Virus-like particle
vvDD	Double deleted vaccinia virus
YE-NEO	Neoepitope yeast vaccine

References

1. Muller AJ, Thomas S, Prendergast GC. A brief overview of cancer vaccines. Cancer J. 2023;29(1):34–37. doi:10.1097/PPO.0000640.
2. DeMaria PJ, Bilusic M. Cancer vaccines. Hematol Oncol Clin N Am. 2019;33(2):199–214. doi:10.1016/j.hoc.2018.12.001.
3. Thomas S, Prendergast GC. Cancer vaccines: a brief overview. Methods Mol Biol. 2016;1403:755–761.
4. Herlyn D, Birebent B. Advances in cancer vaccine development. Ann Med. 1999;31(1):66–78. doi:10.3109/07859264.
5. Buonaguro L, Tagliamonte M. Selecting target antigens for cancer vaccine development. Vaccines (Basel). 2020;8(4):615. doi:10.3390/vaccines0615.
6. Chiappinelli KB, Strissel PL, Desrichard A, Li H, Henke C, Akman B, Hein A, Rote N, Cope L, Snyder A, et al. Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses. Cell. 2015;162(5):974–986. doi:10.1016/j.cell.2015.07.011.
7. Roulois D, Loo Yau H, Singhania R, Wang Y, Danesh A, Shen SY, Han H, Liang G, Jones P, Pugh T, et al. DNA-Demethylating agents target colorectal cancer cells by inducing viral mimicry by endogenous transcripts. Cell. 2015;162(5):961–973. doi:10.1016/j.cell.2015.07.056.
8. Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022;15(1):28. doi:10.1186/s3045-022-01247-x.

9. Toussaint B, Chauchet X, Wang Y, Polack B, Le Gouellec A. Live-attenuated bacteria as a cancer vaccine vector. Expert Rev Vaccines. 2013;12(10):1139–1154. doi:10.1586/10584.2013.86914.
10. Paston SJ, Brentville VA, Symonds P, Durrant LG. Cancer vaccines, adjuvants, and delivery systems. Front Immunol. 2021;12:67932. doi:10.3389/fimmu.2021.67932.
11. Bolhassani A, Safaiyan S, Rafati S. Improvement of different vaccine delivery systems for cancer therapy. Mol Cancer. 2011;10(1):3. doi:10.1186/1476-4598-10-3.
12. Hoption Cann SA, van Netten JP, van Netten C. Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J. 2003;79(938):672–680. doi:10.1093/postgradmedj/79.938.672.
13. Pearl R. Cancer and tuberculosis. Am J Epidemiol. 1929;9(1):97–159. doi:10.1093/oxfordjournals.aje.a1646.
14. Holmgren I. Employment of B.C.G. especially in intravenous injection. Acta Medica Scandinavica. 1936;90(S78):350–361. doi:10.1111/j.0954-6820.1936.tb5958.x.
15. Mukherjee N, Julian E, Torrelles JB, Svatek RS. Effects of mycobacterium bovis Calmette et Guérin (BCG) in oncotherapy: bladder cancer and beyond. Vaccine. 2021;39(50):7332–7340. doi:10.1016/j.vaccine.2021.09.053.
16. Radoshevich L, Cossart P. Listeria monocytogenes: towards a complete picture of its physiology and pathogenesis. Nat Rev Microbiol. 2018;16(1):32–46. doi:10.1038/nrmicro.2017.126.
17. Kawai K, Kawai A. Increased serum lactate dehydrogenase and changes in its isozymes pattern correlated to the atypical lymphocytes in adult rubella. Nihon Naika Gakkai Zasshi. 1989;78(4):500–505.
18. Leong ML, Hampl J, Liu W, Mathur S, Bahjat KS, Luckett W, Dubensky TW, Brockstedt DG. Impact of preexisting vector-specific immunity on vaccine potency: characterization of listeria monocytogenes-specific humoral and cellular immunity in humans and modeling studies using recombinant vaccines in mice. Infect Immun. 2009;77(9):3958–3968. doi:10.1128/IAI.01274-08.
19. Wood LM, Paterson Y. Attenuated listeria monocytogenes: a powerful and versatile vector for the future of tumor immunotherapy. Front Cell Infect Microbiol. 2014;4:51. doi:10.3389/fcimb.2014.00051.
20. Deng W, Lira V, Hudson TE, Lemmens EE, Hanson WG, Flores R, Barajas G, Katibah GE, Desbien AL, Lauer P, et al. Recombinant listeria promotes tumor rejection by CD8 T cell-dependent remodeling of the tumor microenvironment. Proc Natl Acad Sci USA. 2018;115(32):8179–8184. doi:10.1073/pnas.10115.
21. Edelson BT, Unanue ER. MyD88-dependent but toll-like receptor 2-independent innate immunity to listeria: no role for either in macrophage listericidal activity. J Immunol. 2002;169(7):3869–3875. doi:10.4049/jimmunol.169.7.3869.
22. Brunt LM, Portnoy DA, Unanue ER. Presentation of listeria monocytogenes to CD8+ T cells requires secretion of hemolysin and intracellular bacterial growth. J Immunol. 1990;145(11):3540–3546. doi:10.4049/jimmunol.145.11.3540.
23. Flickinger JC Jr., Rodeck U, Snook AE. Listeria monocytogenes as a vector for cancer immunotherapy: current understanding and progress. Vaccines (Basel). 2018;6(3):48. doi:10.3390/vaccines0048.
24. Le DT, Brockstedt DG, Nir-Paz R, Hampl J, Mathur S, Nemunaitis J, Sterman DH, Hassan R, Lutz E, Moyer B, et al. A live-attenuated listeria vaccine (ANZ-100) and a live-attenuated listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. Clin Cancer Res. 2012;18(3):858–868. doi:10.1158/1078-0432.CCR-11-2121.
25. Denham JD, Lee DH, Castro M, Pandya S, Aslam S, Nanjappa S, Greene JN. Two cases of disseminated infection following live organism anti-cancer vaccine administration in cancer patients. Int J Infect Dis. 2018;72:1–2. doi:10.1016/j.ijid.2018.04.004.
26. Morrow ZT, Powers ZM, Sauer JD. Listeria monocytogenes cancer vaccines: bridging innate and adaptive immunity. Curr Clin Microbiol Rep. 2019;6(4):213–224. doi:10.1007/s0588-019-00133-4.
27. ClinicalTrials.gov. A phase 1 safety and tolerability study of personalized live, attenuated, double-deleted listeria monocytogenes (pLADD) immunotherapy in adults with metastatic colorectal cancer. ClinicalTrials.Gov identifier: NCT9030. https://clinicaltrials.gov/ct2/show/NCT9030.
28. ClinicalTrials.gov. Epacadostat, pembrolizumab, and CRS-207, with or without CY/GVAX pancreas in patients with metastatic pancreas cancer. ClinicalTrials.Gov identifier: NCT6302. https://clinicaltrials.gov/ct2/show/NCT6302.
29. Wallecha A, Maciag PC, Rivera S, Paterson Y, Shahabi V. Construction and characterization of an attenuated listeria monocytogenes strain for clinical use in cancer immunotherapy. Clin Vaccine Immunol. 2009;16(1):96–103. doi:10.1128/CVI.00274-08 .
30. Stein MN, Fong L, Tutrone R, Mega A, Lam ET, Parsi M, Vangala S, Gutierrez AA, Haas NB. ADXS1142 immunotherapy ± pembrolizumab treatment for metastatic castration-resistant prostate cancer: open-label phase I/II KEYNOTE-046 study. The Oncologist. 2022;27(6):453–461. doi:10.1093/oncolo/oyac048.
31. Galicia-Carmona T, Arango-Bravo E, Serrano-Olvera JA, Flores-de La Torre C, Cruz-Esquivel I, Villalobos-Valencia R, Morán-Mendoza A, Castro-Eguiluz D, Cetina-Pérez L. ADXS11-001 LM-LLO as specific immunotherapy in cervical cancer. Hum Vaccin Immunother. 2021;17(8):2617–2625. doi:10.1080/25515.2021.13036.
32. Mason NJ, Gnanandarajah JS, Engiles JB, Gray F, Laughlin D, Gaurnier-Hausser A, Wallecha A, Huebner M, Paterson Y. Immunotherapy with a HER2-targeting listeria induces HER2-specific immunity and demonstrates potential therapeutic effects in a phase I trial in canine osteosarcoma. Clin Cancer Res. 2016;22(17):4380–4390. doi:10.1158/1078-0432.CCR-16-0088.
33. ClinicalTrials.gov. A study of the clinical activity and safety of JNJ-61809, a live attenuated listeria monocytogenes immunotherapy, in combination with apalutamide versus apalutamide in subjects with metastatic castration-resistant prostate cancer. ClinicalTrials.Gov identifier: NCT6605. https://clinicaltrials.gov/ct2/show/NCT6605.
34. Brahmer JR, Johnson ML, Cobo M, Viteri S, Sarto JC, Sukari A, Awad MM, Salgia R, Papadimitrakopoulou VA, Rajan A, et al. JNJ-61757 (JNJ-757), a live, attenuated, double-deleted listeria monocytogenes–based immunotherapy in patients with NSCLC: results from two phase 1 studies. JTO Clin Res Rep. 2021;2(2):10103. doi:10.1016/j.jtocrr.2020.10103.
35. Drake CG, Pachynski RK, Subudhi SK, McNeel DG, Antonarakis ES, Bauer TM, Lauer P, Brockstedt D, Patricia D, Wade M, et al. Safety and preliminary immunogenicity of JNJ-61809, a live-attenuated, double-deleted listeria monocytogenes-based immunotherapy, in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2022;25(2):219–228. doi:10.1038/s1391-021-00402-8.
36. ClinicalTrials.gov. RT201 (tumor antigen-specific macrophage tumor vaccine). ClinicalTrials.Gov identifier: NCT0301. https://clinicaltrials.gov/ct2/show/NCT0301.
37. Ding YD, Shu LZ, He RS, Chen KY, Deng YJ, Zhou ZB, Xiong Y, Deng H. Listeria monocytogenes: a promising vector for tumor immunotherapy. Front Immunol. 2023;14:18011. doi:10.3389/fimmu.2023.18011.
38. Brockstedt DG, Bahjat KS, Giedlin MA, Liu W, Leong M, Luckett W, Gao Y, Schnupf P, Kapadia D, Castro G, et al. Killed but metabolically active microbes: a new vaccine paradigm for eliciting effector T-cell responses and protective immunity. Nat Med. 2005;11(8):853–860. doi:10.1038/nm1276.
39. Skoberne M, Yewdall A, Bahjat KS, Godefroy E, Lauer P, Lemmens E, Liu W, Luckett W, Leong M, Dubensky TW, et al. KBMA listeria monocytogenes is an effective vector for dc-mediated induction of antitumor immunity. J Clin Invest. 2008;118(12):3990–4001. doi:10.1172/JCI1350.
40. Hanson WG, Benanti EL, Lemmens EE, Liu W, Skoble J, Leong ML, Rae CS, Fassò M, Brockstedt DG, Chen C, et al. A potent and effective suicidal listeria vaccine platform. Infect Immun. 2019;87(8). doi:10.1128/IAI.00144-19.

41. Eisenstark A, Kazmierczak RA, Dino A, Khreis R, Newman D, Schatten H. Development of salmonella strains as cancer therapy agents and testing in tumor cell lines. Methods Mol Biol. 2007;394:323–354.
42. Yang Z, Zou L, Yue B, Hu M. Salmonella typhimurium may support cancer treatment: a review. Acta Biochim Biophys Sin (Shanghai). 2023;55(3):331–342. doi:10.3724/abbs.23007.
43. Lee CH, Lin ST, Liu JJ, Chang WW, Hsieh JL, Wang WK. Salmonella induce autophagy in melanoma by the downregulation of AKT/mTOR pathway. Gene Ther. 2014;21(3):309–316. doi:10.1038/gt.2013.86.
44. Tu DG, Chang WW, Lin ST, Kuo CY, Tsao YT, Lee CH. Salmonella inhibits tumor angiogenesis by downregulation of vascular endothelial growth factor. Oncotarget. 2016;7(25):37513–37523. doi:10.18632/oncotarget.7038.
45. Tsao YT, Kuo CY, Cheng SP, Lee CH. Downregulations of AKT/mTOR signaling pathway for salmonella-mediated suppression of matrix metalloproteinases-9 expression in mouse tumor models. Int J Mol Sci. 2018;19(6):1630. doi:10.3390/ijms1630.
46. Yang CJ, Chang WW, Lin ST, Chen MC, Lee CH. Salmonella overcomes drug resistance in tumor through P-glycoprotein downregulation. Int J Med Sci. 2018;15(6):574–579. doi:10.7150/ijms.23285.
47. Toso JF, Gill VJ, Hwu P, Marincola FM, Restifo NP, Schwartzentruber DJ, Sherry RM, Topalian SL, Yang JC, Stock F, et al. Phase I study of the intravenous administration of attenuated salmonella typhimurium to patients with metastatic melanoma. J Clin Oncol. 2002;20(1):142–152. doi:10.1200/JCO.2002.20.1.142.
48. Heimann DM, Rosenberg SA. Continuous intravenous administration of live genetically modified salmonella typhimurium in patients with metastatic melanoma. J Immunother. 2003;26(2):179–180. doi:10.1097/02371-23000-00011.
49. Schmitz-Winnenthal FH, Hohmann N, Schmidt T, Podola L, Friedrich T, Lubenau H, Springer M, Wieckowski S, Breiner KM, Mikus G, et al. A phase 1 trial extension to assess immunologic efficacy and safety of prime-boost vaccination with VXM01, an oral T cell vaccine against VEGFR2, in patients with advanced pancreatic cancer. Oncoimmunology. 2018;7(4):e3584. doi:10.1080/22402X.2017.13584.
50. Gniadek TJ, Augustin L, Schottel J, Leonard A, Saltzman D, Greeno E, Batist G. A phase I, dose escalation, single dose trial of oral attenuated salmonella typhimurium containing human IL-2 in patients with metastatic gastrointestinal cancers. J Immunother. 2020;43(7):217–221. doi:10.1097/CJI.0000325.
51. ClinicalTrials.gov. Saltikva for metastatic pancreatic cancer. NCT9234. Sponsor: Salispera LLC. [Active, not recruiting] [accessed 2024 Apr 24]. https://clinicaltrials.gov/.
52. Zhou S, Zhang S, Zheng K, Li Z, Hu E, Mu Y, Mai J, Zhao A, Zhao Z, Li F. Salmonella-mediated methionine deprivation drives immune activation and enhances immune checkpoint blockade therapy in melanoma. J Immunother Cancer. 2024;12(2):e8238. doi:10.1136/jitc-2023-08238.
53. ClinicalTrials.gov. Study of SGN1 administered via intratumoral injection in patients with advanced solid tumor. ClinicalTrials.Gov identifier: NCT3345. https://clinicaltrials.gov/study/NCT3345 .
54. ClinicalTrials.gov. Study of SGN1 in patients with advanced solid tumor. ClinicalTrials.Gov identifier: NCT8150. https://clinicaltrials.gov/study/NCT8150.
55. Li Y, Lu W, Yang J, Edwards M, Jiang S. Survivin as a biological biomarker for diagnosis and therapy. Expert Opin Biol Ther. 2021;21(11):1429–1441. doi:10.1080/12598.2021.18672.
56. ClinicalTrials.gov. Multiple myeloma trial of orally administered salmonella based survivin vaccine (MAPSS). ClinicalTrials.Gov identifier: NCT2291. https://www.clinicaltrials.gov/study/NCT2291.
57. Chorobik P, Marcinkiewicz J. Therapeutic vaccines based on genetically modified salmonella: a novel strategy in cancer immunotherapy. Pol Arch Med Wewn. 2011;121(12):461–467. doi:10.20452/pamw.1117.
58. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116(2):180–182. doi:10.1016/S0022-5347(17)58737-6.
59. Babjuk M, Burger M, Capoun O, Cohen D, Comperat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, et al. European Association of Urology guidelines on non–muscle-invasive bladder cancer (ta, t1, and carcinoma in situ). Eur Urol. 2022;81(1):75–94. doi:10.1016/j.eururo.2021.08.010.
60. Abou Chakra M, Luo Y, Duquesne I, M AOD. Update on the mechanism of action of intravesical BCG therapy to treat non-muscle-invasive bladder cancer. Front Biosci (Landmark Ed). 2024;29(8):295. doi:10.31083/j.fbl8295.
61. Jiang S, Redelman-Sidi G. BCG in bladder cancer immunotherapy. Cancers (Basel). 2022;14(13):3073. doi:10.3390/cancers3073.
62. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol. 2018;15(10):615–625. doi:10.1038/s1585-018-0055-4.
63. Yu DS, Wu CL, Ping SY, Keng C, Shen KH. Bacille Calmette-Guerin can induce cellular apoptosis of urothelial cancer directly through toll-like receptor 7 activation. Kaohsiung J Med Sci. 2015;31(8):391–397. doi:10.1016/j.kjms.2015.05.005.
64. Martinez-Lopez MF, de Almeida CR, Fontes M, Mendes RV, Kaufmann SHE, Fior R. Macrophages directly kill bladder cancer cells through TNF signaling as an early response to BCG therapy. Dis Model Mech. 2024;17(8). doi:10.1242/dmm.00693.
65. Sharma P, Bajorin DF, Jungbluth AA, Herr H, Old LJ, Gnjatic S. Immune responses detected in urothelial carcinoma patients after vaccination with NY-ESO-1 protein plus BCG and GM-CSF. J Immunother. 2008;31(9):849–857. doi:10.1097/CJI.0b013e1574.
66. ClinicalTrials.gov. Different strains of BCG with or without vaccine in high grade non-muscle invasive bladder cancer. (S1602). ClinicalTrials.Gov identifier: NCT1660. https://www.clinicaltrials.gov/study/NCT1660.
67. ClinicalTrials.gov. Multicenter clinical trial on the effectiveness and safety of instillation of BCG and Alternative BCG protocols for intermediate and high-risk non-muscle invasive bladder cancer. ClinicalTrials.Gov identifier: NCT1110. https://www.clinicaltrials.gov/study/NCT1110.
68. Chabalgoity JA, Dougan G, Mastroeni P, Aspinall RJ. Live bacteria as the basis for immunotherapies against cancer. Expert Rev Vaccines. 2002;1(4):495–505. doi:10.1586/10584.1.4.495.
69. Liu SC, Ahn GO, Kioi M, Dorie MJ, Patterson AV, Brown JM. Optimized clostridium-directed enzyme prodrug therapy improves the antitumor activity of the novel DNA cross-linking agent PR-104. Cancer Res. 2008;68(19):7995–8003. doi:10.1158/0008-5472.CAN-08-1698.
70. Shinnoh M, Horinaka M, Yasuda T, Yoshikawa S, Morita M, Yamada T, Miki T, Sakai T. Clostridium butyricum MIYAIRI 588 shows antitumor effects by enhancing the release of TRAIL from neutrophils through MMP-8. Int J Oncol. 2013;42(3):903–911. doi:10.3892/ijo.2013.1790.
71. Abedi Jafari F, Abdoli A, Pilehchian R, Soleimani N, Hosseini SM. The oncolytic activity of clostridium novyi nontoxic spores in breast cancer. Bioimpacts. 2022;12(5):405–414. doi:10.34172/bi.2021.25.
72. Sharafabad BE, Abdoli A, Abdolmohammadi Khiav L, Meskini M, Jamur P, Dilmaghani A. Therapeutic potential of clostridium novyi-nt in cancer: current knowledge and future perspectives. Curr Cancer Drug Targets. 2023;23(9):682–696. doi:10.2174/1568009623664253.
73. Patyar S, Joshi R, Byrav DS, Prakash A, Medhi B, Das BK. Bacteria in cancer therapy: a novel experimental strategy. J Biomed Sci. 2010;17(1):21. doi:10.1186/1423-0127-17-21.
74. Kucerova P, Cervinkova M. Spontaneous regression of tumour and the role of microbial infection–possibilities for cancer treatment. Anticancer Drugs. 2016;27(4):269–277. doi:10.1097/CAD.0000337.

75. Slingluff CL Jr., Yamshchikov G, Neese P, Galavotti H, Eastham S, Engelhard VH, Kittlesen D, Deacon D, Hibbitts S, Grosh WW, et al. Phase I trial of a melanoma vaccine with gp100(280-288) peptide and tetanus helper peptide in adjuvant: immunologic and clinical outcomes. Clin Cancer Res. 2001;7(10):3012–3024.
76. Reisinger KS, Block SL, Collins-Ogle M, Marchant C, Catlett M, Radley D, Sings HL, Haupt RM, Garner EIO. Safety, tolerability, and immunogenicity of gardasil given concomitantly with menactra and Adacel. Pediatrics. 2010;125(6):1142–1151. doi:10.1542/peds.2009-2336.
77. Kaufman HL, Lenz HJ, Marshall J, Singh D, Garett C, Cripps C, Moore M, von Mehren M, Dalfen R, Heim WJ, et al. Combination chemotherapy and ALVAC-CEA/B7.1 vaccine in patients with metastatic colorectal cancer. Clin Cancer Res. 2008;14(15):4843–4849. doi:10.1158/1078-0432.CCR-08-0276.
78. Kumar R, Kumar P. Yeast-based vaccines: new perspective in vaccine development and application. FEMS Yeast Res. 2019;19(2). doi:10.1093/femsyr/foz007.
79. Srivastava V, Nand KN, Ahmad A, Kumar R. Yeast-based virus-like particles as an emerging platform for vaccine development and delivery. Vaccines (Basel). 2023;11(2):479. doi:10.3390/vaccines0479.
80. Sauerwein H, Schmitz S, Hiss S. Effects of a dietary application of a yeast cell wall extract on innate and acquired immunity, on oxidative status and growth performance in weanling piglets and on the ileal epithelium in fattened pigs. J Anim Physiol Anim Nutr (Berl). 2007;91(9–10):369–380. doi:10.1111/j.1439-0396.2006.00663.x.
81. Ardiani A, Higgins JP, Hodge JW. Vaccines based on whole recombinant Saccharomyces cerevisiae cells. FEMS Yeast Res. 2010;10(8):1060–1069. doi:10.1111/j.1567-1364.2010.00665.x.
82. Jung V, Fischer E, Imig J, Kleber S, Nuber N, Reinshagen F, Kamradt J, Grobholz R, Knuth A, Renner C, et al. Yeast-based identification of prostate tumor antigens provides an effective vaccine platform. Anticancer Res. 2010;30(3):895–902.
83. Tanaka A, Jensen JD, Prado R, Riemann H, Shellman YG, Norris DA, Chin L, Yee C, Fujita M. Whole recombinant yeast vaccine induces antitumor immunity and improves survival in a genetically engineered mouse model of melanoma. Gene Ther. 2011;18(8):827–834. doi:10.1038/gt.2011.28.
84. Hamilton DH, Litzinger MT, Jales A, Huang B, Fernando RI, Hodge JW, Ardiani A, Apelian D, Schlom J, Palena C. Immunological targeting of tumor cells undergoing an epithelial-mesenchymal transition via a recombinant brachyury-yeast vaccine. Oncotarget. 2013;4(10):1777–1790. doi:10.18632/oncotarget.1295.
85. Wansley EK, Chakraborty M, Hance KW, Bernstein MB, Boehm AL, Guo Z, Quick D, Franzusoff A, Greiner JW, Schlom J, et al. Vaccination with a recombinant Saccharomyces cerevisiae expressing a tumor antigen breaks immune tolerance and elicits therapeutic antitumor responses. Clin Cancer Res. 2008;14(13):4316–4325. doi:10.1158/1078-0432.CCR-08-0393.
86. Bernstein MB, Chakraborty M, Wansley EK, Guo Z, Franzusoff A, Mostbock S, Sabzevari H, Schlom J, Hodge JW. Recombinant Saccharomyces cerevisiae (yeast-CEA) as a potent activator of murine dendritic cells. Vaccine. 2008;26(4):509–521. doi:10.1016/j.vaccine.2007.11.033.
87. Bilusic M, Heery CR, Arlen PM, Rauckhorst M, Apelian D, Tsang KY, Tucker JA, Jochems C, Schlom J, Gulley JL, et al. Phase I trial of a recombinant yeast-cea vaccine (GI-6207) in adults with metastatic cea-expressing carcinoma. Cancer Immunol Immunother. 2014;63(3):225–234. doi:10.1007/s0262-013-1505-8.
88. Chaft JE, Litvak A, Arcila ME, Patel P, D'Angelo SP, Krug LM, Rusch V, Mattson A, Coeshott C, Park B, et al. Phase II study of the GI-4000 KRAS vaccine after curative therapy in patients with stage I-III lung adenocarcinoma harboring a KRAS G12C, G12D, or G12V mutation. Clin Lung Cancer. 2014;15(6):405–410. doi:10.1016/j.cllc.2014.06.002.
89. Muscarella P, Bekaii-Saab T, McIntyre K, Rosemurgy A, Ross SB, Richards DA, Fisher WE, Flynn PJ, Mattson A, Coeshott C, et al. A phase 2 randomized placebo-controlled adjuvant trial of GI-4000, a recombinant yeast expressing mutated RAS proteins in patients with resected pancreas cancer. J Pancreat Cancer. 2021;7(1):8–19. doi:10.1089/pancan.2020.0021.
90. Asimgil H, Ertetik U, Cevik NC, Ekizce M, Dogruoz A, Gokalp M, Arık-Sever E, Istvanffy R, Friess H, Ceyhan GO, et al. Targeting the undruggable oncogenic KRAS: the dawn of hope. JCI Insight. 2022;7(1). doi:10.1172/jci.insight.13688.
91. ClinicalTrials.gov. Cancer vaccine targeting brachyury protein in tumors. ClinicalTrials.Gov identifier: NCT9817. https://clinicaltrials.gov/study/NCT9817.
92. Heery CR, Singh BH, Rauckhorst M, Marte JL, Donahue RN, Grenga I, Rodell TC, Dahut W, Arlen PM, Madan RA, et al. Phase I trial of a yeast-based therapeutic cancer vaccine (GI-6301) targeting the transcription factor brachyury. Cancer Immunol Res. 2015;3(11):1248–1256. doi:10.1158/2326-6066.CIR-15-0119.
93. DeMaria PJ, Bilusic M, Park DM, Heery CR, Donahue RN, Madan RA, Bagheri MH, Strauss J, Shen V, Marté JL, et al. Randomized, double-blind, placebo-controlled phase II study of yeast-brachyury vaccine (GI-6301) in combination with standard-of-care radiotherapy in locally advanced, Unresectable Chordoma. Oncologist. 2021;26(5):e847–e858. doi:10.1002/onco.13720.
94. DeMaria PJ, Lee-Wisdom K, Donahue RN, Madan RA, Karzai F, Schwab A, Palena C, Jochems C, Floudas C, Strauss J, et al. Phase 1 open-label trial of intravenous administration of MVA-BN-brachyury-tricom vaccine in patients with advanced cancer. J Immunother Cancer. 2021;9(9):e3238. doi:10.1136/jitc-2021-03238.
95. ClinicalTrials.gov. QUILT-3.080: NANT pancreatic cancer vaccine. ClinicalTrials.Gov identifier: NCT6869. https://www.clinicaltrials.gov/study/NCT6869.
96. ClinicalTrials.gov. QUILT-3.060: NANT pancreatic cancer vaccine: molecularly informed integrated immunotherapy in subjects with pancreatic cancer who have progressed on or after standard-of-care therapy. ClinicalTrials.Gov identifier: NCT9248. https://www.clinicaltrials.gov/study/NCT9248.
97. ClinicalTrials.gov. QUILT 3.071: NANT colorectal cancer (CRC) vaccine. ClinicalTrials.Gov identifier: NCT3157. https://www.clinicaltrials.gov/study/NCT3157.
98. Nangia CS, Kistler M, Sender LS, Lee JH, Jones FR, Jafari O, Soon-Shiong P. Innate and adaptive immunotherapy: an orchestration of immunogenic cell death by overcoming immune suppression and activating NK and T-cell therapy in patients with third-line or greater TNBC. J Clin Oncol. 2019;37(15_suppl):abstract e2566. doi:10.1200/JCO.2019.37.15_suppl.e2566.
99. ClinicalTrials.gov. QUILT-3.067: NANT triple negative breast cancer (TNBC) vaccine: molecularly informed integrated immunotherapy in subjects with TNBC who have progressed on or after standard-of-care therapy. ClinicalTrials.Gov identifier: NCT7085. https://www.clinicaltrials.gov/study/NCT7085.
100. Kelly E, Russell SJ. History of oncolytic viruses: genesis to genetic engineering. Mol Ther. 2007;15(4):651–659. doi:10.1038/sj.mt.60108.
101. Larocca C, Schlom J. Viral vector-based therapeutic cancer vaccines. Cancer J. 2011;17(5):359–371. doi:10.1097/PPO.0b013e2325e63.
102. Kooti W, Esmaeili Gouvarchin Ghaleh H, Farzanehpour M, Dorostkar R, Jalali Kondori B, Bolandian M. Oncolytic viruses and cancer, do you know the main mechanism? Front Oncol. 2021;11:71015. doi:10.3389/fonc.2021.71015.
103. Yun CO, Hong J, Yoon AR. Current clinical landscape of oncolytic viruses as novel cancer immunotherapeutic and recent preclinical advancements. Front Immunol. 2022;13:93410. doi:10.3389/fimmu.2022.93410.
104. Pol J, Kroemer G, Galluzzi L. First oncolytic virus approved for melanoma immunotherapy. Oncoimmunology. 2016;5(1):e5641. doi:10.1080/22402X.2015.15641.
105. ClinicalTrials.gov. Oncolytic virus studies. [accessed 2024 Sep 15]. https://www.clinicaltrials.gov/search?term=oncolytic%20virus&aggFilters=status:act%20not%20rec.

106. Crystal RG. Adenovirus: the first effective in vivo gene delivery vector. Hum Gene Ther. 2014;25(1):3–11. doi:10.1089/hum.2013.2527.
107. Bett AJ, Haddara W, Prevec L, Graham FL. An efficient and flexible system for construction of adenovirus vectors with insertions or deletions in early regions 1 and 3. Proc Natl Acad Sci USA. 1994;91(19):8802–8806. doi:10.1073/pnas.91.19.8802.
108. Sutter G, Wyatt LS, Foley PL, Bennink JR, Moss B. A recombinant vector derived from the host range-restricted and highly attenuated MVA strain of vaccinia virus stimulates protective immunity in mice to influenza virus. Vaccine. 1994;12(11):1032–1040. doi:10.1016/0264-410X(94)90341-7.
109. Harrop R, John J, Carroll MW. Recombinant viral vectors: cancer vaccines. Adv Drug Deliv Rev. 2006;58(8):931–947. doi:10.1016/j.addr.2006.05.005.
110. Bezeljak U. Cancer gene therapy goes viral: viral vector platforms come of age. Radiol Oncol. 2022;56(1):1–13. doi:10.2478/raon-2022-0002.
111. Morse MA, Hobeika AC, Osada T, Berglund P, Hubby B, Negri S, Niedzwiecki D, Devi GR, Burnett BK, Clay TM, et al. An alphavirus vector overcomes the presence of neutralizing antibodies and elevated numbers of tregs to induce immune responses in humans with advanced cancer. J Clin Invest. 2010;120(9):3234–3241. doi:10.1172/JCI2672.
112. Waibler Z, Anzaghe M, Ludwig H, Akira S, Weiss S, Sutter G, Kalinke U. Modified vaccinia virus Ankara induces toll-like receptor-independent type I interferon responses. J Virol. 2007;81(22):12102–12110. doi:10.1128/JVI.01190-07.
113. Shinohara S, Sawada T, Nishioka Y, Tohma S, Kisaki T, Inoue T, Ando K, Ikeda M, Fujii H, Ito K. Differential expression of fas antigen and Bcl-2 protein on CD4+ T cells, CD8+ T cells, and monocytes. Cell Immunol. 1995;163(2):303–308. doi:10.1006/cimm.1995.1130.
114. Vollmar J, Arndtz N, Eckl KM, Thomsen T, Petzold B, Mateo L, Schlereth B, Handley A, King L, Hülsemann V, et al. Safety and immunogenicity of IMVAMUNE, a promising candidate as a third generation smallpox vaccine. Vaccine. 2006;24(12):2065–2070. doi:10.1016/j.vaccine.2005.11.022.
115. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. Cancer Res. 2004;64(12):4328–4337. doi:10.1158/0008-5472.CAN-04-0073.
116. Hodge JW, Sabzevari H, Yafal AG, Gritz L, Lorenz MG, Schlom J. A triad of costimulatory molecules synergize to amplify T-cell activation. Cancer Res. 1999;59(22):5800–5807.
117. Fernando RI, Castillo MD, Litzinger M, Hamilton DH, Palena C. IL-8 signaling plays a critical role in the epithelial–mesenchymal transition of human carcinoma cells. Cancer Res. 2011;71(15):5296–5306. doi:10.1158/0008-5472.CAN-11-0156.
118. Heery CR, Palena C, McMahon S, Donahue RN, Lepone LM, Grenga I, Dirmeier U, Cordes L, Marté J, Dahut W, et al. Phase I study of a poxviral TRICOM-Based vaccine directed against the transcription factor brachyury. Clin Cancer Res. 2017;23(22):6833–6845. doi:10.1158/1078-0432.CCR-17-1087.
119. Madan RA, Gulley JL, Schlom J, Steinberg SM, Liewehr DJ, Dahut WL, Arlen PM. Analysis of overall survival in patients with non-metastatic castration-resistant prostate cancer treated with vaccine, nilutamide, and combination therapy. Clin Cancer Res. 2008;14(14):4526–4531. doi:10.1158/1078-0432.CCR-07-5048.
120. Cripe TP, Ngo MC, Geller JI, Louis CU, Currier MA, Racadio JM, Towbin AJ, Rooney CM, Pelusio A, Moon A, et al. Phase 1 study of intratumoral pexa-vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus, in pediatric cancer patients. Mol Ther. 2015;23(3):602–608. doi:10.1038/mt.2014.243.
121. ClinicalTrials.gov. Hepatocellular carcinoma study comparing vaccinia virus based immunotherapy plus sorafenib vs sorafenib alone (PHOCUS). ClinicalTrials.Gov identifier: NCT2755. https://www.clinicaltrials.gov/study/NCT2755.
122. ClinicalTrials.gov. A study of recombinant vaccinia virus in combination with cemiplimab for renal cell carcinoma. ClinicalTrials.Gov identifier: NCT4083. https://www.clinicaltrials.gov/study/NCT4083.
123. Zeh HJ, Downs-Canner S, McCart JA, Guo ZS, Rao UN, Ramalingam L, Thorne SH, Jones HL, Kalinski P, Wieckowski E, et al. First-in-man study of western reserve strain oncolytic vaccinia virus: safety, systemic spread, and antitumor activity. Mol Ther. 2015;23(1):202–214. doi:10.1038/mt.2014.194.
124. Downs-Canner S, Guo ZS, Ravindranathan R, Breitbach CJ, O'Malley ME, Jones HL, Moon A, McCart JA, Shuai Y, Zeh HJ, et al. Phase 1 study of intravenous oncolytic poxvirus (vvDD) in patients with advanced solid cancers. Mol Ther. 2016;24(8):1492–1501. doi:10.1038/mt.2016.101.
125. ClinicalTrials.gov. Safety of recombinant human IL-21 oncolytic vaccinia virus Injection□hV01) in advanced tumors. ClinicalTrials.Gov identifier: NCT4376. https://www.clinicaltrials.gov/study/NCT4376.
126. ClinicalTrials.gov. A clinical study on evaluating intravenous administration of IDOV-SAFE. ClinicalTrials.Gov identifier: NCT0309. https://www.clinicaltrials.gov/study/NCT0309.
127. ClinicalTrials.gov. A phase I clinical study of intratumoral injection oncolytic vaccinia virus GC001 in patient with advanced solid tumors. ClinicalTrials.Gov identifier: NCT8307. https://www.clinicaltrials.gov/study/NCT8307.
128. ClinicalTrials.gov. A clinical trial of TG6050 in patients with metastatic non-small cell lung cancer (Delivir). ClinicalTrials.Gov identifier: NCT8926. https://www.clinicaltrials.gov/study/NCT8926.
129. ClinicalTrials.gov. Exploratory study of a novel oncolytic vaccinia virus RGV004 in the treatment of refractory/relapsed B-cell lymphoma. ClinicalTrials.Gov identifier: NCT7025. https://www.clinicaltrials.gov/study/NCT7025.
130. ClinicalTrials.gov. Safety and efficacy of KM1 in subjects with recurrent or refractory ovarian cancer (K9017-004). ClinicalTrials.Gov identifier: NCT4731. https://www.clinicaltrials.gov/study/NCT4731.
131. ClinicalTrials.gov. Efficacy & safety of olvimulogene nanivacirepvec & platinum-doublet + physician's choice of immune checkpoint inhibitor compared to docetaxel in NSCL cancer (VIRO-25). ClinicalTrials.Gov identifier: NCT3665. https://www.clinicaltrials.gov/study/NCT3665.
132. ClinicalTrials.gov. Efficacy & safety of olvi-vec and platinum-doublet + bevacizumab compared to physician's choice of chemotherapy and bevacizumab in platinum-resistant/refractory ovarian cancer (PRROC) (OnPrime, GOG-3076). ClinicalTrials.Gov identifier: NCT1471. https://www.clinicaltrials.gov/study/NCT1471.
133. ClinicalTrials.gov. A study of VET3-TGI in patients with solid tumors (STEALTH-001). ClinicalTrials.Gov identifier: NCT4815. https://www.clinicaltrials.gov/study/NCT4815.
134. ClinicalTrials.gov. A clinical trial assessing BT-001 alone and in combination with pembrolizumab in metastatic or advanced solid tumors. ClinicalTrials.Gov identifier: NCT5331. https://www.clinicaltrials.gov/study/NCT5331.
135. Chang J. Adenovirus vectors: excellent tools for vaccine development. Immune Netw. 2021;21(1):e6.
136. Wold WS, Toth K. Adenovirus vectors for gene therapy, vaccination and cancer gene therapy. Curr Gene Ther. 2013;13(6):421–433. doi:10.2174/1566523213665046.
137. Sato-Dahlman M, LaRocca CJ, Yanagiba C, Yamamoto M. Adenovirus and immunotherapy: advancing cancer treatment by combination. Cancers (Basel). 2020;12(5):1295. doi:10.3390/cancers1295.
138. Balint JP, Gabitzsch ES, Rice A, Latchman Y, Xu Y, Messerschmidt GL, Chaudhry A, Morse MA, Jones FR. Extended evaluation of a phase 1/2 trial on dosing, safety, immunogenicity, and overall survival after immunizations with an advanced-generation Ad5 [E1-, E2b-]-CEA(6D) vaccine in late-stage colorectal cancer.

Cancer Immunol Immunother. 2015;64(8):977–987. doi:10.1007/s0262-015-1706-4.
139. Morse MA, Chaudhry A, Gabitzsch ES, Hobeika AC, Osada T, Clay TM, Amalfitano A, Burnett BK, Devi GR, Hsu DS, et al. Novel adenoviral vector induces T-cell responses despite anti-adenoviral neutralizing antibodies in colorectal cancer patients. Cancer Immunol Immunother. 2013;62(8):1293–1301. doi:10.1007/s0262-013-1400-3.
140. Redman JM, Tsai YT, Weinberg BA, Donahue RN, Gandhy S, Gatti-Mays ME, Abdul Sater H, Bilusic M, Cordes L, Steinberg SM, et al. A randomized phase II trial of mFOLFOX6 + bevacizumab alone or with AdCEA vaccine + avelumab immunotherapy for untreated metastatic colorectal cancer. Oncologist. 2022;27(3):198–209. doi:10.1093/oncolo/oyab046.
141. Gabitzsch ES, Tsang KY, Palena C, David JM, Fantini M, Kwilas A, Rice AE, Latchman Y, Hodge JW, Gulley JL, et al. The generation and analyses of a novel combination of recombinant adenovirus vaccines targeting three tumor antigens as an immunotherapeutic. Oncotarget. 2015;6(31):31344–31359. doi:10.18632/oncotarget.5181.
142. ClinicalTrials.gov. Testing a combination of vaccines for cancer prevention in lynch syndrome. ClinicalTrials.Gov identifier: NCT9011. https://www.clinicaltrials.gov/study/NCT9011.
143. Karan D, Dubey S, Van Veldhuizen P, Holzbeierlein JM, Tawfik O, Thrasher JB. Dual antigen target-based immunotherapy for prostate cancer eliminates the growth of established tumors in mice. Immunotherapy. 2011;3(6):735–746. doi:10.2217/imt.11.59.
144. Lubaroff DM, Konety B, Link BK, Ratliff TL, Madsen T, Shannon M, Ecklund D, Williams RD. Clinical protocol: phase I study of an adenovirus/prostate-specific antigen vaccine in men with metastatic prostate cancer. Hum Gene Ther. 2006;17(2):220–229. doi:10.1089/hum.2006.17.220.
145. Bilusic M, McMahon S, Madan RA, Karzai F, Tsai YT, Donahue RN, Palena C, Jochems C, Marté JL, Floudas C, et al. Phase I study of a multitargeted recombinant Ad5 PSA/MUC-1/brachyury-based immunotherapy vaccine in patients with metastatic castration-resistant prostate cancer (mCRPC). J Immunother Cancer. 2021;9(3):e2374. doi:10.1136/jitc-2021-02374.
146. ClinicalTrials.gov. MG1 Maraba/MAGE-A3, with and without adenovirus vaccine with transgenic MAGE-A3 insertion in incurable MAGE-A3-Expressing solid tumours. ClinicalTrials.Gov identifier: NCT5816. https://www.clinicaltrials.gov/study/NCT5816.
147. Jonker DJ, Hotte SJ, Abdul Razak AR, Renouf DJ, Lichty B, Bell JC, Powers J, Dancey J, Stojdl DF, Stephenson KB, et al. Phase I study of oncolytic virus (OV) MG1 maraba/MAGE-A3 (MG1MA3), with and without transgenic MAGE-A3 adenovirus vaccine (AdMA3) in incurable advanced/metastatic MAGE-A3-expressing solid tumours: CCTG IND.214. J Clin Oncol. 2017;35(15_suppl):e4637. doi:10.1200/JCO.2017.35.15_suppl.e4637.
148. ClinicalTrials.gov. Oncolytic MG1-MAGEA3 with ad-MAGEA3 vaccine in combination with pembrolizumab for non-small cell lung cancer patients. ClinicalTrials.Gov identifier: NCT9760. https://www.clinicaltrials.gov/study/NCT9760.
149. Pellom ST, Rumfield CS, Y Maurice Morillon II, Roller N, Poppe LK, Brough DE, Sabzevari H, Schlom J, Jochems C. Characterization of recombinant gorilla adenovirus HPV therapeutic vaccine PRGN-2009. JCI Insight. 2021;6(7). doi:10.1172/jci.insight.11912.
150. Floudas CS, Strauss J, Redman JM, Pastor DM, Turkbey EB, Donahue RN, Jochems C, Gulley JL, Lamping E, Cordes LM, et al. Phase I evaluation of PRGN-2009 alone and in combination with bintrafusp alfa in patients (pts) with recurrent/metastatic (R/M) hpv-associated cancers (HPV-C). J Clin Oncol. 2023;41(16_suppl):2628. doi:10.1200/JCO.2023.41.16_suppl.2628.
151. Tschernia N, Birrer MJ, Liao JB, Lankford A, Disis ML, Gulley JL. A phase 2 study to evaluate efficacy and safety of PRGN-2009, a novel gorilla adenovirus-based immunotherapy, in combination with pembrolizumab versus pembrolizumab monotherapy in patients with recurrent or metastatic cervical cancer. J Clin Oncol. 2024;42(16_suppl):TPS5623. doi:10.1200/JCO.2024.42.16_suppl.TPS5623.
152. Leoni G, D'Alise AM, Cotugno G, Langone F, Garzia I, De Lucia M, Fichera I, Vitale R, Bignone V, Tucci FG, et al. A genetic vaccine encoding shared cancer neoantigens to treat tumors with microsatellite instability. Cancer Res. 2020;80(18):3972–3982. doi:10.1158/0008-5472.CAN-20-1072.
153. Bartolomeo R, Troise F, Allocca S, Sdruscia G, Vitale R, Bignone V, Petrone AM, Romano G, D'Alise AM, Ruzza V, et al. Development of a potency assay for nous-209, a multivalent neoantigens-based genetic cancer vaccine. Vaccines (Basel). 2024;12(3):325. doi:10.3390/vaccines0325.
154. ClinicalTrials.gov. Nous-209 genetic vaccine for the treatment of microsatellite unstable solid tumors. ClinicalTrials.Gov identifier: NCT1310. https://www.clinicaltrials.gov/study/NCT1310.
155. Overman M, Fakih M, Le D, Shields A, Pedersen K, Shah M, Mukherjee S, Faivre T, Leoni G, D'Alise AM, et al. Phase I interim study results of nous-209, an off-the-shelf immunotherapy, with pembrolizumab, for the treatment of tumors with a deficiency in mismatch repair/microsatellite instability (dMMR/MSI). J Immunother Cancer. 2021;9(Suppl_2):A441. doi:10.1136/jitc-2021-ITOC.444.
156. ClinicalTrials.gov. Cancer preventive vaccine nous-209 for lynch syndrome patients. ClinicalTrials.Gov identifier: NCT8866. https://www.clinicaltrials.gov/study/NCT8866.
157. ClinicalTrials.gov. A vaccine trial for patients with stage IIIB, IV, or recurrent non-small cell lung cancer (VTNSCLC). ClinicalTrials.Gov identifier: NCT4222. https://www.clinicaltrials.gov/study/NCT4222.
158. ClinicalTrials.gov. Vaccine therapy in treating patients with stage IIIB, stage IV, or recurrent non-small cell lung cancer. ClinicalTrials.Gov identifier: NCT1094. https://www.clinicaltrials.gov/study/NCT1094.
159. ClinicalTrials.gov. CCL21-gene modified dendritic cell vaccine and pembrolizumab in treating patients with stage IV non-small cell lung cancer. ClinicalTrials.Gov identifier: NCT6361. https://www.clinicaltrials.gov/study/NCT6361.
160. ClinicalTrials.gov. DCs vaccine combined with cytokine-induced killer cells in patients with AML. ClinicalTrials.Gov identifier: NCT8663. https://www.clinicaltrials.gov/study/NCT8663.
161. Giaginis CT, Zarros AC, Papaefthymiou MA, Papadopouli AE, Sfiniadakis IK, Theocharis SE. Coxsackievirus and adenovirus receptor expression in human endometrial adenocarcinoma: possible clinical implications. World J Surg Oncol. 2008;6(1):59. doi:10.1186/1477-7819-6-59.
162. Reeh M, Bockhorn M, Gorgens D, Vieth M, Hoffmann T, Simon R, Izbicki JR, Sauter G, Schumacher U, Anders M. Presence of the coxsackievirus and adenovirus receptor (CAR) in human neoplasms: a multitumour array analysis. Br J Cancer. 2013;109(7):1848–1858. doi:10.1038/bjc.2013.509.
163. ClinicalTrials.gov. Trial investigating an immunostimulatory oncolytic adenovirus for cancer. ClinicalTrials.Gov identifier: NCT5989. https://www.clinicaltrials.gov/study/NCT5989.a
164. Musher BL, Rowinsky EK, Smaglo BG, Abidi W, Othman M, Patel K, Jawaid S, Jing J, Brisco A, Leen AM, et al. LOAd703, an oncolytic virus-based immunostimulatory gene therapy, combined with chemotherapy for unresectable or metastatic pancreatic cancer (LOKON001): results from arm 1 of a non-randomised, single-centre, phase 1/2 study. Lancet Oncol. 2024;25(4):488–500. doi:10.1016/S1470-2045(24)00079-2.
165. Wenthe J, Eriksson E, Naseri S, Sandin L, Hahn A, Irenaeus S, Sundin A, Leja-Jarblad J, Ullenhag G, Lövgren T, et al. Immunostimulatory gene therapy targeting CD40/4-1BB in combination with chemotherapy induces an inflammatory gene profile in tumors from patients with advanced disease [abstract]. In: proceedings of the American association for cancer research annual meeting 2023; part 1 (regular and invited abstracts); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR. Cancer Res. 2023;83(7_Suppl):Abstract nr 6663.

166. ClinicalTrials.gov. LOAd703 oncolytic virus therapy for pancreatic cancer. ClinicalTrials.Gov identifier: NCT5196. https://www.clinicaltrials.gov/study/NCT5196.
167. ClinicalTrials.gov. H101 recombinant human adenovirus type 5 plus HAIC of FOLFOX for intrahepatic cholangiocarcinoma. ClinicalTrials.Gov identifier: NCT4002. https://www.clinicaltrials.gov/study/NCT4002.
168. ClinicalTrials.gov. H101 oncolytic Adenovirus(H101) combined with PD-1 inhibitors in patients with advanced malignant pleural mesothelioma. ClinicalTrials.Gov identifier: NCT1636. https://www.clinicaltrials.gov/study/NCT1636.
169. ClinicalTrials.gov. H101 combined with camrelizumab for recurrent cervical cancer. ClinicalTrials.Gov identifier: NCT4905. https://www.clinicaltrials.gov/study/NCT4905.
170. ClinicalTrials.gov. Oncolytic adenovirus TILT-123 and avelumab for treatment of solid tumors refractory to or progressing after anti-PD(L)1. AVENTIL. ClinicalTrials.Gov identifier: NCT2932. https://www.clinicaltrials.gov/study/NCT2932.
171. ClinicalTrials.gov. Oncolytic adenovirus coding for TNFa and IL2 (TILT-123) with pembrolizumab or pembrolizumab and pegylated liposomal doxorubicin as treatment for ovarian cancer. (PROTA). ClinicalTrials.Gov identifier: NCT1318. https://www.clinicaltrials.gov/study/NCT1318.
172. ClinicalTrials.gov. TNFα and IL-2 coding oncolytic adenovirus TILT-123 monotherapy (TUNIMO). ClinicalTrials.Gov identifier: NCT5327. https://www.clinicaltrials.gov/study/NCT5327.
173. ClinicalTrials.gov. TNFalpha and interleukin 2 coding oncolytic adenovirus TILT-123 during TIL treatment of advanced melanoma (TUNINTIL). ClinicalTrials.Gov identifier: NCT7473. https://www.clinicaltrials.gov/study/NCT7473.
174. Pakola SA, Peltola KJ, Clubb JHA, Jirovec E, Haybout L, Kudling TV, Alanko T, Korpisaari R, Juteau S, Jaakkola M, et al. Safety, efficacy, and biological data of T-Cell–enabling oncolytic adenovirus TILT-123 in advanced solid cancers from the TUNIMO monotherapy phase I trial. Clin Cancer Res. 2024;30(17):3715–3725. doi:10.1158/1078-0432.CCR-23-3874.
175. Jirovec E, Quixabeira DCA, Clubb JHA, Pakola SA, Kudling T, Arias V, Haybout L, Jalkanen K, Alanko T, Monberg T, et al. Single intravenous administration of oncolytic adenovirus TILT-123 results in systemic tumor transduction and immune response in patients with advanced solid tumors. J Exp Clin Cancer Res. 2024;43(1):297. doi:10.1186/s3046-024-03219-0.
176. Li R, Villa NY, Yu X, Johnson JO, Borjas G, Dhillon J. Oncolytic immunotherapy with nivolumab in muscle-invasive bladder cancer: a phase 1b trial. Nat Med. 2024;31(1):176–188.
177. Reddy PS, Burroughs KD, Hales LM, Ganesh S, Jones BH, Idamakanti N, Hay C, Li SS, Skele KL, Vasko A-J, et al. Seneca Valley virus, a systemically deliverable oncolytic picornavirus, and the treatment of neuroendocrine cancers. J Natl Cancer Inst. 2007;99(21):1623–1633. doi:10.1093/jnci/djm198.
178. Rudin CM, Poirier JT, Senzer NN, Stephenson J Jr., Loesch D, Burroughs KD, Reddy PS, Hann CL, Hallenbeck PL. Phase I clinical study of Seneca Valley virus (SVV-001), a replication-competent picornavirus, in advanced solid tumors with neuroendocrine features. Clin Cancer Res. 2011;17(4):888–895. doi:10.1158/1078-0432.CCR-10-1706.
179. ClinicalTrials.gov. First in man clinical study to evaluate safety and tolerability of an oncolytic adenovirus in prostate cancer patients. ClinicalTrials.Gov identifier: NCT7002. https://www.clinicaltrials.gov/study/NCT7002.
180. ClinicalTrials.gov. MSC-DNX-2401 in treating patients with recurrent high-grade glioma. ClinicalTrials.Gov identifier: NCT6568. https://www.clinicaltrials.gov/study/NCT6568.
181. ClinicalTrials.gov. MEM-288 oncolytic virus alone and in combination with nivolumab in solid tumors including non-small cell lung cancer. ClinicalTrials.Gov identifier: NCT6760. https://www.clinicaltrials.gov/study/NCT6760.
182. ClinicalTrials.gov. Ixovex-1 single agent and combination therapy (IXACT). ClinicalTrials.Gov identifier: NCT9946. https://www.clinicaltrials.gov/study/NCT9946.
183. ClinicalTrials.gov. Binary oncolytic adenovirus in combination with HER2-specific autologous CAR VST, advanced HER2 positive solid tumors (VISTA). ClinicalTrials.Gov identifier: NCT0256. https://www.clinicaltrials.gov/study/NCT0256.
184. ClinicalTrials.gov. A clinical study of BioTTT001 in combination with SOX and toripalimab in patients with gastric cancer. ClinicalTrials.Gov identifier: NCT3121. https://www.clinicaltrials.gov/study/NCT3121.
185. ClinicalTrials.gov. A clinical study evaluating the safety and efficacy of BioTTT001 in patients with malignant solid tumors. ClinicalTrials.Gov identifier: NCT5846. https://www.clinicaltrials.gov/study/NCT5846.
186. ClinicalTrials.gov. A clinical study of BioTTT001 in combination with toripalimab and regorafenib in patients with colorectal cancer. ClinicalTrials.Gov identifier: NCT3134. https://www.clinicaltrials.gov/study/NCT3134.
187. Dilloo D, Rill D, Entwistle C, Boursnell M, Zhong W, Holden W, Holladay M, Inglis S, Brenner M. A novel herpes vector for the high-efficiency transduction of normal and malignant human hematopoietic cells. Blood. 1997;89(1):119–127. doi:10.1182/blood.V89.1.119.
188. Boursnell ME, Entwisle C, Blakeley D, Roberts C, Duncan IA, Chisholm SE, Martin GM, Jennings R, Ni Challanain D, Sobek I, et al. A genetically inactivated herpes simplex virus type 2 (HSV-2) vaccine provides effective protection against primary and recurrent HSV-2 disease. J Infect Dis. 1997;175(1):16–25. doi:10.1093/infdis/175.1.16.
189. Sanchala DS, Bhatt LK, Prabhavalkar KS. Oncolytic herpes simplex viral therapy: a stride toward selective targeting of cancer cells. Front Pharmacol. 2017;8:270. doi:10.3389/fphar.2017.00270.
190. Stanway PA, Samloff IM, Brace CJ, Renwick JH. Predisposition to spina bifida: search for a relation to maternal gastric acid secretion. J Med Genet. 1977;14(5):332–334. doi:10.1136/jmg.14.5.332. PMID: 53466; PMCID: PMC3615.
191. Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene Laherparepvec (T-VEC): an intralesional cancer immunotherapy for advanced melanoma. Cancers (Basel). 2021;13(6):1383. doi:10.3390/cancers1383.
192. ClinicalTrials.gov. Talimogene Laherparepvec in combination with neoadjuvant chemotherapy in triple negative breast cancer. ClinicalTrials.Gov identifier: NCT9855. https://www.clinicaltrials.gov/study/NCT9855.
193. CAN-3110 receives FDA fast track designation for treatment of recurrent high-grade glioma. News release. Candel therapeutics. 2024 Feb 13 [accessed 2024 Sep 15]. https://ir.candeltx.com/news-releases/news-release-details/can-3110-receives-fda-fast-track-designation-treatment-recurrent.
194. Ling AL, Solomon IH, Landivar AM, Nakashima H, Woods JK, Santos A, Masud N, Fell G, Mo X, Yilmaz AS, et al. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. Nature. 2023;623(7985):157–166. doi:10.1038/s1586-023-06623-2.
195. Ghonime MG, Jackson J, Shah A, Roth J, Li M, Saunders U, Coleman J, Gillespie GY, Markert JM, Cassady KA. Chimeric HCMV/HSV-1 and Δγ134.5 oncolytic herpes simplex virus elicit immune mediated antigliomal effect and antitumor memory. Transl Oncol. 2018;11(1):86–93. doi:10.1016/j.tranon.2017.10.005.
196. ClinicalTrials.gov. HSV G207 in children with recurrent or refractory cerebellar brain tumors. ClinicalTrials.Gov identifier: NCT1388. https://www.clinicaltrials.gov/study/NCT1388.
197. ClinicalTrials.gov. Trial of C134 in patients with recurrent GBM (C134-HSV-1). ClinicalTrials.Gov identifier: NCT7576. https://www.clinicaltrials.gov/study/NCT7576.
198. ClinicalTrials.gov. Genetically engineered HSV-1 phase 1 study for the treatment of recurrent malignant glioma (M032-HSV-1). ClinicalTrials.Gov identifier: NCT2827. https://www.clinicaltrials.gov/study/NCT2827.
199. ClinicalTrials.gov. Study of Pembrolizumab and M032 (NSC 73972). ClinicalTrials.Gov identifier: nCT4430. https://clinicaltrials.gov/study/NCT4430.

200. Patel DM, Foreman PM, Nabors LB, Riley KO, Gillespie GY, Markert JM. Design of a phase I clinical trial to evaluate M032, a genetically engineered HSV-1 expressing IL-12, in patients with Recurrent/Progressive glioblastoma multiforme, anaplastic astrocytoma, or Gliosarcoma. Hum Gene Ther Clin Dev. 2016;27(2):69–78. doi:10.1089/humc.2016.031.
201. Menotti L, Avitabile E. Herpes simplex virus Oncolytic Immunovirotherapy: the blossoming branch of multimodal therapy. Int J Mol Sci. 2020;21(21):8310. doi:10.3390/ijms8310.
202. Peters C, Rabkin SD. Designing herpes viruses as Oncolytics. Mol Ther Oncolytics. 2015;2:15010–. doi:10.1038/mto.2015.10.
203. ClinicalTrials.gov. A phase 1B/2 study of RP1 in solid organ transplant patients with advanced cutaneous malignancies (ARTACUS). ClinicalTrials.Gov identifier: NCT9436. https://www.clinicaltrials.gov/study/NCT9436.
204. ClinicalTrials.gov. Study evaluating cemiplimab alone and combined with RP1 in treating advanced squamous skin cancer (CERPASS). ClinicalTrials.Gov identifier: NCT0436. https://www.clinicaltrials.gov/study/NCT0436.
205. ClinicalTrials.gov. A randomized, phase 2/3 study to investigate the efficacy and safety of RP2 in combination with nivolumab in immune checkpoint inhibitor-naïve adult patients with metastatic uveal melanoma (RP2-202). ClinicalTrials.Gov identifier: NCT1406. https://www.clinicaltrials.gov/study/NCT1406.
206. ClinicalTrials.gov. RP2/RP3 in combination with atezolizumab and Bevacizumab for the treatment of patients with CRC. ClinicalTrials.Gov identifier: NCT3611. https://www.clinicaltrials.gov/study/NCT3611.
207. ClinicalTrials.gov. A clinical study on oncolytic virus injection (R130) for the treatment of advanced solid tumors. ClinicalTrials.Gov identifier: NCT0374. https://www.clinicaltrials.gov/study/NCT0374.
208. ClinicalTrials.gov. A clinical study on oncolytic virus injection (R130) for the treatment of relapsed/refractory advanced solid tumors. ClinicalTrials.Gov identifier: NCT6075. https://www.clinicaltrials.gov/study/NCT6075 .
209. ClinicalTrials.gov. A clinical study on oncolytic virus injection (R130) for the treatment of relapsed/refractory cervical and endometrial cancer. ClinicalTrials.Gov identifier: NCT2677. https://www.clinicaltrials.gov/study/NCT2677.
210. ClinicalTrials.gov. First-in-human (FIH) phase I trial of BS-006 in cervical cancer (CC-OV01). ClinicalTrials.Gov identifier: NCT3440. https://www.clinicaltrials.gov/study/NCT3440.
211. ClinicalTrials.gov. OH2 oncolytic viral therapy in solid tumors. ClinicalTrials.Gov identifier: NCT6525. https://www.clinicaltrials.gov/study/NCT6525.
212. ClinicalTrials.gov. OH2 oncolytic viral therapy in advanced bladder cancer. ClinicalTrials.Gov identifier: NCT8789. https://www.clinicaltrials.gov/study/NCT8789.
213. ClinicalTrials.gov. OH2 OH2 oncolytic viral therapy in non-muscle-invasive bladder cancer. ClinicalTrials.Gov identifier: NCT2136. https://www.clinicaltrials.gov/study/NCT2136.
214. ClinicalTrials.gov. OH2 injection in solid tumors. ClinicalTrials.Gov identifier: NCT6967. https://www.clinicaltrials.gov/study/NCT6967.
215. Zhang B, Huang J, Tang J, Hu S, Luo S, Luo Z, Zhou F, Tan S, Ying J, Chang Q, et al. Intratumoral OH2, an oncolytic herpes simplex virus 2, in patients with advanced solid tumors: a multicenter, phase I/II clinical trial. J Immunother Cancer. 2021;9(4):e2224. doi:10.1136/jitc-2020-02224.
216. ClinicalTrials.gov. A clinical study of T3011 in combination with toripalimab and regorafenib in patients with colorectal cancer. ClinicalTrials.Gov identifier: NCT3303. https://www.clinicaltrials.gov/study/NCT3303.
217. ClinicalTrials.gov. A study of T3011 administered via intravenously in patients with advanced solid tumors. ClinicalTrials.Gov identifier: NCT8268. https://www.clinicaltrials.gov/study/NCT8268.
218. Ji D, Weitao Y, Tong X, Zhang C, Wang F, Chen Z, Zhou Y, Li Z, Deng Y, Huang G, et al. A phase 1/2a study of T3011, an oncolytic HSV expressing IL-12 and PD-1 antibody, administered via intratumoral (IT) injection as monotherapy in advanced solid tumors. J Clin Oncol. 2023;41(16_suppl):2520. doi:10.1200/JCO.2023.41.16_suppl.2520.