



Oncolytic viral vectors in the era of diversified cancer therapy: from preclinical to clinical

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Abstract

With the in-depth research and wide application of immunotherapy recently, new therapies based on oncolytic viruses are expected to create new prospects for cancer treatment via eliminating the suppression of the immune system by tumors. Currently, an increasing number of viruses are developed and engineered, and various virus vectors based on effectively stimulating human immune system to kill tumor cells have been approved for clinical treatment. Although the virus can retard the proliferation of tumor cells, the choice of oncolytic viruses in biological cancer therapy is equally critical given their therapeutic efficacy, safety and adverse effects. Moreover, previously known oncolytic viruses have not been systematically classified. Therefore, in this review, we summarized and distinguished the characteristics of several common types of oncolytic viruses: herpes simplex virus, adenovirus, measles virus, Newcastle disease virus, reovirus and respiratory syncytial virus. Subsequently, we outlined that these oncolytic viral vectors have been transformed from preclinical studies in combination with immunotherapy, radiotherapy, chemotherapy, and nanoparticles into clinical therapeutic strategies for various advanced solid malignancies or circulatory system cancers.

Keywords Oncolytic virus · Tumor immunity · Clinical trials

Abbreviations

ADP	Adenoviral death protein	DC	Dendritic cell
APMV-1	Paramyxovirus type 1	DLT	Dose limited toxicity
CAR	Coxsackie and adenovirus receptor	DOX	Doxorubicin
CAR-T	Chimeric antigen receptor T-cells	eIF2a	Eukaryotic initiation factor 2a
CD	Cytosine deaminase	FAP	Fibroblast activation protein
CLTA-4	Cytotoxic T lymphocyte associated protein 4	GM-CSF	Granulocyte–macrophage colony stimulating factor
CpHV-1	Caprine herpesvirus	HSV	Herpes simplex virus
CR	Complete remission	HSV-tk	Herpes simplex virus-1 thymidine kinase
CTL	Cytotoxic T lymphocytes	HVR1	Hypervariable region 1
		ICB	Immune checkpoint blockade
		ICD	Immunogenic cell death
		ICIs	Immune checkpoint inhibitors
		IFN-1	Interferon-1
		IFN- α	Interferon α
		IgM	Immunoglobulin M
		IL-12	Interleukin 12
		IL-2	Interleukin-2
		mCRPC	Metastatic castration-resistant prostate cancer
		MDSC	Marrow-derived suppressor cell
		MHC-1	Major histocompatibility complex 1
		MM	Malignant mesothelioma
		MTD	Maximum tolerated dose

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Mucin-1	MUC-1
MV	Measles virus
NDV	Newcastle disease virus
OV	Oncolytic virus
pCR	Pathological complete remission
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
Pfu	Plasmid forming units
PKR	Protein kinase R
PR	Partial remission
PSA	Prostate-specific antigen
Reovirus	Respiratory and enteric orphan virus
SBRT	Hypofractionated stereotaxic body radiotherapy
SD	Stable disease
TAA	Tumor-associated antigens
TCID ₅₀	Median tissue culture infective dose
TNF-α	Tumor necrosis factor alpha

TRAIL	TNF-related apoptosis-inducing ligand
T-Vec	Talimogene laherparepvec

Introduction

Oncolytic virus (OV) is a biologically effective preparation that can enter the body through intravenous drip, intratumor injection, intraspinal drip and other methods of administration to enter the body to play a role. It has the potential to treat solid tumors or non-solid tumors [1]. OVs can selectively proliferate and replicate in tumor cells, thereby activating the host’s anti-tumor immune system, and recruiting more effector lymphocytes in the tumor microenvironment to achieve the effect of killing tumor cells [2], the mechanism can be seen in Fig. 1. At the end of the twentieth century, it was reported that the genetically edited herpes simplex virus (HSV) could inhibit the growth of malignant glioma [3]. In the following decades, with the rapid

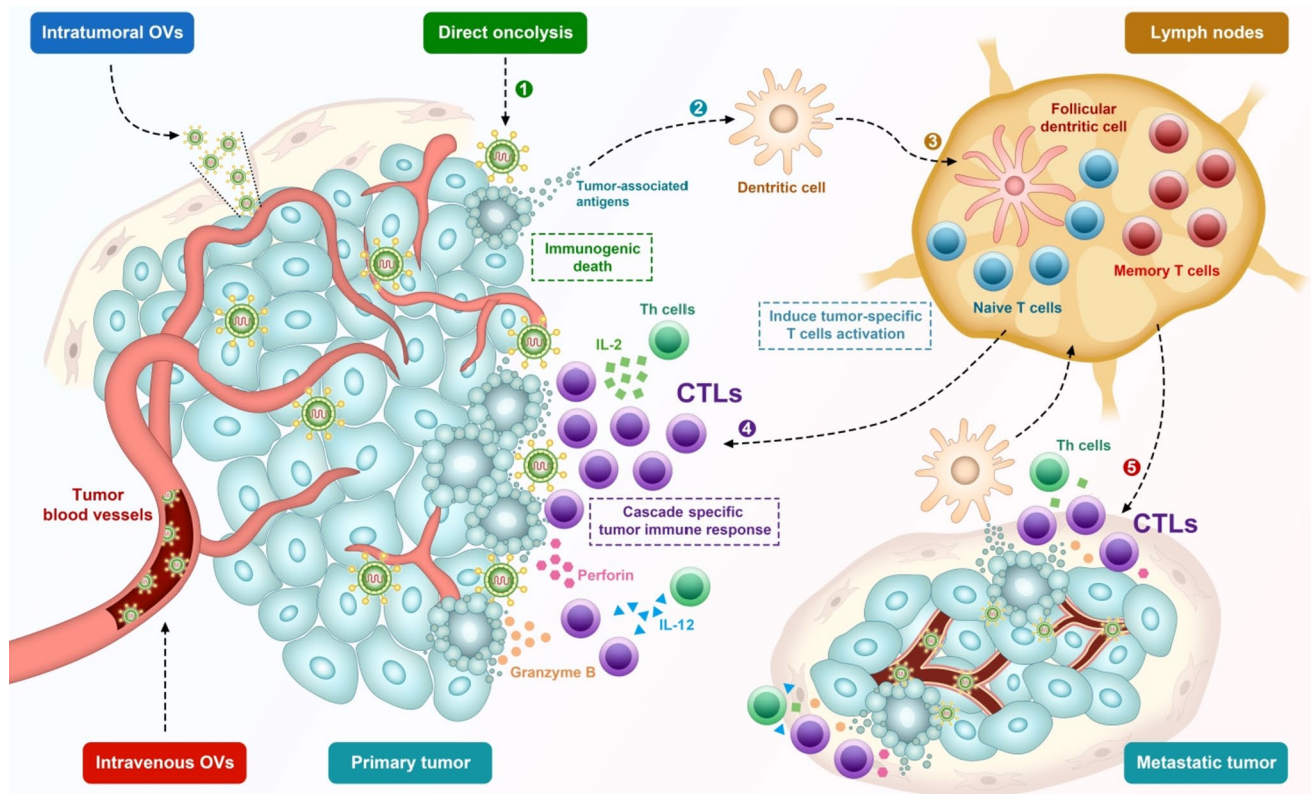


Fig. 1 Schematic diagram of anticancer mechanism of oncolytic virus. OVs can enter the tumor site through various routes of administration (such as intratumoral injection or intravenous injection). Oncolytic viruses that enter the tumor site can first cause immunogenic death of tumor cells through direct oncolysis (1), release a variety of tumor-associated antigens, after being taken up by DC (2), enter the lymph nodes through lymphatic reflux, present tumor antigen information to naive T cells in the lymph nodes, induce differentiation to produce tumor-specific effector T cells cells (3), which acti-

vate the tumor immune response. With the continuous oncolysis and T cell-specific immune attack, more tumor-associated antigens are released, and more effector T cells are generated through the presentation of DCs, causing a cascade of specific tumor immune responses (4). In addition, memory T cells distributed in lymph nodes or local inflammation sites of tumors will conduct immune tracking of distant tumors, differentiate into effector T cells to kill tumor cells, and reduce malignant metastasis and recurrence (5)

development of reverse genetic manipulation technology, gene-edited OVs also showed broad application prospects [4, 5]. In 2015, the American pharmaceutical manufacturer Amgen prepared a gene-edited attenuated HSV-1, which can be injected into the tumor to treat unresectable melanoma recurring after surgery, and it was approved by the U.S. Food and Drug Administration [6]. This is the first appearance of OV therapy among many anti-tumor therapies, and it is also a major milestone in the field of OV research. Given that the favorable anti-tumor efficacy of the virus in clinical trials, phase 3 clinical trials in combination with PD-1 antagonists have been carried out [7]. Biotechnology has promoted the research progress of OVs and deepened people's understanding of the mechanism of OVs and tumor molecular mechanisms. This review discusses several OVs that have been studied in depth and their characteristics, and analyzes the progress of these OVs in clinical applications.

Types and characteristics of OVs

As a new force in tumor immunotherapy, more and more viral vectors are being developed to obtain the best therapeutic effect. The following lists several main representative OVs and their structural characteristics. More OVs that are still in the preclinical research stage are shown in Table 1.

Herpes simplex virus

As a member of the alpha-herpesvirus subfamily, herpes simplex virus (HSV) contains a double-stranded DNA genome of approximately 125–250 kb that encodes more than 70 proteins [18] (Fig. 2A). Knockout or mutation of HSV gene RL1 by gene editing technology can reduce the expression of neurotoxic protein ICP34.5, greatly reducing the neurotoxicity of HSV [19], making it selectively used in interferon-deficient cancer cells copying [20]. The genome of HSV is large and easy to modify. Multiple foreign genes can be inserted to improve the anti-tumor effect [21], and the modification of the glycoprotein on the surface of HSV can improve tumor targeting [22]. The key to using HSV for oncolytic therapy is genetic engineering technology, which is to knock out the main genes that infect normal cells and replicate and proliferate in normal cells to improve the targeting of HSV infecting tumor cells, and more in tumor cells selective replication. Currently known HSV mutants that can be used as oncolytic vectors are as follows:

- (1) Dlsptk, the first known type 1 HSV mutant, has a mutation in its *UL23* gene, which can encode thymidine kinase and restrain the metastasis of glioma in mice [23], but increasing the dose will cause serious encephalitis and other adverse reactions [24];
- (2) R3616 is derived from HSV-1(F) strain, knocking out two genes encoding ICP34.5 can effectively enhance the anti-tumor ability in vivo [25]. Relevant experiments have shown that R3616 can infect tumor antigen-specific lymphocytes, not only can kill the primary tumor, but also have an inhibitory effect on distant metastasis and recurrence [26];
- (3) HSV1716, sourced from the HSV-1 (17+) strain, deletes two copies of the neurotoxicity-determining gene *RL1*. Protein kinase R (PKR) phosphorylates not only eukaryotic initiation factor 2a (eIF2a), thereby inhibiting protein translation and inducing tumor cell apoptosis, but also viral death [27]. The ICP34.5-mediated dephosphorylation of eIF2a can promote protein translation and inhibit cell apoptosis, so HSV1716 can be used in tumor cells with uncontrolled protein synthesis [28];
- (4) G207 was the first HSV to be used in oncology clinical trials. The *LacZ* gene was inserted into the deleted *ICP34.5* locus, allowing the virus to selectively replicate in malignant cells. The deletion mutant *ICP34.5* induces downregulation of late viral genes including *US11* through *PKR* [29]. G207 induces systemic anti-tumor immunity in the host and activates cytotoxic T lymphocytes (CTL) [30];
- (5) G47 Δ , isolated from the G207 strain of HSV, has mutations in *RL1* and *ICP47* in its genome, and inserts the *LacZ* gene fragment into the *ICP6* gene, resulting in a reduction in the large subunit of the encoding ribonucleic acid reductase, resulting in inactivation of ribonucleic acid reductase leads to further induction of selective replication of oncolytic HSV in tumor cells [31, 32]. In addition, the *ICP47* mutation can effectively stimulate the specific tumor immune response by increasing the expression of major histocompatibility complex 1 (MHC-1) [33];
- (6) HF10 is deleted the 3.9 kb junction between the right end of *UL* and *UL/IRL*, resulting in the loss of *UL56* expression and the enhanced expression of *UL53* (gK), *UL54* (ICP27) and *UL55* [34]. In addition, HF10 can enhance angiogenesis and induce anti-tumor responses of cytotoxic T lymphocytes [35].
- (7) Oncovex^{GM-CSF} delete HSV genes encoding *ICP34.5* and *ICP47*, and a series of encoding cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), human interleukin-12 (IL-12), interferon alpha (IFN- α) and tumor necrosis factor alpha (TNF- α), etc., were integrated into the *ICP34.5* locus factor genes. Thereby, enhancing the anti-tumor immune function of oncolytic HSV, improving the immune response ability of antigen-specific T cells, reducing the negative immune regulation of CD4⁺ T cells, and

Table 1 Preclinical studies of oncolytic virus therapy alone in recent years

Oncolytic Virus	Cancers	Description	Main therapeutic effect	Treatment results	References
Vaccinia virus	Breast cancer Melanoma Colon adenocarcinoma	Co-expression of PD-L1 inhibitor and GM-CSF	Activate tumor-specific T cell immunity, GM-CSF, PD-L1 inhibitor and oncolytic virus present a synergistic anti-tumor effect	The growth of primary and distal tumors in mice was significantly inhibited, and the infiltration of immune cells in the tumor microenvironment was increased, providing a new answer to the problem of PD-1/PD-L1 drug resistance	Guan Wang et al. [8]
Herpes simplex virus	Glioblastoma	Expressing a full-length anti(α)-human CD47 IgG1 or IgG4 antibody	Activate the natural immune system, the virus persists in the tumor microenvironment, and stimulates the production of antibodies in situ	Blocking the SIRPα and CD47 in the glioma microenvironment of mice inhibited the growth and invasion of gliomas in mice, and significantly prolonged the survival of mice	Bo Xu et al. [9]
Vesicular stomatitis virus	Colorectal adenocarcinoma	Expression of tumor-associated antigens and pseudotyped with LCMV-GP	Produce a strong CD8 ⁺ T cell response, transform the tumor microenvironment from immunosuppressive type to immune support type	In mice, the proportion of memory T cells was significantly increased, the immune response of CD8 ⁺ T cells in the tumor microenvironment was enhanced, and the secretion of IFN-γ and TNF-α was increased	Krishna Das et al. [10]
Adenovirus	High-grade glioma	Delta-24-RGD has an RGD-4C peptide motif inserted into the adenovirus fiber, which allows the adenovirus to anchor directly to the integrin	By expressing RGD-4C peptide, the active targeting ability of recombinant oncolytic adenovirus is improved to lyse and kill tumor cells	T cell infiltration was significantly increased in Delta-24-RGD-infected tumors, indicating immune activation. Treatment of tumor-bearing hamsters with Delta-24-RGD significantly improved survival compared to hamsters treated with control group	Lynette M Phillips et al. [11]
Poliovirus	Melanoma Breast cancer	Internal ribosome entry site on poliovirus replaced by IRES of human rhinovirus type 2 to avoid neurovirulence	PVSRIP0 can selectively replicate in cells expressing CD155/Nect15, which is highly expressed on malignant glioma cells, resulting in efficient oncolysis	Pro-inflammatory cytokines were produced in tumor-bearing mice, effectively activating the proliferation of functional anti-tumor T cells, but failed to induce broader infiltration of immune cells such as T cells or durable anti-tumor efficacy	Michael C Brow et al. [12]

Table 1 (continued)

Oncolytic Virus	Cancers	Description	Main therapeutic effect	Treatment results	References
Adenovirus	Hepatocellular carcinoma	Oncolytic adenovirus encapsulated by cell membrane nanovesicles	Avoid neutralizing antibodies to weaken the efficacy of oncolytic adenovirus and improve its active targeting and biocompatibility	The oncolytic virus replicates and expands significantly in the tumor site of mice, inhibits the growth of tumor tissue, induces tumor cell apoptosis, and does not induce the mice to produce obvious neutralizing antibodies to inhibit the anti-tumor effect of the oncolytic virus	Peng Lv et al. [13]
Adenovirus	Lung cancer	Natural immunoglobulin M (IgM) antibodies binds to the hypervariable region 1 (HVR1) of the oncolytic adenovirus capsid protein hexon	The engineered and modified oncolytic adenovirus can escape the body's natural immune system and exert its anti-tumor efficacy better	The sequestration of oncolytic virus in the liver was significantly reduced, and the oncolytic virus injected by the tail vein could be more enriched in orthotopic lung cancer in mice, inhibited tumor growth, and had no toxic response to the liver	Svetlana Atasheva et al. [14]
Rotavirus	Neuroblastoma Lymphoma Breast carcinoma	Attenuated rotavirus for intratumoral injection	Improve the resistance of immune checkpoint blocking therapy in the tumor microenvironment, and activate the IFN- γ pathway to kill tumors	It can significantly inhibit the growth of neuroblastoma in mice, and significantly increase the proportion of tumor-infiltrating myeloid cells and CD8+ T lymphocytes. The anti-tumor effect of intratumoral injection is better than that of intravenous injection	Tala Shekarian et al. [15]
Herpes simplex virus	Glioblastoma	Recombinant oncolytic herpes simplex virus expressing E-cadherin	Improve the spread of oncolytic HSV in the tumor microenvironment, and weaken its killing of oncolytic HSV without affecting the activity of NK cells	Expression of E-cadherin in a mouse glioma model further promotes the spread of oncolytic virus between tumor cells, reduces the clearance rate of oncolytic virus by NK cells, and significantly prolongs the survival of mice	Bo Xu et al. [16]
Adenovirus	Pancreatic cancer	Oncolytic adenovirus expressing non-secretory IL-12 (without N-terminal signal peptide)	The IL-12 is enriched in the tumor site, which can cure the cancer foci that spread to the peritoneum while producing oncolytic effect, significantly improving the survival rate of tumor-bearing animals	By intraperitoneal injection, the survival rate of the Syrian hamster pancreatic cancer model was significantly improved, and the intraperitoneal metastatic tumor lesions were cured without toxic side effects to important organs	Pengju Wang et al. [17]

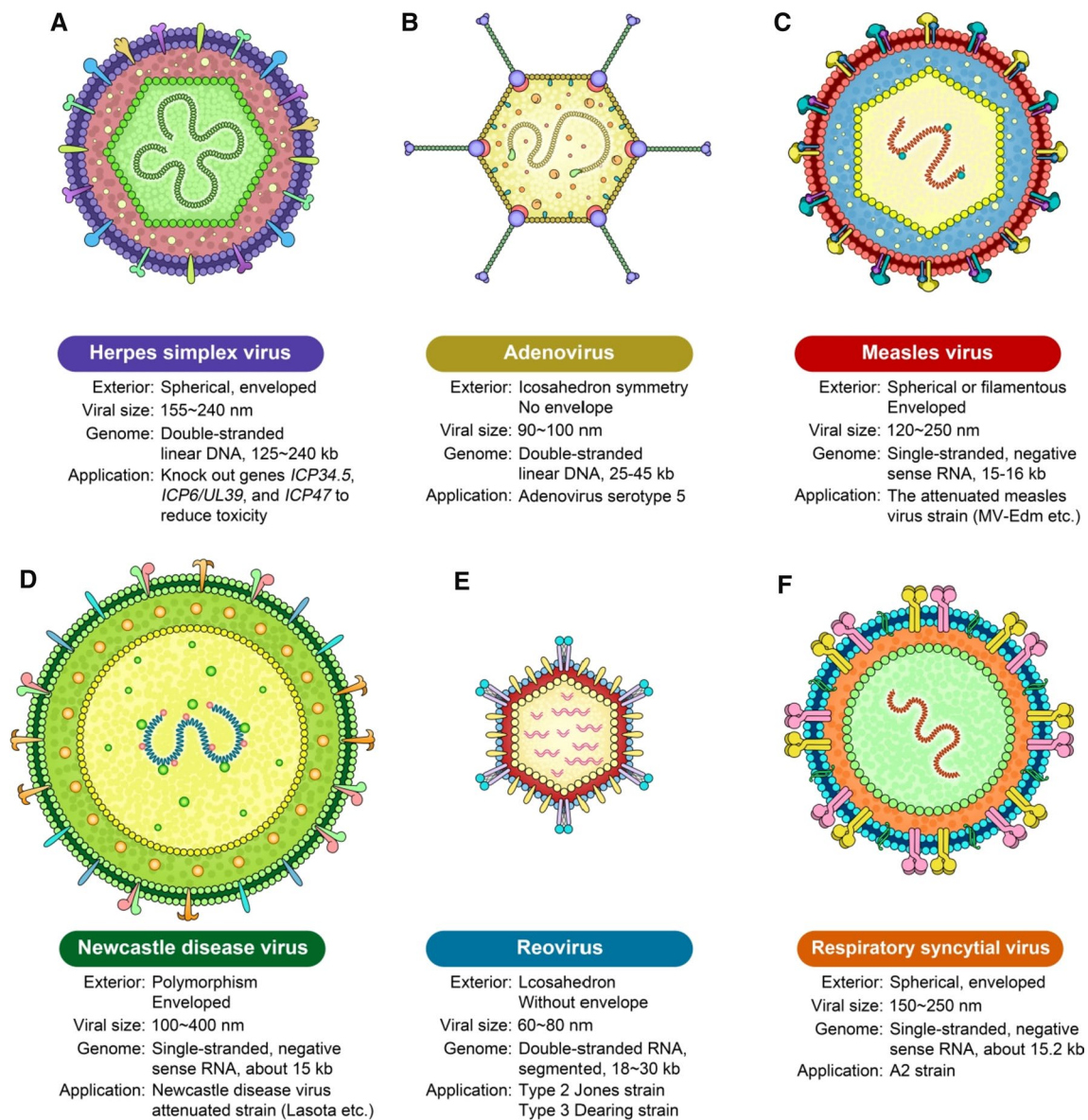


Fig. 2 Characteristics of different types of oncolytic viruses. **A** Herpes simplex virus. **B** Adenovirus. **C** Measles virus. **D** Newcastle disease virus. **E** Reovirus. **F** Respiratory Syncytial Virus

achieving a specific anti-tumor effect in CD8⁺ T cells [36].

Adenovirus

Adenovirus is a DNA virus with icosahedral symmetry and no viral envelope, and it is also a major research hotspot in the field of OV [37] (Fig. 2B). However, the coxsackie and adenovirus receptor (CAR) expression on the surface of most tumor cells is low or absent, resulting in insufficient efficiency of the commonly used oncolytic adenovirus vector, human serotype 5 adenovirus, to infect tumor cells [38]. Therefore, some studies insert RGD (a short peptide

composed of arginine, glycine and aspartic acid) into the fibers of the virus capsid [39]. RGD can specifically target the highly expressed integrin $\alpha_v\beta_3$ receptors in tumor tissues [40], thereby enhancing the ability of oncolytic adenovirus vectors to actively target tumor cells. In addition to RGD, adenovirus can also be modified with other functional targeting groups, such as targeting CD46 that is up-regulated in breast and colorectal cancer [41], or targeting desmoglein which is overexpressed in a variety of malignant epithelial cancers [42]. After a variety of modification methods, adenovirus can selectively replicate in malignant cells. The replication of adenovirus is initiated by the first adenovirus transcription unit E1A [43]. The product encoded by the

E1A gene can separate the complex of retinoblastoma and *E2F* gene product, resulting in the activation of E1B, E2, E3, E4 and other early transcription units by free E2F transcription factors [44]. Most of the current oncolytic adenovirus vectors insert a mutation sequence into the *E1A* gene, which can destroy the retinoblastoma binding domain, so that more E2F transcription factor complexes are freed from the retinoblastoma complex to regulate transcription of adenovirus in tumor cells [45]. After ensuring that adenovirus can selectively replicate in tumor cells in large numbers, the researchers integrated various exogenous genes with the function of promoting tumor cell apoptosis into the genome of the oncolytic adenovirus vector, like TNF-related apoptosis-inducing ligand (TRAIL) [46] or adenoviral death protein (ADP) [47], etc. Another type of gene that has been exploited is the prodrug activator, whose expression promotes the conversion of nontoxic prodrugs to toxic substances in the localized area of the tumor and is also delivered to nearby uninfected tumor cells through gap junctions between tumor cells, thus achieve better tumor suppressor effect [48]. For example, viruses capable of encoding bacterial cytosine deaminase (CD) [49] or herpes simplex virus-1 thymidine kinase (HSV-tk) [50]. These encoded proteins can promote the conversion of prodrugs such as 5-fluorocytosine or oriclovir into toxic substances in cancer lesions, significantly enhancing the antitumor activity of adenovirus [51]. Adenovirus can not only kill tumor cells directly, but also produce persistent specific anti-tumor immune memory in the body, which is very important for the long-term prognosis of the body. However, the maintenance of this immune activation depends on the continuous replication of adenovirus [52]. When the tumor cells die, part of the adenovirus in the cell will also die, reducing the total number of viruses and weakening the long-term therapeutic effect. In the past ten years, the research direction of oncolytic adenovirus has evolved from the use of genes to maximize the immediate killing of tumor cells to amplify the immune response induced by viral oncolysis. Inspired by this concept, more oncolytic adenoviral vectors are loaded with immunomodulatory factors, including GM-CSF, CD40 ligands, or interferon-1 (IFN-1) [53].

Measles virus

From the 1970s to the 1980s, clinicians observed a phenomenon: patients suffering from leukemia or lymphoma after infection with measles virus (MV) appeared remission [54], based on this clinical phenomenon, MV has been gradually developed as a cancer immunotherapy. MV is spherical or filamentous, with a diameter of about 120–250 nm. The core is a single negative-stranded RNA, which is not segmented. The full length of the genome is about 16 kb (Fig. 2C). In subsequent research, the effective replication of MV in malignant tumor cells and the lysis and death of

tumor cells mediated by MV have been confirmed in a number of basic studies [55–57]. Oncolytic MV can enter tumor cells through the mediation of cell membrane receptors such as CD46 and CD150 [58]. CD46 expression is expressed in most normal tissue cells, but because normal cells can clear the virus through the IFN anti-virus pathway, the oncolytic attenuated MV is not sufficiently amplified in normal cells to a pathogenic level [59]. Compared with normal tissue cells, most cancer cells typically highly express CD46, resulting in oncolytic MVs preferentially infecting tumor cells and spreading in tumor tissue, especially some malignant tumor cells with defective anti-virus response, such as the lack of type 1 IFN system, which is more conducive to allowing the virus to enter and spread in tumor cells. replication and proliferation [60]. The P, V, and C proteins of pathogenic MVs are the weapons of MV against the host cell IFN system, but these arms have been unloaded in oncolytic MVs, so oncolytic MVs show high sensitivity to the IFN system [61]. The sequences encoding P protein, V protein and C protein are different in different MV strains, so engineering MVs into oncolytic MVs also requires certain precise regulation [62]. However, there is no systematic study of the interaction between these differences and the efficacy of oncolytic MVs.

The oncolytic effect of MV is related to the cytopathic effect. The infected tumor cells fuse into multinucleated syncytia, lose the integrity of the cell membrane, and eventually lead to cell death. MV replication, protein expression, syncytium formation and oncolytic effects have been verified in several human-derived cancer animal models, including circulatory system cancer such as leukemia [63] and myeloma [64], as well as solids tumors such as ovarian carcinoma [65], glioblastoma [66], liver cancer [67], pancreatic cancer [68], breast cancer [69] and gastric cancer [70].

Newcastle disease virus

Newcastle disease virus (NDV) is a paramyxovirus type 1 (APMV-1), which has a negative sense single-stranded RNA genome (Fig. 2D). NDV uses poultry as its host, and has evolved a virus immune escape mechanism in the poultry body, that is, interferes with the host response mediated by IFN-1. Importantly, this viral escape mechanism is not species-specific and works neither in accepted nor non-accepted hosts [71]. Some NDV strains exhibit natural eosinophilia and immunostimulatory properties in non-receptive hosts [72]. According to the pathogenic type and virulence of NDV virus, it can be divided into chronic (low), intermediate (medium) and rapid (high) [73]. The whole genome sizes of NDV are in line with the principle of 6 times that of APMV-1. Genomic RNA contains two extragenic regions, namely a 30 bp leader region and a 50 bp trailing region [74]. These regions are used to control the transcription and replication of the virus, and are also used to embed newly

synthesized RNA into virus particles. NDV has 6 genomes (3'-N-NP-M-F-HN-L-5'), *N* gene encodes nuclear protein, *P* gene encodes phosphoprotein, *M* encodes matrix protein, *F* gene encodes fusion protein, and *HN* gene encodes hemagglutinin-neural enzyme protein, *L* gene encoding and large protein [75]. It can be seen that exogenous genes with anti-tumor function can also be easily inserted into the huge genome of NDV by gene editing technology.

NDV-infected cells first connect the cell-binding domain through the HN molecule. Under the action of α 2,6-sialic acid, HN and NDV bind to the surface of the host cell. After the virus binds to the cell surface, the fusion protein F is activated. The synergistic effect of HN and F causes the virus to fuse with the host cell membrane, allowing the viral genome to enter the cytoplasm of the host cell [76]. NDV can also use clathrin-mediated endocytosis and endocytosis as another way to enter cells [77]. In the cytoplasm, NDV's RNA is transcribed into messenger RNA (mRNA). Compared with mammalian mRNA, viral mRNA is still polyadenylated and carries 50-phosphate (50-PPP). Then the viral mRNA occupies the host cell's translation system and substrate to translate the genome into the corresponding viral protein. The next step is to use the newly generated nucleocapsid as the positive chain "antigenome" [78] for virus replication. The viral nucleocapsid consists of a single viral RNA (about 15,000 nucleotides in length) with NP, P, and L proteins. Binding of viral proteins P and L requires the RNA-dependent RNA polymerase, which is required for viral replication. There are 10^3 – 10^4 viruses that can replicate in each cell. The newly generated viral genome is encapsulated in the plasma membrane, and new viral particles are released through a process of budding from the cell membrane.

The infection of normal cells from non-receptive hosts (such as mice or humans) usually only stops at the step where NDV mRNA is transcribed into protein, and does not enter the subsequent virus replication and proliferation process [79]. NDV infection of tumor cells is related to the cleavage site of F and the second sialic acid binding site of HN. Persistent infection can avoid direct cell lysis and death, and can mediate immunogenic cell death (ICD) of tumor cells and promote the spread of viruses between cells. This is a potential mechanism for evading host antiviral responses [80]. Wild-type and engineered NDVs can be used alone or in combination with clinically routine cancer therapies to treat human cancers [81].

Reovirus

Reovirus (respiratory and enteric orphan virus) is a non-enveloped double-stranded RNA virus with a regular icosahedral structure and a diameter of about 60–80 nm (Fig. 2E), which is widespread in nature. Reovirus is able to block

mutations in Ras (PKR signaling pathway), thereby maintaining its ability to selectively infect tumor cells [82]. More importantly, human normal cells are resistant to reovirus infection and replication, so the biosafety of reovirus has been validated in both preclinical studies and clinical trials [83].

Respiratory syncytial virus

Respiratory syncytial virus (RSV) belongs to the family Paramyxoviridae. The diameter of the virus particle is about 150–250 nm kb (Fig. 2F). RSV can cause lesions in the human respiratory tract, but it has been reported that RSV has oncolytic ability in cancers such as prostate cancer and lung cancer [84, 85], which may be related to the ability of RSV to directly or indirectly promote apoptosis in tumor cells or the obstruction of the IFN system in tumor cells [86], but the specific mechanism remains to be explored.

Preclinical studies of OV

In order to achieve satisfactory results in antitumor therapy, a surging number of novel combination therapy methods have emerged in the preclinical studies of OVs (Table 2). Given that the strong ability of OV to activate host-specific anti-tumor immunity [87], the combination therapy of OVs with immunotherapy, radiotherapy and chemotherapy or other biological materials will be a major direction in the future. (Fig. 3).

Combination therapy of OV therapy and immunotherapy

Tumor cells in the body often exhibit behaviors such as escaping from immune monitoring and losing immune response. Therefore, the higher the degree of malignancy, the faster the spread of cancer, and the worse the prognosis of cancer patients. These biological phenomena of tumor cells are related to the immune examination mechanism in the host, namely, programmed cell death ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) is closely related to the up-regulation of cytotoxic T lymphocyte associated protein 4 (CTLA-4) [100]. More importantly, the up-regulation of CLTA-4 and PD-1 was detected in tumor treatment after administration [101]. Therefore, the combination of viral therapy and immune checkpoint inhibitors (ICIs) will be a promising cancer treatment strategy. Despite the undisputed success of ICIs, there are still relatively few cancer patients who can benefit from a single ICI therapy. OVs can promote the anti-tumor immune response by inducing tumor cell immunogenic cell death [102]. During the oncolytic process of the virus on tumor cells, it releases

Table 2 Preclinical research on oncolytic virus combined with immunotherapy, chemotherapy, radiotherapy or bionanomaterials therapy in recent years

Oncolytic Virus	Combination therapy	Cancers	Treatment results	References
Zika virus	Anti PD-L1	Glioblastoma	A strong inflammatory response was induced in a mouse glioma model, increased infiltration of CD4 ⁺ T cells and CD8 ⁺ T cells in the tumor site, and restored glioma sensitivity to anti-PD-L1 therapy	Lishu Chen et al. [88]
Vesicular stomatitis virus	Anti PD-1 NK cells	Pancreatic cancer	The addition of anti-PD-1 to the combined regimen of oncolytic virus and NK cells can maintain the activation state of immune cells in mice and the effector function of immune organs, and the cured mice are re-bearing with tumors, showing increased tumor growth volume. decreasing trend	Adam Nelson et al. [89]
Adenovirus	Anti PD-1 Anti CLTA-4	Triple-negative breast cancer	Significantly inhibited tumor growth in mice, prolonged mouse survival, massive recruitment of CD8 ⁺ T cells and memory T cells in the tumor microenvironment, decreased numbers of Treg and tumor-associated macrophages, and promoted the transition of macrophages from the M2 phenotype Polarization towards the M1 phenotype	Huan Zhang et al. [90]
Adenovirus	DOX	Liver cancer	DOX promotes the gene expression of oncolytic adenovirus and the replication of viral progeny by activating the phosphorylation of Smad3, and enhances the antitumor effect of oncolytic adenovirus by promoting apoptosis and pyroptosis	Boduan Xiao, et al. [91]
Measles virus	Anti PD-1 Ruxolitinib	Glioblastoma	The combination regimen promoted a systemic anti-tumor immune response in mice, decreased PD-L1 expression on myeloid suppressor cells, inhibited tumor growth in the mouse brain, and reversed glioblastoma resistance to ICB	Eleni Panagioti et al. [92]

Table 2 (continued)

Oncolytic Virus	Combination therapy	Cancers	Treatment results	References
Vaccinia virus	Anti PD-1 Anti CLTA-4	Melanoma Colon carcinoma Lung carcinoma	The infiltration of CD4 ⁺ T cells, CD8 ⁺ T cells, and NK cells was significantly increased at tumor area in mice, and four of the seven mice achieved complete tumor regression	Shinsuke Nakao et al. [93]
Caprine herpesvirus (CpHV-1)	Cisplatin	Malignant mesothelioma (MM)	CpHV-1 can reduce cell viability and clonogenic potential in MM cell lines without affecting non-tumor cells, and has a strong synergistic effect with the chemotherapeutic drug cisplatin to kill tumor cells	Iris Maria Forte et al. [94]
Vaccinia virus	Cyclophosphamide	Lung adenocarcinoma	The combination of oncolytic vaccinia virus and cyclophosphamide effectively infects human lung adenocarcinoma cells in vitro, where it replicates continuously, resulting in the lysis of tumor cells; tumor growth rate in tumor-bearing mice is significantly inhibited, pro-inflammatory cytokines and The secretion of chemokines was significantly increased, showing the characteristics of synergistic tumor killing	Elisabeth Hofmann et al. [95]
Adenovirus	Radiotherapy	Osteosarcoma	Radiation therapy can increase the replication of recombinant oncolytic adenovirus in human osteosarcoma cell lines U2OS and Saos2 and lyse tumor cells	Elora Hossain et al. [96]
Adenovirus	Radiotherapy	Cervical cancer	Oncolytic adenovirus can effectively produce radiosensitization effect, and the combination of the two has obvious synergistic antitumor effect on cervical cancer cells	Yixin Duan et al. [97]

Table 2 (continued)

Oncolytic Virus	Combination therapy	Cancers	Treatment results	References
Herpes simplex virus	Nanomaterials	Breast cancer	Co-assembly of the oncolytic herpes simplex virus HSV1716 with biocompatible magnetic nanoparticles from magnetotactic bacteria can target tumors from the circulation through magnetic guidance, protect the virus from host neutralizing antibodies, and enhance intratumoral Viral replication, which also enhances intratumoral recruitment of activated immune cells, promotes antitumor immunity and immune cell death, induces tumor shrinkage and improves survival in syngeneic mouse models of breast cancer	Faith H N Howard et al. [98]
Measles virus	Nanomaterials	Breast cancer	The natural compound ursolic acid nanoparticles were used as oncolytic sensitizers to enhance the oncolytic activity of measles virus on breast cancer cells by inducing apoptosis, and synergistically trigger apoptosis to kill various breast cancer cell lines	Ching-Hsuan Liu et al. [99]

tumor-associated antigens (TAAs) and produces inflammatory cytokines [103]. The result is that OV_s can transform the immunosuppressive “cold” tumor microenvironment into a “hot” immune stimulation environment. ICIs inhibit the relevant pathways of negative immune regulation, allowing CD4⁺ and CD8⁺ effector T cells to regain their immune function in the tumor microenvironment, while OV_s release TAA by causing tumor cell immunogenic death to stimulate the tree in the tumor microenvironment dendritic cells (DCs) enhance their antigen presentation function and stimulate the maturation of primitive T cells [104]. Based on the immune properties of the above-mentioned OV_s in the tumor microenvironment, anti-PD-L1/PD-1 antibody, anti-CTLA-4 antibody and other ICIs are used in combination with OV_s to achieve the anti-tumor immunity. The synergistic effect of two-pronged approach to kill tumor cells. Yuan et al. developed a recombinant oncolytic adenovirus that could open the blood–brain barrier. In a glioblastoma model, the combination with PD-L1 antibody was found to synergistically improve oncolysis and induce tumor cell pyroptosis [105]. In addition, some small-molecule immune adjuvants such

as Toll-like receptors and Chimeric antigen receptor T-cells (CAR-T) can also be combined with OV_s, which are safe and effective [106]. Therefore, OV_s and ICIs are complementary and can cascade to amplify specific anti-tumor immune effects and achieve better anti-tumor effects.

Combination therapy of OV_s, radiotherapy and chemotherapy

Radiotherapy and chemotherapy are still the conventional methods for the treatment of tumors in the world. Some advanced malignant tumors with poor surgical treatment, or some tumors that are sensitive to radiotherapy and chemotherapy are often treated with these methods. The anti-tumor mechanism of conventional chemotherapeutic drugs is to achieve anti-tumor effect by inhibiting DNA synthesis in the cell cycle of tumor cells [107]. Radiotherapy is to fight cancer through direct and irreparable damage to DNA by double-strand breaks. Therefore, a single chemotherapy or radiotherapy often brings certain adverse reactions to the patient, which affects the therapeutic effect and prognosis of

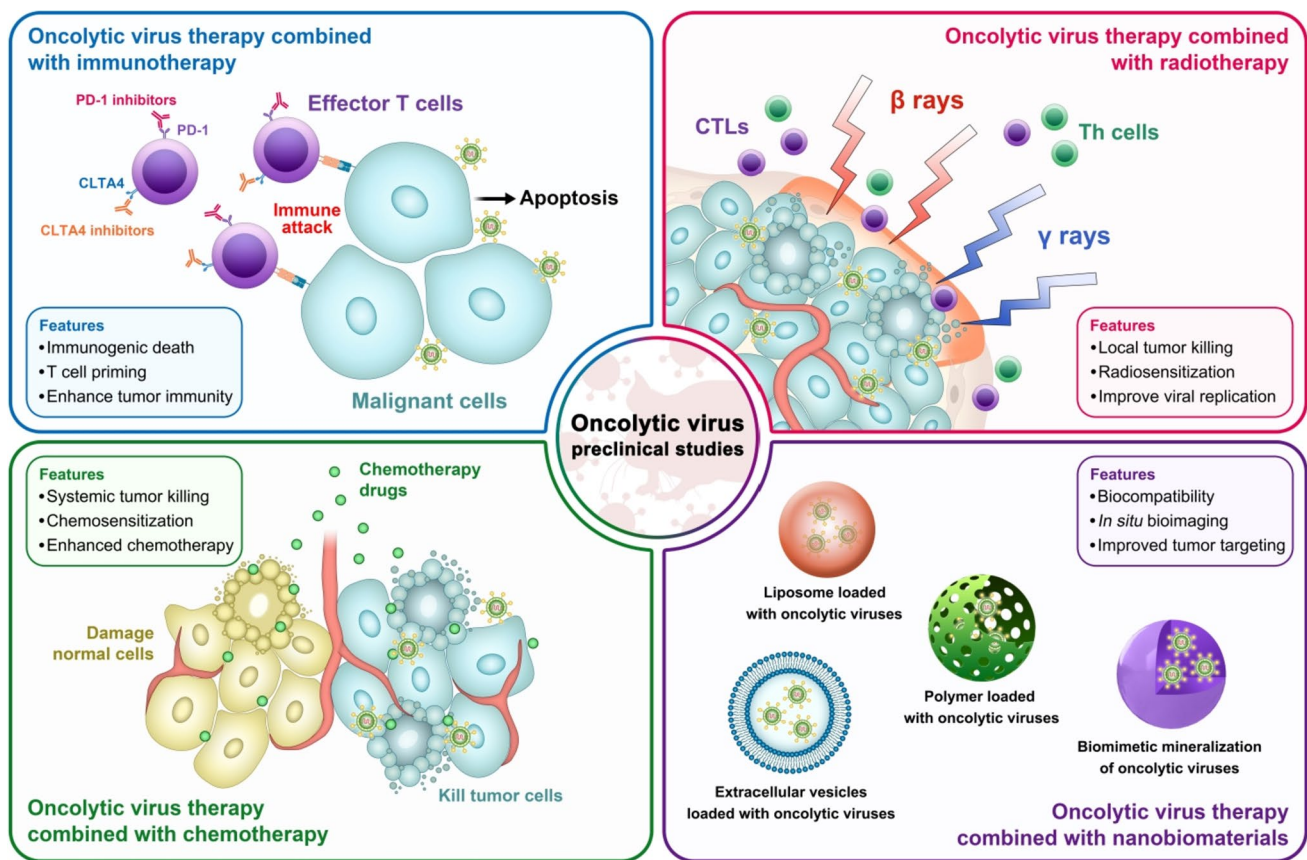


Fig. 3 Preclinical characteristics of oncolytic virus combination therapy. Combined immunotherapy (top left); combined with radiotherapy (top right); combined with chemotherapy (bottom left); combined with nanobiomaterial therapy (bottom right)

the tumor. The OV is suitable for tumors of various stages, and its administration methods are diverse and suitable for combined administration. Nowadays, many research results have confirmed that the combined application of chemotherapeutic drugs and OVs can exert better anti-tumor effects in some human-derived xenogeneic living tumor models. This synergy has two advantages: first, it can reduce possible adverse reactions without affecting the overall efficacy of OVs; second, it can reduce the amount of OVs used under the same time and space conditions. This reduces the adverse reactions that the drug may bring to the body, and at the same time reduces the possibility of tumor cells developing drug resistance [108–110]. Cyclophosphamide, which is used to treat leukemia and some solid tumors, is the first chemotherapeutic drug used in combination with OVs [111]. With the development of more targeted drugs, the use of new, less toxic drugs in combination with OVs to treat tumors has better prospects for clinical applications. Song et al. constructed a recombinant oncolytic adenovirus Ad-VT, and inserted an exogenous gene encoding Apoptin into the downstream of the E1a gene to promote tumor cell apoptosis. At the same time, the combination of Ad-VT and paclitaxel showed that the tumor growth could

be significantly inhibited in the nude mouse model of drug-resistant xenografts, which provided a new idea for solving the clinical dilemma of paclitaxel resistance [112]. Mistarz et al. demonstrated that the combination of oncolytic vaccinia virus and doxorubicin (DOX) synergistically induces immunogenic cell death in chemotherapy-resistant ovarian cancer cells and prolongs survival in a xenograft animal model [113]. In addition to chemotherapy, radiotherapy is also a classic treatment for tumors. During radiotherapy, some signal pathways of the tumor will be activated, and some related genes can be down-regulated or up-regulated so that the OV can replicate and proliferate in tumor cells. Chen et al. investigated the synergistic antitumor effect of radiation therapy and oncolytic vaccinia virus on the basis of a mouse tumor model, in tumor-bearing mice receiving high-dose hypofractionated stereotaxic body radiotherapy (SBRT) and oncolytic vaccinia virus. After treatment, the infiltrating numbers of CD4⁺ and CD8⁺ cells in the tumor area were increased, while the infiltration of Treg cells was decreased, and the ratio of M1/M2 macrophages was increased [114]. The combined application of OV, radiotherapy and chemotherapy has demonstrated good efficacy and has been confirmed by many pre-clinical studies, and

it is safer and more effective than single medication. However, according to the tumor type, size, stage, and the overall physiological condition of the host, as well as the different types of OV and chemotherapeutic drugs, the synergistic anti-tumor effect and specific molecular mechanisms of this combined application need to be further studied.

Combination therapy of OV and nanomaterials

In recent years, with the rapid development of the field of nanotechnology, the application of bio-nanomaterials in tumor therapy is receiving extensive attention [115]. They have good drug-carrying capacity. bio-imaging, activation of tumor immunity and other functions are integrated, and after a certain modification, it can be specifically targeted to tumor cells. Whether in tumor diagnosis or treatment, it shows high potential application prospects. Therefore, biological materials can be used to load OVs to achieve the purpose of blocking virus immunogenicity and achieving tumor targeted delivery. Currently used for loading OVs are mainly liposomes, cells or exosomes [116, 117], and some non-biological material carriers such as high-molecular polymers [118].

Clinical application of OV

There are many kinds of OVs that have been clinically tested. Compared with traditional surgical treatment, radiotherapy, chemotherapy and other conventional methods of treating tumors, these OVs show a certain degree of novelty and synergistically enhance the effect of curative effect (Table 3). The following summarizes the latest clinical applications of several popular OVs.

HSV

T-Vec, an oncolytic HSV, is currently marketed for the treatment of melanoma that cannot be treated by surgical therapy [119]. A phase II clinical trial (NCT02211131) used T-Vec as an adjuvant drug after melanoma surgery 150 postoperative patients with stage IIIB-IVM1a melanoma were equally divided into two groups (with or without T-Vec postoperatively) for postoperative risk assessment of melanoma recurrence. After three years of observation, 17.1% of patients who underwent T-VEC therapy after surgery achieved pathological complete remission (pCR) and increased CD8⁺ in tumor lesions. Compared with the surgery alone group, postoperative adjuvant use overall melanoma recurrence was reduced by 25% in the T-Vec arm [120]. HSV1716 demonstrated well-tolerated and antitumor properties in an OV clinical trial in malignant pleural mesothelioma (NCT01721018).

Replication and presence of HSV were consistently detected in tumor lesions in 7 of 12 patients. And half of the patients reported stable disease (SD) at week eight [121].

Adenovirus

In 2017, Northwestern University Feinberg School of Medicine developed an engineered oncolytic adenovirus called NSC-CRAAd-S-pk7, and its safety was confirmed in a 3-year phase 1 clinical trial (NCT03072134), at the maximum dose in the trial (1.875×10^{11} viral particles), the patients had no obvious adverse reactions, and showed a certain anti-tumor effect, 1 of the 12 patients had partial remission (PR), and 10 had SD. Immunological examination confirmed the increase of peripheral blood circulating immune cells and the increase of CD8⁺:CD4⁺ ratio of tumor lesions in the brain [122]. In addition to oncolytic therapy alone, oncolytic adenovirus can be used in combination with radiation therapy to enhance antitumor efficacy [123, 124]. In a phase 1 clinical trial investigating the relationship between oncolytic adenovirus and radiosensitization (NCT03213054), 13 patients with esophageal cancer who were ineligible for surgery and chemotherapy were recruited after 3 intravenous injections of OV (NCT03213054). Eight patients had local complete remission (CR) after six weeks of conventional radiotherapy on day 1, day 18, and day 32) and a total of 60 Gy, and none of the tumor biopsy specimens showed viable pathology. There were three cases of partial remission. Immunohistochemical examination of tumor tissues from all patients revealed increased PD-L1 expression and massive infiltration of CD8⁺ cells [125]. Astoundingly, the National Institutes of Health Clinical Center proposed the mixed use of oncolytic adenoviruses to enhance tumor targeting. They developed three oncolytic adenoviruses expressing prostate-specific antigen (PSA), Mucin-1 (MUC-1) and brachyury, respectively. The C-terminus of brachyury and MUC-1 are overexpressed in metastatic castration-resistant prostate cancer (mCRPC) and have been shown to be important in response to chemotherapy, epithelial-mesenchymal transition, and metastasis. play an important role in resistance [126]. Enrolled patients in this phase 1 clinical trial (NCT03481816) received concurrent subcutaneous injections of all three oncolytic adenoviruses (subcutaneously every 3 weeks, 5×10^{11} viral particles per dose, up to 3 doses, followed by every 8 weeks) Booster vaccine for 1 year), one patient had a partial response, five patients had stable disease for more than 6 months, median progression-free survival was 22 weeks, and pluripotent T cells were also detected in most patients after vaccination No dose toxicity was seen in response to these three tumor-associated antigens [127].

Table 3 Recent ongoing oncolytic virus clinical trials

Name	Type of virus	Diseases	Therapeutic properties	Stage and status	Identifier	Expected expire date
OVV-01	Vesicular Stomatitis Virus	Advanced solid tumors	Combined PD-1/PD-L1 immune checkpoint inhibitors in the treatment of patients with advanced solid tumors	Phase 1, recruiting	NCT04787003	February 28, 2024
ASP9801	Vaccinia virus	Metastatic cancer Solid tumors Advanced cancer	Encoding IL-7 and IL-12, enhance the anti-tumor efficacy of oncolytic viruses, and improve the immune status of the tumor microenvironment	Phase 1, recruiting	NCT03954067	October 31, 2024
MEDI9253	Newcastle Disease Virus	Advanced/Metastatic solid tumors	Combined use of recombinant Newcastle disease oncolytic virus encoding IL-12 and Durvalumab to synergistically enhance anti-tumor efficacy	Phase 1, recruiting	NCT04613492	November 7, 2025
OH2	Herpes simplex virus	Pancreatic Cancer	Insert the human <i>GM-CSF</i> gene in the transcriptome, express and deliver <i>GM-CSF</i> in the tumor microenvironment, and induce more effective anti-tumor immune response	Phase 2, recruiting	NCT04637698	November 30, 2022
LOAd703	Adenovirus	Pancreatic Cancer	Encoding TMZ-CD40L and 4-1BBL, induce anti-tumor cytotoxic T cell immune response, reduce the infiltration of suppressive immune cells such as bone marrow-derived suppressor cells (MDSC), and induce tumor regression	Phase 2, recruiting	NCT02705196	December 2021
RGV004	Vaccinia virus	B-cell Lymphoma	Encoding CD3/CD19 bispecific antibody to more accurately target B cell malignant tumors	Phase 1, not yet recruiting	NCT04887025	March 15, 2025
TILT-123	Adenovirus	Solid Tumor	The oncolytic adenovirus expressing TNF- α and interleukin-2 (IL-2) can kill tumor cells while activating T cells and induce specific tumor T cell immune responses	Phase 1, recruiting	NCT04695327	March 31, 2025
NG-641	Adenovirus	Metastatic Cancer Epithelial Tumor	The oncolytic adenovirus expresses fibroblast activation protein (FAP) antibodies and immune enhancing molecules, which can target cancer-related fibroblasts and regulate tumor immunity	Phase 1, recruiting	NCT04053283	December 31, 2022

Table 3 (continued)

Name	Type of virus	Diseases	Therapeutic properties	Stage and status	Identifier	Expected expire date
NG-350A	Adenovirus	Metastatic Cancer Epithelial Tumor	The oncolytic adenovirus expresses agonistic CD40 antibody, which can replace the role of CD4 + T cells to a certain extent, and reverse the tumor microenvironment from immune-suppressive to immune-supportive	Phase 1, recruiting	NCT03852511	December 2021
MV-s-NAP	Measles Virus	Breast Carcinoma	This oncolytic measles virus expresses <i>Helicobacter pylori</i> neutrophil activating protein, activates tumor inflammation, and produces reactive oxygen species to kill tumors	Phase 1, recruiting	NCT04521764	August 10, 2023
VSV-hlFNbeta-NIS	Vesicular Stomatitis Virus	Endometrial carcinoma Endometrial adenocarcinoma	The oncolytic virus expresses interferon β , which can prevent cells from producing growth factors that promote tumor angiogenesis and inhibit tumor angiogenesis	Phase 1, recruiting	NCT03120624	July 15, 2023

Measles virus

In addition to solid tumors, OV_s can also be used in the treatment of circulatory malignancies [128, 129]. MV-NIS is a recombinant oncolytic measles virus that encodes a sodium iodide homologue and mediated entry into tumor cells through the CD46 receptor in vivo [130]. It has been reported that myeloma plasma cells typically overexpress CD46 [131] and are sensitive to MV-NIS. Inspired by this, Stephen et al. conducted a phase 1 clinical trial (NCT00450814) in multiple myeloma. After MV-NIS treatment, the proportion of CD3⁺ and CD8⁺ T cells in the peripheral blood of the patients was significantly increased. There was also a certain increase in central memory T cells and effector memory T cells, suggesting that MV-NIS specifically captured hematological tumors and caused a systemic anti-tumor immune response, which improved the long-term prognosis of multiple myeloma [132].

Newcastle disease virus

Compared with other OV_s, there are relatively few clinical trials related to NDV. The oncolytic effect of wild-type NDV was reported as early as in a phase 1 clinical trial in 2002 [133]. With the maturity of gene editing technology and the development of the genetic engineering technology industry, people are also constantly developing the clinical translation application value of oncolytic NDV [134–136]. The German Cancer Center infected autologous tumor cells with NDV, and then administered an irradiation dose of 200 Gy to prepare an NDV anti-cancer vaccine, which was then combined with a bispecific anti-CD28 fusion protein to conduct phase 1 clinical trial on 14 advanced colorectal cancer patients' clinical trials. Of these, tumor-reactive T cells were detected in all patients during treatment, suggesting the ability to reactivate nonviable T cells in advanced cancer [137]. Surprisingly, the combination of NDV and different therapies showed amazing therapeutic effects. In two case reports, researchers administered NDV, local hyperthermia, NDV, and DC vaccines to a prostate cancer patient and a breast cancer patient who had failed standard therapy. Combination therapy, after continuous follow-up confirmed that the patient achieved long-term complete remission [138, 139].

Reovirus

Pelareorep (Reolysin) is an oncolytic viral biological product that shows overall survival benefit by intravenous injection. It is a non-genetically modified non-pathogenic reovirus that overcomes the effect of neutralizing antibodies and activates the body's own immune system by activating the body's own immune system. It can selectively infect and destroy tumor cells and is used to treat a variety of solid

tumors and hematological malignancies. In a phase I trial of Pelareorep, a median tissue culture infective dose (TCID₅₀) of 1×10^8 to 3×10^{10} was divided into 6 graded doses of intravenous Pelareorep administered 4 weeks apart. No dose limited toxicity (DLT) was observed in all evaluable patients with advanced solid tumors, and treatment outcomes in 15 patients showed 1 PR and 7 SD [140]. Besides, in a clinical trial of children with extracranial solid tumors with a median age of 12.5 years (3.0–20.2 years), the safety of intravenous Reolysin at a dose of 5×10^8 TCID₅₀/kg (once daily for 5 days) was also demonstrated [141].

Respiratory syncytial virus

In recent years, RSV has made some progress in preclinical studies of human hepatocellular carcinoma [142] and human skin cancer [143], but there is no clinical trial results of RSV in oncolysis research. Astonishingly, a case report found that COVID-19, the respiratory virus ravaging the world, alleviated the progression of Hodgkin's lymphoma unexpectedly, shedding a new perspective on the development of respiratory virus oncolytic engineering [144].

Outlook

Oncolytic viruses have shown broad application prospects in pre-clinical research and clinical trials. At present, patients with relapsed or refractory advanced tumors are the main participants in clinical trials of OV therapy, and almost all viral therapies are performed on patients with advanced solid tumors. In order to enhance the anti-tumor effect, a growing number of natural viruses have been developed and modified to improve the infectivity or immune activity of the virus to tumor cells. In addition, new strategies for combination therapy are constantly increasing to improve the effectiveness of cancer treatment. Although the use of most viruses and combination therapies are adopted, there are still some improvements in clinical trials of virus treatments. For example, the OV itself has strong immunogenicity, and most of them will be cleared after entering the host body, leading to aggregation. The total amount of OV at the tumor site is reduced, which affects the efficacy of OV. In order to further improve the therapeutic effect of OVs and further extend the survival period of patients, it is necessary to develop more safe vectors to reduce the killing of the virus by the host's immune system. In addition, more clinical trials are needed to ensure the biological safety of OVs.

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Declarations

Conflict of interest The authors report no conflicts of interest.

Ethical statement This manuscript does not contain any original experimental data and patient data, and the preclinical studies and clinical trials cited are published results.

Informed consent statement This review did not contain any privacy of patients or original unpublished experimental data, we just discussed some clinical trials results that have been published and did not conduct any clinical trials. Furthermore, in this review, it can be found in the cited clinical trials articles that all patients have signed informed consent and agreed to participate in the clinical trial. Relevant statements can be found in the Ethical statement.

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