Journal of Clinical Pharmacy and Therapeutics / Volume 2025, Issue 1 / 6036890

Review Article | Open Access

Oncolytic Viruses Reshape PD-1/PD-L1 Signaling: Mechanisms and Clinical Synergy With Immune Checkpoint Blockade

Seyedeh Nasim Mirbahari, Mehdi Bakhtiyaridovvombaygi, Hamid Mahdizadeh, Amirhossein Izadpanah, Elham Roshandel, Mehdi Totonchi

First published: 31 July 2025
https://doi.org/10.1155/jcpt/6036890

Academic Editor: Hongda Liu

Abstract

Oncolytic viruses (OVs) are naturally occurring or genetically engineered viruses that selectively target and destroy cancer cells. They act through multiple mechanisms, including direct tumor cell lysis, stimulation of immune-mediated cytotoxicity, and modulation of the tumor microenvironment (TME). Recent studies have shown that, beyond their direct oncolytic activity, OVs also influence the immune landscape by modulating the expression of PD-1/PD-L1 axis. In many cases, OVs trigger the release of proinflammatory cytokines, leading to increased PD-L1 levels on immune cells. This upregulation plays a key role in modulating the TME and shaping immune checkpoint signaling. While there is also evidence that OVs can directly reduce PD-L1 expression on tumor cells, the most prominent effect appears to be the boost in PD-L1 expression. This shift is

thought to be crucial in influencing how the immune system responds to tumors. These changes could modulate PD-L1-mediated immune suppression and alter the exhaustion and anergy rate of the effector tumor-specific T cells infiltrated into th TME. This review discusses how OVs influence PD-1 and PD-L1 ex on innate and adaptive immune activation, inte pathways, and engineered OVs designed to exp immunomodulatory cytokines and chemokines these mechanisms can be leveraged to enhanc particularly in combination with ICIs. Furthermo potential of OVs to remodel the TME, modulate and promote immune-mediated tumor clearan highlights the evolving role of OVs in cancer the potential to augment the effectiveness of curre strategies.

1. Introduction

Oncolytic viruses (OVs) are viruses that occur natu to selectively infect and replicate within cancer cell destruction through cell lysis [1]. OVs eliminate tur direct cytolysis but also by activating antitumor im modulating the tumor microenvironment (TME) [2, evidence indicates that OVs also modulate immun molecules such as PD-1 and its ligand PD-L1, there [4]. The PD-1/PD-L1 pathway is one of the central i allowing immune tolerance against cancer cells. PD receptors on T cells, delivering inhibitory signals th cytotoxic activity against tumor cells [5]. OVs may i pathway through various mechanisms. Some stimu proinflammatory cytokines, leading to increased PI

immune cells. Conversely, certain OVs have been found to directly reduce PD-L1 levels on tumor cells. Additionally, all OVs have the potential to enhance T-cell infiltration, particularly cytotoxic T lymphocytes (CTLs), within tumors, thereby counteracting immune suppression driven by PD-L1 expression [6, 7]. The immunomodulatory effects of OVs on the PD-1/PD-L1 axis depend on viral tropism, dosage, and tumor-specific factors [8]. This review investigates the emerging role of OVs in cancer therapy, with a focus on their ability to modulate the PD-1/PD-L1 immune checkpoint pathway a key regulator of antitumor immune evasion. We analyze the mechanisms through which OVs alter PD-1 and PD-L1 expression to potentiate immune-mediated tumor clearance, while also exploring synergistic strategies to amplify therapeutic efficacy. The discussion further encompasses the crosstalk between innate and adaptive immune activation triggered by OVs, the role of interferon signaling pathways in shaping antitumor responses, and innovative approaches to engineer OVs for targeted delivery of immunostimulatory cytokines and chemokines. By synthesizing current preclinical and clinical evidence, this review underscores the transformative potential of combining OVs with immune checkpoint inhibitors (ICIs), offering a roadmap to enhance durable responses and overcome resistance in cancer immunotherapy.

2. OVs and Their Mechanism of Action

OVs offer a novel therapeutic strategy for cancer by leveraging viral replication to selectively target and kill malignant cells [9]. They exploit the defective antiviral pathways in tumor cells to replicate, thereby inducing cell lysis, while sparing normal tissues with intact immune surveillance. This approach addresses several limitations of conventional therapies, particularly in targeting immunologically ‘cold’ tumors and inducing systemic antitumor immunity [10] (Figure 1). Commonly utilized viral platforms include adenovirus, herpes simplex virus (HSV), vaccinia

virus, poliovirus, reovirus, vesicular stomatitis virus (VSV), and measles virus (MV), among others [11, 12]. The mechanisms by which OVs exert antitumor effects are multifaceted and context-dependent. These include exploiting defective interferon signaling in tumor cells, inducing immunogenic cell death (ICD), and activating both innate and adaptive immune responses against tumor-associated antigens (TAAs). Numerous preclinical studies have demonstrated the efficacy of OVs in various animal models and cancer types [13]. They have demonstrated that OVs not only reduce tumor burden but also enhance antigen presentation, increase T-cell infiltration, and improve responsiveness to chemotherapy and immune checkpoint blockade [14, 15]. Classifying OVs based on viral origin, genetic modification, and replication strategy helps elucidate their design principles and therapeutic potential. Classification systems consider factors such as viral genus, replication dependency, tumor selectivity, and immunomodulatory capabilities [16]. Each viral platform offers distinct advantages based on its replication kinetics, tropism, and ability to evade or engage the host immune system. Genetic modifications are incorporated into OVs to enhance their tumor specificity, enhance anticancer efficacy, or improve safety profiles [17]. Genetic modifications include deleting or introducing specific viral genes, incorporating tumor-specific promoters, or enabling the expression of immunostimulatory cytokines within the viral genome [18]. Importantly, OVs can modulate the TME, including immune checkpoint pathways like PD-1/PD-L1, thereby enhancing the efficacy of antitumor immune responses. Such immune modulation underscores the multifunctional potential of OVs and supports their integration with current immunotherapy strategies.

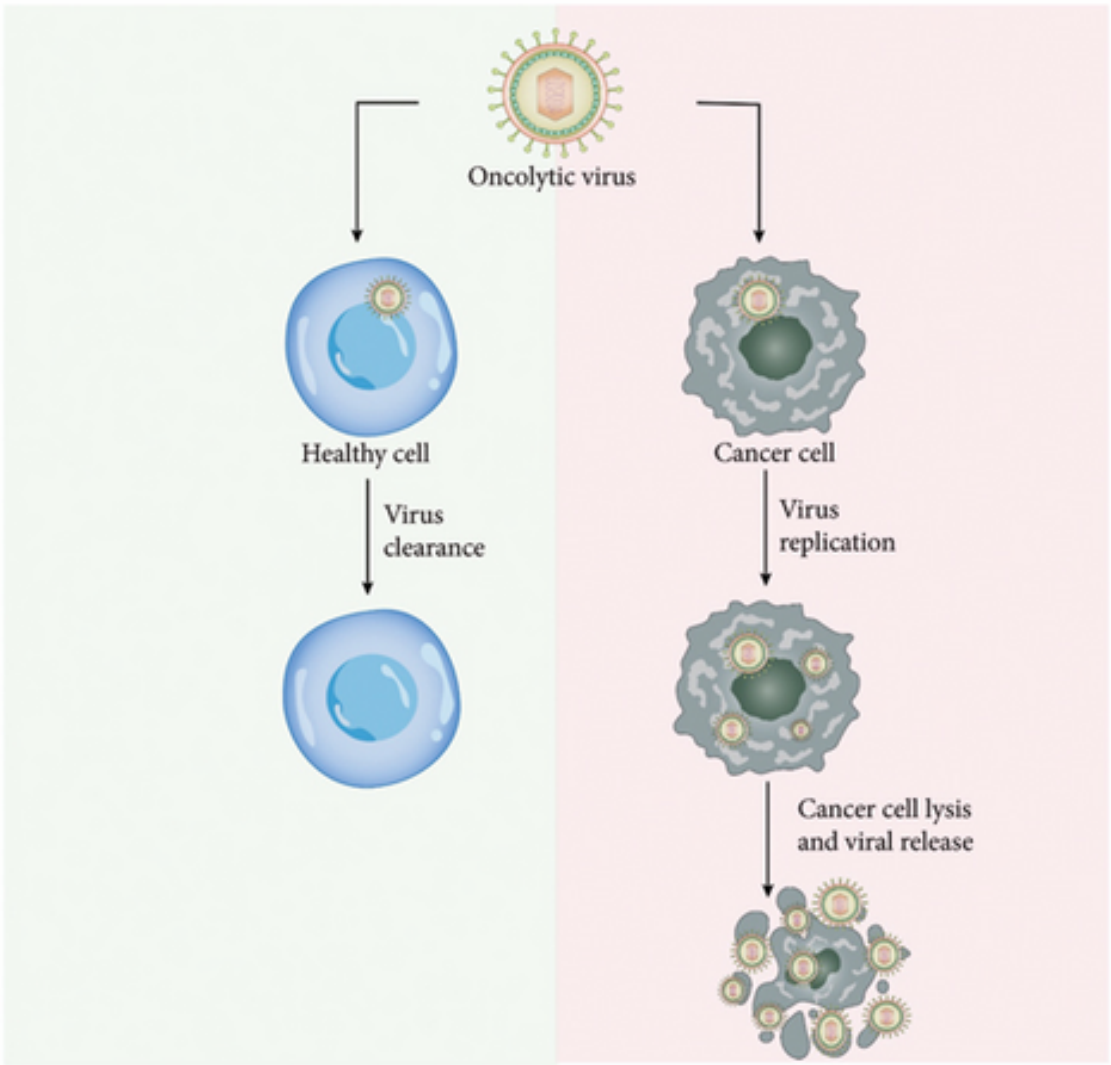

Figure 1

Open in figure viewer | PowerPoint

Oncolytic virus selectivity. This image depicts the selective nature of OVs. While healthy cells are able to clear the virus, cancer cells provide a favorable environment for viral replication. This leads to the lysis of cancer cells and the release of new virus particles, which can then infect and kill more tumor cells, ultimately contributing to tumor regression.

3. The Discovery and Mechanisms of the

PD-1/PD-L1 Pathway in Immune Regulation

PD-1, discovered by Honjo et al., was initially believed to be involved in programmed cell death [19]. Later studies clarified that PD-1 plays a pivotal role in maintaining immune homeostasis by negatively regulating T-cell activity. PD-L1, identified in 1999 as a primary ligand for PD-1, was shown to inhibit T-cell activation [20]. The PD-1/PD-L1 axis suppresses effector T-cell function, contributing to immune tolerance and preventing autoimmune pathology. Mice lacking PD-1 or PD-L1 exhibit autoimmune phenotypes, underscoring the importance of this pathway in immune regulation [21]. A second PD-1 ligand, PD-L2, was identified in 2001 and shown to inhibit T-cell responses through similar mechanisms [22]. Under physiological conditions, PD-L1 and PD-L2 are expressed by multiple cell types, including macrophages, epithelial, and endothelial cells. Their expression contributes to peripheral tolerance by dampening excessive or self-reactive immune responses. PD-L2 also binds repulsive guidance molecule 2 (RGM-2, a molecule abundant in pulmonary macrophages), playing a role in maintaining respiratory immune tolerance [23]. PD-L1 and PD-L2 have also been shown to bind B7-1 (CD80), a costimulatory molecule classically associated with CD28 and CTLA-4 signaling. This interaction adds another layer of complexity to T-cell regulation. The binding of PD-L1/PD-L2 to B7-1 transmits inhibitory signals that suppress T-cell activation, reinforcing peripheral tolerance [24]. This was a surprising discovery, given that B7-1 was previously considered exclusive to CD28 and CTLA-4 pathways. The PD-1/PD-L1 axis exerts its immunosuppressive effects through a well-defined signaling pathway. Upon PD-1 engagement with PD-L1, the Src homology 2-containing protein tyrosine phosphatase 2 (SHP-2) is recruited, leading to the dephosphorylation of key signaling molecules in the T-cell receptor (TCR) pathway, including ZAP-70, PI3K, and phospholipase C-gamma-2 [25]. This signaling cascade dampens T-cell activation and

cytokine production, ultimately limiting immune-mediated tissue damage and preventing autoimmunity (Figure 2).

Figure 2

Open in figure viewer | PowerPoint

T-cell signaling in tumor immunity. This figure depicts the intricate signaling networks that govern T-cell activation and suppression within the tumor immune environment. T cells are essential for identifying and targeting cancer cells, but tumor cells can evade immune detection by expressing inhibitory molecules such as PD-L1 and PD-L2. These molecules bind to PD-1 receptors on T cells, leading to their inhibition. At the same time, activation signals from the TCR and costimulatory molecules like CD28 enhance T-cell activation and effector functions. The outcome of tumor immunity is determined by the balance between these activating and inhibitory signals, which influences the ability of T cells to eliminate tumor cells.

3.1. Integrated Structural and Functional Roles of PD-1, PD-L1, and PD-L2 in Immune Regulation and Cancer Immune Evasion

PD-1 is a type I transmembrane glycoprotein composed of 288 amino acids, consisting of an extracellular immunoglobulin V-like (IgV) domain, a transmembrane region, and a cytoplasmic tail. The IgV domain facilitates the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [25]. The transmembrane domain anchors PD-1 in the plasma membrane, whereas the cytoplasmic tail contains two conserved motifs: an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). This motif plays a vital role in recruiting inhibitory proteins that mediate PD-1's suppressive effects on T-cell activation [26]. PD-1 is expressed on

multiple immune cell subsets, including activated T cells, B cells, and natural killer (NK) cells. Its primary function is to attenuate T-cell activation and effector function, thereby preventing immune-mediated tissue damage and autoimmunity. However, tumors frequently hijack this regulatory pathway to escape immune surveillance [27]. PD-1 expression is tightly regulated and is upregulated upon TCR engagement and activation. The *Pdcd1* gene encodes PD-1, and its transcription is driven by multiple transcription factors, including NFATc1 and AP-1, which are activated through TCR signaling [28]. Upon binding to its ligands, PD-1 initiates a signaling cascade that leads to functional changes in T cells, including anergy and apoptosis. This process involves the recruitment of SHP-1 and SHP-2 phosphatases to the ITSM motif, leading to downstream inhibition of TCR signaling. These phosphatases dephosphorylate key signaling molecules in the TCR pathway, including ZAP-70, PI3K, and AKT, effectively halting T-cell activation, proliferation, and effector functions [29]. While this regulatory mechanism is essential for immune homeostasis, its dysregulation in cancer contributes to immune evasion and tumor progression. In addition to its role in T-cell regulation, PD-1 blockade has been shown to enhance the activity of NK cells and promote antibody production by activating PD-1+ B cells. This highlights the broader impact of PD-1 signaling across the immune system. PD-1 expression is also modulated by cytokine signaling, particularly in the inflammatory milieu. For instance, proinflammatory cytokines such as IFN-γ, IL-2, and IL-12 have been shown to upregulate PD-1 expression on T cells, creating a feedback loop that fine-tunes immune activation and prevents excessive inflammation [30]. The PD-1 signaling pathway plays a pivotal role in regulating immune responses, primarily through T-cell anergy and apoptosis induction. Its interaction with PD-L1 and PD-L2, coupled with the influence of cytokines and transcription factors, underscores its importance in both immune homeostasis and cancer immunotherapy. Building upon the pivotal role of PD-1, a deeper understanding of its ligands, PD-L1 and PD-L2, further

elucidates the mechanisms underlying immune suppression and tumor immune evasion. PD-L1 and PD-L2 are type I transmembrane glycoproteins that function as key immune checkpoint ligands by interacting with PD-1 to negatively regulate T-cell activation. While PD-L1 and PD-L2 share similar inhibitory functions, they differ significantly in sequence homology and tissue distribution [31]. PD-L1 exerts immunosuppressive effects through multiple mechanisms. It contributes to T-cell apoptosis, induces the production of immunoregulatory cytokines such as IL-10, impairs effector T-cell function, and interacts directly with CD80, thereby dampening immune responses. These regulatory functions have been demonstrated in both murine and human immune systems [32]. PD-L1 is expressed on a broad range of cells, including tumor cells and various immune cell subsets, whereas PD-L2 expression is largely restricted to professional antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages [33]. The expression of PD-L1 is regulated at multiple levels. Transcription factors such as HIF-1α, MYC, AP-1, and IRF family members promote PD-L1 transcription in response to oncogenic signaling and hypoxic or inflammatory conditions [34, 35]. Additionally, genetic alterations such as chromosomal translocations and focal amplifications can lead to PD-L1 overexpression [36]. MicroRNAs also contribute to posttranscriptional control by targeting pathways involved in PD-L1 protein stability, trafficking, and membrane localization [37]. PD-L1 upregulation may also occur in response to viral infection or cytokine signaling. Inflammatory mediators such as TNF-α, IFN-γ, and IL-4 have been shown to induce PD-L1 expression, contributing to $CD8^+$ T-cell exhaustion in the TME [38]. Although PD-L1 is typically absent in most healthy tissues, its expression is strongly induced in nucleated cells in response to IFN-γ released during tumor antigen-specific immune responses. This serves as a mechanism of adaptive resistance, particularly within tumor-infiltrating lymphocytes (TILs) [39]. Through its engagement with PD-1 and B7-1, PD-L1 transmits inhibitory signals that reduce T-cell proliferation and

cytokine secretion. While this immune dampening limits inflammation and prevents tissue damage, it also impedes effective antitumor immunity. Notably, PD-L1 can be upregulated even in the absence of TILs, driven by intrinsic oncogenic signaling pathways or noncoding RNAs, further supporting immune evasion in “cold” tumors [40].

4. Impact of OVs on PD-1/PD-L1 Pathway

OVs exert antitumor effects not only through direct cytolysis but also by modulating the TME and reshaping immune responses. The interaction between viral infection and the PD-1/PD-L1 axis was initially described in herpetic stromal keratitis. Adjustments of immune responses were demonstrated through the induction of expression of PD-1 in T cells and PD-L1 in macrophages in the cornea and lymph node by infectious HSV-1, called ocular infection. Other literature also suggested that interactions with the virus upregulate PD-1/PD-L1, leading to an immune dysregulation known as T-cell exhaustion, which further promotes viral replication and colonization [41]. From one viewpoint, the release of TAAs, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) triggers an immune response, along with the secretion of cytokines, which can result in reduced PD-L1 expression on cancer cells. On the other hand, some OVs may induce the upregulation of PD-L1 (Table 1). VZV infection profoundly affects the induction of PD-L1 expression in different cell types, as VZV directly downregulates PD-L1 protein expression in various cell types, including fibroblasts [49]. In contrast, HSV-1 infection of DCs leads to a direct upregulation of PD-L1 levels. Inflammatory cytokines produced during viral infection may play a crucial role in driving virus-induced PD-L1 expression, as well as PD-L1 induction through TLR activation triggered by PAMPs [50]. Immune cell surface PD-1 interacts with tumor cell surface PD-L1, generating an immunosuppressive environment that fails to attack tumor cells. A reduction in the inhibitory molecules PD-1 and

PD-L1 on immune cells would prevent the immune system from being reactivated by immune checkpoint blockades, potentially leading to the progressive elimination of tumor cells. OV-infected tumor cell lysis causes ICD and releases of TAAs, allowing an antigen-driven T-cell response and production of IFN-γ, triggering a reduction in PD-L1 expression on the tumor cell surface (Figure 3) [51]. Although ICIs such as anti-PD1 have shown promise in various malignancies, their efficacy in immunologically cold tumors like hepatocellular carcinoma (HCC) remains limited. One of the key reasons for this resistance is the immunosuppressive TME, which prevents adequate T-cell infiltration and activation. A study by Chiu et al. revealed that HCCs often upregulate PVRL1, a molecule that stabilizes PVR on the tumor cell surface, facilitating interaction with TIGIT, an inhibitory receptor on $CD8^+$ effector memory T cells. This PVR–TIGIT axis effectively dampens T-cell responses, contributing to resistance against PD1 blockade. Notably, knockdown of PVRL1 in tumor cells enhanced $CD8^+$ T-cell infiltration and tumor suppression in mice, especially when combined with dual PD1/TIGIT blockade. These findings support the rationale for combining OVs, which can convert cold tumors into hot by enhancing T-cell infiltration and antigen presentation with ICIs, particularly in tumors that express high levels of inhibitory molecules like PVRL1. Thus, OV-based therapies can help overcome immune resistance mechanisms inherent to cold tumors, potentially improving responses to checkpoint inhibitors [52]. Oncolytic treatment of neoplasms is likely to induce ICD of the tumor, which in turn activates NK cells and reduces PD-L1 expression through the production of cytokines that promote PD-L1 downregulation [53]. These mechanisms therefore suggest that the role of OVs in modulating the inhibitory molecules PD-1 or PD-L1 may intensify the patient's immune responses against tumor cells. Recent evidence highlights the importance of spatiotemporal coordination between OV therapy and ICI administration. For instance, the early inflammatory remodeling of the TME induced by OVs is essential for subsequent T-cell

activation and expansion. In a recent clinical report, T-VEC was used intratumorally in a patient with refractory adult T-cell leukemia/lymphoma (ATLL), demonstrating significant tumor regression and immune modulation. Single-cell RNA sequencing of pre- and posttreatment fine-needle aspiration samples revealed enhanced infiltration and activation of CTLs following OV treatment [54]. This underscores the importance of administering OVs prior to PD-1 blockade, allowing sufficient time for the TME to transition into an immune-inflamed state, thereby enabling optimal clonal expansion of effector T cells. In addition to sequential combination strategies, an emerging and promising approach involves engineering OVs to encode ICIs such as anti-PD-1 antibodies within their genomes. This strategy not only ensures localized production of checkpoint inhibitors at the tumor site, minimizing systemic toxicity, but also aligns the peak ICI activity with OV-induced immune activation. Given that the systemic half-life of monoclonal antibodies like anti-PD-1 (pembrolizumab or nivolumab) can range from 2 to 3weeks [55, 56]. Local expression via OVs can provide a more controlled and dynamic checkpoint blockade. Such integrated constructs can maximize therapeutic synergy while reducing the risk of immune-related adverse events, making OVs powerful vehicles for precise and context-specific immunomodulation.

Table 1. Effects of various OVs on the regulation of PD-1 and PD-L1. This table summarizes the impact of different OVs on the expression of PD-1 and PD-L1, critical immune checkpoints involved in suppressing antitumor immunity. The regulation of these checkpoints by OVs is crucial in overcoming immune evasion by tumors, thereby enhancing the efficacy of cancer immunotherapy. Reovirus-induced PD-L1 upregulation may reflect TLR-driven inflammation, whereas vaccinia virus downregulates PD-L1 via IFN-γ induction. The table includes the mechanisms through which each virus modulates PD-1 and PD-L1 levels,

primarily through the induction of ICD, activation of T cells, and production of inflammatory cytokines.

Virus	PD-1/PD-L1 regulation	Tumor type	Ref
Oncolytic virus alphavirus M1 (OVM1)	Downregulation	Prostate cancer and glioma	[42]
Oncolytic vaccinia virus	Downregulation	Ovarian and colon cancer cells	[43]
Oncolytic adenovirus (hTertAd)	Downregulation	Primary liver tumors and lung metastasis	[44]
Semliki forest virus-based vector encoding IL12	Upregulation	Colorectal cancer cells	[45]
Oncolytic reovirus	Upregulation	Multiple myeloma cells	[46]
Oncolytic adenovirus (delta-24-RGD)	Upregulation	Glioma	[47]
Oncolytic vesicular stomatitis virus VSVΔ51-YF	Downregulation	Prostate	[48]

Figure 3

Oncolytic immunovirotherapy for cancer. This figure depicts the mechanisms underlying OV-mediated immunotherapy in cancer treatment. Injection of OVs leads to viral replication within tumor cells, releasing tumor antigens, viral antigens, and DAMPs. These molecules activate DCs, which present tumor antigens to CD8+ T cells in the lymph node. The interaction between tumor antigens and TCRs leads to the activation and expansion of tumor-specific CD8+ T cells. However, tumor cells often express PD-L1, which binds to PD-1 receptors on T cells, inhibiting their antitumor activity. Anti-PD-1 therapy can block this inhibitory pathway, enhancing the killing capacity of CD8+ T cells and leading to tumor regression. The effectiveness of OV therapy depends on the tumor's immunogenicity and its sensitivity to viral infection. Cold tumors, which are less responsive to ICIs, may benefit from the combined use of OVs and ICIs.

4.1. Innate Immune Activation and Modulation of PD-1/PD-L1 Expression by OVs

A key mechanism by which OVs exert antitumor activity is through the activation of the innate immune system. Among the components of this response, NK cells play a central role in recognizing and eliminating virally infected and transformed cells [57]. Upon OV administration, NK cells are activated and secrete proinflammatory cytokines such as IFN-γ and TNF-α, initiate a cascade of immune-stimulatory events within the TME [58–60]. These cytokines not only contribute to the recruitment and activation of APCs, such as DCs and macrophages, but also influence the expression of immune checkpoint molecules. Specifically, IFN-γ can downregulate PD-L1 expression on tumor cells under certain conditions, while simultaneously enhancing MHC class I presentation and the activation of CTLs.

4.2. Interferon Signaling Pathways and Their Impact on PD-L1 Expression in OV Therapy

Interferons are essential in enhancing the efficiency of OVs because they induce a type of immune response known as type I interferon signaling, which is favorable for effective antitumor immunity. OVs selectively target and destroy cancer cells by exploiting defects in the IFN pathway, which cancer cells often lack. While OVs use this vulnerability to replicate and lyse tumor cells, they also trigger an immune response in the surrounding healthy tissue. This leads to the release of type I IFNs (such as IFN-α and IFN-β) by immune and stromal cells, activating antitumor immunity, recruiting CTLs and NK cells, and reducing PD-L1 expression on tumor cells. Thus, OVs not only directly kill cancer cells but also enhance immune-mediated tumor destruction through IFN pathway activation in the TME [61]. Type I IFNs lead to a decrease in the PD-L1 expression on tumor cells by supporting immune cell recruitment and facilitating CTL activities [62]. It has been shown that OVs increase type I IFN pathway activation and decrease PD-L1 expression in tumor cells, enhancing tumor destruction by CTLs [63]. Various OVs activate type I IFN signaling, which disrupts the PD-1/PD-L1 immune checkpoint axis and enhances the recruitment of NK cells and T cells to the tumor site. This boosts the immune system's ability to attack and destroy the tumor [64–66].

4.3. Cytokine and Chemokine Engineering in OVs: Modulating PD-1 and PD-L1 Expression for Enhanced Antitumor Immunity

OVs can be created to produce specific cytokines and chemokines, thereby regulating PD-1 and PD-L1 expression and augmenting the antitumor immune response [8]. For instance, GM-CSF-expressing oncolytic vaccinia virus, JX-594, causes further recruitment and activation

of DCs and T cells into the TME, which increases IFN-γ and other proinflammatory cytokines and leads to decreased PD-L1 expression on tumor cells [67]. Woller et al. showed that oncolytic adenovirus infection of PD-1-resistant tumors elicited robust $CD8^+$ T-cell responses against conserved neoepitopes, responses that were not effectively induced by PD-1 inhibition alone. Notably, the combination therapy broadened the neoantigen-specific T-cell repertoire and led to complete tumor regression in a $CD8^+$ T-cell-dependent manner. In addition, the use of oncolytic adenoviruses expressing IL-12 further enhances the antitumor immune response by promoting the differentiation of naïve T cells into Th1 cells and activating NK cells, resulting in elevated production of IFN-γ and TNF-α. These cytokines subsequently reduce PD-L1 expression on tumor cells. Together, these findings highlight the potential of OVs not only to overcome immunotherapy resistance by reprogramming the tumor immune microenvironment but also to enhance the efficacy of ICIs such as PD-1/PD-L1 blockade [44]. In the same manner, treating oncolytic MV expressing IL-12 enhances the activation and proliferation of T cells and NK cells, leading to a strong Th1 immune response that downregulates PD-L1 on tumor cells [68]. HSV-1 with IL-12 insertion selects and activates various populations of DCs, T cells, and NK cells, which results in a higher amount of IFN-γ and subsequently leads to loosened PD-L1 levels in the TME [69]. Oncolytic adenoviruses programmed to express TNF-related apoptosis-inducing ligands show enhanced induction of apoptosis in tumor cells along with remodeling of the TME, thereby decreasing the levels of PD-L1 in tumor cells [70]. Oncolytic parvoviruses expressing IL-2 activated and proliferated T and NK cells and stimulated the immune response, resulting in an increase in IFN-γ production and a decreased PD-L1 expression on cancer cells [71]. Coxsackievirus A21 (CVA21), an OV that selectively targets and destroys tumor cells, can also be incorporated into the body, and the infection will enhance the secretion of type I interferon that antagonizes the action of PD-L [72]. In conclusion, the OVs designed to secrete chemokines and

cytokines markedly affected the design-modulated CD8+ T-cell tumor immune response due to polarization of the tumor immune response and PDL and PD-L1 modulation. Tumor-associated inflammation and immune activation can also be achieved by the application of GM-CSF, IL-12, or IL-2, whose receptors are expressed on T cells, NK cells, and DCs and support their expansion, increasing the synthesis of IFN-γ and other inflammatory cytokines in proinflammatory cytokines. Notably, these cytokines downregulate the PD-L1 molecule on the surface of tumor cells, thereby enhancing immune activity against the tumor.

4.4. Immunogenic Cell Death Induction and Antigen Presentation in OV Therapy

OVs not only exert direct lytic effects on tumor cells but also remodel the tumor TME through the induction of ICD and enhancement of antigen presentation, thereby significantly improving the efficacy of PD-1/PD-L1 inhibitors [73]. ICD, triggered by OVs, leads to the release of TAAs along with DAMPs, including ATP, calreticulin, and HMGB1, which activate DCs and facilitate effective T-cell priming [74]. Additionally, OVs upregulate the expression of major histocompatibility complex (MHC) molecules on tumor cells, enhancing antigen presentation and increasing tumor visibility to the immune system [75, 76]. These changes support robust adaptive immune responses and help overcome the immunosuppressive effects of PD-L1 within the TME. Furthermore, studies in nonsmall cell lung cancer (NSCLC) have demonstrated that engineering OVs to target tumor-specific pathways can improve responses to PD-1 inhibitors by addressing the heterogeneity and immune resistance of the TME [77]. Overall, the synergy between ICD induction, improved antigen presentation, and immune checkpoint blockade offers a powerful approach for enhancing antitumor immunity and overcoming resistance in various cancer types.

5. Influence of OVs on PD-1/PD-L1 Pathway in Acquired Immune Activation

The role of adaptive immune activation, particularly T-cell-mediated responses, is critical to the therapeutic efficacy of OVs. While OVs primarily trigger innate immunity, they also influence adaptive immune pathways, including the PD-1/PD-L1 immune checkpoint axis [78]. The OVs could enhance the activation and proliferation of CTLs, modulating the expression of PD-1 and PD-L1. There are several experiments that demonstrated the upregulation of PDL-1 on tumor cells after OV treatment, and in the opposite manner, there are several studies that showed OVs would downregulate the PDL-1 expression in cancer cells (Table 1). This is important because high levels of PD-1 on T cells and PD-L1 on tumor cells help to advance an immunosuppressive TME, inhibiting efficient antitumor immune responses. OVs enhance acquired immunity by inducing ICDs in tumor cells, which release TAAs and activate DCs. This process promotes the activation and infiltration of CTLs into the TME [51, 79]. Activated CTLs release IFN-γ, which reduces PD-L1 expression on tumor cells, thereby increasing their vulnerability to immune-mediated destruction. Additionally, OVs stimulate the production of type I interferons and other proinflammatory cytokines, reinforcing both innate and adaptive immune responses. These cytokines enhance the cytolytic activity of NK cells and support the persistence and functionality of CTLs, contributing to a sustained antitumor immune effect [80]. In summary, OVs exert a great influence on the PD-1/PD-L1 pathway via immunologic activation. By augmenting CTL activation and proliferation, these viruses have been known to downregulate PD-1 and PD-L1 expression, thus effectively overturning the immune checkpoint blockade, leading to enhanced antitumor immunity. This capacity to reprogram the adaptive immune response positions OVs as valuable agents in the context of cancer immunotherapy, particularly in combination with immune checkpoint

blockade. Mechanistic studies have shown that OVs modulate PD-1/PD-L1 expression and reshape the TME, providing the rationale for combining OVs with ICIs. These insights guide clinical trial design by identifying optimal timing, tumor types, and immune targets to enhance therapeutic synergy.

6. PD-1/PD-L1 Blockade in Combination With Oncolytic Virotherapy for Cancer Treatment

The clinical introduction of monoclonal antibodies targeting the PD-1/PD-L1 pathway markedly advanced cancer immunotherapy by restoring T-cell-mediated tumor surveillance. To date, the U.S. Food and Drug Administration (FDA) has approved ten ICIs targeting PD-1 or PD-L1, including anti–PD-1 agents such as Pembrolizumab (Keytruda), Nivolumab (Opdivo), Atezolizumab (Tecentriq), Avelumab (Bavencio), Durvalumab (Imfinzi), Cemiplimab (Libtayo), Dostarlimab (Jemperli), Retifanlimab (Zynyz), Toripalimab (Loqtorzi), and Tislelizumab (Tevimbra). Among them, some are anti PD-1 (Pembrolizumab, Nivolumab, Cemiplimab, Dostarlimab, Retifanlimab, Toripalimab, and Tislelizumab), and some others are anti PDL-1 (Atezolizumab, Avelumab, and Durvalumab) [81]. These agents function by preventing the inhibitory PD-1/PD-L1 interaction, thereby sustaining T-cell effector functions in the TME. Anti-PD-1/PDL-1 drugs are effective in treating a variety of cancers, including melanoma, lung cancer, kidney cancer, lymphoma, esophageal, gastric cancer, breast cancer, head and neck cancer, cervical cancer, and bladder cancer [82]. They are often used in combination with other cancer treatments, such as chemotherapy or radiation therapy. For instance, combining oncolytic vaccinia virus with anti-PD-1 therapy has demonstrated synergistic effects, where the virus-induced immune activation reduces PD-L1 expression on tumor cells,

making them more susceptible to PD-1/PDL-1 blockade [15]. Emerging biomarkers such as baseline $CD8^+$ T-cell infiltration and PD-L1 combined positive score (CPS) may further guide patient selection for OV-ICI combination therapies. In the following sections, we critically evaluate key clinical trials combining OVs with PD-1/PD-L1 inhibitors, summarize mechanistic insights underlying their synergy, and discuss the implications for future combination strategies in immuno-oncology. Table 2 summarizes the most prominent clinical trials using both OV therapy and ICI therapy simultaneously.

Table 2. Clinical trials of OVs in combination with ICIs.

Virus	Variant	Genetic modification	NCT	Study
HSV	T-VEC	Deletion of ICP34.5 and ICP47 genes and insertion of hGM-CSF	NCT02263508	Phase I label, si st
			NCT02263508	Pha rando doubl pla cont

6.1. OHSV and PD-L1/PD-1 Inhibitors

Talimogene laherparepvec (T-VEC) is a modified HSV type 1-based OV encoding GM-CSF. Expression of the gene encoding GM-CSF leads to the local production of GM-CSF, which facilitates tumor-specific T-cell activation and the infiltration of ACPs. In addition, genes for infectious cell proteins 34.5 and 47 were deleted in T-VEC, which increased tumor-selective virus replication and enhanced antigen presentation in infected tumor cells, respectively [104]. Intralesional T-VEC has been tested in several studies as monotherapy and with PD-1 inhibitors [83, 105]. In a small phase-Ib clinical trial (MASTERKEY-265; NCT02263508), T-VEC and pembrolizumab combination therapy in melanoma patients (n=21) yielded an overall response rate (ORR) of 62% and a complete response rate (CRR) of 33%. Post-treatment tumor biopsies of responding patients exhibited increased $CD8^+$ T-cell infiltration, PD-L1 expression, and IFN-γ mRNA [83]. These results suggest that T-VEC likely improves of PD-1 inhibitors efficacy in combination therapy through favorably modulating the TME. More recently, Chesney and colleagues completed the Phase-III trial of KEYNOTE-034/MASTERKEY-265. In this study, 692 anti-PD1 naïve, unresectable stage IIIB-IVM1c melanoma patients were randomized to pembrolizumab plus T-VEC (n=346) and pembrolizumab plus placebo (n =346). Compared with placebo plus pembrolizumab, T-VEC plus pembrolizumab did not significantly extend progression-free survival (PFS) or overall survival (OS). Although the T-VEC plus pembrolizumab group showed higher ORR (48.6%) and disease-related response (42.2%) rates than the pembrolizumab plus placebo group (ORR: 41.3%; DRR: 34.1%), these differences did not reach statistical significance [84]. The

reasons for the lack of statistical significance in survival are not entirely clear; however, it may be partly attributable to the inclusion of patients with more advanced stage) in this trial Approximately 41% of patients in the KEYNOTE-034 trial had IVM1c or IVM1b disease, which involves distant organ metastases, whereas a previous trial excluded patients with extensive visceral disease who were unlikely to benefit from single-agent OV therapy, focusing instead on individuals with predominantly early-stage disease [106]. Another crucial factor in evaluating the results of phases I and III of the MASTERKEY-265 study lies in the treatment regimen. In the phase-Ib trial, T-VEC was injected before pembrolizumab to facilitate seroconversion and establish a protective immune response against the oncolytic viral vector. However, in the phase-III trial, T-VEC and pembrolizumab were administered concomitantly from the beginning [107]. Preclinical studies indicate that the administration schedule of anti-PD-1 and OVs influences therapeutic efficacy, whereby OV administration preceding anti-PD-1 results in improved outcomes compared to alternative schedules [108]. In fact, initial OV treatment creates an immunologically hot TME through APCs recruitment and activation, primed $CD8^+$ T cells, and their infiltration into the TME. In addition, OV treatment upregulates PD-L1 and MHC-I expression on tumor cells and inflammatory cytokine production, further supporting the immunologically hot TME. Furthermore, administering anti-PD-1 in such optimized TME enhances the activation of $CD8^+$ T cells and effectively mitigates T-cell exhaustion mediated by PD-L1/PD-1 interaction [108, 109].

The phase-II MASTERKEY-115 clinical trial (NCT04068181) investigated the therapeutic potential of combining T-VEC with pembrolizumab in advanced melanoma patients who experienced disease progression or recurrence following prior anti-PD-1 therapy. This multicenter study enrolled 71 participants categorized into four distinct subgroups based on treatment history: cohort 1 (n=26) comprised patients with primary

resistance to anti-PD-1 agents, cohort 2 (*n*=15) included those demonstrating acquired resistance after initial response, cohort 3 (*n*=15) involved individuals recurring within 6months post-adjuvant anti-PD-1 treatment, and cohort 4 (*n*=15) encompassed patients with disease-free intervals exceeding 6months following adjuvant therapy. While cohorts 1 and 2 received prior anti-PD-1 regimens for metastatic or locally recurrent disease, clinical outcomes varied significantly across groups. Minimal response rates were observed in cohorts 1 (0% ORR) and 2 (6.7% ORR), whereas cohorts 3 and 4 exhibited substantially improved outcomes, achieving ORRs of 53.3% and 46.7%, respectively [110].

Sarcoma and head and neck cancer are among the other cancers for which the combination of pembrolizumab with T-VEC has been investigated. A phase-II trials (NCT03069378) of pembrolizumab in combination with T-VEC in locally advanced sarcoma (*n*=20) reported a 35% ORR with a favorable safety profile [85]. In another trial (MASTERKEY-232; NCT02626000) involving 36 patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with T-VEC plus pembrolizumab, the ORR was 13.9%, and the median OS and PFS were 5.8 and 3.0months, respectively. However, the combination therapy did not improve efficacy over pembrolizumab monotherapy; thus, phase III was not pursued. In this study, all patients who responded to treatment exhibited PD-L1 expression, with four demonstrating a baseline CPS PD-L1 greater than 50. This finding suggests a potential association between elevated baseline PD-L1 CPS and therapeutic response. It is important to note that significant adverse events were observed, including one case of fatal arterial bleeding, which was possibly related to T-VEC [86].

Vusolimogene oderparepvec (also referred to as RP1) is another genetically modified HSV-1-based OV designed to express GM-CSF and fusogenic glycoprotein from gibbon ape leukemia virus (GALV-GP R-)

[111]. In preclinical lung and breast cancer studies, RP1 induced GALV-GP-enhanced ICD and host antitumor immunity. In addition, the virus increased PD-L1 expression and showed augmented activity in combination with anti-PD-1 therapy [111]. Intratumoral RP1 combined with nivolumab has been studied in a phase I/II trial for patients with skin cancers (NCT03767348). The ORR was 62.5% (5/8) in patients with anti-PD-1-naive cutaneous melanoma and 37.5% (6/16) in patients with prior anti-PD1/anti-PDL-1 plus anti-CTLA-4 failure. Among patients with anti-PD-1-naive cutaneous squamous cell carcinoma, 47.1% (8/17) experienced a complete remission (CR) and 17.6% (3/17) a partial response (PR). Additionally, the combination of RP1 and nivolumab was well tolerated, with no new safety signals detected. Most importantly, robust $CD8^+$ T-cell infiltration and elevated PD-L1 expression were observed in post-treatment tumor biopsies. The clinical responses were independent of the baseline tumor PD-L1 expression and correlated with increased gene signatures reflective of cytotoxic *T*, Th1, and, NK cells activation, Notably, key genes previously implicated in responsiveness to anti–PD-1 therapy including *CD8*, *CXCL9*, *CD27*, and *TIGIT*—were upregulated in patients who responded to treatment [112, 113]. A phase-III study of RP1 in combination with nivolumab (IGNYTE-3; NCT06264180) is also underway for patients who have not responded to previous anti-PD-1 treatment [114].

OrienX010 is another HSV-1-derived oncolytic immunotherapy collected from the oral cavity of a Chinese patient infected with HSV-1 of Han ethnicity and genetically modified to delete ICP34.5 and ICP47 while expressing human GM-CSF [115]. In a phase Ib study, intratumoral injection of OrienX010 in four dose groups, including 10^6pfu, 10^7pfu, 10^8 pfu and 4×10^8pfu was evaluated in patients with unresectable stage IIIC-IV melanoma. No dose-limiting toxicities (DLTs) were observed in this study, and promising efficacy results were obtained, including an ORR of 28.6%, a disease control rate (DCR) of 57.1%, a median mPFS of 3.0

months, and a median OS of 17.4months [116]. Recently, the efficacy and tolerability of intratumoral OrienX010 (Ori) in combination with toripalimab (Tori) as a neoadjuvant regimen (neoadjuvant) were evaluated in patients with stage IIIB/IVM1a acral melanoma. Following surgical resection, adjuvant tori was administered starting 3weeks postoperatively and continued for up to 1year. Of the 30 patients enrolled, 27 patients underwent surgery after receiving neoadjuvant therapy and subsequently received adjuvant therapy. Three patients did not undergo surgery due to disease progression during neoadjuvant therapy. The ori+tori combination therapy was well-tolerated, with all patients experiencing at least one TRAE, predominantly Grade 1–2. Only two grade 3 TRAEs were observed, including one case of alanine aminotransferase elevation and one case of peripheral neuropathy, both of which were in the adjuvant setting. Among the 27 patients who underwent surgery, 4 patients (14.8%) achieved a pathological (CR), 5 (18.5%) a near-pathological CR, 12 (44.4%) a pathological partial response PR), and 6 (22.2%) did not achieve a pathological response. Pathologic responses were associated with robust immune infiltrates displaying signs of activation and hyaline fibrosis in the treated tumor specimens. Furthermore, analysis of cytokines and chemokines in the serum of responding patients showed that the combination therapy significantly increased the secretion of immune factors that are effective in tumor elimination through various mechanisms. This increase included cytotoxic cytokines such as TNF, TNFR, IFN-γ, and Fas ligand, which directly kill tumor cells, along with granzymes GZMA, GZMH, and GZMB, which are secreted by immune cells and play a role in tumor destruction. Also, chemokines CXCL9, CXCL10, CXCL11, CXCL13, CCL19, and CCL23, which enhance the recruitment and activation of immune cells, and regulatory interleukins such as IL-12, IL-18, and IL-10, which modulate the immune response, were significantly increased [88].

6.2. Oncolytic Coxsackievirus and ICI Therapy

Coxsackievirus A21 (V937, formerly CVA21 or Cavatak™) is a wild-type OV with tropism for malignant cells overexpressing intracellular adhesion molecule (ICAM)-1 and decay-accelerating factor (DAF) [117]. Increased immune cell infiltration, IFN-γ gene regulation, PD-L1 expression, tumor cell lysis, and a systemic antitumor immune response have all been linked to CavatakTM administration. Preclinical studies have demonstrated that intratumoral CVA21 with anti-PD1 has a considerably stronger antitumor effect compared to using either individually [118]. Phase-Ib study KEYNOTE-200 investigated the safety and efficacy of intravenous CVA21 with pembrolizumab in patients with advanced NSCLC and bladder cancer [119]. Combination therapy was generally well tolerated and associated with ORRs of 23% and 31% in the immunotherapy-naive NSCLC patients (those who did not previously receive immunotherapy) and the immunotherapy-naive bladder cancer patients, respectively. The biopsy specimens from evaluable patients with negative or low baseline PD-L1 expression exhibited a substantial increase in PD-L1 expressing tumor cells by 62% at Day 15 post-CVA21plus pembrolizumab treatment [119]. The CAPRA trial evaluated intratumoral V937 plus pembrolizumab in metastatic/unresectable stage IIIB-IV melanoma, reporting a 47% (17/36) confirmed ORR, based on immune-related response criteria. Among 17 responders, 14 (82%) had responses more than 6months. Biomarker analysis revealed that pretreatment intratumoral infiltration of $CD3^+$ and $CD8^+$ T lymphocytes was lower in responders. In contrast, clinical responses correlated with increased serum CXCL10 and CCL22 levels, indicating viral replication drives antitumor immunity, even within tumors exhibiting a nonimmunologically “active” microenvironment [92].

6.3. Oncolytic Reovirus and ICI Therapy

Pelareorep (REOLYSIN®) is a live, nongenetically modified reovirus isolate from the type 3 Dearing strain. After intravenous administration,

pelareorep selectively infects and lyses tumor cells with an activated RAS pathway. The preferential elimination of RAS-activated cells by pelareorep is primarily due to the inhibition of autophosphorylation of double-stranded RNA-activated protein kinase (PKR) in these cells, enabling viral replication [120]. Pelareorep induces innate and adaptive antitumor immune responses and promotes an inflammatory tumor phenotype characterized by increased T-cell and NK cell infiltration into the TME and PD-L1 expression [93]. Several preclinical and clinical initiatives have investigated the safety and efficacy of pelareorep with other therapies, including chemotherapy. Chemotherapy combinations were utilized in OV therapy studies to attenuate neutralizing antiretroviral antibodies formation and improve systemic viral delivery to tumor tissues [121]. A phase-II trial demonstrated that pelareorep combined with gemcitabine was well tolerated and exhibited moderate clinical activity in advanced pancreatic ductal adenocarcinoma (PDAC). Analysis of an on-treatment biopsy from a patient with stable disease revealed viral replication, PD-L1 upregulation, and tumor cell apoptosis [122]. Upregulation of PD-L1 following pelareorep suggests the logic of combination therapy with anti-PD-L1 inhibitors [122]. To address this therapeutic method, a phase-Ib clinical trial of the efficacy and safety of the combination of intravenous pelareorep, pembrolizumab, and chemotherapy (5-FU, gemcitabine, or irinotecan) was conducted in 11 patients with advanced PDAC. Combination therapy was again well tolerated; one patient had a clinical response (ORR: 9%), and median PFS and median OS were 2.0 and 3.1 months, respectively. Similar to previous studies with pelareorep, viral proliferation was demonstrated in most on-treatment biopsy specimens. Increased intertumoral $CD8^+$ T cells, LILRA4, and ICOS expression were observed in patients with clinical benefit. It should be noted that both of the above genes are involved in IFN production upon reovirus infection. In addition, an increase in blood levels of IFN-inducible chemokines (CXCL9/10/11) was demonstrated during the first treatment cycle [123].

While chemotherapy combinations can effectively attenuate the development of NARA, prior chemotherapy may modulate OVs-induced antitumor responses. To evaluate whether eliminating chemotherapy could improve virus-induced antitumor immune responses, Mahalingam et al. conducted a phase-II study in which pelareorep plus pembrolizumab was administered as a chemotherapy-free second-line treatment for PDAC patients. The simultaneous administration of pelareorep and pembrolizumab was well tolerated and showed moderate efficacy with a clinical benefit rate of 42% (1 PR and 4 SD) among 12 patients. Significant immunological changes, characterized by decreased VDAC1 expression in $CD8^+$ T cells and reduced peripheral Treg abundance, were observed in on-treatment biopsies from responders to pelareorep plus pembrolizumab. Furthermore, post-treatment samples revealed a tendency for increased PD-L1 expression and higher frequencies of $CD8^+$ T cell and NK cell interactions with PD-$L1^+$ cells following combination therapy [93].

6.4. Oncolytic Adenovirus and ICI Therapy

ONCOS-102, a modified serotype 5 adenovirus, features a serotype 3 fiber knob to improve gene delivery to cancer cells and a 24-base-pair deletion in the E1A Rb-binding site, limiting replication to cancer cells. In addition, the virus is equipped with GM-CSF to enhance antitumor immunity [124]. Adenoviruses are predominantly lytic and possess a restricted repertoire of immune evasion genes, and some studies indicate that adenovirus-based OVs exhibit enhanced immune activation compared to HSV, vaccinia virus, and reovirus [125]. Intratumoral injection of ONCOS-102 with cyclophosphamide in refractory solid tumors leads to increased $CD8^+$ T cells infiltration and upregulation of type 1T helper cytokines within TME. Importantly, ONCOS-102 upregulates tumor PD-L1 expression, suggesting its potential as an immunosensitizing agent for combination with PD-1/PD-L1 inhibitors

[126]. More recently, Shoushtari et al. reported a 35% ORR in anti-PD-1 refractory melanoma patient treated with ONCOS-102+pembrolizumab. A favorable safety profile was observed, with no DLTs; pyrexia, chills, and nausea were the predominant treatment-related adverse events. Notably, eight patients (53%) exhibited a reduction in at least one noninjected lesion, indicating that local ONCOS-102 delivery can elicit a systemic antitumor response. Significantly elevated baseline infiltration of both $CD8^+$ and $CD4^+$ lymphocytes was observed in patients who achieved subsequent disease control relative to those experiencing progressive disease. Furthermore, a further increase in tumor infiltration of $CD4^+$ and $CD8^+$ T cells was observed following OV administration in patients with disease control. This finding is not observed in patients with PD. Moreover, distinct gene expression profiles were identified between patients achieving disease control and those experiencing progressive disease, characterized by increased cytotoxicity, stimulatory, and checkpoint inhibitor gene expression. Interestingly, ONCOS-102 elicited early T-cell activation, as evidenced by an increase in these markers from baseline to week 3 (before ONCOS-102 and before pembrolizumab) in all patients. However, at week 9, these markers remained elevated only in patients with disease control, whereas patients experiencing disease progression exhibited a reduction in expression [94, 127].

DNX-2401 is another oncolytic adenovirus with a deletion of 24bps in the E1A gene, which restricts viral replication to cells with dysregulated RB signaling. Additionally, DNX-2401 incorporates an RGD motif in its fiber knob, allowing viral entry via αvβ3 or αvβ5 integrins, commonly overexpressed on tumor cells. Previous studies have shown that injection of DNX-2401 is safe and triggers cancer cell death initially by direct oncolysis and then by induction of immune responses that establish sustained antitumor immunity and drive tumor regression [128]. DNX-2401 has also been shown to markedly increase PD-1

expression in preclinical models, effectively conditioning the immune microenvironment to respond more synergistically to subsequent anti–PD-1 treatment [129]. CAPTIVE phase I/II trial evaluated a combination therapy of intratumoral DNX-2401 plus multiple intravenous doses of pembrolizumab in a cohort of 49 adult patients with relapsed glioblastoma. Full-dose combined treatment was generally well tolerated, and AEs were mostly grade 3 or lower events, indicating the safety of such combinations. The median OS was 12.5months, and the OS at 12months was 52.7%, while the 12-month OS in the DNX-2401 monotherapy trial was 32%. In this study, patients were stratified into three groups: low, medium, and high-based on the level of TME inflammation at the time of intervention. The results showed that complete response to treatment and the longest survival occurred exclusively in the medium inflammation group (TME^{medium}), likely due to an optimal balance between immune cell infiltration and PD-1 expression. In contrast, despite high immune cell infiltration, tumors with high inflammation (TME^{high}) exhibited poor response to PD-1 blockade, attributed to excessive expression of multiple immunosuppressive checkpoint molecules that induced immune exhaustion. Interestingly, combination therapy with DNX-2401 significantly enhanced the response to anti–PD-1 treatment in TME^{medium} tumors by inducing CTL infiltration and upregulating PD-1 expression. It should be mentioned that three patients had stable responses and survived for 45, 48, and 60months [96].

Enadenotucirev (formerly known as ColoAd1), is a group B chimeric Ad11p/Ad3 oncolytic adenovirus that has been identified by a process of bio-selected for the ability to selectively replicate and kill cancer cells rapidly [130]. One distinct advantage of enadenotucirev is that the capsid is entirely generated from Ad11p, which has a lower incidence of neutralizing antibodies in humans than other serotypes [130]. Enadenotucirev has been explored in numerous studies; a phase-I

mechanism of action research discovered that it can be successfully delivered by IV or IT infusion in patients with colorectal cancer and epithelial malignancies with a predictable and controlled safety profile [131, 132]. This study also showed that the virus gains access to and replicates within them and was associated with infiltration of $CD8^+$ T cells into the TME [132]. In a recent phase I clinical trial [121], 51 CRC patients with advanced/metastatic epithelial cancer were treated with nivolumab in combination with enadenotucirev. 31 patients experienced grade 3-4 AEs, including anemia, infusion-related reaction, hyponatremia, and sizable intestinal obstruction. Regarding efficacy, median long-term OS was 16months, median PFS was 1.6months, and ORR was 2% (one PR for 10months). Biopsies obtained postcombination therapy from responding patients revealed enhanced CD8+ T-cell infiltration within the TME and increased expression of granzyme B, a marker of $CD8^+$ T-cell cytolytic activity [97]. The data suggest that enadenotucirev, through its immunostimulatory payloads, facilitates immune cell infiltration, potentially augmenting nivolumab efficacy in the context of anti-PD-1 resistance [133].

6.5. Oncolytic Vaccinia Virus and ICI Therapy

PexaVec (JX-594) is a replication-competent oncolytic vaccinia virus engineered for deletion of the viral thymidine kinase gene and expression of human GM-CSF and β-galactosidase genes under the control of synthetic early/late and p7.5 promoters [134]. PexaVec targets cancer cells through various methods, whereby virus replication and spread are activated by EGFR/Ras signaling, a pathway that is frequently active in cancer, and high cellular levels of thymidine kinase are observed in growing cancer cells [135, 136]. Administration of PexaVec induces a proinflammatory tumor environment through direct lysis of tumor cells and subsequent release of tumor antigens, which is optimal for combination with immunotherapy [137]. A phase-II clinical trial

evaluated PexaVec plus cemiplimab (anti-PD-1) in 89 renal cell carcinoma patients, randomly assigning them to four cohorts: ICI-naive with accessible tumors (Group A, IT virus+cemiplimab, *n*=15), ICI-naive with accessible tumors receiving cemiplimab followed by IT virus at progression (Group B, *n*=16), ICI-naive with nonaccessible tumors (Group C, IV virus+cemiplimab, *n*=30), and prior ICI-treated patients (Group D, IV virus+cemiplimab, *n*=28) [103]. With an average follow-up of 22.2 months, ORR was 13.3% in group A, 12.5% in group B, 23.3% in group C, and 17.9% in group D. Another phase I/II trial studied the safety and efficacy of PexaVec plus durvalumab (anti-PD-1) with or without tremelimumab (anti-CTLA-4) in patients with refractory colorectal cancer [137]. In this study, patients were divided into two groups receiving PexaVec/durvalumab (*n*=16) and PexaVec/durvalumab/tremelimumab (*n*=18) treatment. The combined therapy of PexaVec with ICIs did not cause any unexpected AEs, and the most common AEs were in grades 1–2, while fever and decreased lymphocyte count were the most common AEs in grades 3–4. In 14 patients receiving PexaVec/durvalumab therapy, one PR lasting 9months, one SD, a median PFS of 2.3months, and a median OS of 5.2months were observed. PexaVec/durvalumab/tremelimumab therapy in 11 evaluable patients resulted in 3 cases of SD, a median PFS of 2.1months, and a median OS of 7.5months [137].

7. Conclusion

OVs represent a unique class of immunotherapeutics capable of directly lysing tumor cells while reshaping the TME to enhance antitumor immunity. Central to this dual functionality is their capacity to modulate the PD-1/PD-L1 immune checkpoint axis as a critical barrier to sustained cytotoxic T-cell responses in many malignancies. As reviewed in this article, OVs exhibit divergent effects on PD-1 and PD-L1 expression, either amplifying or attenuating immune suppression depending on viral

tropism, infection kinetics, and the immunologic composition of the host microenvironment. These context-dependent effects underscore the necessity for a mechanistic dissection of how specific OVs interact with tumor and immune cell signaling pathways. Differential modulation of the PD-1/PD-L1 axis by OVs is influenced by viral genome architecture, host pattern recognition receptor engagement, cytokine milieu, and the immunogenicity of viral oncolysis. Elucidating these mechanisms will be essential for rational viral vector design and for identifying biomarkers predictive of response. Interestingly, the interaction between OVs and the PD-1/PD-L1 pathway is context-dependent and influenced by multiple factors such as virus type, tumor type, and the TME. For instance, some OVs like alphavirus M1 (OVM1) and oncolytic vaccinia virus and adenovirus delta-24-RGD have been shown to downregulate PD-L1 expression in prostate, glioma, ovarian, and colon cancer cells [42–44]. In contrast, oncolytic reovirus, Semliki Forest virus encoding IL-12, upregulate PD-L1 expression in tumor models like multiple myeloma, colorectal cancer, and glioma, respectively [45, 46]. This dual behavior underscores the influence of tumor-specific immune environments and cytokine profiles, which may determine whether PD-L1 is induced as a compensatory immune resistance mechanism. Moreover, the timing of ICI administration relative to OV treatment is critical: early administration might impair virus replication and priming, while delayed administration after TME modulation and T-cell infiltration is likely to enhance antitumor efficacy. These nuanced interactions emphasize the need for tailored combination schedules based on tumor biology, immune dynamics, and virus properties. Therapeutically, the integration of OVs with immune checkpoint blockade represents a mechanistically synergistic strategy. Preclinical and early clinical data support the notion that OVs can convert immunologically quiescent tumors into inflamed, T-cell-infiltrated environments responsive to PD-1/PD-L1 inhibition. This combinatorial approach warrants prioritization in earlier lines of therapy, particularly for patients with immune-excluded or

nonresponsive tumors. Looking forward, advances in synthetic virology, immunogenomics, and high-resolution tumor profiling are likely to accelerate the development of next-generation OVs. Engineering approaches that couple selective replication with immunostimulatory payloads, cytokine tuning, or ligand masking may enhance the safety and efficacy of OV-based strategies. Moreover, integration of OVs with personalized immunotherapy platforms, such as neoantigen vaccines, adoptive cell transfer, and metabolic reprogramming, offers an opportunity to overcome current limitations of immune checkpoint therapy. Furthermore, combining advanced OV engineering approaches such as CRISPR-based genome editing, insertion of immunomodulatory genes, and cytokine or chemokine payloads with personalized immunotherapies, including patient-specific neoantigen vaccines, represents a promising frontier. This integrated strategy not only enhances tumor selectivity and immune activation but also tailors treatment to individual tumor profiles, potentially improving efficacy across diverse cancer types. In conclusion, the capacity of OVs to modulate the PD-1/PD-L1 pathway adds a powerful immunologic dimension to their clinical utility. Moving forward, their deliberate incorporation into combination regimens, guided by mechanistic insight and precision immunology, may redefine the therapeutic landscape of cancer immunotherapy.

Nomenclature

OV
: Oncolytic virus

PD-1
: Programmed cell death protein 1

PD-L1
: Programmed death-ligand 1

HSV
: Herpes simplex virus

VSV
: Vesicular stomatitis virus

TAA
: Tumor-associated antigen

CPS
: Combined positive score

DC
: Dendritic cell

NK
: Natural killer (cells)

ICD
: Immunogenic cell death

IFN
: Interferon

TIL
: Tumor-infiltrating lymphocyte

APC
: Antigen-presenting cell

SHP2
: Src homology 2-containing protein tyrosine phosphatase 2

ITSM
: Immunoreceptor tyrosine-based switch motif

TCR
: T-cell receptor

NFAT
: Nuclear factor of activated *T* cells

AP-1
: Activator protein 1

IL
: Interleukin

TNF
: Tumor necrosis factor

B7-1
: CD80 (cluster of differentiation 80)

CTL

Cytotoxic T lymphocyte

GM-CSF

Granulocyte-macrophage colony-stimulating factor

CVA21

Coxsackievirus A21

NDV

Newcastle disease virus

MV

Measles virus

ICI

Immune checkpoint inhibitor

FDA

Food and Drug Administration

ICP

Infectious cell protein

ORR

Overall response rate

CRR

Complete response rate

TME

Tumor microenvironment

PFS

Progression-free survival

OS

Overall survival

NSCLC

Nonsmall cell lung cancer

RAS

Rat sarcoma virus

PKR

Protein kinase R

PDAC

Pancreatic ductal adenocarcinoma

5-FU

5-Fluorouracil

LILRA4
: Leukocyte immunoglobulin-like receptor subfamily A Member 4

ICOS
: Inducible T-cell costimulator

VDAC1
: Voltage-dependent anion channel 1

Treg
: Regulatory *T* cells

NARA
: Neutralizing antiretroviral antibodies

RP1
: Vusolimogene oderparepvec (also known as RP1)

ICAM-1
: Intercellular adhesion molecule 1

DAF
: Decay-accelerating factor

CXCL10
: C-X-C motif chemokine ligand 10

CCL22
: C-C motif chemokine ligand 22

CR
: Complete remission

PR
: Partial response

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Seyedeh Nasim Mirbahari: conceptualization, investigation, and writing original draft. Mehdi Bakhtiyaridovvombaygi: investigation and writing original draft. Amirhossein Izadpanah and Hamid Mahdizadeh: investigation, review, and editing. Elham Roshandel and Mehdi Totonchi: review, editing, validation of final draft, and supervision. All authors read and approved the submitted version.

Funding

This work was supported by the Genetic Department of Royan Institute (ACECR), Iran National Innovation Fund (INIF), Royan Lotus Charity Foundation (Grant No. 402000238), and Royan TuCAGene Ltd.

Acknowledgments

The authors gratefully acknowledge the support provided by the Genetic Department of Royan Institute (ACECR), Iran National Innovation Fund (INIF), the Royan Lotus Charity Foundation, and Royan TuCAGene Ltd. for their contributions to this research.

Data Availability Statement

All the data generated or analysed during this study have been included in this published article.

1 Ma R., Li Z., Chiocca E. A., Caligiuri M. A., and Yu J., The Emerging Field of Oncolytic Virus-Based Cancer Immunotherapy, *Trends in Cancer*. (2023) **9**, no. 2, 122–139, https://doi.org/10.1016/j.trecan.2022.10.003.

Google Scholar

2 Wan P. K., Ryan A. J., and Seymour L. W., Beyond Cancer Cells: Targeting the Tumor Microenvironment With Gene Therapy and Armed Oncolytic Virus, *Molecular Therapy*. (2021) **29**, no. 5, 1668–1682, https://doi.org/10.1016/j.ymthe.2021.04.015.

Google Scholar

3 Beder N., Mirbahari S. N., Belkhelfa M., Mahdizadeh H., and Totonchi M., Unmasking the Potential: Mechanisms of Neuroinflammatory Modulation by Oncolytic Viruses in Glioblastoma, *Exploration of Targeted Anti-Tumor Therapy*. (2025) **6**, https://doi.org/10.37349/etat.2025.1002294.

Google Scholar

4 Duan Q., Zhang H., Zheng J., and Zhang L., Turning Cold Into Hot: Firing up the Tumor Microenvironment, *Trends in Cancer*. (2020) **6**, no. 7, 605–618, https://doi.org/10.1016/j.trecan.2020.02.022.

Google Scholar

5 Han Y., Liu D., and Li L., PD-1/PD-L1 Pathway: Current Researches in Cancer, *American Journal of Cancer Research*. (2020) **10**, no. 3, 727–742.

Google Scholar

6 Russell L., Peng K. W., Russell S. J., and Diaz R. M., Oncolytic Viruses: Priming Time for Cancer Immunotherapy, *BioDrugs*. (2019) **33**, no. 5, 485–501, https://doi.org/10.1007/s40259-019-00367-0, 2-s2.0-85069498549.

Google Scholar

7 Zamarin D., Ricca J. M., Sadekova S. et al., PD-L1 in Tumor Microenvironment Mediates Resistance to Oncolytic Immunotherapy, *Journal of Clinical Investigation*. (2018) **128**, no. 4, 1413–1428, https://doi.org/10.1172/JCI98047, 2-s2.0-85045052376.

Google Scholar

8 Tian Y., Xie D., and Yang L., Engineering Strategies to Enhance Oncolytic Viruses in Cancer Immunotherapy, *Signal Transduction and Targeted Therapy*. (2022) **7**, no. 1, https://doi.org/10.1038/s41392-022-00951-x.

Google Scholar

9 Hemminki O., Dos Santos J. M., and Hemminki A., Oncolytic Viruses for Cancer Immunotherapy, *Journal of Hematology & Oncology*. (2020) **13**, no. 1, https://doi.org/10.1186/s13045-020-00922-1.

Google Scholar

10 Rahman M. M. and McFadden G., Oncolytic Viruses: Newest Frontier for Cancer Immunotherapy, *Cancers (Basel)*. (2021) **13**, no. 21, https://doi.org/10.3390/cancers13215452.

Google Scholar

11 Mondal M., Guo J., He P., and Zhou D., Recent Advances of Oncolytic Virus in Cancer Therapy, *Human Vaccines & Immunotherapeutics*. (2020) **16**, no. 10, 2389–2402, https://doi.org/10.1080/21645515.2020.1723363.

Google Scholar

12 Fatemi N., Mirbahari S. N., Tierling S. et al., Emerging Frontiers in Colorectal Cancer Therapy: From Targeted Molecules to Immunomodulatory Breakthroughs and Cell-Based Approaches, *Digestive Diseases and Sciences*. (2025) **70**, no. 3, 919–942, https://doi.org/10.1007/s10620-024-08774-2.

Google Scholar

13 Bai Y., Hui P., Du X., and Su X., Updates to the Antitumor Mechanism of Oncolytic Virus, *Thoracic Cancer*. (2019) **10**, no. 5, 1031–1035, https://doi.org/10.1111/1759-7714.13043, 2-s2.0-85065249060.

Google Scholar

14 Huang Z., Guo H., Lin L. et al., Application of Oncolytic Virus in Tumor Therapy, *Journal of Medical Virology*. (2023) **95**, no. 4, https://doi.org/10.1002/jmv.28729.

Google Scholar

15 Mirbahari S. N., Da Silva M., Zúñiga A. I. M. et al., Recent Progress in Combination Therapy of Oncolytic Vaccinia Virus, *Frontiers in Immunology*. (2024) **15**, https://doi.org/10.3389/fimmu.2024.1272351.

Google Scholar

16 Lin D., Shen Y., and Liang T., Oncolytic Virotherapy: Basic Principles, Recent Advances and Future Directions, *Signal Transduction and Targeted Therapy*. (2023) **8**, no. 1, https://doi.org/10.1038/s41392-023-01407-6.

Google Scholar

17 Kelly E. and Russell S. J., History of Oncolytic Viruses: Genesis to Genetic Engineering, *Molecular Therapy*. (2007) **15**, no. 4, 651–659, https://doi.org/10.1038/sj.mt.6300108, 2-s2.0-33947245441.

Google Scholar

18 Kingsak M., Meethong T., Jongkhumkrong J., Cai L., and Wang Q., Therapeutic Potential of Oncolytic Viruses in the Era of Precision Oncology, *Biomaterials Translational*. (2023) **4**, no. 2, 67–84, https://doi.org/10.12336/biomatertransl.2023.02.003.

Google Scholar

19 Ishida Y., Agata Y., Shibahara K., and Honjo T., Induced Expression of PD-1, a Novel Member of the Immunoglobulin Gene Superfamily, Upon Programmed Cell Death, *The EMBO Journal*. (1992) **11**, no. 11, 3887–3895, https://doi.org/10.1002/j.1460-2075.1992.tb05481.x.

Google Scholar

20 Dong H., Zhu G., Tamada K., and Chen L., B7-H1, a Third Member of the B7 Family, Co-Stimulates T-Cell Proliferation and Interleukin-10 Secretion, *Nature Medicine*. (1999) **5**, no. 12, 1365–1369, https://doi.org/10.1038/70932, 2-s2.0-0032736029.

Google Scholar

21 Latchman Y. E., Liang S. C., Wu Y. et al., PD-L1-Deficient Mice Show that PD-L1 on T Cells, Antigen-Presenting Cells, and Host Tissues Negatively Regulates T Cells, *Proceedings of the National Academy of Sciences of the USA*. (2004) **101**, no. 29, 10691–10696, https://doi.org/10.1073/pnas.0307252101, 2-s2.0-3242677686.

Google Scholar

22 Latchman Y., Wood C. R., Chernova T. et al., PD-L2 is a Second Ligand for PD-1 and Inhibits T Cell Activation, *Nature Immunology*. (2001) **2**, no. 3, 261–268, https://doi.org/10.1038/85330, 2-s2.0-5844264920.

Google Scholar

23 Xiao Y., Yu S., Zhu B. et al., RGMb is a Novel Binding Partner for PD-L2 and Its Engagement With PD-L2 Promotes Respiratory Tolerance, *Journal of Experimental Medicine*. (2014) **211**, no. 5, 943–959, https://doi.org/10.1084/jem.20130790, 2-s2.0-84899758346.

Google Scholar

24 Park J. J., Omiya R., Matsumura Y. et al., B7-H1/CD80 Interaction is Required for the Induction and Maintenance of Peripheral T-Cell Tolerance, *Blood*. (2010) **116**, no. 8, 1291–1298, https://doi.org/10.1182/blood-2010-01-265975, 2-s2.0-77956496386.

Google Scholar

25 Zhang X., Schwartz J. C., Guo X. et al., Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1, *Immunity*. (2004) **20**, no. 3, 337–347, https://doi.org/10.1016/s1074-7613(04)00051-2, 2-s2.0-12144290320.

Google Scholar

26 Lázár-Molnár E., Yan Q., Cao E., Ramagopal U., Nathenson S. G., and Almo S. C., Crystal Structure of the Complex Between Programmed Death-1 (PD-1) and its Ligand PD-L2, *Proceedings of the National Academy of Sciences of the USA*. (2008) **105**, no. 30, 10483–10488, https://doi.org/10.1073/pnas.0804453105, 2-s2.0-48749095324.

Google Scholar

27 Quatrini L., Mariotti F. R., Munari E., Tumino N., Vacca P., and Moretta L., The Immune Checkpoint PD-1 in Natural Killer Cells: Expression, Function and Targeting in Tumour Immunotherapy, *Cancers (Basel)*. (2020) **12**, no. 11, https://doi.org/10.3390/cancers12113285.

Google Scholar

28 Liu R., Li H. F., and Li S., PD-1-Mediated Inhibition of T Cell Activation: Mechanisms and Strategies for Cancer Combination Immunotherapy, *Cell Insight*. (2024) **3**, no. 2, https://doi.org/10.1016/j.cellin.2024.100146.

Google Scholar

29 Arasanz H., Gato-Cañas M., Zuazo M. et al., PD1 Signal Transduction Pathways in T Cells, *Oncotarget*. (2017) **8**, no. 31, 51936–51945, https://doi.org/10.18632/oncotarget.17232, 2-s2.0-85026750421.

Google Scholar

30 Lin X., Kang K., Chen P. et al., Regulatory Mechanisms of PD-1/pd-L1 in Cancers, *Molecular Cancer*. (2024) **23**, no. 1, https://doi.org/10.1186/s12943-0

24-02023-w.

Google Scholar

31 Keir M. E., Butte M. J., Freeman G. J., and Sharpe A. H., PD-1 and Its Ligands in Tolerance and Immunity, *Annual Review of Immunology*. (2008) **26**, no. 1, 677–704, https://doi.org/10.1146/annurev.immunol.26.021607.090331, 2-s2.0-42649125225.

Google Scholar

32 Taylor A., Verhagen J., Blaser K., Akdis M., and Akdis C. A., Mechanisms of Immune Suppression by Interleukin-10 and Transforming Growth Factor-β: The Role of T Regulatory Cells, *Immunology*. (2006) **117**, no. 4, 433–442, https://doi.org/10.1111/j.1365-2567.2006.02321.x, 2-s2.0-33645023639.

Google Scholar

33 Zheng Y., Fang Y. C., and Li J., PD-L1 Expression Levels on Tumor Cells Affect Their Immunosuppressive Activity, *Oncology Letters*. (2019) **18**, no. 5, 5399–5407, https://doi.org/10.3892/ol.2019.10903, 2-s2.0-85073759189.

Google Scholar

34 Ju X., Zhang H., Zhou Z., and Wang Q., Regulation of PD-L1 Expression in Cancer and Clinical Implications in Immunotherapy, *American Journal of Cancer Research*. (2020) **10**, no. 1, 1–11.

Google Scholar

35 Lin Q., Wang X., and Hu Y., The Opportunities and Challenges in Immunotherapy: Insights From the Regulation of PD-L1 in Cancer Cells,

Cancer Letters. (2023) **569**, https://doi.org/10.1016/j.canlet.2023.216318.

Google Scholar

36 Kataoka K., Miyoshi H., Sakata S. et al., Frequent Structural Variations Involving Programmed Death Ligands in Epstein-Barr Virus-Associated Lymphomas, *Leukemia*. (2019) **33**, no. 7, 1687–1699, https://doi.org/10.1038/s41375-019-0380-5, 2-s2.0-85060671911.

Google Scholar

37 Yi M., Niu M., Xu L., Luo S., and Wu K., Regulation of PD-L1 Expression in the Tumor Microenvironment, *Journal of Hematology & Oncology*. (2021) **14**, no. 1, https://doi.org/10.1186/s13045-020-01027-5.

Google Scholar

38 Huang H. C., Wang S. H., Fang G. C. et al., Upregulation of PD-L1 by SARS-CoV-2 Promotes Immune Evasion, *Journal of Medical Virology*. (2023) **95**, no. 2, https://doi.org/10.1002/jmv.28478.

Google Scholar

39 Lu C., Redd P. S., Lee J. R., Savage N., and Liu K., The Expression Profiles and Regulation of PD-L1 in Tumor-Induced Myeloid-Derived Suppressor Cells, *OncoImmunology*. (2016) **5**, no. 12, https://doi.org/10.1080/2162402x.2016.1247135, 2-s2.0-85007499773.

Google Scholar

40 Yin S., Chen Z., Chen D., and Yan D., Strategies Targeting PD-L1 Expression and Associated Opportunities for Cancer Combination Therapy,

Theranostics. (2023) **13**, no. 5, 1520–1544, https://doi.org/10.7150/thno.80091.

 Google Scholar

41 Jun H., Seo S. K., Jeong H. Y. et al., B7-H1 (CD274) Inhibits the Development of Herpetic Stromal Keratitis (HSK), *FEBS Letters*. (2005) **579**, no. 27, 6259–6264, https://doi.org/10.1016/j.febslet.2005.09.098, 2-s2.0-27544462006.

 Google Scholar

42 Bai W., Tang X., Xiao T. et al., Enhancing Antitumor Efficacy of Oncolytic Virus M1 via Albendazole-Sustained CD8+ T Cell Activation, *Molecular Therapy Oncology*. (2024) **32**, no. 2, https://doi.org/10.1016/j.omton.2024.200813.

 Google Scholar

43 Liu Z., Ravindranathan R., Kalinski P., Guo Z. S., and Bartlett D. L., Rational Combination of Oncolytic Vaccinia Virus and PD-L1 Blockade Works Synergistically to Enhance Therapeutic Efficacy, *Nature Communications*. (2017) **8**, no. 1, https://doi.org/10.1038/ncomms14754, 2-s2.0-85016152800.

 Google Scholar

44 Woller N., Gürlevik E., Fleischmann-Mundt B. et al., Viral Infection of Tumors Overcomes Resistance to PD-1-Immunotherapy by Broadening Neoantigenome-Directed T-Cell Responses, *Molecular Therapy*. (2015) **23**, no. 10, 1630–1640, https://doi.org/10.1038/mt.2015.115, 2-s2.0-84943582368.

 Google Scholar

45 Quetglas J. I., Labiano S., Aznar M. et al., Virotherapy With a Semliki Forest Virus-Based Vector Encoding IL12 Synergizes With PD-1/pd-L1 Blockade, *Cancer Immunology Research*. (2015) **3**, no. 5, 449–454, https://doi.org/10.1158/2326-6066.cir-14-0216, 2-s2.0-84962219179.

Google Scholar

46 Kelly K. R., Espitia C. M., Zhao W. et al., Oncolytic Reovirus Sensitizes Multiple Myeloma Cells to Anti-PD-L1 Therapy, *Leukemia*. (2018) **32**, no. 1, 230–233, https://doi.org/10.1038/leu.2017.272, 2-s2.0-85048474247.

Google Scholar

47 Jiang H., Rivera-Molina Y., Gomez-Manzano C. et al., Oncolytic Adenovirus and Tumor-Targeting Immune Modulatory Therapy Improve Autologous Cancer Vaccination, *Cancer Research*. (2017) **77**, no. 14, 3894–3907, https://doi.org/10.1158/0008-5472.can-17-0468, 2-s2.0-85023741536.

Google Scholar

48 Hodgins J. J., Abou-Hamad J., O'Dwyer C. E. et al., PD-L1 Promotes Oncolytic Virus Infection via a Metabolic Shift That Inhibits the Type I IFN Pathway, *Journal of Experimental Medicine*. (2024) **221**, no. 7, https://doi.org/10.1084/jem.20221721.

Google Scholar

49 Jones D., Blackmon A., Neff C. P. et al., Varicella-Zoster Virus Downregulates Programmed Death Ligand 1 and Major Histocompatibility Complex Class I in Human Brain Vascular Adventitial Fibroblasts, Perineurial Cells, and Lung Fibroblasts, *Journal of Virology*. (2016) **90**, no. 23, 10527–10534, https://doi.org/10.1128/jvi.01546-16, 2-s2.0-85000879102.

Google Scholar

50 Bryant-Hudson K. M. and Carr D. J., PD-L1-expressing Dendritic Cells Contribute to Viral Resistance During Acute HSV-1 Infection, *Clinical and Developmental Immunology*. (2012) **2012**, 1–9, https://doi.org/10.1155/2012/924619, 2-s2.0-84858206022.

Google Scholar

51 Nasar R. T., Uche I. K., and Kousoulas K. G., Targeting Cancers With oHSV-Based Oncolytic Viral Immunotherapy, *Current Issues in Molecular Biology*. (2024) **46**, no. 6, 5582–5594, https://doi.org/10.3390/cimb46060334.

Google Scholar

52 Chiu D. K., Yuen V. W., Cheu J. W. et al., Hepatocellular Carcinoma Cells Up-Regulate PVRL1, Stabilizing PVR and Inhibiting the Cytotoxic T-Cell Response via TIGIT to Mediate Tumor Resistance to PD1 Inhibitors in Mice, *Gastroenterology*. (2020) **159**, no. 2, 609–623, https://doi.org/10.1053/j.gastro.2020.03.074.

Google Scholar

53 Shen W., Patnaik M. M., Ruiz A., Russell S. J., and Peng K. W., Immunovirotherapy With Vesicular Stomatitis Virus and PD-L1 Blockade Enhances Therapeutic Outcome in Murine Acute Myeloid Leukemia, *Blood*. (2016) **127**, no. 11, 1449–1458, https://doi.org/10.1182/blood-2015-06-652503, 2-s2.0-84962607727.

Google Scholar

54 An J., Hu E., Shi Y. et al., Single-Cell Analysis of Oncolytic Virotherapy in Adult T-Cell Leukemia/Lymphoma, *The Journal for ImmunoTherapy of Cancer*. (2025) **13**, no. 3, https://doi.org/10.1136/jitc-2024-011265.

Google Scholar

55 Kwok G., Yau T. C., Chiu J. W., Tse E., and Kwong Y. L., Pembrolizumab (Keytruda), *Human Vaccines & Immunotherapeutics*. (2016) **12**, no. 11, 2777–2789, https://doi.org/10.1080/21645515.2016.1199310, 2-s2.0-85009785163.

Google Scholar

56 Shinno Y., Goto Y., Ohuchi M. et al., The Long Half-Life of Programmed Cell Death Protein 1 Inhibitors May Increase the Frequency of Immune-Related Adverse Events After Subsequent EGFR Tyrosine Kinase Inhibitor Therapy, *JTO Clinical and Research Reports*. (2020) **1**, no. 1, https://doi.org/10.1016/j.jtocrr.2020.100008.

Google Scholar

57 Franks M. L., An J.-H., and Leavenworth J. W., The Role of Natural Killer Cells in Oncolytic Virotherapy: Friends or Foes?, *Vaccines*. (2024) **12**, no. 7, https://doi.org/10.3390/vaccines12070721.

Google Scholar

58 Kanerva A., Nokisalmi P., Diaconu I. et al., Antiviral and Antitumor T-Cell Immunity in Patients Treated With GM-CSF-Coding Oncolytic Adenovirus, *Clinical Cancer Research*. (2013) **19**, no. 10, 2734–2744, https://doi.org/10.1158/1078-0432.ccr-12-2546, 2-s2.0-84878074018.

Google Scholar

59 Miyamoto S., Inoue H., Nakamura T. et al., Coxsackievirus B3 is an Oncolytic Virus With Immunostimulatory Properties That is Active Against Lung Adenocarcinoma, *Cancer Research*. (2012) **72**, no. 10, 2609–2621, https://doi.org/10.1158/0008-5472.can-11-3185, 2-s2.0-84861112821.

Google Scholar

60 Samson A., Bentham M. J., Scott K. et al., Oncolytic Reovirus as a Combined Antiviral and Anti-Tumour Agent for the Treatment of Liver Cancer, *Gut*. (2018) **67**, no. 3, 562–573, https://doi.org/10.1136/gutjnl-2016-312009, 2-s2.0-85001697099.

Google Scholar

61 Geoffroy K. and Bourgeois-Daigneault M.-C., The Pros and Cons of Interferons for Oncolytic Virotherapy, *Cytokine & Growth Factor Reviews*. (2020) **56**, 49–58, https://doi.org/10.1016/j.cytogfr.2020.07.002.

Google Scholar

62 Fenton S. E., Saleiro D., and Platanias L. C., Type I and II Interferons in the Anti-Tumor Immune Response, *Cancers (Basel)*. (2021) **13**, no. 5, https://doi.org/10.3390/cancers13051037.

Google Scholar

63 Jiang K., Li Y., Zhu Q. et al., Pharmacological Modulation of Autophagy Enhances Newcastle Disease Virus-Mediated Oncolysis in Drug-Resistant Lung Cancer Cells, *BMC Cancer*. (2014) **14**, 551–615, https://doi.org/10.1186/1471-2407-14-551, 2-s2.0-84904847712.

Google Scholar

64 Mousavinasab F. and Razani E., Harnessing the Potential of Vesicular Stomatitis Virus as a Novel Therapeutic Strategy for Cancer Treatment, *Iranian Journal of Blood and Cancer*. (2023) **15**, no. 2, 117–127, https://doi.org/10.58209/ijbc.15.2.117.

Google Scholar

65 Annels N. E., Simpson G. R., Denyer M. et al., Oncolytic Reovirus-Mediated Recruitment of Early Innate Immune Responses Reverses Immunotherapy Resistance in Prostate Tumors, *Molecular Therapy Oncolytics*. (2021) **20**, 434–446, https://doi.org/10.1016/j.omto.2020.09.010.

Google Scholar

66 Chatelain C., Berland L., Grard M. et al., Interplay Between Oncolytic Measles Virus, Macrophages and Cancer Cells Induces a Proinflammatory Tumor Microenvironment, *OncoImmunology*. (2024) **13**, no. 1, https://doi.org/10.1080/2162402x.2024.2377830.

Google Scholar

67 Deng L., Fan J., Guo M., and Huang B., Oncolytic and Immunologic Cancer Therapy With GM-CSF-Armed Vaccinia Virus of Tian Tan Strain Guang9, *Cancer Letters*. (2016) **372**, no. 2, 251–257, https://doi.org/10.1016/j.canlet.2016.01.025, 2-s2.0-84957713781.

Google Scholar

68 Veinalde R., Grossardt C., Hartmann L. et al., Oncolytic Measles Virus Encoding Interleukin-12 Mediates Potent Antitumor Effects Through T Cell Activation, *OncoImmunology*. (2017) **6**, no. 4, https://doi.org/10.1080/2162402x.2017.1285992, 2-s2.0-85017124160.

Google Scholar

69 Zhang W., Fulci G., Wakimoto H. et al., Combination of Oncolytic Herpes Simplex Viruses Armed With Angiostatin and IL-12 Enhances Antitumor Efficacy in Human Glioblastoma Models, *Neoplasia*. (2013) **15**, no. 6, 591–599, https://doi.org/10.1593/neo.13158, 2-s2.0-84878664183.

Google Scholar

70 Zhu W., Zhang H., Shi Y., Song M., Zhu B., and Wei L., Oncolytic Adenovirus Encoding Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TRAIL) Inhibits the Growth and Metastasis of Triple-Negative Breast Cancer, *Cancer Biology & Therapy*. (2013) **14**, no. 11, 1016–1023, https://doi.org/10.4161/cbt.26043, 2-s2.0-84885971231.

Google Scholar

71 Geletneky K., Hajda J., Angelova A. L. et al., Oncolytic H-1 Parvovirus Shows Safety and Signs of Immunogenic Activity in a First Phase I/IIa Glioblastoma Trial, *Molecular Therapy*. (2017) **25**, no. 12, 2620–2634, https://doi.org/10.1016/j.ymthe.2017.08.016, 2-s2.0-85030167053.

Google Scholar

72 Müller L. M. E., Holmes M., Michael J. L. et al., Plasmacytoid Dendritic Cells Orchestrate Innate and Adaptive Anti-Tumor Immunity Induced by Oncolytic Coxsackievirus A21, *The Journal for ImmunoTherapy of Cancer*. (2019) **7**, no. 1, https://doi.org/10.1186/s40425-019-0632-y, 2-s2.0-85068505252.

Google Scholar

73 Wu Y. Y., Sun T. K., Chen M. S., Munir M., and Liu H. J., Oncolytic Viruses-Modulated Immunogenic Cell Death, Apoptosis and Autophagy Linking to Virotherapy and Cancer Immune Response, *Frontiers in Cellular and Infection Microbiology*. (2023) **13**, https://doi.org/10.3389/fcimb.2023.1142172.

Google Scholar

74 Mardi A., Shirokova A. V., Mohammed R. N. et al., Biological Causes of Immunogenic Cancer Cell Death (ICD) and Anti-Tumor Therapy; Combination of Oncolytic Virus-Based Immunotherapy and CAR T-Cell Therapy for ICD Induction, *Cancer Cell International*. (2022) **22**, no. 1, https://doi.org/10.1186/s12935-022-02585-z.

Google Scholar

75 Todo T., Martuza R. L., Rabkin S. D., and Johnson P. A., Oncolytic Herpes Simplex Virus Vector With Enhanced MHC Class I Presentation and Tumor Cell Killing, *Proceedings of the National Academy of Sciences of the USA*. (2001) **98**, no. 11, 6396–6401, https://doi.org/10.1073/pnas.101136398, 2-s2.0-0035933088.

Google Scholar

76 Zhao L. and Liu H., Newcastle Disease Virus: A Promising Agent for Tumour Immunotherapy, *Clinical and Experimental Pharmacology and Physiology*. (2012) **39**, no. 8, 725–730, https://doi.org/10.1111/j.1440-1681.2011.05662.x, 2-s2.0-84864316905.

Google Scholar

77 Roussot N., Kaderbhai C., and Ghiringhelli F., Targeting Immune Checkpoint Inhibitors for Non-Small-Cell Lung Cancer: Beyond PD-1/pd-L1 Monoclonal Antibodies, *Cancers (Basel)*. (2025) **17**, no. 5, https://doi.org/10.33

90/cancers17050906.

 Google Scholar

78 Lemos de Matos A., Franco L. S., and McFadden G., Oncolytic Viruses and the Immune System: The Dynamic Duo, *Molecular Therapy-Methods & Clinical Development*. (2020) **17**, 349–358, https://doi.org/10.1016/j.omtm.2020.01.001.

 Google Scholar

79 Tan E. W., Abd-Aziz N., Poh C. L., and Tan K. O., Engineered Oncolytic Adenoviruses: An Emerging Approach for Cancer Therapy, *Pathogens*. (2022) **11**, no. 10, https://doi.org/10.3390/pathogens11101146.

 Google Scholar

80 Bishnoi S., Tiwari R., Gupta S., Byrareddy S. N., and Nayak D., Oncotargeting by Vesicular Stomatitis Virus (VSV): Advances in Cancer Therapy, *Viruses*. (2018) **10**, no. 2, https://doi.org/10.3390/v10020090, 2-s2.0-85042551623.

 Google Scholar

81 Mayrhofer P. and Kunert R., Nomenclature of Humanized mAbs: Early Concepts, Current Challenges and Future Perspectives, *Human Antibodies*. (2018) **27**, no. 1, 37–51, https://doi.org/10.3233/hab-180347, 2-s2.0-85058526251.

 Google Scholar

82 Munari E., Mariotti F. R., Quatrini L. et al., PD-1/PD-L1 in Cancer:

Pathophysiological, Diagnostic and Therapeutic Aspects, *International Journal of Molecular Sciences*. (2021) **22**, no. 10, https://doi.org/10.3390/ijms22105123.

Google Scholar

83 Ribas A., Dummer R., Puzanov I. et al., Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy, *Cell*. (2018) **174**, no. 4, 1031–1032, https://doi.org/10.1016/j.cell.2018.07.035, 2-s2.0-85050944829.

Google Scholar

84 Chesney J. A., Ribas A., Long G. V. et al., Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined With Pembrolizumab for Advanced Melanoma, *Journal of Clinical Oncology*. (2023) **41**, no. 3, 528–540, https://doi.org/10.1200/jco.22.00343.

Google Scholar

85 Kelly C. M., Antonescu C. R., Bowler T. et al., Objective Response Rate Among Patients With Locally Advanced or Metastatic Sarcoma Treated With Talimogene Laherparepvec in Combination With Pembrolizumab: A Phase 2 Clinical Trial, *JAMA Oncology*. (2020) **6**, no. 3, 402–408, https://doi.org/10.1001/jamaoncol.2019.6152.

Google Scholar

86 Harrington K. J., Kong A., Mach N. et al., Talimogene Laherparepvec and Pembrolizumab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (MASTERKEY-232): A Multicenter, Phase 1b Study, *Clinical Cancer Research*. (2020) **26**, no. 19, 5153–5161, https://doi.org/10.1158/1078-0432.Ccr-20-1170.

[redacted] Google Scholar

87 Wong M. K., Sacco J. J., Robert C. et al., *Efficacy and Safety of RP1 Combined With Nivolumab in Patients With Anti–PD-1–failed Melanoma From the IGNYTE Clinical Trial*, 2024, American Society of Clinical Oncology.

[redacted] Google Scholar

88 Liu J., Wang X., Li Z. et al., Neoadjuvant Oncolytic Virus Orienx010 and Toripalimab in Resectable Acral Melanoma: A Phase Ib Trial, *Signal Transduction and Targeted Therapy*. (2024) **9**, no. 1, https://doi.org/10.1038/s41392-024-02029-2.

[redacted] Google Scholar

89 Zhang H., Ren Y., Wang F. et al., The Long-Term Effectiveness and Mechanism of Oncolytic Virotherapy Combined With Anti-PD-L1 Antibody in Colorectal Cancer Patient, *Cancer Gene Therapy*. (2024) **31**, no. 9, 1412–1426, https://doi.org/10.1038/s41417-024-00807-2.

[redacted] Google Scholar

90 Rudin C. M., Pandha H. S., Zibelman M. et al., Phase 1, Open-Label, Dose-Escalation Study on the Safety, Pharmacokinetics, and Preliminary Efficacy of Intravenous Coxsackievirus A21 (V937), With or Without Pembrolizumab, in Patients With Advanced Solid Tumors, *The Journal for ImmunoTherapy of Cancer*. (2023) **11**, no. 1, https://doi.org/10.1136/jitc-2022-005007.

[redacted] Google Scholar

91 Dummer R., Robert C., Scolyer R. A. et al., Neoadjuvant Anti-PD-1 Alone

or in Combination With Anti-TIGIT or an Oncolytic Virus in Resectable Stage IIIB–D Melanoma: A Phase 1/2 Trial, *Nature Medicine*. (2025) **31**, no. 1, 144–151, https://doi.org/10.1038/s41591-024-03411-x.

Google Scholar

92 Silk A. W., O'Day S. J., Kaufman H. L. et al., A Phase 1b Single-Arm Trial of Intratumoral Oncolytic Virus V937 in Combination With Pembrolizumab in Patients With Advanced Melanoma: Results From the CAPRA Study, *Cancer Immunology Immunotherapy*. (2023) **72**, no. 6, 1405–1415, https://doi.org/10.1007/s00262-022-03314-1.

Google Scholar

93 Mahalingam D., Chen S., Xie P. et al., Combination of Pembrolizumab and Pelareorep Promotes Anti-Tumour Immunity in Advanced Pancreatic Adenocarcinoma (PDAC), *British Journal of Cancer*. (2023) **129**, no. 5, 782–790, https://doi.org/10.1038/s41416-023-02344-5.

Google Scholar

94 Shoushtari A. N., Olszanski A. J., Nyakas M. et al., Pilot Study of ONCOS-102 and Pembrolizumab: Remodeling of the Tumor Microenvironment and Clinical Outcomes in Anti-PD-1-Resistant Advanced Melanoma, *Clinical Cancer Research*. (2023) **29**, no. 1, 100–109, https://doi.org/10.1158/1078-0432.Ccr-22-2046.

Google Scholar

95 Zamarin D., Odunsi K., Slomovitz B. M. et al., *Phase I/II Study to Evaluate Systemic Durvalumab+ Intraperitoneal (IP) ONCOS-102 in Patients With Peritoneal Disease Who Have Epithelial Ovarian (OC) or Metastatic Colorectal Cancer (CRC): Interim Phase I Clinical and Translational Results*, 2020, American Society of

Clinical Oncology.

 Google Scholar

96 Nassiri F., Patil V., Yefet L. S. et al., Oncolytic DNX-2401 Virotherapy Plus Pembrolizumab in Recurrent Glioblastoma: A Phase 1/2 Trial, *Nature Medicine*. (2023) **29**, no. 6, 1370–1378, https://doi.org/10.1038/s41591-023-02347-y.

 Google Scholar

97 Fakih M., Harb W., Mahadevan D. et al., Safety and Efficacy of the Tumor-Selective Adenovirus Enadenotucirev, in Combination With Nivolumab, in Patients With Advanced/metastatic Epithelial Cancer: A Phase I Clinical Trial (SPICE), *The Journal for ImmunoTherapy of Cancer*. (2023) **11**, no. 4, https://doi.org/10.1136/jitc-2022-006561.

 Google Scholar

98 Yi L., Ning Z., Xu L. et al., The Combination Treatment of Oncolytic Adenovirus H101 With Nivolumab for Refractory Advanced Hepatocellular Carcinoma: An Open-Label, Single-Arm, Pilot Study, *ESMO Open*. (2024) **9**, no. 2, https://doi.org/10.1016/j.esmoop.2024.102239.

 Google Scholar

99 Li R., Shah P. H., Stewart T. F. et al., Oncolytic Adenoviral Therapy Plus Pembrolizumab in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer: The Phase 2 CORE-001 Trial, *Nature Medicine*. (2024) **30**, no. 8, 2216–2223, https://doi.org/10.1038/s41591-024-03025-3.

 Google Scholar

100 Li R., Villa N. Y., Yu X. et al., Oncolytic Immunotherapy With Nivolumab in Muscle-Invasive Bladder Cancer: A Phase 1b Trial, *Nature Medicine*. (2025) **31**, no. 1, 176–188, https://doi.org/10.1038/s41591-024-03324-9.

Google Scholar

101 Block M. S., Clubb J. H. A., Mäenpää J. et al., The Oncolytic Adenovirus TILT-123 With Pembrolizumab in Platinum Resistant or Refractory Ovarian Cancer: The Phase 1a PROTA Trial, *Nature Communications*. (2025) **16**, no. 1, https://doi.org/10.1038/s41467-025-56482-w.

Google Scholar

102 Chen N., Wang D., Porter C. E. et al., Abstract P3-06-04: Treatment of Metastatic Breast Cancer With Multipotent Oncolytic/Helper Adenovirus CAdVEC, *Cancer Research*. (2023) **83**, no. 5, P3–04, https://doi.org/10.1158/1538-7445.sabcs22-p3-06-04.

Google Scholar

103 Rha S., Bae W., Kim C. et al., 1885P Pexa-Vec (Thymidine Kinase-Deactivated Vaccinia Virus Plus GM-CSF) in Combination With Cemiplimab (REGN2810; ANTI-PD-1) for Metastatic or Unresectable Renal Cell Carcinoma REN026: Results From a Phase II Study, *Annals of Oncology*. (2023) **34**, S1013–S1014, https://doi.org/10.1016/j.annonc.2023.09.1115.

Google Scholar

104 Liu B. L., Robinson M., Han Z. Q. et al., ICP34.5 Deleted Herpes Simplex Virus With Enhanced Oncolytic, Immune Stimulating, and Anti-Tumour Properties, *Gene Therapy*. (2003) **10**, no. 4, 292–303, https://doi.org/10.1038/sj.gt.3301885, 2-s2.0-0037295403.

Google Scholar

105 Andtbacka R. H., Kaufman H. L., Collichio F. et al., Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma, *Journal of Clinical Oncology*. (2015) **33**, no. 25, 2780–2788, https://doi.org/10.1200/jco.2014.58.3377, 2-s2.0-84933586864.

Google Scholar

106 Andtbacka R. H. I., Collichio F., Harrington K. J. et al., Final Analyses of OPTiM: A Randomized Phase III Trial of Talimogene Laherparepvec Versus Granulocyte-Macrophage Colony-Stimulating Factor in Unresectable Stage III-IV Melanoma, *The Journal for ImmunoTherapy of Cancer*. (2019) **7**, no. 1, https://doi.org/10.1186/s40425-019-0623-z, 2-s2.0-85066852382.

Google Scholar

107 Kaufman H. L., Shalhout S. Z., and Iodice G., Talimogene Laherparepvec: Moving From First-In-Class to Best-In-Class, *Frontiers in Molecular Biosciences*. (2022) **9**, https://doi.org/10.3389/fmolb.2022.834841.

Google Scholar

108 Nguyen H. M., Bommareddy P. K., Silk A. W., and Saha D., Optimal Timing of PD-1 Blockade in Combination With Oncolytic Virus Therapy, *Seminars in Cancer Biology*. (2022) **86**, no. 3, 971–980, https://doi.org/10.1016/j.semcancer.2021.05.019.

Google Scholar

109 Wongariyapak A., Roulstone V., Melcher A. A., Pedersen M., and

Harrington K. J., Combination Strategies Incorporating Oncolytic Viruses and Immune Checkpoint Inhibitors for Advanced Melanoma: What is the Evidence?, *Annals of Translational Medicine*. (2023) **11**, no. 10, https://doi.org/10.21037/atm-2023-5.

Google Scholar

110 Robert C., Gastman B., Gogas H. et al., Open-Label, Phase II Study of Talimogene Laherparepvec Plus Pembrolizumab for the Treatment of Advanced Melanoma That Progressed on Prior Anti-PD-1 Therapy: MASTERKEY-115, *European Journal of Cancer*. (2024) **207**, https://doi.org/10.1016/j.ejca.2024.114120.

Google Scholar

111 Thomas S., Kuncheria L., Roulstone V. et al., Development of a New Fusion-Enhanced Oncolytic Immunotherapy Platform Based on Herpes Simplex Virus Type 1, *The Journal for ImmunoTherapy of Cancer*. (2019) **7**, no. 1, https://doi.org/10.1186/s40425-019-0682-1, 2-s2.0-85070581794.

Google Scholar

112 Milhem M. M., Vanderwalde A. M., Bowles T. L. et al., Updated Results From the Skin Cancer Cohorts From an Ongoing Phase 1/2 Multicohort Study of Rp1, An Enhanced Potency Oncolytic HSV, Combined With Nivolumab (IGNYTE), *Journal of Clinical Orthodontics*. (2022) **40**, no. 16, https://doi.org/10.1200/jco.2022.40.16_suppl.9553.

Google Scholar

113 Harrington K., Nenclares P., Leslie I. et al., 610 Immune Biomarker Analysis of RP1 in Combination With Nivolumab in Patients With Advanced Solid Tumors, *Regular and Young Investigator Award Abstracts*. (2022) https://d

oi.org/10.1136/jitc-2022-sitc2022.0610.

 Google Scholar

114 Luke J. J., Kong G., Gullo G., and Robert C., A Randomized, Controlled, Multicenter, Phase 3 Study of Vusolimogene Oderparepvec (VO) Combined With Nivolumab vs Treatment of Physician's Choice in Patients With Advanced Melanoma That has Progressed on Anti–PD-1 and Anti–CTLA-4 Therapy (IGNYTE-3), 2024, American Society of Clinical Oncology.

 Google Scholar

115 Ren J., Gwin W. R., Zhou X. et al., Adaptive T Cell Responses Induced by Oncolytic Herpes Simplex Virus-Granulocyte Macrophage-Colony-Stimulating Factor Therapy Expanded by Dendritic Cell and Cytokine-Induced Killer Cell Adoptive Therapy, *OncoImmunology*. (2017) **6**, no. 4, https://doi.org/10.1080/2162402x.2016.1264563, 2-s2.0-85017115902.

 Google Scholar

116 Cui C., Wang X., Lian B. et al., OrienX010, an Oncolytic Virus, in Patients With Unresectable Stage IIIC-IV Melanoma: A Phase Ib Study, *The Journal for ImmunoTherapy of Cancer*. (2022) **10**, no. 4, https://doi.org/10.1136/jitc-2021-004307.

 Google Scholar

117 Annels N. E., Mansfield D., Arif M. et al., Phase I Trial of an ICAM-1-Targeted Immunotherapeutic-Coxsackievirus A21 (CVA21) as an Oncolytic Agent Against Non Muscle-Invasive Bladder Cancer, *Clinical Cancer Research*. (2019) **25**, no. 19, 5818–5831, https://doi.org/10.1158/1078-0432.CCR-18-4022, 2-s2.0-85072820084.

[redacted] Google Scholar

118 Silk A. W., Kaufman H., Gabrail N. et al., Abstract CT026: Phase 1b Study of Intratumoral Coxsackievirus A21 (*C* V *A* 21) and Systemic *P* Emb *R* Olizumab in *a* Dvanced Melanoma Patients: Interim Results of the CAPRA Clinical Trial, *Cancer Research*. (2017) **77**, no. 13, https://doi.org/10.1158/1538-7445.am2017-ct026.

[redacted] Google Scholar

119 Rudin C., Pandha H., Gupta S. et al., Phase Ib KEYNOTE-200: A Study of an Intravenously Delivered Oncolytic Virus, Coxsackievirus A21 in Combination With Pembrolizumab in Advanced NSCLC and Bladder Cancer Patients, *Annals of Oncology*. (2018) **29**, https://doi.org/10.1093/annonc/mdy424.050.

[redacted] Google Scholar

120 Mahalingam D., Fountzilas C., Moseley J. et al., A Phase II Study of REOLYSIN(®) (Pelareorep) in Combination With Carboplatin and Paclitaxel for Patients With Advanced Malignant Melanoma, *Cancer Chemotherapy and Pharmacology*. (2017) **79**, no. 4, 697–703, https://doi.org/10.1007/s00280-017-3260-6, 2-s2.0-85015071483.

[redacted] Google Scholar

121 Roulstone V., Mansfield D., Harris R. J. et al., Antiviral Antibody Responses to Systemic Administration of an Oncolytic RNA Virus: The Impact of Standard Concomitant Anticancer Chemotherapies, *The Journal for ImmunoTherapy of Cancer*. (2021) **9**, no. 7, https://doi.org/10.1136/jitc-2021-002673.

Google Scholar

122 Mahalingam D., Goel S., Aparo S. et al., A Phase II Study of Pelareorep (REOLYSIN(®)) in Combination With Gemcitabine for Patients With Advanced Pancreatic Adenocarcinoma, *Cancers (Basel)*. (2018) **10**, no. 6, https://doi.org/10.3390/cancers10060160, 2-s2.0-85047822244.

Google Scholar

123 Mahalingam D., Wilkinson G. A., Eng K. H. et al., Pembrolizumab in Combination With the Oncolytic Virus Pelareorep and Chemotherapy in Patients With Advanced Pancreatic Adenocarcinoma: A Phase Ib Study, *Clinical Cancer Research*. (2020) **26**, no. 1, 71–81, https://doi.org/10.1158/1078-0432.ccr-19-2078.

Google Scholar

124 Saffarzadeh N., Foord E., O'Leary E. et al., Inducing Expression of ICOS-L by Oncolytic Adenovirus to Enhance Tumor-Specific Bi-Specific Antibody Efficacy, *Journal of Translational Medicine*. (2024) **22**, no. 1, https://doi.org/10.1186/s12967-024-05049-2.

Google Scholar

125 Ponce S., Cedrés S., Ricordel C. et al., ONCOS-102 Plus Pemetrexed and Platinum Chemotherapy in Malignant Pleural Mesothelioma: A Randomized Phase 2 Study Investigating Clinical Outcomes and the Tumor Microenvironment, *The Journal for ImmunoTherapy of Cancer*. (2023) **11**, no. 9, https://doi.org/10.1136/jitc-2023-007552.

Google Scholar

126 Ranki T., Pesonen S., Hemminki A. et al., Phase I Study With ONCOS-102 for the Treatment of Solid Tumors-An Evaluation of Clinical Response and Exploratory Analyses of Immune Markers, *The Journal for ImmunoTherapy of Cancer*. (2016) **4**, no. 1, https://doi.org/10.1186/s40425-016-0121-5, 2-s2.0-84997285773.

Google Scholar

127 Levi S. T. and Boland G. M., ONCOS-102: A Step Forward or Sideways?, *Clinical Cancer Research*. (2023) **29**, no. 1, 3–4, https://doi.org/10.1158/1078-0432.Ccr-22-2887.

Google Scholar

128 Lang F. F., Conrad C., Gomez-Manzano C. et al., Phase I Study of DNX-2401 (Delta-24-RGD) Oncolytic Adenovirus: Replication and Immunotherapeutic Effects in Recurrent Malignant Glioma, *Journal of Clinical Oncology*. (2018) **36**, no. 14, 1419–1427, https://doi.org/10.1200/jco.2017.75.8219, 2-s2.0-85043530708.

Google Scholar

129 Gállego Pérez-Larraya J., Garcia-Moure M., Labiano S. et al., Oncolytic DNX-2401 Virus for Pediatric Diffuse Intrinsic Pontine Glioma, *New England Journal of Medicine*. (2022) **386**, no. 26, 2471–2481, https://doi.org/10.1056/NEJMoa2202028.

Google Scholar

130 Illingworth S., Di Y., Bauzon M. et al., Preclinical Safety Studies of Enadenotucirev, a Chimeric Group B Human-Specific Oncolytic Adenovirus, *Molecular Therapy Oncolytics*. (2017) **5**, 62–74, https://doi.org/10.1016/j.omto.2017.03.003, 2-s2.0-85020550693.

Google Scholar

131 Machiels J. P., Salazar R., Rottey S. et al., A Phase 1 Dose Escalation Study of the Oncolytic Adenovirus Enadenotucirev, Administered Intravenously to Patients With Epithelial Solid Tumors (EVOLVE), *The Journal for ImmunoTherapy of Cancer*. (2019) **7**, no. 1, https://doi.org/10.1186/s40425-019-0510-7, 2-s2.0-85060579717.

Google Scholar

132 Garcia-Carbonero R., Salazar R., Duran I. et al., Phase 1 Study of Intravenous Administration of the Chimeric Adenovirus Enadenotucirev in Patients Undergoing Primary Tumor Resection, *The Journal for ImmunoTherapy of Cancer*. (2017) **5**, no. 1, https://doi.org/10.1186/s40425-017-0277-7, 2-s2.0-85029639192.

Google Scholar

133 Das S. and Acharya D., Immunological Assessment of Recent Immunotherapy for Colorectal Cancer, *Immunological Investigations*. (2023) **52**, no. 8, 1065–1095, https://doi.org/10.1080/08820139.2023.2264906.

Google Scholar

134 Cripe T. P., Ngo M. C., Geller J. I. et al., Phase 1 Study of Intratumoral Pexa-Vec (JX-594), An Oncolytic and Immunotherapeutic Vaccinia Virus, in Pediatric Cancer Patients, *Molecular Therapy*. (2015) **23**, no. 3, 602–608, https://doi.org/10.1038/mt.2014.243, 2-s2.0-84924071637.

Google Scholar

135 Toulmonde M., Cousin S., Bessede A. et al., A Phase Ib Trial of JX-594 (Pexa-Vec), a Targeted Multimechanistic Oncolytic Vaccinia Virus, in Combination With Low-Dose Cyclophosphamide in Patients With Advanced Solid Tumors, *Annals of Oncology*. (2017) **28**, v137–v138, https://doi.org/10.1093/annonc/mdx367.047.

Google Scholar

136 Parato K. A., Breitbach C. J., Le Boeuf F. et al., The Oncolytic Poxvirus JX-594 Selectively Replicates in and Destroys Cancer Cells Driven by Genetic Pathways Commonly Activated in Cancers, *Molecular Therapy*. (2012) **20**, no. 4, 749–758, https://doi.org/10.1038/mt.2011.276, 2-s2.0-84859443203.

Google Scholar

137 Monge C., Xie C., Myojin Y. et al., Phase I/II Study of PexaVec in Combination With Immune Checkpoint Inhibition in Refractory Metastatic Colorectal Cancer, *The Journal for ImmunoTherapy of Cancer*. (2023) **11**, no. 2, https://doi.org/10.1136/jitc-2022-005640.

Google Scholar