

Herpes virus-based therapeutics in dermatology – Past, present and future perspectives

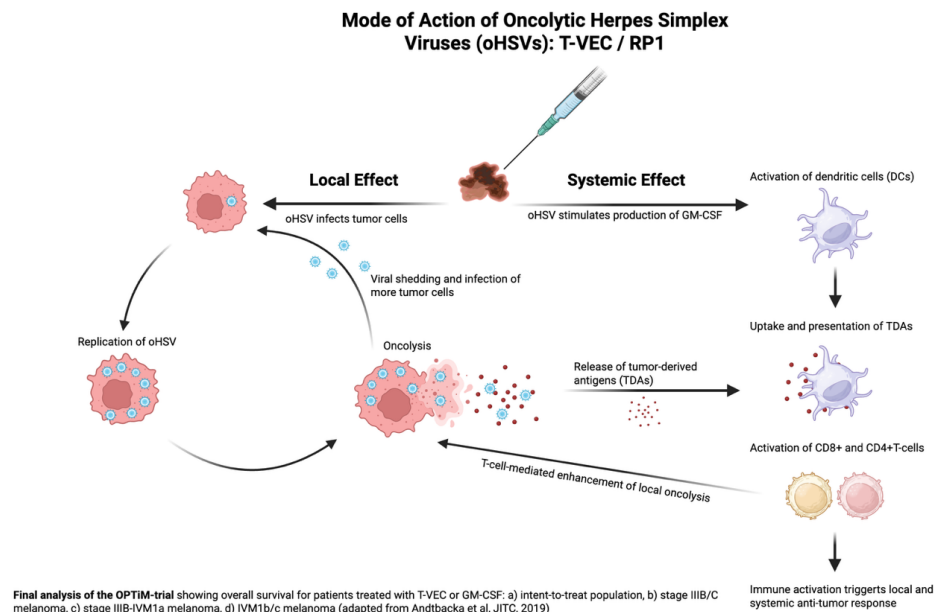
Maximilian Krecu¹, Paul Fiebiger¹, Verena Wally^{1,2}, Peter Koelblinger¹

¹ Department of Dermatology and Allergy, Paracelsus Medical University, Muellner Hauptstraße 48, 5020 Salzburg, Austria

² EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology & Allergy, University Hospital of the Paracelsus Medical University, 5020 Salzburg, Austria

Corresponding author: Maximilian Krecu (m.krecu@salk.at)

Graphical Abstract



Subject editor: Georg Stengl
Received: 25 October 2025
Accepted: 6 March 2026
Published: 3 April 2026

Citation: Krecu M, Fiebiger P, Wally V, Koelblinger P (2026) Herpes virus-based therapeutics in dermatology – Past, present and future perspectives. SKINdeep 2: e176050. <https://doi.org/10.1553/skindeep.2026.176050>

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Mode of action of oHSVs (T-VEC / RP1): oHSVs are injected into tumor cells, where viral DNA replicates and replaces tumor DNA. The HSV US11 gene enhances viral replication, while GM-CSF expression is intended to trigger an additional systemic anti-tumor immune response through the recruitment and activation of macrophages, dendritic cells, and other leukocytes, thereby enhancing the spread of immune-mediated oncolysis beyond the injected lesion. In RP1, GALV-GP-R- expression shall promote systemic anti-tumor activity. Viral replication leads to oncolysis and the release of tumor-derived antigens (TDAs), which are taken up by dendritic cells to activate CD4⁺ and CD8⁺ T cells. This process triggers both local inflammation and a pronounced anti-tumor immune response, ultimately inducing further tumor cell death through apoptosis. GM-CSF = granulocyte-macrophage colony-stimulating factor; Created in <https://BioRender.com>.

Abstract

The growing incidence of skin cancers, including malignant melanoma and non-melanoma skin cancers, presents an ongoing challenge in dermato-oncology. In recent years, herpes virus-based therapeutics, particularly oncolytic herpes simplex virus (oHSV), have gained attention as promising treatment strategies. Engineered to selectively infect and destroy cancer cells while preserving healthy tissue, oHSV induces direct oncolysis and in some patients also promotes systemic anti-tumor immune responses. These mechanisms make oHSV-based approaches especially appealing in cutaneous malignancies, where local and immune-mediated systemic tumor control is critical. Various oHSV variants have been developed to enhance tumor specificity, immune activation, and clinical efficacy. In this review, we highlight the role of herpes virus-based therapies in dermato-oncology, focusing on their mechanisms of action, clinical development, and therapeutic potential in skin cancer treatment.

Key words: Oncolytic herpes simplex virus (oHSV), T-VEC, RP1, oncolytic virotherapy, cancer immunotherapy, melanoma, non-melanoma skin cancer

1. Introduction

In Western countries, melanoma and non-melanoma skin cancers (NMSC) – primarily basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) – are the most common malignancies among Caucasians, with incidence rates continuing to rise [1, 2]. NMSC, when detected at early stages, and melanoma, if excised in situ, are typically well treatable and curable through surgical excision.

However, relapses are frequent, and prognosis is still poor in many patients with locally advanced or metastatic disease stages, despite the introduction of effective immuno- and targeted therapies during the last decade [3–5]. Melanoma and NMSCs are known for their high tumor mutational burden and their corresponding abundant number of neoantigens [6]. However, comparative studies between the different types of skin cancer have revealed key proteomic, genomic, and immunologic differences [7–10]. This has helped to understand how malignant cells interact with different types of immune cells within the tumor microenvironment (TME), eventually enabling immune evasion that leads to tumor growth and/or metastasis development [11]. Of note, this knowledge laid the foundation for the concept of immune checkpoint inhibition, nowadays a key treatment strategy for a plethora of malignancies.

Immune checkpoint inhibitors (ICIs) and targeted therapies (TTs) have transformed dermato-oncology, with the NADINA trial redefining neoadjuvant therapy in resectable stage III melanoma and CheckMate-067 confirming the long-term efficacy of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-antibody ipilimumab in combination with the Programmed cell death protein 1 (PD-1) antibody nivolumab (Ipi/Nivo) in advanced disease [12, 13]. For NMSC and melanoma, available treatment options include surgery, radiotherapy, hedgehog inhibitors, ICIs and TTs, as demonstrated by the efficacy of vismodegib, sonidegib, and cemiplimab in BCC, as well as cemiplimab and pembrolizumab in CSCC [14–19]. Collectively, these data highlight the expanding and durable impact of modern systemic therapies across skin cancer subtypes.

Despite these therapeutic advances – nowadays enabling long-term survival in a significant proportion of even metastasized patients – treatment resistance and treatment-related adverse events (TRAEs) remain critical challenges. Oncolytic viruses (OVs) have emerged as a complementary class of immunotherapeutic agents and may help to overcome primary and secondary resistance to systemic skin cancer treatments. They are characterized by their non-overlapping mechanisms of action and distinct toxicity profiles mainly limited to temporary local and febrile systemic reactions. The concept of viral-based intraleisional therapy is not new: early reports date back over a century, with periods of intense research during the 1950s and 1960s, followed by significant drawbacks due to low efficacy and severe toxicities observed in early human trials [20, 21].

Recent progress in molecular biology and genetic engineering facilitated the development of genetically modified OVs capable of replicating selectively in tumor cells while exhibiting attenuated natural neurovirulence leading to HSV-related diseases in healthy tissues.

This review provides an overview of the mechanism of action of herpes-based OVs, past and present pivotal trials, challenges and limitations, and concludes with an outlook on potential future treatment strategies.

2. Mechanism of action of herpes virus-based oncolytics

Cytolytic viruses, whether naturally occurring or genetically engineered (“armed”), can selectively replicate within tumor cells, causing their lysis and the release of tumor-derived antigens (TDAs), viral pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and pro-inflammatory cytokines [22]. The intra-tumoral administration of oncolytic viruses (OVs) promotes the recruitment of dendritic cells (DCs) to the TME, enhances antigen cross-presentation, and may prime T cells to mount a systemic, polyclonal anti-tumor response, potentially overcoming both intra- and intertumoral heterogeneity [23]. OV-mediated induction of type I interferons (e.g., IFN- α), along with the deletion of viral immune evasion genes such as ICP47 in herpes simplex virus (HSV)-1, enhances major histocompatibility complex class I (MHC-I) expression and improves antigen processing and presentation [24, 25]. Another mechanism of action of engineered OVs is based on the delivery of immunostimulatory transgenes, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), or the expression of costimulatory ligands to further boost the activation and proliferation of tumor-specific T cells, [26]. As a result, OV-induced oncolysis not only reduces tumor burden at the injection site but can also elicit a broader antitumor immune response capable of targeting distant, non-injected lesions [26–28].

Herpes viruses are currently extensively studied candidates for oncolytic virotherapy in skin cancers. However, oncolytic herpes simplex virus (oHSV) variants have also been tested in preclinical models for the treatment of other malignancies, including glioblastoma, glioma, meningioma, colon carcinoma, sarcoma as well as cervical, ovarian, breast, urological, thyroid and liver cancers [29–43].

Prominent examples of oHSV include **Talimogen laherparepvec** (T-VEC) and **Vusolimogene oderparepvec** (RP1), for which the most preclinical and clinical data is available.

Herpes viruses possess a large double-stranded DNA genome (152 kb) enclosed within an enveloped icosahedral capsid [44]. HSV exists in two major

variants, HSV-1 and HSV-2, and is also referred to as a neurotropic virus, given its capability of infecting nerve tissue, specifically neurons, where it can establish stable latent infections. Three key characteristics render HSV a major candidate for tumor-targeting therapies. First, its genome contains approximately 30 kb of nonessential genes, allowing for genetic modifications through gene addition or replacement [45]. Second, herpes viruses exhibit a favorable safety profile, as they do not integrate into the host cell's genome and replicate as a rolling circle from its episomal DNA [46]. Third, effective anti-herpetic drugs are available in case of an undesired spread.

For cellular uptake, unlike viruses that rely on a single-entry receptor, HSV uses four distinct receptors, enabling it to infect a broad range of cancer cell lines. This multi-receptor mechanism enhances its potency and reduces the likelihood of resistance, as frequently observed with adenoviruses [27].

HSV's tumor-selective replication relies on deleting the virus' infected cell protein (ICP)34.5 and ICP47 genes. Removing ICP34.5 allows the virus to replicate and lyse tumor cells through reduction of neurovirulence. Deleting ICP47 further boosts this tumor-specific killing ability by reducing immune evasion [28]. Furthermore, incorporation of the GM-CSF-gene into the viral DNA also promotes immune activation by driving progenitor cells to differentiate into dendritic cells [28]. This was reported to trigger a broader – GM-CSF-driven – and potentially systemic immune response [47].

Based on these findings, the first T-VEC prototype was developed, genotypically described as: JS1/ICP34.5⁻/ICP47⁻/GM-CSF⁺ HSV-1. Noteworthy, in 2015 the FDA approved T-VEC as the first OV for the treatment of unresectable recurrent melanoma following initial surgery [48].

The development of RP1 has built upon the T-VEC platform by retaining the ICP34.5 and ICP47 deletions and GM-CSF transgene, but additionally incorporating the fusogenic protein GALV-GP-R⁻ (Gibbon Ape Leukemia Virus – Glycoprotein – Retargeted version) to enhance immunogenic cell death [49–51]. These modifications intensify the intratumoral inflammation and further potentiate DC activation and T cell priming within the TME. The key properties of T-VEC, RP1 and other relevant herpesvirus-based vectors are summarized in Table 1.

3. Oncolytic HSVs in melanoma treatment

In 2006, a phase I clinical trial with T-VEC, the first-in-class HSV-1 OV, laid the groundwork for the therapeutic use of HSV in dermato-oncology [52]. While T-VEC remains the benchmark in melanoma therapy, RP1's enhanced design shows broader potential, particularly in tumors with resistance to checkpoint blockade. However, RP1 is still under investigation in clinical trials and not approved as a therapeutic agent for melanoma [53]. Since then, several studies using oHSVs for the treatment of melanoma have been registered (Table 2).

3.1. T-VEC in melanoma treatment

Preclinical studies showed that T-VEC and its murine variant OncoVEX^ΔmGM-CSF induced strong local and also systemic antitumor responses, showing synergistic effects in combination with ICI [54, 55]. These findings laid the foundation for clinical trials evaluating T-VEC alone or in combination with other treatments.

Table 1. Main properties of herpes virus-based vectors.

Vector	Modifications and Features
T-VEC	Engineered for intratumoral administration.
	HSV-1 JS1 strain improves tumor selectivity.
	Deletion of ICP34.5 gene enables replication in tumor cells while reducing neurovirulence and increasing cellular stress response.
	Deletion of ICP47 gene prevents suppression of antigen presentation and enhances expression of the HSV US11 gene.
RP1	Integration of the GM-CSF cassette triggers systemic anti-tumor immune response.
	Engineered for intratumoral administration.
	HSV-1 RH018 strain enhances tumor cell cytotoxicity.
	Loss of UL56 gene lowers neurovirulence without impairing in vitro replication.
HF-10	GALV-GP-R- expression promotes systemic tumor cell killing.
	Engineered for intratumoral administration.
	Deletion in BamHI-B fragment (including UL43, UL49.5, UL55, LAT) boosts tumor selectivity and reduces the natural neurovirulence:
MVR-T3011	Increased expression of UL53 and UL54 support viral replication.
	Engineered for intratumoral and intravenous administration.
	HSV-1-based vector encoding IL-12 and anti-PD-1 antibody fragment.
	Local expression of IL-12 promotes T cell and NK activation.
OrienX010	Anti-PD-1 expression enables checkpoint blockade directly in the tumor microenvironment (TME).
	Engineered for intratumoral administration.
	HSV-1-based vector with deletions in ICP34.5 and ICP47 for tumor selectivity and reduced neurovirulence and increases cellular stress response.
	GM-CSF gene integration to stimulate antitumor immunity.

HSV-1 = herpes simplex virus type 1.

GALV-GP-R-: codon-optimized form of highly fusogenic membrane glycoprotein (GP) from gibbon ape leukemia virus (GALV).

Initial clinical experience was obtained in a first-in-human Phase I trial conducted between 2003 and 2007, which demonstrated the safety, tolerability, and preliminary antitumor activity of T-VEC in 30 patients with advanced solid tumors [56]. Building on these findings, a subsequent Phase II study in 50 patients with unresectable melanoma conducted from 2004 to 2008 (**NCT00289016**) confirmed clinically meaningful and durable response rates [57]. The encouraging results from these early clinical studies provided the rationale for initiating the phase III open-label, randomized OP-TiM trial (**NCT00769704**) in 2009. This trial compared intratumoral T-VEC to subcutaneous GM-CSF in 436 patients with unresectable stage IIIB–IVM1c melanoma. The final analysis was published in 2019. With a median follow-up of 49 months, median overall survival (OS) was 23.3 months in the T-VEC group compared to 18.9 months in the GM-CSF arm (HR 0.79; 95% CI, 0.62–1.00; $p = 0.0494$). T-VEC showed greater efficacy with a durable response rate (DRR) of 19.0% vs. 1.4%, and an ORR of 31.5% vs. 6.4%. CR occurred in 16.9% of patients treated with T-VEC, with a median time to CR of 8.6 months and an estimated 5-year survival of 88.5% among CR patients. The strongest benefit was seen in stage IIIB (advanced regional disease) – IVM1a (metastatic disease limited to skin, subcutis, or lymph nodes; no visceral organ metastases). Immunologic analyses demonstrated systemic activity through increased CD8⁺ T cell and NK cell infiltration in non-injected tumor lesions [58].

Promising preliminary data had already supported the FDA approval of T-VEC for advanced melanoma in 2015, as well as its further evaluation in combination with other therapies.

Initiated in 2016, a phase II randomized controlled trial (RCT) (**NCT02819843**) investigated T-VEC with or without radiotherapy (RT) in 19 patients with cutaneous metastases from solid tumors, including melanoma and NMSC (T-VEC: n = 9; T-VEC+RT: n = 10). One patient in each arm achieved a complete remission (CR) in a non-target lesion, but no overall modified WHO responses were observed. Median PFS was 1.2 months (T-VEC) and 2.5 months (T-VEC+RT), with OS of 4.9 and 17.3 months, respectively. Treatment-related adverse events (TRAE) were consistent with prior T-VEC data (e.g., flu-like symptoms, chills, pyrexia, fatigue, and injection-site reactions), and skin-related quality of life remained poor throughout. The trial was terminated early due to slow accrual, lack of systemic responses, and the COVID-19 pandemic. The authors suggested that more effective strategies are needed to induce systemic antitumor immunity with immunoradiotherapy combinations [59].

Beginning in 2018, a phase I trial (**NCT03747744**) evaluated intratumoral T-VEC administration combined with CD1c⁺ (BDCA-1) and/or CD141⁺ (BDCA-3) myeloid dendritic cells (myDCs) in 13 patients with advanced, ICI-refractory melanoma. T-VEC was given on day 1, followed by myDCs on day 2, with repeated T-VEC injections every 2–3 weeks. The treatment was well tolerated, with fatigue, fever, and flu-like symptoms being the most common side effects. Two out of three patients in the highest CD1c⁺ dose cohort achieved durable complete responses (> 33 months), while in cohort 4 (patients treated with the combination of CD1c⁺ and CD141⁺ myDCs) one unconfirmed partial and two mixed responses were observed. Of note, biopsies revealed strong tumor immune infiltration, suggesting that this combination may offer clinical benefit in heavily pretreated melanoma [60].

Starting in 2019, T-VEC was further evaluated in combination with ICIs. Consequently, the MASTERKEY-265 phase III trial (**NCT02263508**) evaluated T-VEC combined with the PD1 inhibitor pembrolizumab versus pembrolizumab alone in unresectable stage IIIB–IVM1c melanoma with injectable metastases. While the combinatorial treatment showed slightly higher response rates (ORR 48.6% vs. 41.3%; CRR 17.9% vs. 11.6%; DRR 42.2% vs. 34.1%), it did not significantly improve the primary endpoint PFS (14.3 vs. 8.5 months; HR 0.86; *p* = 0.13) or OS, leading to a negative final outcome. Improved PFS was seen in subgroups with lower lactate dehydrogenase (LDH) levels or smaller baseline tumor burden, suggesting that patient selection may be crucial and influence outcomes [61].

Subsequently, the open-label phase II MASTERKEY-115 trial (**NCT04068181**) evaluated T-VEC plus pembrolizumab in 72 patients with PD-1–refractory stage IIIB–IVM1d melanoma. Cohorts 1 and 2 included patients with unresectable disease and primary or acquired resistance, respectively, within 12 weeks of their last anti-PD-1 dose. Cohorts 3 and 4 included resected patients who relapsed < 6 or ≥ 6 months after starting adjuvant anti-PD-1. Confirmed ORRs were 0%, 6.7%, 40.0%, and 46.7% across cohorts 1–4; ORRs were 3.8%, 6.7%, 53.3%, and 46.7%. CRRs reached 13.3% in cohorts 3 and 4. Median PFS was 5.5 and 8.2 months in cohorts 1 and 2 and not estimable in cohorts 3 and 4. Thus, the combination showed limited benefit in primary resistance but meaningful activity in patients relapsing after adjuvant PD-1 therapy [62].

Notably, a real-world analysis from Austria reported real-life outcomes of T-VEC across 10 melanoma centers in Austria, Switzerland, and Germany, including 88 patients treated between May 2016 and January 2020. The ORR was 63.7%, with CRR in 43.2% and partial responses in 20.5%, while 9.1% had stable disease and 27.3% progressed. Median time to response was ~4 months; median PFS was 9 months, with 1-, 2-, 3-year PFS rates of 45%, 35%, 28%, respectively. OS was 82%, 71%, 65%, 65% at 1, 2, 3, 4 years, and the median was not reached. Together, these data support meaningful real-world activity and favorable tolerability of T-VEC in routine practice [63].

T-VEC has also been examined in a neoadjuvant setting. Final 5-year results from an open-label, randomized phase II trial (**NCT02211131**) evaluated neoadjuvant T-VEC followed by surgery versus upfront surgery in 150 patients with resectable stage IIIB–IVM1a melanoma and injectable lesions. Patients in the T-VEC arm received up to six doses prior to surgery; both groups could receive adjuvant therapy per investigator discretion. At a median follow-up of 63.3 months, the neoadjuvant T-VEC arm showed improved 5-year recurrence-free survival (RFS; 22.3% vs. 15.2%), event free survival (EFS; 43.7% vs. 27.4%), and overall survival (OS; 77.3% vs. 62.7%) compared to surgery alone. Distant metastasis-free survival (DMFS) also favored the T-VEC group (hazard ratio 0.73). No new safety concerns were identified [64]. These findings could be indicative that intratumoral T-VEC possibly induces durable systemic effects and supports its use as a neoadjuvant strategy in resectable advanced melanoma.

Moreover, T-VEC is being investigated in combination with BRAF/MEK inhibitors to enhance its therapeutic effect. Preclinical studies in both murine and human xenograft models have shown that combining T-VEC with the mitogen-activated protein kinase (MEK)1/2 inhibitor trametinib boosts viral replication within tumors, leading to increased melanoma cell death and delayed tumor progression. This dual approach also promoted cytotoxic T cell infiltration and raised PD-1 expression in the TME, suggesting enhanced immune engagement [65]. Further, adding an anti-PD-1 antibody to this regimen has resulted in complete tumor clearance in over 80% of treated mice, along with extended survival and minimal toxicity [66]. Based on these promising findings, a phase Ib clinical trial (**NCT03088176**) is currently underway to evaluate T-VEC in combination with the BRAF-/MEK-inhibitor combination dabrafenib plus trametinib in patients with advanced BRAF-positive melanoma [67].

Across all studies, T-VEC demonstrated a favorable safety profile, with the most common adverse events being mild systemic symptoms and local injection site reactions. Grade ≥ 3 TRAEs were reported in 7.3–29.7% of patients. (Table 2) Similar to other immunotherapies, cases of vitiligo have been observed following T-VEC treatment, likely reflecting an exaggerated immune response targeting melanocytes [68].

3.2. RP1 in melanoma treatment

RP1 is a next-generation oHSV-1 designed to improve efficacy compared to T-VEC. It uses a more cytotoxic HSV-1 backbone and retains T-VEC's transgenes whilst incorporating the fusogenic GALV-GP-R- protein. This enhancement is intended to boost tumor cell killing and immune activation. In preclinical models including murine lymphoma and human lung and breast cancer cells RP1 showed

superior efficacy, particularly when combined with anti-PD-1 therapy [50]. This prompted clinical trials of RP1 in solid tumors, including melanoma, with ICI.

An update of the Phase I/II trial **IGNYTE (NCT03767348)** combining RP1 with nivolumab in advanced anti-PD1-refractory melanoma was presented at the 2025 ASCO Annual Meeting. In 140 patients, the confirmed ORR was 32.9% (CR 15%, PR 17.9%), median duration of response was 33.7 months, with 1-, 2-, and 3-year overall survival rates of 75.3%, 63.3%, and 54.8%, respectively. [53] Deep/visceral injections (lung or liver) yielded a better outcome than superficial injections alone (ORR 42.9% vs 30%), without introducing major safety issues; low-grade pneumothoraces were observed in lung-injection subjects. Grade 3 TRAEs occurred in 9 and grade 4 events in 4 percent of patients. No grade 5 events were reported. The long-lasting systemic response of this combination in a difficult-to-treat setting will advance to a confirmatory Phase III **IGNYTE-3 (NCT06264180)** trial. Recruitment started in July 2024; primary completion is expected by January 2029. Notably, the FDA had granted *Priority Review* for RP1; however, in July 2025, the agency issued a Complete Response Letter (CRL), stating that the available data from IGNYTE were insufficiently controlled to support approval [69].

3.3. Other herpes-based OV therapies in melanoma treatment

The Phase Ib trial **NCT04197882** investigated **OrienX010**, an HSV-1–based OV expressing GM-CSF, in combination with toripalimab as neoadjuvant therapy for resectable stage IIIb–IV (M1a) acral melanoma. Among 30 enrolled patients, 27 completed surgery and neoadjuvant toripalimab therapy. The study reported radiological and pathological ORRs of 36.7% and 77.8%, respectively, including complete response rates (CRR) of 3.3% and 14.8%. Pathological response rate refers to the proportion of patients whose resected tumor specimens show a defined degree of tumor regression, defined by the proportion of remaining viable tumor cells on histopathologic examination after neoadjuvant therapy [70]. At a median follow-up of 35.7 months, the 1- and 2-year RFS rates were 85.2% and 81.5%, while the EFS rates were 83% and 73%, respectively. Grade 3 TRAEs occurred in 17% of patients, but no grade 4 events were observed. Notably, pathologic responses were associated with high densities of tertiary lymphoid structures and tumor-infiltrating lymphocytes [71]. These results underscore the potential of HSV-1–based OVs in hard-to-treat melanoma subtypes like acral and uveal melanoma.

MVR-T3011 is a novel oncolytic HSV-1, similar in design to T-VEC and RP1. Delivered intratumorally, it selectively targets tumor cells while sparing healthy tissue, by exploiting defects in the immune response pathways specific to cancer cells. Its dual expression of IL-12 and the fragment antigen-binding region (Fab) fragment of an anti-human PD-1 antibody allows it to modulate the TME in a unique way by simultaneously stimulating local immune activation and relieving checkpoint-mediated suppression directly within the tumor [72]. Currently, a Phase I/IIa trial (**NCT04370587**) is assessing the agent alone or in combination with pembrolizumab in advanced solid tumors, including melanoma. A recent update from the 2023 Annual Meeting of the American Society of Clinical Oncology (ASCO) presented data from 29 patients who received MVR-T3011 alone or with pembrolizumab, with a median follow-up of

Table 2. Clinical trials investigating oHSVs in melanoma registered at clinicaltrials.gov and clinicaltrialsregister.eu as of September 2025.

Year	NCT/Study Name/ Author	Stage of Melanoma	Therapy (Combination)	Phase (Status)	N	ORR (%)	Main outcomes	TRAE (Grade 3-4)
2006	Hu JC et al.	Different stage IV malignancies including melanoma	T-VEC	I (Completed)	30	N/A	N/A	Pyrexia, local erythema or inflammation
2008	(NCT02574260)	IIIB-IV	T-VEC	II (Completed)	3	N/A	Maximum of 24 treatments under NCT00289016; inclusion/ exclusion criteria fulfilled.	N/A
2009	(NCT00289016) Senzer et al.	IIIC-IV	T-VEC	II (Completed)	50	26	mDoR = 7.4m (223d)	Pain, fatigue, dyspnea
2009	(NCT00769704, EudraCT 2008- 006140-20) OPTiM, Andtbacka RH et al.	IIIB-IV	T-VEC vs. GM- CSF	III (Completed)	437	31.5 vs. 6.4	mDoR = n.r. vs. 2.8m	Cellulitis, pain, vomiting, fatigue
2010	(NCT01368276)	IIIB-IV	T-VEC vs. GM- CSF	III (Completed)	31	57.1 vs. 100	Safety study for eligible pts of NCT00769704	Cardiovascular and respiratory disorders, kidney injury
2015	(NCT01017185) Robert L Ferris et al.	Various skin cancers including melanoma	HF10 + Ipi	I (Completed)	28	N/A	N/A	N/A
2015	(NCT02297529)	IIIB-IVM1c	T-VEC	IIIB	41	26	CR in 3 pts. Median treatment duration 13.1w	7.3% TRAEs G3+: Nausea, pyrexia, wound infection
2016	(NCT02965716)	IIIA-IV	T-VEC + pembrolizumab	II (Active, not recruiting)	71	46.7	iPFS 5.5m for cohort 1, 8.2m for cohort 2.	12.7% TRAEs G3+ Pyrexia, influenza-like illness
2016	(NCT02819843)	Various solid tumors including melanoma and NMSC	T-VEC + radiotherapy vs. T-VEC	II (Completed)	19	0%	N/A	fatigue, chills, fever, nausea
2017	(NCT02272855) Andtbacka RH et al.	IIIB-IV	HF10 + Ipi	II (Completed)	46	41	mPFS = 19m	Embolism, lymphedema, diarrhea, hypoglycemia, groin pain
2017	NCT03088176	BRAF-positive, advanced melanoma	T-VEC + dabrafenib + trametinib	I (Unknown status)	4	N/A	N/A	N/A
2018	(NCT03747744)	Advanced/ metastatic Melanoma	CD1c (BDCA-1) + myDC + T-VEC	I (Completed)	13	Durable CR in 2 pts;	N/A	Fatigue, pyrexia, chills, injection site reactions
2018	(NCT03064763) Yamazaki N et al.	IIIB-IV	T-VEC	I (Active, not recruiting)	18	35	N/A	Diarrhea, worsening of BPH, epiglottitis, pneumonia
2018	(NCT03259425)	IIIB-IVM1a	HF10 + Nivo	II (Terminated, DSMC recommendation)	7	N/A	N/A	Anemia, cutaneous and subcutaneous tissue disorders

Year	NCT/Study Name/ Author	Stage of Melanoma	Therapy (Combination)	Phase (Status)	N	ORR (%)	Main outcomes	TRAE (Grade 3-4)
2019	(NCT02014441) Andtbacka RH et al.	IIIB-IVM1c	T-VEC	II (Completed)	61	35	mDoR = n.r.	Pyrexia, delirium
2019	(NCT01740297) Chesney J et al.	IIIC-IV	T-VEC + Ipi vs. Ipi-monotherapy	II (Completed)	198	36.7 vs. 16	mDoR = n.r. mPFS = 13.5m vs. 4.5m	Colitis, diarrhea, pyrexia, lymphopenia
2019	(NCT03153085) Yokota K et al.	IIIB-IV	HF10 + Ipi	II (Completed)	28	BORR = 11.1%	DCR = 55.6%	35.7% G3 TRAEs
2019	(NCT02263508) Long G et al.	IIIB-IVM1c	T-VEC + pembrolizumab	Ib (Completed)	21	62	mDoR = n.r. mPFS = n.r. 4-year PFS = 55.9%	Fatigue, pyrexia, chills
2019	(NCT03842943)	III	T-VEC + pembrolizumab	II (Completed)	N/A	N/A	N/A	N/A
2019	(NCT03767348) IGNYTE Thomas S et al.	Various solid tumors including melanoma	RP1 vs. RP1 + Nivo	II (Recruiting in expansion cohorts)	156	32.9-33.6	DOR: 33.7m	9.3% TRAEs G3+ Fatigue, chills, fever, nausea
2020	(NCT04330430) NIVEC	IIIB-IVM1a	Neoadjuvant T-VEC + Nivo for 8 weeks	II (Active, recruiting)	13	N/A	N/A	N/A
2020	(NCT04068181) Masterkey-115	IIIB-IVM1d anti-PD1-refractory Melanoma	T-VEC + pembrolizumab	II (Completed)	72	40-46.7	5.5-8.2m	12.7% TRAEs G3+ Pyrexia, fatigue.
2020	(NCT04427306)	High-risk, resectable melanoma	T-VEC	II (Recruiting)	N/A	N/A	N/A	N/A
2020	(NCT04370587)	Advanced or metastatic solid tumors including melanoma	T3011 vs. T3011 + pembrolizumab	I/IIa (Recruiting)	29	25	12-m PFS = 36.4%	10.3% TRAEs G3+ Pyrexia, fatigue, flu-like-symptoms.
2021	(NCT03555032 NCT02094391 NCT03685890 NCT03555032) Tulokas SKA et al., 2021	IIIB-IV	Ipi vs. Nivo vs. T-VEC	I/II (Completed)	60	77	mPFS = 6.1m	Cellulitis, gastrointestinal disorders, pyrexia, influenza, pain, post-operative wound infection
2021	(NCT02211131) Dummer R et al.	IIIB-IVM1a	Neoadjuvant T-VEC + resection vs. immediate resection	II (Completed)	57	N/A	5-year OS = 77.3% vs. 62.7% 5y-RFS: 22.3% vs. 15.2% EFS: 43.7% vs. 27.4%	29.7% TRAEs G3+ GI hemorrhage, cellulitis, pyrexia, cholecystitis
2021	(NCT02263508) Ribas A et al. MASTERKEY-265/ KEYNOTE-034	IIIB-IVM1c	T-VEC + pembrolizumab vs. Placebo + pembrolizumab	III (Completed)	692	48.6 vs. 41.3	mDoR = 43.7m vs. n.r. mPFS = 14.3m vs. 8.5m	Fatigue, pyrexia, chills
2021	(NCT04197882) Wang X et al.	IIIB-IVM1a	OrienX010 + toripalimab	Ib (completed)	30	36.7	1-y RFS: 85.2% 2-y-RFS: 81.5	17% TRAEs G3. Transaminitis, wound infections.
2021	(NCT04206358) Guo J et al.	IV (M1c)	OrienX010 + JS001	Ib (Recruiting)	15	40% in injected lesions, 28.5% non-injected liver, 23% extrahepatic	mPFS = n.r.	10% TRAEs G3. Pyrexia, chills, transaminitis, vomiting

Year	NCT/Study Name/ Author	Stage of Melanoma	Therapy (Combination)	Phase (Status)	N	ORR (%)	Main outcomes	TRAE (Grade 3-4)
2021	(NCT02366195) (TVEC-325) Malvey J et al.	IIB-IVM1c	T-VEC	II (Completed)	112	32	mDoR = n.r. mTTF = 8.1m	CNS metastases, overall decline, pyrexia, lumbalgia
2024	(NCT06264180) IGNUYE-3	Advanced melanoma refractory to anti-PD-1 and anti-CTLA-4 therapy	RP1+Nivo vs physicians treatment of choice	III (Recruiting)	400	N/A	N/A	N/A

Abbreviations: SCC = squamous cell carcinoma; CSCC = cutaneous squamous cell carcinoma; N/A = not available; n.r. = not reached; Pembro = Pembrolizumab; N = number of patients; ORR = objective response rate; DoR = duration of response; mDoR = median duration of response; PFS = progression free survival; iPFS = immune-related progression free survival; mPFS = median progression free survival; DCR = disease control rate; TTF = time to treatment failure; RFS = regression free survival; BORR = best overall response rate; TRAE = treatment-related adverse events; T-VEC = talimogene laherparepvec; GM-CSF = granulocyte-macrophage colony-stimulating factor; DSMC = Data and Safety Monitoring Committee; ICI = immune checkpoint inhibitor; CR = complete response; w = weeks; pts = patients; BPH: benign prostate hyperplasia; GI = gastrointestinal; CBR = Clinical benefit rate; DCR = disease control rate; m = months; w = weeks; d = days; G3 = Grade 3.

14.1 months. Among 12 advanced melanoma patients previously treated with PD-1 or PD-1/CTLA-4 therapy, MVR-T3011 monotherapy resulted in an ORR of 25% and a 12-month PFS rate of 36.4%. TRAEs occurred in 76% of patients (10% with \geq G3), with pyrexia, fatigue, and flu-like symptoms being most common; no dose-limiting toxicities or new safety concerns were observed. CD8+ T cell infiltration increased in 47% of evaluable tumors and was more pronounced in those with clinical benefit [73]. The study is projected to complete by October 2025.

HF10 is a mutated strain of Herpes Simplex Virus type 1 (HSV-1) which has previously demonstrated oncolytic activity [74]. A phase II trial published in 2017 evaluated intratumoral HF10 in combination with ipilimumab in patients with unresectable metastatic melanoma and reported an objective response rate (ORR) of 41% at 24 weeks [75]. Another single-arm phase II study assessed the safety and efficacy of a 12-week neoadjuvant regimen combining nivolumab with HF10 in patients with resectable stage IIB-IVM1a melanoma. Pathologic analysis revealed a complete response (0% viable tumor) in 5 of 6 participants. The sixth patient experienced disease progression that precluded surgery. Upon recommendation from the Data and Safety Monitoring Committee (DSMC), the study was terminated early in 2022 [76].

4. Oncolytic HSVs in NMSC treatment

Given the high aggressivity of melanoma compared to most NMSCs, a lot of effort went into the development of oHSVs for the treatment of melanoma in the first years of respective research. This resulted in a first FDA-approval of T-VEC for melanoma and a lower number of trials registered for NMSCs [77]. Still, patients with advanced NMSC represent a distinct and clinically important subgroup – particularly solid organ transplant recipients (SOTRs), for whom systemic immunotherapies are often contraindicated due to rejection risk, thus calling for local treatment options [78]. Therefore, the use of oHSVs for the treatment of NMSC is increasingly coming into focus. The following section highlights relevant and recent clinical trials investigating oHSV therapies in NMSC, as depicted in Table 3.

4.1. T-VEC in NMSC treatment

The Phase I/II trial **NCT03458117**, completed in 2023, evaluated T-VEC monotherapy in patients with cutaneous lymphomas and advanced NMSC. Among 26 treated participants, the cohort included cutaneous B-cell lymphoma (n = 19), cutaneous T cell lymphoma (n = 5), CSCC (n = 1), and Merkel cell carcinoma (n = 1). An ORR of 32% was observed, with 84% of injected lesions showing clinical improvement. Notably, a 40% response in non-injected lesions was reported [79]. These findings confirm tolerability and also systemic activity of T-VEC monotherapy in NMSC and suggest a rationale for future trials exploring OV alone and in combination with ICI.

Another phase II trial (**NCT03714828**) presented at the American Association of Cancer Research (AACR) Annual Meeting 2024 evaluating T-VEC in cSCC showed a 100% ORR, with 90.9% achieving a CR and 9.1% a PR. Of 24 injected lesions, 96% showed a CR. Median time to response was 35 days, and median duration of response (mDoR) was 209 days. Compared to 2022 interim data, responses were faster and more durable, and patients had significantly fewer invasive tumors one and two years after treatment compared to prior timepoints ($p = 0.0156$ and 0.0312) [80, 81].

An ongoing phase II trial (**NCT03069378**) is assessing the efficacy of T-VEC combined with pembrolizumab in patients with locally advanced or metastatic cutaneous sarcomas. Both agents were administered concurrently on day 1 and every 3 weeks. In an expansion cohort, ORRs of 11% for undifferentiated pleomorphic sarcoma (UPS)/myxofibrosarcoma (MFS), 43% for angiosarcoma (AS), and 0% for epithelioid sarcoma (ES) were reported. The highest observed ORR was 71% in AS (5/7). Median PFS was 14.9 weeks for UPS/MFS and 54 weeks for angiosarcoma. The treatment regimen was generally well tolerated with only one patient developing a grade 3 TRAE (immune-mediated hepatitis) [82]. The results support the safety and potential efficacy of OV-ICI therapy in advanced sarcomas, especially angiosarcoma.

T-VEC is also being investigated in other rare NMSCs. **NCT04065152** (KAPVEC) is a Phase II, multicenter intralesional T-VEC trial targeting classic and endemic Kaposi sarcoma. The study aims to determine whether the agent's combined PR/CR rate exceeds 40%, following a lead-in phase of T-VEC administration every 2 weeks for up to 6 cycles. Results have not yet been reported, and data are currently pending.

T-VEC is also being explored in the neoadjuvant treatment of NMSC. In a phase II exploratory study involving 18 patients with BCC deemed difficult to resect, intralesional T-VEC was administered over six cycles (13 weeks) prior to surgery. The primary endpoint—avoiding the need for skin grafting or flap reconstruction—was achieved in 53% of patients. Additionally, partial and complete responses were reported in 24% and 35% of cases, respectively [83].

Across these studies, T-VEC demonstrated a similarly favorable safety profile, with adverse events primarily consisting of mild constitutional symptoms (fever, flu-like symptoms, and local ulceration) and injection site reactions. Grade ≥ 3 TRAEs were reported in 3.4–12% of patients.

4.2. RP1 in NMSC treatment

As outlined in Table 2, the Phase I/II trial **IGNYTE (NCT03767348)** investigates RP1 alone or in combination with nivolumab in a variety of advanced solid tumors, including melanoma and NMSCs. The ASCO 2025 update focused exclusively on anti-PD1-refractory melanoma. However, interim results also showed promising ORRs for CSCC (47.1%), BCC (25%), Merkel cell carcinoma (75%) and angiosarcoma (66.7%) [84].

The Phase II **CERPASS** trial (**NCT04050436**) is evaluating cemiplimab with or without RP1 in unresectable CSCC. In December 2023 Replimune reported that the trial did not meet its two primary endpoints (ORR and CRR) as the pre-defined threshold for statistical significance ($p < 0.025$) had not been reached. The ORR was similar in both study groups (52.5% for RP1 plus cemiplimab vs. 51.4% for cemiplimab alone, $p = 0.692$). CRR, however, was increased in the combination arm with RP1 versus cemiplimab alone (38.1% vs. 25%, $p = 0.040$), almost reaching statistical significance. Duration of response was also increased with an HR of 0.45. Final results of the trial regarding DoR, PFS, OS as well as biomarker analyses are awaited [85].

The ongoing Phase Ib/II **ARTACUS** trial (**NCT04349436**) is testing RP1 monotherapy every two weeks up to a maximum of 25 doses in 23 SOTRs with advanced skin cancers. Interim data show an ORR of 34.8%, CRR of 21.7% and PR of 13%, with a DCR of 39.1%. Common side effects included fatigue, chills, and fever [86]. Importantly, no case of allograft rejection was reported in this cohort including patients with hepatic and lung allografts. These results are especially significant, as SOTRs are generally at high risk for NMSCs and are usually excluded from immunotherapy due to rejection risk. Continued investigation may establish RP1 as a valuable option for these immunocompromised patients, potentially expanding beyond skin cancers.

4.3. Other herpes-based OV therapies in NMSC treatment

The mechanism of action of the novel oHSV-1 MVR-T3011 has been elucidated above and is summarized in Table 1 [72]. Currently, there are two trials for NMSCs investigating this OV: an ongoing Phase I/IIa trial (**NCT05602792**) is evaluating MVR-T3011 as monotherapy in a variety of solid tumors. Interim results presented at the 2023 ASCO Annual Meeting showed an ORR of 11% and a DCR of 49% among 55 evaluable patients (however, only for HNSCC, sarcoma, melanoma, and breast cancer). Common TRAEs included pyrexia, flu-like symptoms, elevated TSH, proteinuria, facial edema, leukocytosis, transaminitis, and anemia [87]. Results on NMSC are currently being awaited.

Another Phase I/IIa trial (**NCT04370587**) is assessing MVR-T3011 alone or in combination with pembrolizumab in a variety of advanced solid tumors. In the latest update from January 2023, 29 patients had been treated with MVR-T3011 alone or in combination with pembrolizumab. However, reported outcomes focused solely on melanoma patients, while data on NMSC are still pending [73]. Analysis of the final results will help elucidate the potential of this therapeutic approach.

Table 3. Clinical trials investigating oHSVs in NMSC registered at clinicaltrials.gov and clinicaltrialsregister.eu as of September 2025.

Year	Author, Study Name, (NCT#)	Kind of skin cancer / Stage	Therapy (Combination)	Phase (Status)	N	ORR (%)	Main outcomes	TRAE (Grade 3-4)
2015	(NCT03714828)	Low risk CSCC	T-VEC	II (Completed)	11	100	mDOR = 209d	Flu-like symptoms
2016	(NCT02819843)	Various solid tumors including melanoma and NMSC	T-VEC + radiotherapy vs. T-VEC	II (Completed)	19	0%	Composite RR: 22% (combination) vs 7% (T-VEC)	10.5% TRAEs 3+ Nausea, flu-like-symptoms,
2017	(NCT03069378) Kelly CM et al.	Locally advanced/ metastatic sarcoma	T-VEC + pembrolizumab	II (Active, not recruiting)	41	N/A	mDoR = 14m (56.1w) mPFS = 4.3m (17.1w)	5% TRAEs 3+ (ir Hepatitis); Pneumonitis, anemia, fever, hypophosphatemia
2018	(NCT03458117)	Various locally advanced cutaneous lymphomas and NMSC	T-VEC	I (Completed)	26	32	Non-injected response rate = 40%	12% TRAEs 3+. Pyrexia, flu-like-symptoms, Ulceration of tumor
2019	(NCT04163952)	Advanced CSCC	T-VEC + panitumumab	I (Active, nor recruiting)	N/A	N/A	N/A	N/A
2019	(NCT04050436) CERPASS	Advanced CSCC	RP1 + cemiplimab vs. cemiplimab	II (Active, not recruiting)	231	Combination: 52.5 Mono: 51.4	CRR 38.1% vs 25% PFS not yet reported	16.5% TRAEs 3. 1 TRAE Grade 4 (myocarditis)
2019	(NCT03921073)	Locally advanced cutaneous angiosarcoma	T-VEC	II (Active, recruiting)	5	N/A	N/A	N/A
2019	(EudraCT -number 2018-002165-19) NeoBCC	IaBCC	Neoadjuvant T-VEC	II (Completed)	18	55.6	6m-RFS 100% primary endpoint met in 50%: resection without skin graft or flap.	No TRAEs 3+
2020	(NCT04349436) ARTACUS	Locally advanced NMSC in SOTR	RP1	Ib/II (Recruiting)	23	34.8	DCR: 39.1%	Flu-like-symptoms, nausea, diarrhea
2020	(NCT04370587)	Advanced or metastatic solid tumors	MVR-T3011 vs. MVR-T3011 + pembrolizumab	I/IIa (Recruiting)	29	N/A	N/A	N/A
2020	(NCT05602792)	Advanced solid tumors	MVR-T3011	I/IIa (Unknown status)	55	11%	DCR 49%	3.4% TRAEs 3+. Pyrexia, flu-like-symptoms, transaminitis, leucocytosis, edema
2021	(NCT04065152) KAPVEC	Kaposi Sarcoma (KS) not requiring systemic therapy	T-VEC	II (Unknown status)	N/A	N/A	N/A	N/A

Abbreviations: SCC = squamous cell carcinoma; BCC = basal cell carcinoma; MCC = Merkel cell carcinoma; HNSCC = head and neck SCC. SOTR: solid organ transplant recipient; RR: response rate.

5. Summary, limitations and outlook

Current evidence suggests that OV_s offer a certain benefit in achieving durable locoregional control of unresectable melanoma and NMSC, rather than significantly extending overall survival. Until now the only completed phase III clinical trial comparing a combination strategy with PD-1 monotherapy thus far was negative. However, a potential benefit of the OV/ICI combination was observed in certain subgroups in this study including patients with lower LDH levels or limited baseline tumor burden. The optimal timing and regimen for combining OV_s with other agents remains subject of ongoing research. Currently, the com-

bination of RP1 with nivolumab in checkpoint inhibitor-refractory melanoma appears most promising.

T-VEC is generally contraindicated in immunosuppressed individuals due to the elevated risk of localized or systemic herpesvirus infection [88]. Additionally, biosafety concerns stem from the use of a live, replicating virus, which carries a potential risk of transmission—particularly through accidental exposure such as needlestick injuries during preparation or administration. Importantly, T-VEC remains sensitive to antiviral agents like acyclovir, which can be used in the event of accidental exposure [89]. As a result, established safety and handling protocols exist for T-VEC [90]. Also, many institutions have implemented specific standard operating procedures for its preparation, storage, and administration. However, in recent years, theoretical concerns have not translated into measurable harm or risk in clinical practice – i.e. a significant rate of symptomatic herpes infections in treated patients or treating health care professionals – leading to a significant reduction of safety concerns and measures. Yet use of T-VEC is often limited to specialized centers.

Regarding safety, a recent study reported that combining T-VEC with ICIs is associated with a two-fold increase in cutaneous immune-related adverse events compared to ICI monotherapy (hazard ratio: 2.03, $P = 0.006$) [91]. These toxicities are dose-dependent and clinically diverse, ranging from mild pruritus to vitiligo and severe conditions like toxic epidermal necrolysis [92]. Management typically involves topical or short-term systemic corticosteroids, which, in the context of prior ICI therapy, have not been shown to compromise antitumor efficacy [93].

Another important point to consider regarding the postulated mechanisms of action of oHSVs concerns the extent of tumour cell infection after intraleisional treatment.

Patient studies on biodistribution of T-VEC show detectable viral DNA in injected lesions, yet viral copy numbers differ substantially between treated individuals. Also, replication-competent viruses are recovered infrequently outside of early treatment cycles. These findings indicate that while viral genomes are present in most injected lesions, sustained productive infection is not uniformly demonstrable and appears heterogeneous across patients [94].

Mechanistic modelling of oHSV biodistribution further indicates patient-to-patient variability in key virologic parameters including viral infection rate and suggests that differences in these parameters influence the dynamics of tumor cell infection and viral propagation [95].

Preclinical evidence also shows heterogeneous susceptibility of melanoma cell lines to oHSV infection and lysis, consistent with the notion that tumor intrinsic factors, as well as the tumor microenvironment contribute to variable infection – and thus possibly also treatment – efficiency [25, 96].

Concerning RP1, similar data regarding interindividual variability of tumor cell infection in treated patients, as well as data on quantitative assessments of intratumoral infection rates have not yet been published.

In addition to expanding indications for the use of OV, efforts are underway to identify biomarkers that help predict which patients are most likely to respond to a distinct treatment or treatment combination, as investigated in an ongoing trial (**NCT04330430**) at the Netherlands Cancer Institute regarding the combination of T-VEC with nivolumab [97].

Identifying genetic or immunologic predictors of response could help stratify patients more effectively and optimize therapeutic outcomes. For instance, mutations in the IFN γ -JAK-STAT pathway, known markers of ICI resistance, have been shown to increase sensitivity to oHSVs like HSV1-dICP0 and VSV- Δ 51 in melanoma models [98, 99]. Similarly, durable responses have been observed in ICI-resistant melanoma patients with B2M mutations treated with T-VEC-based combinations, though the relative contribution of oHSV versus other agents remains unclear [100]. These findings again underscore the necessity of biomarker discovery in tailoring OV-based therapy to individual patients.

Moreover, ongoing preclinical studies suggest that the therapeutic potential of oHSVs may be enhanced through rational combinations with other agents. MEK inhibitors, for instance, have demonstrated the ability to augment T-VEC activity and upregulate PD-L1 expression in murine models, suggesting a synergistic potential when combined with checkpoint blockade [65]. However, these combinatorial strategies remain largely unexplored in the clinical setting and warrant further investigation.

The recent success of neoadjuvant immunotherapies, as exemplified by the NADINA trial, has revitalized interest in applying oHSV-based regimens in earlier treatment settings. There is a growing rationale for evaluating oHSVs as part of neoadjuvant strategies, particularly in patients with resectable melanoma who exhibit high T cell infiltration at baseline, or in NMSC patients with limited resection or radiation options [71, 101]. The neoadjuvant setting offers a unique immunological window where the tumor can serve as an *in situ* vaccine. Thus, utilization of the patient's own tumor as a source of antigens can potentially enhance the systemic immune response initiated by oHSVs. Recent data from trials such as **NCT02211131**, which showed improved EFS and OS with neoadjuvant T-VEC plus surgery, further support this approach.

Finally, OVs may provide an alternative immunotherapeutic option for immunocompromised patients, such as SOTRs with NMSCs, who are often ineligible for standard checkpoint blockade therapy. Trials like ARTACUS (**NCT04349436**) explore this unmet medical need and may expand the therapeutic reach of virotherapy [86].

In summary, apart from T-VEC monotherapy in melanoma, oHSVs have not yet demonstrated consistent benefit in late-stage clinical trials. Ongoing phase III trials investigating oHSVs, particularly RP1, in PD-1-refractory patients are due to be completed. These novel treatment approaches might offer another therapeutic option after disease progression in this patient subgroup, provided that injectable lesions are present. In patients experiencing locally limited progression during systemic therapy, i.e. development of satellite- or intransit metastases, intralesional treatment with T-VEC can already provide durable clinical control in certain cases, although specific evidence regarding this particular scenario is limited. Taken together, oHSVs remain a promising and useful treatment modality, particularly when applied earlier during treatment when visceral metastases are absent or of limited extent. Future studies should focus on refining patient selection criteria – possibly through the utilization of yet to be discovered biomarkers, optimizing combination strategies, and exploring the neoadjuvant potential of oHSVs to fully establish their role in the dynamic landscape of skin cancer treatment.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Use of AI

No use of AI was reported.

Funding

No funding was reported.

Author contributions

Conceptualization: MK, PK. Writing – original draft: MK. Writing – review and editing: VW, PK, PF. All authors edited, read and approved the final manuscript. All authors agreed to the published version of the manuscript.

Author ORCIDs

Maximilian Kreu  <https://orcid.org/0000-0001-9606-1390>

Verena Wally  <https://orcid.org/0000-0001-8705-3890>

Peter Koelblinger  <https://orcid.org/0000-0002-5897-2780>

Data availability

All of the data that support the findings of this study are available in the main text.

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