

Review

Oncolytic Viruses as an Adjunct to Immune Checkpoint Inhibition

Jacob Ripp¹, Stijn Hentzen¹, Anwaar Saeed^{2,*}

¹Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS 66160, USA

²Department of Internal Medicine, Division of Medical Oncology, University of Kansas Medical Center, Kansas City, KS 66205, USA

*Correspondence: asaheed@kumc.edu (Anwaar Saeed)

Academic Editor: Roberto Bei

Submitted: 24 February 2022 Revised: 18 April 2022 Accepted: 22 April 2022 Published: 10 May 2022

Abstract

Utilizing viruses in the treatment of cancer, or oncolytic viral therapy (OVT), began in the 1950s with the idea that viruses could invade and destroy cancer cells. Barriers to this approach included a lack of specificity towards cancer cells and intolerable toxicities. However, it was discovered that OVT increases cytokines such as interferon gamma and interleukins within the tumor microenvironment. This “priming” of the tumor microenvironment can lead to an improved innate immunologic response to tumor cells. An “OVT-as-mono-therapy” approach has led to modest tumor response rates that have unfortunately not translated well in clinical trials. Currently, only one OVT agent—talimogene laherparevec (TVEC)—has been approved by the FDA for unresectable melanoma with limited visceral metastases. Further advancements in immunotherapy combined with improved viral engineering over the last decade have paved the way for a renewed focus on OVT. For example, various viruses have been modified to infiltrate and upregulate PD-L1 signaling within tumor cells. Upregulation of PD-L1 on tumor cells can increase tumor cell response to immunotherapies that utilize the interaction between PD-L1 on tumor cells and PD-1 on lymphocytes to allow for immune cell destruction of cancer cells. Combining OVT and immunotherapy offers more promise than OVT as monotherapy. Currently, several are actively investigating the combinatorial approach of OVT and immunotherapy in treating non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer, melanoma, pancreatic cancer, multiple myeloma, and head and neck squamous cell carcinoma. In this review, we will discuss the history of OVT including its limitations as a monotherapy. We will also discuss the background of combining OVT and immunotherapy including possible benefits and pitfalls of this approach. Lastly, we will review current clinical trials investigating OVT and immunotherapy in multiple cancers.

Keywords: oncolytic viral therapy; immunotherapy; immune checkpoint inhibition

1. Introduction

The idea of using viruses to treat cancer cells has been around nearly as long as the discovery of viruses themselves. In 1892, Dmitri Ivanovsky [1] described an agent which was “non-bacterial” affecting the tobacco plant, naming this the tobacco mosaic virus. Six years later, “foot and mouth virus” was not only filtered out by scientists but was directly implicated in causing animal disease [2]. Three years later, in 1901, the yellow fever virus became the first virus discovered by scientists causing disease in humans [3]. Finally, in 1931, Max Knoll and Ernst Ruska obtained the first images of viruses with the invention of electron microscopy [4].

During the forty years between Ivanovsky’s discovery and Knoll and Ruska’s images, several case reports were published detailing patients with cancers who magically improved after becoming infected with viral illnesses. In 1897, roughly 5 years after the Ivanovsky’s discovery of the tobacco mosaic virus, George Dock [5] published a case report of a 42-year-old woman with leukemia who became afflicted with influenza. Notably, this was roughly 4 decades before it was known that a virus was responsible for influenza. Dock reported that after his patient developed “tonsillitis and coryza” as well as severe fatigue and weakness, her white blood cell count decreased roughly 70-fold

with a concordant reduction in her hepatosplenomegaly as well. She was able to live for roughly one more year after this infection, a remarkable achievement for a patient with acute leukemia at that time. In 1951, there was another case report involving a four year-old boy with profound hepatosplenomegaly and lymphocytic leukemia with a white blood cell count of 300,000, hemoglobin of 5.6 grams per deciliter, and a platelet count of 150,000 [6]. He was treated with intravenous iron for 33 days with no effect and discharged home. About 12 days later, he had a fever of 38.6 degrees Celsius with new, enlarged cervical lymph nodes and vesicles on his face, scalp, and neck consistent with varicella. After seven days, his white blood cell count decreased to 7500 and he no longer had any hepatosplenomegaly. This “remission” lasted roughly 1 month, and he unfortunately died shortly afterwards from “acute lymphatic leukemia”. While the ultimate outcome of these case reports of patients with mostly hematologic malignancies typically ended in death after a few months, they offered a possible window into new cancer therapeutics. This window could be summarized with the following principle: In mostly hematologic malignancies, which tended to have the most rapid cell growth and produce the most depleted immune systems in patients, certain viruses under the right contexts could induce short remissions.



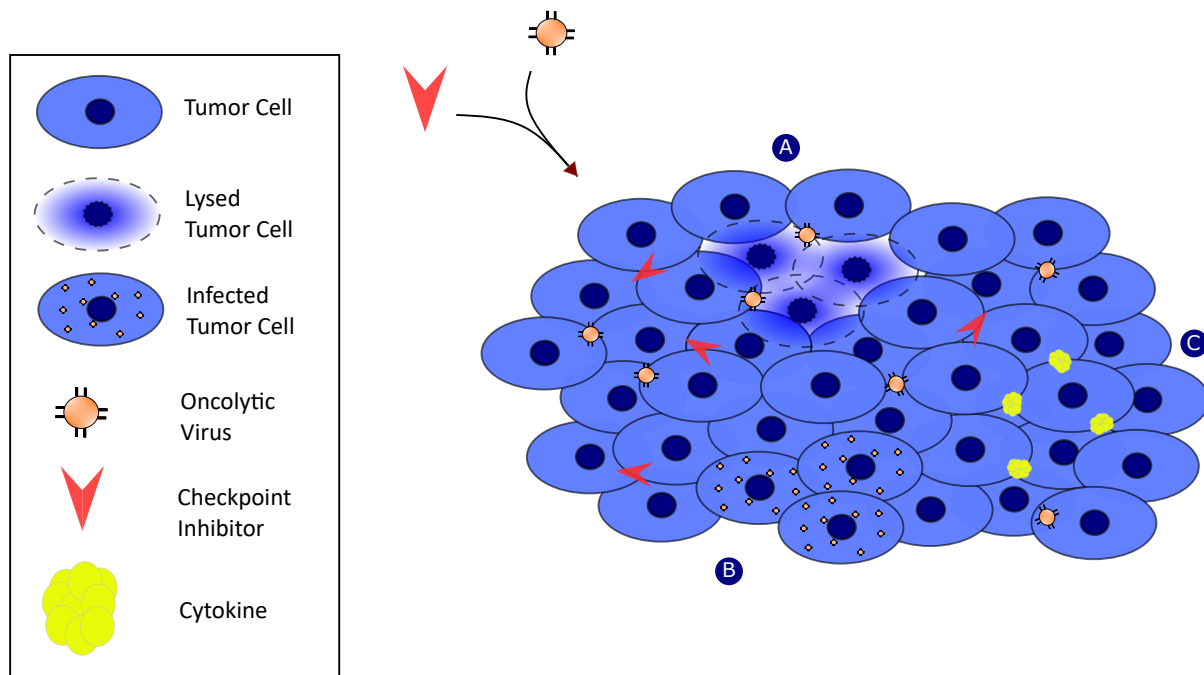


Fig. 1. Oncolytic viruses mediate antitumor response synergistically with checkpoint inhibitor activity through multiple mechanisms of action. Mechanism-A: viral replication within tumor cells. Mechanism-B: Induction of tumor cell death via Mechanism-A. Mechanism-C: release of cytokines and initiation of innate immunity.

2. OVT Trials

In 1947, Sidney Farber [7] published the results of his study utilizing aminopterin—often considered the first successful chemotherapy agent—to induce remissions in children with leukemia from his basement lab in Boston. Two years later, alongside the infancy of chemotherapy, a clinical trial was presented at the American Association for Cancer Research in which 22 patients with Hodgkin’s lymphoma were “treated” with the hepatitis B virus [8]. In this study, 7 out of 22 patients had a demonstrable clinical response with 4 out of 22 patients experiencing a reduction in tumor size. Unfortunately, 14 out of 22 patients developed hepatitis. Over the next 30 years, there were at least three other clinical trials in which cancer patients were infected with viruses. In 1952, 34 patients with various cancers were infected with Egypt Virus 101 in which only 4 patients demonstrated tumor regression [9]. In 1956, 30 patients with cervical cancer were infected with adenovirus with no tumor responses seen [10]. In 1974, 90 patients with various cancers were treated with the mumps virus in which 37 patients experienced either a complete regression or tumor shrinkage of >50% [11].

Owing to both the lack of a positive signal and improved ethical guidelines in clinical trials in the 1970s, there was a pause on treating cancer patients with non-attenuated viruses. Instead, the ability to develop *ex vivo* culture of human cells allowed researchers to use rodent models to further test oncolytic viral therapies. One study utilized various cancer rodent models and infected them with very large

doses of the Russian Far East encephalitis virus producing complete regressions [12]. Unfortunately, in each case, all rodents died of encephalitis shortly afterwards. Clearly, viruses showed great potential although their unpredictability and pathogenicity continued to prevent any meaningful progress until viral engineering became available in the 1990s.

Historically, oncolytic viral therapy (OVT) focused on direct entry and replication of viruses within rapidly dividing tumor cells causing their destruction. However, this paradigm has changed, and more promising potential lies in OVT transforming the tumor microenvironment from an immunosuppressed environment into an immunostimulatory environment in combination with checkpoint inhibitor therapies (see Fig. 1). In normal cells, protein fragments are expressed on major histocompatibility (MHC) class I molecules on the surface of the cell [13]. Cytotoxic T cells (CTL) then recognize either healthy or viral/tumoral antigens via an interaction between T cell receptors (TCRs) and MHC class I molecules. This interaction causes the CTL to either spare the cell (if healthy) or kill the cell (if viral/tumoral). However, tumor cells manipulate this interaction in many ways including by evading recognition by the CTL or suppressing antigen presentation [14]. Either through viral engineering or naturally occurring mechanisms, OVT offers a therapeutic strategy that circumvents this problem.

3. Herpes Viruses

The first OVT approved by the FDA in 2015 was Talimogene laherparepvec (T-VEC), an intralesional therapy for unresectable melanoma with limited visceral disease [15]. T-VEC is an attenuated herpes simplex virus 1 (HSV-1) that is genetically modified to specifically infect and lyse cancer cells and preserve normal cells. Normal cells block viral replication via the enzyme protein kinase R (PKR) which phosphorylates eukaryotic initiation factor 2 (eIF2). Activated eIF2 causes the disruption of viral protein synthesis [16]. HSV-1 contains infected cell protein 34.5 (ICP34.5) which dephosphorylates eIF2 and allows viral protein synthesis and subsequent viral replication to succeed [17]. Infected cell protein 47 (ICP47) is another protein produced by herpes viruses that inhibits antigen presentation to CTSs and allow for further viral proliferation [18]. In T-VEC, the genes for both ICP34.5 and ICP47 are deleted and replaced with human granulocyte-macrophage colony stimulating factor (GM-CSF) [19]. In cancer cells, the PKR-eIF2 defense mechanism against viruses is defective [16]. Therefore, T-VEC may safely infect normal cells without replicating within and destroying them and instead target cancer cells causing their destruction. This feat of viral engineering ultimately led to a phase III clinical trial of 436 patients with Stage IIIB–IV unresectable melanoma in which participants were enrolled in a two-to-one ratio to T-VEC and GM-CSF [15]. While T-VEC did not demonstrate an overall survival benefit, patients who were treated with T-VEC had a higher durable response rate compared to GM-CSF, which led to FDA approval.

While T-VEC may be limited as a monotherapy, several trials are evaluating the immunostimulatory action of T-VEC within the tumor microenvironment and combining it with immune checkpoint inhibitors including pembrolizumab and atezolizumab for hepatocellular carcinoma, breast cancer, and other gastrointestinal cancers (see Table 1). As checkpoint inhibitors specifically act to restore normal immune function by blocking immunoinhibitory proteins, combining these therapies with T-VEC may create a powerful synergistic treatment strategy. In 2016, a clinical trial combining T-VEC with the CTLA-4 inhibitor, ipilimumab, in previously untreated and resectable Stage IIIB–IV melanoma revealed a response rate of 50% [20]. This is an improvement from previous response rates with ipilimumab monotherapy (11%) and T-VEC monotherapy (26%) [20]. Other possible combinatorial therapies with OVT include PD-L1 and PD-1 inhibitors [21]. As OVTs like T-VEC specifically attract T-cells to the tumor microenvironment and upregulate tumor expression of PD-L1, for example, combining T-VEC with pembrolizumab offers a mechanism to enhance treatment response of an already effective therapy [22]. One of the limitations of anti-PD-1 therapy is that it is most effective against tumors which express a high amount of PD-L1. If PD-L1 levels were artificially enhanced by OVTs like T-VEC, then deeper re-

sponses may be observed [22]. Currently, there are several clinical trials evaluating the efficacy of T-VEC monotherapy or in combination with immune checkpoint inhibitors against melanoma, non-melanoma skin cancer, pancreatic cancer, unresectable gastrointestinal or ovarian cancer, angiosarcoma, sarcoma, rectal cancer, liver cancer, and breast cancer (see Table 1).

While T-VEC is the only FDA-approved OVT, there are several other herpes-based OVTs that are under investigation as monotherapies, in combination with immune checkpoint inhibitors, or in combination with chemotherapies. HF-10 is a naturally occurring HSV-1 OVT which has deletions in *UL56* and *LAT* and increased expression of *UL53* [23]. While the ultimate purpose of these natural genetic mutations is unknown, HF-10 has demonstrated antitumor responses in murine models of melanoma [24]. M032 is another herpes-based OVT that has been reengineered with a deletion of the γ 34.5 subunit, which causes its neurovirulence, and instead expressed interleukin-12 (IL-12) [25]. Once tumor cell destruction occurs, IL-12 is released into the tumor microenvironment and causing T-cell recruitment and response [25]. There are currently 2 clinical trials evaluating the efficacy of M032 in glioblastoma multiforme. Similarly, G207 is another HSV-1-based OVT which, like T-VEC, has a deletion in ICP34.5 which eliminates its virulence [26]. Uniquely, G207 substitutes infected cell protein 6 (ICP6) with LacZ—this allows it to target tumor cells with p16 tumor suppressor defects [26]. G207 is currently being evaluated in clinical trials for glioblastoma multiforme (see Table 1). One newer HSV2-based OVT, OH2, which also has ICP34.5 removed. ICP34.5, along with infected cell protein 47 (ICP47), allows the virus to present antigens within tumor cells to further promote oncolytic activity [27]. OH2 is being evaluated in several trials against melanoma, and GI cancers—including in combination with checkpoint inhibitor therapies (see Table 1).

4. Adenoviruses

Like herpes-based OVTs, adenovirus-based OVTs are modified to include deletions in genes that promote virulence in healthy cells. The first adenovirus-based OVT was H101, which includes *E1B* and *E3* gene partial deletions. H101 was approved by the China Food and Drug Administration Department in 2005 for nasopharyngeal carcinoma [28]. One of the more successful trials of H101 was a study of 165 patients with unresectable hepatocellular carcinoma who were treated with TACE and with or without H101. TACE with H101 showed an overall survival benefit of 12.8 months (TACE with H101) versus 10.49 months (TACE without H101) ($p = 0.046$) [29]. H101, along with other adenovirus-based OVTs, is currently under investigation for several cancers including intratumoral injections for gynecologic malignancies, hepatocellular carcinoma, and cholangiocarcinoma (see Table 2).

Table 1. Clinical trials for herpes simplex virus-based oncolytic viral therapies.

Study title	Identifier	Interventions	Condition	Phase	Status
Neo-adjuvant T-VEC + nivolumab combination therapy for resectable early metastatic (Stage IIIB/C/D–IV M1a) melanoma with injectable disease	NCT04330430	Talimogene laherparepvec (TVEC)	Stage III melanoma Stage IV melanoma	Phase II	Recruiting
Study of talimogene laherparepvec (T-VEC) in pancreatic cancer	NCT03086642	Talimogene laherparepvec (TVEC)	Pancreatic cancer	Phase I	Recruiting
Talimogene laherparepvec for the treatment of peritoneal surface malignancies	NCT03663712	Talimogene laherparepvec (TVEC)	Stage IV Peritoneal Surface Dissemination From Gastrointestinal or Recurrent, Platinum-resistant Ovarian Cancer That Cannot be Completely Resected	Phase I	Recruiting
Combination of talimogene laherparepvec with atezolizumab in early breast cancer	NCT03802604	Talimogene laherparepvec (TVEC) Atezolizumab	Breast cancer	Phase I	Recruiting
A study of talimogene laherparepvec (T-VEC) in combination with pembrolizumab in patients with metastatic and/or locally advanced sarcoma	NCT03069378	Talimogene Laherparepvec (TVEC)	Sarcoma Epitheloid sarcoma Cutaneous angiosarcoma	Phase II	Recruiting
Talimogene laherparepvec in combination with neoadjuvant chemotherapy in triple negative breast cancer	NCT02779855	Talimogene Laherparepvec (TVEC) Paclitaxel	Breast cancer Ductal carcinoma Invasive breast carcinoma Invasive ductal breast carcinoma	Phase I/II	Active, not recruiting
Talimogene laherparepvec with pembrolizumab in melanoma following progression on prior anti-PD-1 based therapy (MASTERKEY-115) (Mk-3475-A07/KEYNOTE-A07)	NCT04068181	Talimogene Laherparepvec (TVEC) Pembrolizumab	Melanoma	Phase II	Active, not recruiting
Talimogene laherparepvec, nivolumab and trabectedin for sarcoma	NCT03886311	Talimogene Laherparepvec (TVEC) Nivolumab Trabectedin	Sarcoma	Phase II	Recruiting
Talimogene laherparepvec, chemotherapy, and radiation therapy before surgery in treating patients with locally advanced or metastatic rectal cancer	NCT03300544	Talimogene Laherparepvec (TVEC) Capecitabine Fluorouracil Leucovorin Oxaliplatin Radiation therapy	Locally advanced rectal adenocarcinoma Metastatic rectal adenocarcinoma Stage IIIA–IVB rectal adenocarcinoma	Phase I	Recruiting
Trial to evaluate the safety of talimogene laherparepvec injected into tumors alone and in combination with systemic pembrolizumab MK-3475-611/Keynote-611	NCT02509507	Talimogene Laherparepvec (TVEC) Pembrolizumab	Hepatocellular carcinoma Liver metastases	Phase I/II	Active, not recruiting
Study of talimogene laherparepvec with atezolizumab for triple negative breast cancer and colorectal cancer with liver metastases	NCT03256344	Talimogene Laherparepvec (TVEC) Atezolizumab	Metastatic triple negative breast cancer Metastatic colorectal cancer with liver metastases	Phase I	Active, not recruiting
Ipilimumab, nivolumab, and talimogene laherparepvec before surgery in treating participants with localized, triple-negative or estrogen receptor positive, HER2 negative breast cancer-deleted	NCT04185311	Talimogene Laherparepvec (TVEC) Ipilimumab Nivolumab	Estrogen receptor positive, HER2 negative localized breast cancer Triple negative localized breast cancer	Phase I	Active, not recruiting

Table 1. Continued.

Study title	Identifier	Interventions	Condition	Phase	Status
Phase I study of TBI-1401(HF10) plus chemotherapy in patients with unresectable pancreatic cancer	NCT03252808	HF10 Gemcitabine Nab-paclitaxel TS-1	Stage III pancreatic cancer Stage IV pancreatic cancer	Phase I	Active, not recruiting
Study of pembrolizumab and M032 (NSC 733972)	NCT05084430	M032 Pembrolizumab	Glioblastoma multiforme Anaplastic astrocytoma Gliosarcoma	Phase I/II	Not yet recruiting
Genetically engineered HSV-1 Phase 1 study for the treatment of recurrent malignant glioma	NCT02062827	M032	Recurrent Glioblastoma multiforme Progressive glioblastoma multiforme Anaplastic astrocytoma Gliosarcoma	Phase I	Recruiting
HSV G207 in children with recurrent or refractory cerebellar brain tumors	NCT03911388	G207	Recurrent or progressive cerebellar neoplasms of the brain	Phase I	Recruiting
HSV G207 alone or with a single radiation dose in children with progressive or recurrent supratentorial brain tumors	NCT02457845	G207	Recurrent or progressive supratentorial neoplasms of the brain	Phase I	Active, not recruiting
OH2 oncolytic viral therapy in pancreatic cancer	NCT04637698	OH2	Pancreatic cancer	Phase I/II	Recruiting
OH2 oncolytic viral therapy in solid tumors	NCT03866525	OH2, with or without irinotecan or HX008	Solid tumors Gastrointestinal cancer	Phase I/II	Recruiting
OH2 injection in solid tumors	NCT04386967	OH2 Pembrolizumab	Solid tumors Melanoma	Phase I/II	Recruiting

Table 2. Clinical trials for adenovirus-based oncolytic viral therapies.

Study title	Identifier	Interventions	Condition	Phase	Status
Intra-tumor injection of oncolytic viruses H101 combined with or without radiotherapy in refractory/recurrent gynecological malignancies	NCT05051696	H101	Female genital neoplasms	Phase I	Recruiting
Intraperitoneal injection of oncolytic viruses h101 for patients with refractory malignant ascites	NCT04771676	H101	Refractory malignant ascites	Phase II	Recruiting
HAIC plus H101 vs HAIC alone for unresectable HCC at BCLC A-B	NCT03780049	Hepatic artery infusion therapy (HAIC) with FOLFOX H101	Unresectable hepatocellular carcinoma	Phase III	Recruiting
Oncolytic adenovirus DNX-2401 in treating patients with recurrent high-grade glioma	NCT03896568	DNX-2401 Therapeutic conventional surgery	Recurrent anaplastic astrocytoma Recurrent glioblastoma Recurrent gliosarcoma Recurrent malignant glioma	Phase I	Recruiting
Oncolytic adenovirus, DNX-2401, for naive diffuse intrinsic pontine gliomas	NCT03178032	DNX-2401	Brainstem glioma Neoadjuvant therapy	Phase I	Active, not recruiting
A randomised phase II open-label study with a phase Ib safety lead-in cohort of ONCOS-102, an immune-priming GM-CSF coding oncolytic adenovirus, and pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma	NCT02879669	ONCOS-102 Pemetrexed Cisplatin/Carboplatin Cyclophosphamide	Unresectable malignant pleural mesothelioma	Phase I/II	Active, not recruiting
A phase 1/2 study to investigate the safety, biologic and anti-tumor activity of ONCOS-102 in combination with durvalumab in subjects with advanced peritoneal malignancies	NCT02963831	ONCOS-102 Durvalumab	Colorectal cancer Platinum-resistant ovarian cancer Appendiceal cancer	Phase I/II	Active, not recruiting

Table 3. Clinical trials for other oncolytic viral therapies.

Study title	Identifier	Interventions	Condition	Phase	Status
A study of MEDI9253 in combination with durvalumab in select solid tumors	NCT04613492	MEDI9253 Durvalumab	Solid tumors	Phase I	Recruiting
A study of metronomic CP and JX-594 in patients with advanced breast cancer and advanced soft-tissue sarcoma (METROmaJX)	NCT02630368	JX-594 and Cyclophosphamide Cyclophosphamide Avelumab, JX-594, and cyclophosphamide	Solid tumors Soft tissue sarcoma Breast cancer	Phase I/II	Recruiting
A study of recombinant vaccinia virus in combination with cemiplimab for renal cell carcinoma	NCT03294083	Pexastimogene Devacirepvec (JX-594) Cemiplimab	Metastatic or unresectable renal cell carcinoma	Phase I/II	Recruiting
A phase I/II study of Pexa-vec oncolytic virus in combination with immune checkpoint inhibition in refractory colorectal cancer	NCT03206073	Pexastimogene Devacirepvec (JX-594) Tremelimumab Durvalumab	Refractory colorectal cancer	Phase I/II	Active, not recruiting
Immunization strategy with intra-tumoral injections of Pexa-vec with ipilimumab in metastatic/advanced solid tumors	NCT02977156	Pexastimogene Devacirepvec (JX-594) Ipilimumab	Advanced and metastatic solid tumors	Phase I	Active, not recruiting

Another adenovirus-based OVT is DNX-2401, which is currently being investigated in clinical trials against recurrent glioma [30]. DNX-2401 specifically deletes E1A, a gene responsible for its virulence, and inserts an RGD-4C motif which allows it to specifically infect tumor cells [31]. Further trials are underway investigating its efficacy against recurrent gliomas in combination with other therapies, including checkpoint inhibitors (see Table 2). In one active phase II trial, DNX-2401 is injected directly into a recurrent glioblastoma or gliosarcoma followed by pembrolizumab every 3 weeks for up to 2 years or until disease progression (NCT02798406).

One last adenovirus-based OVT currently being utilized alongside checkpoint inhibitors is ONCOS-102, which is like H101 and DNX-2401 but is also armed with GM-CSF [32]. The first indication of a positive synergistic effect of ONCOS-102 and checkpoint inhibitor therapy was in a melanoma huNOG mouse model [33]. This paved the way for a phase I trial in which patients with checkpoint inhibitor-refractory, unresectable melanoma were given ONCOS-102 in combination with pembrolizumab [34]. Objective responses were observed in 35% of patients. The FDA has now fast tracked this combination to allow for phase II/III studies for checkpoint inhibitor-refractory, unresectable melanoma. ONCOS-102 is also being utilized in combination with another checkpoint inhibitor, durvalumab, in a current Phase I/II study in patients with peritoneal disease with epithelial ovarian or metastatic colorectal cancer [35] (see Table 2).

5. Other Viruses

Newcastle disease virus (NDV) is often thought of as an ideal candidate for OVT as it does not cause serious illness in humans [36]. MEDI9253, an NDV-based OVT, has emerged as a safe anti-cancer therapy currently being studied with checkpoint inhibitor therapies for several metastatic solid tumors (see Table 3). Like ONCOS-102, MEDI9253 carries a gene for GM-CSF, however, it also encodes an *IL-12* gene, which induces the production of IFN- γ and attracts natural killer and T-cells to the tumor microenvironment [37]. There is currently a large phase I trial investigating MEDI9253 in combination with durvalumab in patients with advanced/metastatic solid tumors (NCT04613492). JX-594 is a vaccinia-based OVT that also carries a gene for GM-CSF and a deletion for thymidine kinase, which allows it to exclusively replicate in cells with high levels of thymidine kinase, namely, tumor cells [38]. JX-594 in combination with sorafenib had promising phase I/II trial results for hepatocellular cancer, however, the phase III PHOCUS trial was discontinued in 2019 after the study was unlikely to meet its primary objective. Other trials are underway including a phase I/II study combining JX-594 with the checkpoint inhibitor, cemiplimab, in metastatic renal cell carcinoma (NCT03294083) (see Table 3).

6. Challenges of OVT and Looking Ahead

There is an abundance of trials utilizing OVT, with most of the promising studies utilizing a synergistic effect with checkpoint inhibitors against solid tumors. One common barrier is the limitation of drug delivery and the challenges of evading immune responses to OVT [39]. While there are trials that are trying to utilize novel viral engineering to deliver OVT intravenously, almost all have poor bioavailability and must be injected intratumorally or locoregionally. This presents a challenge for metastatic cancers with a large tumor burden. One strategy that is being explored involves coating OVTs with biocompatible polymers to block antibodies from binding [40]. Another strategy is to pre-treat patients with a complement-inhibiting peptide [40]. Moreover, due to the intricate engineering process involved with OVT, there is a high cost associated with production and utilization of OVT that may not be practical in real world clinical settings. The estimated cost of T-VEC plus ipilimumab for advanced unresectable melanoma, the most promising OVT thus far, was \$494,983 per patient compared to \$132,950 for ipilimumab monotherapy [41]. If certain OVTs can show a significant PFS or OS benefit in phase III trials, it will be imperative to create sustainable production mechanisms that allow for improved costs, especially when combined with checkpoint inhibitors.

Perhaps the most promising trend with OVT lies in the combination therapy with checkpoint inhibitors, specifically in “cold tumors” with low expressions of PD-L1 on the surface. OVTs promote immunologic responses including type I interferons which increase PD-L1 expression on cancer cells [42]. This would allow for tumors with previously low levels of PD-L1 expression which would have been poor targets for checkpoint inhibition to potentially be ideal targets for checkpoint inhibition.

Author Contributions

JR — drafting of the manuscript; SH — drafting of the manuscript, creation of figure; AS — manuscript revision; All — final approval of the manuscript submitted.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

AS reports research grants (to institution) from AstraZeneca, Bristol Myers Squibb, Merck, Exelixis, Clovis, Kahr medical, Actuate therapeutics, Incyte corporation,

Daiichi sankyo, and advisory board fees from AstraZeneca, Daiichi Sankyo, Bristol Myers Squibb, Pfizer and Exelixis. The remaining authors report no relevant COIs.

References

- [1] Ivanofsky D. Concerning the mosaic disease of the tobacco plant. *St. Petersburg Academy of Imperial Sciences Journal*. 1892; 35: 67–70.
- [2] Fenner F. History of Virology: Vertebrate Viruses. In Mahy BWJ, Van Regenmortel MHV (eds.) *Desk Encyclopedia of General Virology* (pp. 15). Academic Press: Oxford, UK. 2009.
- [3] Staples JE, Monath TP. Yellow Fever: 100 Years of Discovery. *The Journal of the American Medical Association*. 2008; 300: 960–962.
- [4] Ekspång G (ed.) *Nobel Lectures, Physics 1981–1990*. World Scientific: Singapore. 1993.
- [5] Dock G. The influence of complicating diseases upon leukemia. *The American Journal of the Medical Sciences*. 1904; 127: 563–592.
- [6] Bierman HR, Crile DM, Dod KS, Kelly KH, Petraskis NL, White LP, *et al.* Remissions in leukemia of childhood following acute infectious disease: staphylococcus and streptococcus, varicella, and feline panleukopenia. *Cancer*. 1953; 6: 591–605.
- [7] Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *The New England Journal of Medicine*. 1948; 238: 787–793.
- [8] Hoster HA, Zanes RP Jr, Von haam E. Studies in Hodgkin's syndrome; the association of viral hepatitis and Hodgkin's disease; a preliminary report. *Cancer Research*. 1949; 9: 473–480.
- [9] Southam CM, Moore AE. Clinical studies of viruses as antineoplastic agents with particular reference to Egypt 101 virus. *Cancer*. 1952; 5: 1025–1034.
- [10] Georgiades J, Zielinski T, Cicholska A, Jordan E. Research on the oncolytic effect of APC viruses in cancer of the cervix uteri; preliminary report. *Biuletyn Instytutu Medycyny Morskiej w Gdansk*. 1959; 10: 49–57.
- [11] Asada T. Treatment of human cancer with mumps virus. *Cancer*. 1974; 34: 1907–1928.
- [12] Moore AE. Inhibition of growth of five transplantable mouse tumors by the virus of Russian far east encephalitis. *Cancer*. 1951; 4: 375–382.
- [13] Rock KL, York IA, Saric T, Goldberg AL. Protein degradation and the generation of MHC class I-presented peptides. *Advances in Immunology*. 2002; 80: 1–70.
- [14] Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, *et al.* Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Seminars in Cancer Biology*. 2015; 35: S185–S198.
- [15] Andbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, *et al.* Talimogene Laherparepvec Improves Durable Response Rate in Patients with Advanced Melanoma. *Journal of Clinical Oncology*. 2015; 33: 2780–2788.
- [16] Farassati F, Yang A, Lee PWK. Oncogenes in Ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1. *Nature Cell Biology*. 2001; 3: 745–750.
- [17] Smith KD, Mezhir JJ, Bickenbach K, Veerapong J, Charron J, Posner MC, *et al.* Activated MEK suppresses activation of PKR and enables efficient replication and in vivo oncolysis by Delta-gamma(1)34.5 mutants of herpes simplex virus 1. *Journal of Virology*. 2006; 80: 1110–1120.
- [18] Tomazin R, van Schoot NEG, Goldsmith K, Jugovic P, Sempé P, Früh K, *et al.* Herpes Simplex Virus Type 2 ICP47 Inhibits Human TAP but not Mouse TAP. *Journal of Virology*. 1998; 72: 2560–2563.
- [19] Kaufman HL, Ruby CE, Hughes T, Slingluff CL. Current status of granulocyte-macrophage colony-stimulating factor in the immunotherapy of melanoma. *Journal for ImmunoTherapy of Cancer*. 2014; 2: 11.
- [20] Puzanov I, Milhem MM, Minor D, Hamid O, Li A, Chen L, *et al.* Talimogene Laherparepvec in Combination with Ipilimumab in Previously Untreated, Unresectable Stage IIIB–IV Melanoma. *Journal of Clinical Oncology*. 2016; 34: 2619–2626.
- [21] Waibl Polania J, Lerner EC, Wilkinson DS, Hoyt-Miggelbrink A, Fecci PE. Pushing Past the Blockade: Advancements in T Cell-Based Cancer Immunotherapies. *Frontiers in Immunology*. 2021; 12: 777073.
- [22] Bartee MY, Dunlap KM, Bartee E. Tumor-Localized Secretion of Soluble PD1 Enhances Oncolytic Virotherapy. *Cancer Research*. 2017; 77: 2952–2963.
- [23] Eissa IR, Naoe Y, Bustos-Villalobos I, Ichinose T, Tanaka M, Zhiwen W, *et al.* Genomic Signature of the Natural Oncolytic Herpes Simplex Virus HF10 and Its Therapeutic Role in Preclinical and Clinical Trials. *Frontiers in Oncology*. 2017; 7: 149.
- [24] Watanabe D, Goshima F, Mori I, Tamada Y, Matsumoto Y, Nishiyama Y. Oncolytic virotherapy for malignant melanoma with herpes simplex virus type 1 mutant HF10. *Journal of Dermatological Science*. 2008; 50: 185–196.
- [25] Omar NB, Bentley RT, Crossman DK, Foote JB, Koehler JW, Markert JM, *et al.* Safety and interim survival data after intracranial administration of M032, a genetically engineered oncolytic HSV-1 expressing IL-12, in pet dogs with sporadic gliomas. *Neurosurgical Focus*. 2021; 50: E5.
- [26] Aghi MK, Chiocca EA. Phase Ib Trial of Oncolytic Herpes Virus G207 Shows Safety of Multiple Injections and Documents Viral Replication. *Molecular Therapy*. 2009; 17: 8–9.
- [27] Zhang B, Huang J, Tang J, Hu S, Luo S, Luo Z, *et al.* Intratumoral OH2, an oncolytic herpes simplex virus 2, in patients with advanced solid tumors: a multicenter, phase I/II clinical trial. *Journal for ImmunoTherapy of Cancer*. 2021; 9: e002224.
- [28] Cerullo V, Koski A, Vähä-Koskela M, Hemminki A. Chapter eight—Oncolytic adenoviruses for cancer immunotherapy: data from mice, hamsters, and humans. *Advances in Cancer Research*. 2012; 10: 265–318.
- [29] Lin X, Li Q, Lao X, Yang H, Li S. Transarterial injection of recombinant human type-5 adenovirus H101 in combination with transarterial chemoembolization (TACE) improves overall and progressive-free survival in unresectable hepatocellular carcinoma (HCC). *BMC Cancer*. 2015; 15: 707.
- [30] Lang FF, Conrad C, Gomez-Manzano C, Yung WKA, Sawaya R, Weinberg JS, *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: 1419–1427.
- [31] Fuyo J, Alemany R, Gomez-Manzano C, Fuller GN, Khan A, Conrad CA, *et al.* Preclinical Characterization of the Antiglioma Activity of a Tropism-Enhanced Adenovirus Targeted to the Retinoblastoma Pathway. *Journal of the National Cancer Institute*. 2003; 95: 652–660.
- [32] Eissa IR, Bustos-Villalobos I, Ichinose T, Matsumura S, Naoe Y, Miyajima N, *et al.* The Current Status and Future Prospects of Oncolytic Viruses in Clinical Trials against Melanoma, Glioma, Pancreatic, and Breast Cancers. *Cancers*. 2018; 10: 356.
- [33] Kuryk L, Möller AW, Jaderberg M. Combination of immunogenic oncolytic adenovirus ONCOS-102 with anti-PD-1 pembrolizumab exhibits synergistic antitumor effect in humanized a2058 melanoma huNOG mouse model. *OncImmunity*. 2018; 8: e1532763.
- [34] Shoushtari AN, Olszanski AJ, Nyakas M, Hornyak TJ, Wolchok JD, Levitsky V, *et al.* 1083P a pilot study of engineered adenovirus ONCOS-102 in combination with pembrolizumab (pembro) in checkpoint inhibitor refractory advanced or unresectable

- melanoma. *Annals of Oncology*. 2021; 32: 897–898.
- [35] Zamarin D, Odunsi K, Slomovitz BM, Duska LR, Nemunaitis JJ, Reilley 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. *Journal of Clinical Oncology*. 2020; 38: 3017–3017.
- [36] Sinkovics JG, Horvath JC. Newcastle disease virus (NDV): brief history of its oncolytic strains. *Journal of Clinical Virology*. 2000; 16: 1–15.
- [37] Huang Z, Liu M, Huang Y. Oncolytic therapy and gene therapy for cancer: recent advances in antitumor effects of Newcastle disease virus. *Discovery Medicine*. 2020; 30: 39–48.
- [38] Tennesi P, Borad MJ, Babiker HM. Exploring the role of oncolytic viruses in hepatobiliary cancers. *Immunotherapy*. 2018; 10: 971–986.
- [39] Shirley JL, de Jong YP, Terhorst C, Herzog RW. Immune Responses to Viral Gene Therapy Vectors. *Molecular Therapy*. 2020; 28: 709–722.
- [40] Hill C, Carlisle R. Achieving systemic delivery of oncolytic viruses. *Expert Opinion on Drug Delivery*. 2019; 16: 607–620.
- [41] Almutairi AR, Alkhatib NS, Oh M, Curiel-Lewandrowski C, Babiker HM, Cranmer LD, *et al.* Economic Evaluation of Talimogene Laherparepvec Plus Ipilimumab Combination Therapy vs Ipilimumab Monotherapy in Patients with Advanced Unresectable Melanoma. *JAMA Dermatology*. 2019; 155: 22–28.
- [42] Gujar S, Pol JG, Kroemer G. Heating it up: Oncolytic viruses make tumors ‘hot’ and suitable for checkpoint blockade immunotherapies. *Oncoimmunology*. 2018; 7: e1442169.