Oncolytic Virotherapy for Head and Neck Cancer

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Head and neck cancer (HNC) is a significant global health issue, and traditional treatments such as surgery, chemotherapy, and radiation therapy often have limited success, especially in advanced cases. Oncolytic virotherapy (OVT) offers a new approach.

Keywords: head and neck cancer ; oncolytic viruses ; clinical trials ; immunotherapy

1. Introduction

Head and neck cancer (HNC) refers to malignant tumors that occur within the anatomical region extending from the skull base to above the clavicles and in front of the cervical spine. It ranks as the seventh most common malignancy globally, comprising 5% of all cancers in China [1][2][3]. Among all head and neck malignancies, squamous cell carcinoma (SCC) accounts for approximately 90% [4], primarily originating from the oral cavity, nasal cavity, paranasal sinuses, pharynx, and larynx [3]. Due to the complex anatomical and physiological structures in the head and neck region, head and neck squamous cell carcinoma (HNSCC) exhibits high heterogeneity. More than 60% of patients are diagnosed with advanced-stage disease initially, and after comprehensive treatment, the metastasis or recurrence rate ranges from 40% to 60% [5][6], with a five-year survival rate of less than 50% [7][8][9].

Surgery is the primary treatment modality for HNSCC [3][10][11][12], while radiotherapy and chemotherapy are the main treatment options for inoperable cases, advanced-stage disease, or recurrent cases [13][14][15][16]. Digital techniques, navigation surgery, and artificial intelligence have been integrated into the overall management of HNCs, further enhancing the precision, safety, and effectiveness of treatment plans [17][18][19]. In addition to surgical, radiation, and chemotherapy approaches, targeted therapy, hyperthermia [20], and radioactive particle interstitial brachytherapy [21][22] have been utilized. Immunotherapy [23][24][25] has emerged as a crucial treatment option for HNCs, including immune checkpoint inhibitors (ICIs) [26], antiepidermal growth factor receptor monoclonal antibodies [27], and near-infrared photoimmunotherapy [28][29]. Immunotherapy works by harnessing the patient's own immune system to activate antitumor immune responses, control and eliminate tumor cells, and reverse tumor immune suppression [30]. Oncolytic virus (OV) immunotherapy involves using viruses to induce tumor cell death, release tumor antigens, and activate the immune system for long-lasting antitumor responses [31][32]. Genetically modified viruses can enhance the effectiveness of oncolytic virotherapy (OVT) through various antitumor mechanisms [33].

2. Advances of OVT for HNCs

OVT for head and neck tumors is primarily administered through intratumoral or intravenous injection, and has demonstrated good safety profiles in clinical trials. Currently, viruses used in clinical trials for HNCs include DNA viruses such as AD, HSV, and vaccinia virus (VV), as well as RNA viruses such as reovirus (RV), vesicular stomatitis virus (VSV), and measles virus (MV) [34][35][36] (**Table 1**).

Table 1. Clinical trials of OVT for HNC.

Virus Type	Virus Name	Clinical Phase	Route of Administration	Cotherapy	Type of Cancer	Status	ClinicalTrials.Gov ID
Adenovirus	ONYX-015	II	i.t.	cisplatin and fluorouracil	HNSCC	withdrawn	NCT00006106
	OBP-301	II	i.t.	pembrolizumab and SBRT	HNSCC	terminated	NCT04685499
	AdGV.EGR.TNF.11D	I	i.t.	RT + 5FU + hydroxyurea	HNSCC	completed	__
	KH901	II	i.t.	__	HNC	completed	__
	E10A	III	i.t.	paclitaxel + cisplatin	HNSCC	unknown	NCT00634595
	VCN-01	I	i.t.	durvalumab	HNC	active, not recruiting	NCT03799744
	AdAPT-001	I	i.t.	ICIs	solid tumor	recruiting	NCT04673942
	NG-641	Ib	i.v.	pembrolizumab	HNSCC	recruiting	NCT04830592
Herpes Simplex Virus	T-VEC	I/II	i.t.	RT + cisplatin	HNSCC	terminated	NCT01161498
		Ib/III	i.t.	pembrolizumab	HNSCC	completed	NCT02626000
	T-VEC	II	i.t.	pembrolizumab	sarcoma	active, not recruiting	NCT03069378
	HF10	I	i.t.	__	HNSCC, breast cancer, pancreatic cancer, melanoma	completed	NCT01017185
	OH2	I	i.t.	HX 008	solid tumor, gastrointestinal cancer	recruiting	NCT03866525
Reovirus	Reolysin	III	i.v.	carboplatin, paclitaxel	solid tumor	completed	NCT01166542
Measles Virus	MV-NIS	I	i.t.	__	solid tumor	completed	NCT01846091
Vaccinia Virus	GL-ONC1	I	i.v.	RT + cisplatin	HNSCC	completed	NCT01584284
	Pexa-Vec	I	i.t.	ipilimumab	solid tumor	completed	NCT02977156
Vesicular Stomatitis Virus	VSV-IFNβ-NIS	I	i.t./i.v.	avelumab	solid tumor	completed	NCT02923466
	VSV-IFNβ-NIS	I/II	i.v.	pembrolizumab	solid tumor	recruiting	NCT03647163
Newcastle Disease Virus	MEDI5395	I	i.v.	durvalumab	solid tumor	recruiting	NCT04830592

2.1. Adenovirus

AD contains a double-stranded DNA ranging from 26 to 45 kb, and is currently the most frequently used virus vector in cancer biotherapy. It can cause symptoms of upper respiratory tract infections [37][38]. The primary receptor for AD is the Coxsackie-adenovirus receptor (CAR), with other receptors including CD46, CD80, CD86, and desmoglein-2 (DSG2) [39]. Among oncolytic ADs, adenovirus type 5 (AD5) has been extensively studied, and can infect tumor cells through the CAR receptor [40].

In the year 2000, the National Cancer Institute in the United States initiated the phase I clinical trial of the first-generation oncolytic AD, ONYX-015, for the treatment of HNCs. This virus weakened its inhibition of the p53 gene by deleting the E1B55KD gene from its genome, thereby improving tumor targeting. In a phase II clinical trial, 37 recurrent HNSCC patients received intratumor and peritumor injections of ONYX-015. It was observed that the virus caused highly selective destruction of tumor tissue, with significant tumor regression (>50%) observed in 21% of the patients [41]. Unfortunately, the phase III clinical trial was terminated due to funding issues. OBP-301 (Telomelysin), based on AD5, was engineered by inserting the hTERT gene promoter upstream of the E1 gene. Studies have shown that combining OBP-301 with cisplatin enhances its effectiveness against HNSCC, and overcomes its resistance to radiotherapy [42].

AdGV.EGR.TNF.11D is a nonreplicating AD that expresses human TNF-α under the control of the early growth response factor 1 (EGR-1). When administered intratumorally in combination with 5-fluorouracil and hydroxyurea, it achieved an effective rate of 83.3% in recurrent HNSCC patients, with an average survival of 9.6 months [43]. KH901 is a recombinant oncolytic AD constructed through genetic engineering. It is primarily used for intratumoral injection in the treatment of recurrent HNC, and has entered phase II clinical trials [44]. In a phase I clinical trial, 23 patients received single-dose intratumoral injections of KH901 or multiple-dose injections over a period of time, and all patients showed good tolerance. The main toxicities observed were mild to moderate flu-like symptoms. No dose-limiting toxicities (DLTs) were reached in either the single-dose or multiple-dose groups, and all 23 treated patients showed an increase in AD-neutralizing antibodies. E10A is an AD that has been engineered to insert the human endostatin gene. It is primarily used for intratumoral injection in combination with paclitaxel and cisplatin for the treatment of HNSCC, and it is currently undergoing phase III clinical trials. A randomized, open-label, multicenter phase II clinical trial (NCT00634595) demonstrated that intratumoral injection of E10A in combination with paclitaxel and cisplatin could prolong progression-free survival (PFS), and improve the overall disease control rate (DCR) compared to paclitaxel and cisplatin chemotherapy alone [45]. Apart from fever, no other adverse events (AEs) were reported.

Monoclonal antibodies that target the programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocyte-associated protein-4 (CTLA-4) pathways have brought about a permanent transformation in the treatment of various types of tumors, some of which were previously associated with a poor prognosis, including HNSCC [46][47]. The combination of OVs and ICIs in the treatment of HNC holds great research value. Several ongoing clinical trials are dedicated to exploring the combined therapeutic effectiveness of ICIs and OVs in this context [48]. VCN-01 is an oncolytic AD based on AD5, with its genome engineered for selective replication in pRB-defective tumor cells. It carries a fibroblast-specific integrin-binding motif RGD sequence for tumor targeting and expresses hyaluronidase to degrade the extracellular matrix. The efficacy and safety of VCN-01 have been confirmed in various tumor models, including HNC [49]. Clinical trials have been initiated to investigate the combination therapy of VCN-01 with durvalumab in recurrent and metastatic HNSCC (NCT03799744). AdAPT-001 is a virus derived from human AD5 that has undergone two significant modifications [50]. The first modification involves a 50 base pair deletion in the E1A promoter, which makes the virus less likely to affect normal tissues, while maintaining its ability to replicate in and destroy tumor cells. The selectivity of the virus for tumors is also linked to the impaired IFN signaling in cancer cells, which renders them more susceptible to the virus's cytolytic effects. The second modification introduces a chimeric gene consisting of TGF-β receptor II fused with the Fc portion of human IgG-1, creating a soluble TGFβR-IgG fusion protein that effectively neutralizes the activity of the pro-oncogenic cytokine, TGF-β. As demonstrated by Christopher et al. [50], localized oncolytic infection with AdAPT-001 is not only safe, but also overcomes resistance to systemic PD-L1 immunotherapy and provides long-lasting protection against the recurrence of tumors in experiments with syngeneic tumor rechallenge. AdAPT-001 is currently under evaluation in the phase I clinical trial known as BETA PRIME, both with and without ICIs (NCT04673942). NG-641 represents an advanced adenoviral vector for tumor-specific immuno gene therapy (T-SIGn), engineered to be blood-stable and armed with transgenes [51]. The mode-of-action transgene study is a phase Ib clinical trial, conducted across multiple centers and in an open-label format, focusing on dose escalation of NG-641 as a standalone treatment or in combination with pembrolizumab (NCT04830592). Eligible patients include those with newly diagnosed or recurrent locally advanced HNSCC who have definitive surgery scheduled within 8 weeks of the screening.

2.2. Herpes Simplex Virus

HSV is an enveloped virus containing approximately 150 kb of double-stranded DNA and encodes around 80 different proteins, which can be classified into type 1 and type 2 [52]. Due to the broad host range and the ability to carry various foreign DNA, most oncolytic HSVs entering clinical trials are modified from HSV-1 [53]. T-VEC is a recombinant HSV-1 that lacks the γ34.5 and ICP47 genes, but promotes US11 gene expression and encodes GM-CSF [54]. In preoperative lymph node injections for HNSCC, T-VEC promotes highly regressive changes in metastatic lymph nodes [55]. A phase Ib multicenter trial involving 36 patients investigated the safety and preliminary efficacy of T-VEC in combination with pembrolizumab for the treatment of platinum-resistant recurrent or metastatic HNCs (NCT02626000) [56]. The primary endpoint was DLT, and secondary endpoints included objective response rate (ORR), PFS, overall survival (OS), and safety. Most treatment-related AEs were grade 1 or 2, and treatment-related grade 2 or 3 AEs associated with T-VEC and pembrolizumab were 13.9% and 16.7%, respectively. There were no treatment-related fatal AEs. Disease control was observed in 13.9% of cases, and 10 cases (27.8%) were unable to evaluate efficacy due to early death. The median PFS and OS were 3.0 months (95% CI, 2.0–5.8 months) and 5.8 months (95% CI, 2.9–11.4 months), respectively, demonstrating the good safety profile of T-VEC.

Recent research findings indicate that T-VEC has demonstrated encouraging outcomes in the management of melanoma and sarcoma in the head and neck region. As shown in the study conducted by Franke et al. [57], the ORR for T-VEC

monotherapy in cases of head and neck melanoma at the Netherlands Cancer Institute reached 80%, with half of the patients achieving a complete response (CR). The median age at the study's outset was 78.2 years (ranging from 35 to 97), and the median follow-up period extended to 11.6 months. The data present promising outcomes and imply that T-VEC could serve as a viable alternative to systemic therapy for this specific, predominantly elderly patient group. In a phase II clinical trial reported by Kelly et al. [58], the treatment combining T-VEC and pembrolizumab exhibited antitumor activity in advanced sarcoma cases, spanning various histologic subtypes of sarcoma, while maintaining a manageable safety profile (NCT03069378). This combination therapy successfully met its predetermined primary study endpoint, and further assessments of T-VEC in conjunction with pembrolizumab for patients with specific subtypes of sarcoma are in the planning stages.

HF10 is a naturally occurring HSV with a UL56 gene deletion and has cell-fusion capability [59]. Research by Esaki et al. [60] showed that HF10 can replicate within HNSCC cells and kill them. HF10 induces tumor necrosis, CD8+ cell infiltration, and the release of antitumor cytokines, including IL-2, IL-12, TNF-α, and IFN-α, -β, -γ, to inhibit tumor growth and prolong survival. Mace et al. [61] found that HSV1716 was well-tolerated in the treatment of oral SCC, but had minimal biological activity. The main challenges include optimizing the dose, delivery, and distribution of HSV1716 into the dense heterogeneous tumor cell matrix. Increasing understanding of the interactions between HSV1716, HNSCC cells, and the immune system will help optimize antitumor efficacy. OH2, a novel oncolytic HSV-2, robustly triggers the activation of human peripheral blood mononuclear cells, resulting in heightened antitumor effectiveness in vitro and in vivo [62]. At present, it is in the initial phase of clinical trials (phase I) for the treatment of melanoma and various solid tumors (NCT03866525).

2.3. Other OVs

In addition to AD and HSV, various OVs have been used in clinical trials for the treatment of HNC. RV is a naturally occurring OV [63]. Oncolytics Biotech reported the data from a randomized, two-arm, double-blind, multicenter phase III clinical trial of RV in combination with standard chemotherapy for advanced stage HNC. Compared to chemotherapy alone, the combination therapy improved the median PFS of patients (94 days vs. 50 days). However, it was associated with increased side effects such as fever, chills, nausea, and diarrhea, although most patients tolerated it well [64]. Reolysin (Pelareorep) is derived from Reovirus type 3 Dearing, a naturally occurring OV that activates the RAS pathway and has cytotoxic effects on tumor cells [65][66]. The phase III clinical trial of combination therapy involving intravenous Reolysin with paclitaxel and carboplatin in HNC patients has been completed (NCT01166542). In phase I and II clinical trials [67], involving 24 patients with HNSCC and other HNCs, 1 patient achieved CR, 6 patients achieved partial response (PR), 2 patients had a major clinical response (mCR) after initial radiotherapy, 6 patients had stable disease (SD), and 5 patients experienced disease progression (DP).

MV is a negative-sense single-stranded RNA virus [68]. MV-NIS is an OV in which the sodium iodine symporter (NIS) gene is inserted into the MV genome, allowing infected cells to be imaged using single-photon emission computed tomography (SPECT) [69]. A phase I trial of intratumoral administration of MV-NIS for the treatment of HNSCC has been completed at the Mayo Clinic (NCT01846091).

VV is a double-stranded DNA virus, and most adults lack corresponding antibodies. It can infect primary and distant metastatic lesions through intravenous injection [70]. GL-ONC1 (GLV-1H68) is a VV-based oncolytic virus in which the viral thymidine kinase (TK), hemagglutinin (HA), and F14.5L genes are replaced by β-galactosidase, β-glucuronidase, and renilla luciferase/green fluorescence (RLuc-GFP), respectively [71][72]. In a phase I clinical trial, Mell et al. [72] found that intravenous injection of GL-ONC1 in combination with cisplatin chemotherapy and radiotherapy improved overall survival in late-stage HNC patients. The one-year and two-year PFS rates were 74.4% and 64.1%, and the one-year and two-year OS rates were 84.6% and 69.2%, respectively. Pexa-Vec is an oncolytic VV engineered with a deletion in the thymidine kinase gene and carries transgenes for GM-CSF and β-galactosidase [73]. A phase I clinical trial has been completed to evaluate the intratumoral administration of Pexa-Vec in combination with the CTLA-4 inhibitor ipilimumab for patients with metastatic or advanced tumors (NCT02977156).

VSV-hIFNβ-NIS is an oncolytic VSV that expresses human IFN-β and NIS, known to induce rapid and potent tumor regression with systemic treatment [74]. VSV-hIFNβ-NIS is involved in two phase I combination trials: one combines it with the anti-PD-L1 antibody avelumab for patients with refractory metastatic solid tumors (NCT02923466), and the other combines it with the anti-PD1 antibody pembrolizumab for patients with select solid tumors (NCT03647163). MEDI5395 is a recombinant Newcastle disease virus (NDV) carrying a GM-CSF transgene [75]. Recently, MEDI5395 has entered a phase I trial in combination with the PD-L1 inhibitor durvalumab (NCT03889275).

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.
2. Chen, W.; Zheng, R.; Baade, P.D.; Zhang, S.; Zeng, H.; Bray, F.; Jemal, A.; Yu, X.Q.; He, J. Cancer statistics in China, 2015. CA Cancer J. Clin. 2016, 66, 115–132.
3. Chow, L.Q.M. Head and Neck Cancer. N. Engl. J. Med. 2020, 382, 60–72.
4. American Cancer Society. Cancer Facts & Figures 2019; American Cancer Society: Atlanta, GA, USA, 2019.
5. Vermorken, J.B.; Mesia, R.; Rivera, F.; Remenar, E.; Kawecki, A.; Rottey, S.; Erfan, J.; Zabolotnyy, D.; Kienzer, H.R.; Cupissol, D.; et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N. Engl. J. Med. 2008, 359, 1116–1127.
6. Pfister, D.G.; Spencer, S.; Adelstein, D.; Adkins, D.; Anzai, Y.; Brizel, D.M.; Bruce, J.Y.; Busse, P.M.; Caudell, J.J.; Cmelak, A.J.; et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Cancer Netw. 2020, 18, 873–898.
7. Braakhuis, B.J.; Brakenhoff, R.H.; Leemans, C.R. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: Biological risk factors. Ann. Oncol. 2012, 23, x173–x177.
8. Marur, S.; Forastiere, A.A. Head and neck cancer: Changing epidemiology, diagnosis, and treatment. Mayo Clin. Proc. 2008, 83, 489–501.
9. Burtness, B.; Harrington, K.J.; Greil, R.; Soulières, D.; Tahara, M.; de Castro, G.; Psyrri, A., Jr.; Basté, N.; Neupane, P.; Bratland, Å.; et al. KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 2019, 394, 1915–1928.
10. Qiu, S.Y.; Shan, X.F.; Kang, Y.F.; Ding, M.K.; Zhang, L.; Cai, Z.G. Accurate occlusion-driven maxillary reconstruction with deep circumflex iliac artery flap using computer-assisted techniques and intraoral anastomosis: A case series. Int. J. Oral. Maxillofac. Surg. 2023, 52, 744–752.
11. Hu, J.; Liu, J.; Guo, Y.; Cao, Z.; Chen, X.; Zhang, C. A collaborative robotic platform for sensor-aware fibula osteotomies in mandibular reconstruction surgery. Comput. Biol. Med. 2023, 162, 107040.
12. Chen, S.; Alkebsi, K.; Xuan, M.; Wang, X.Y.; Li, L.J.; Li, C.J.; Zhang, Z.; Zhu, G.Q. Single incision-plus approach for gasless endoscopic parotidectomy: A seven-step procedure. Transl. Cancer Res. 2022, 11, 2462–2472.
13. Gordon, K.; Smyk, D.; Gulidov, I.; Golubev, K.; Fatkhudinov, T. An Overview of Head and Neck Tumor Reirradiation: What Has Been Achieved So Far? Cancers 2023, 15, 4409.
14. De Felice, F.; Cattaneo, C.G.; Franco, P. Radiotherapy and Systemic Therapies: Focus on Head and Neck Cancer. Cancers 2023, 15, 4232.
15. Zhong, L.P.; Zhang, C.P.; Ren, G.X.; Guo, W.; William, W.N., Jr.; Sun, J.; Zhu, H.G.; Tu, W.Y.; Li, J.; Cai, Y.L.; et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. J. Clin. Oncol. 2013, 31, 744–751.
16. Yamauchi, M.; Minesaki, A.; Ishida, T.; Sato, Y.; Okamura, S.; Shuto, H.; Tanaka, N.; Hatayama, E.; Shibamiya, N.; Kuratomi, Y. Induction Chemotherapy With 5-Fluorouracil, Cisplatin, and Cetuximab in Advanced Head and Neck Squamous Cell Carcinoma. In Vivo 2023, 37, 1275–1280.
17. Peng, X.; Acero, J.; Yu, G.Y. Application and prospects of computer-assisted surgery in oral and maxillofacial oncology. Sci. Bull. 2023, 68, 236–239.
18. Soh, H.Y.; Hu, L.H.; Yu, Y.; Wang, T.; Zhang, W.B.; Peng, X. Navigation-assisted maxillofacial reconstruction: Accuracy and predictability. Int. J. Oral. Maxillofac. Surg. 2022, 51, 874–882.
19. Zhong, N.N.; Wang, H.Q.; Huang, X.Y.; Li, Z.Z.; Cao, L.M.; Huo, F.Y.; Liu, B.; Bu, L.L. Enhancing head and neck tumor management with artificial intelligence: Integration and perspectives. Semin. Cancer Biol. 2023, 95, 52–74.
20. Drizdal, T.; van Rhoon, G.C.; Fiser, O.; Vrba, D.; van Holthe, N.; Vrba, J.; Paulides, M.M. Assessment of the thermal tissue models for the head and neck hyperthermia treatment planning. J. Therm. Biol. 2023, 115, 103625.
21. Zhong, Y.W.; Lyu, X.M.; Shi, Y.; Guo, C.B.; Zhang, J.G.; Zheng, L. Long-term result of 125 I seed brachytherapy for pediatric desmoid tumor in the head and neck. Pediatr. Blood Cancer. 2023, 70, 30037.
22. Zhang, G.; Wu, Z.; Yu, W.; Lyu, X.; Wu, W.; Fan, Y.; Wang, Y.; Zheng, L.; Huang, M.; Zhang, Y.; et al. Clinical application and accuracy assessment of imaging-based surgical navigation guided 125I interstitial brachytherapy in

deep head and neck regions. J. Radiat. Res. 2022, 63, 741–748.

23. Gildener-Leapman, N.; Ferris, R.L.; Bauman, J.E. Promising systemic immunotherapies in head and neck squamous cell carcinoma. Oral. Oncol. 2013, 49, 1089–1096.
24. Sellars, M.C.; Wu, C.J.; Fritsch, E.F. Cancer vaccines: Building a bridge over troubled waters. Cell 2022, 185, 2770–2788.
25. Kumai, T.; Shinomiya, H.; Shibata, H.; Takahashi, H.; Kishikawa, T.; Okada, R.; Fujieda, S.; Sakashita, M. Translational research in head and neck cancer: Molecular and immunological updates. Auris Nasus Larynx. 2023; in press.
26. O'Meara, C.H.; Jafri, Z.; Khachigian, L.M. Immune Checkpoint Inhibitors, Small-Molecule Immunotherapies and the Emerging Role of Neutrophil Extracellular Traps in Therapeutic Strategies for Head and Neck Cancer. Int. J. Mol. Sci. 2023, 24, 11695.
27. Patel, B.; Saba, N.F. Current Aspects and Future Considerations of EGFR Inhibition in Locally Advanced and Recurrent Metastatic Squamous Cell Carcinoma of the Head and Neck. Cancers 2021, 13, 3545.
28. Miyazaki, N.L.; Furusawa, A.; Choyke, P.L.; Kobayashi, H. Review of RM-1929 Near-Infrared Photoimmunotherapy Clinical Efficacy for Unresectable and/or Recurrent Head and Neck Squamous Cell Carcinoma. Cancers 2023, 15, 5117.
29. Cognetti, D.M.; Johnson, J.M.; Curry, J.M.; Kochuparambil, S.T.; McDonald, D.; Mott, F.; Fidler, M.J.; Stenson, K.; Vasan, N.R.; Razaq, M.A.; et al. Phase 1/2a, open-label, multicenter study of RM-1929 photoimmunotherapy in patients with locoregional, recurrent head and neck squamous cell carcinoma. Head Neck 2021, 43, 3875–3887.
30. Kennedy, L.B.; Salama, A.K.S. A review of cancer immunotherapy toxicity. CA Cancer J. Clin. 2020, 70, 86–104.
31. Matsunaga, W.; Gotoh, A. Adenovirus as a Vector and Oncolytic Virus. Curr. Issues Mol. Biol. 2023, 45, 4826–4840.
32. Hamada, M.; Yura, Y. Efficient Delivery and Replication of Oncolytic Virus for Successful Treatment of Head and Neck Cancer. Int. J. Mol. Sci. 2020, 21, 7073.
33. Raja, J.; Ludwig, J.M.; Gettinger, S.N.; Schalper, K.A.; Kim, H.S. Oncolytic virus immunotherapy: Future prospects for oncology. J. Immunother. Cancer. 2018, 6, 140.
34. Gujar, S.; Bell, J.; Diallo, J.S. SnapShot: Cancer Immunotherapy with Oncolytic Viruses. Cell 2019, 176, 1240–1240.e1.
35. Nenclares, P.; Ap Dafydd, D.; Bagwan, I.; Begg, D.; Kerawala, C.; King, E.; Lingley, K.; Paleri, V.; Paterson, G.; Payne, M.; et al. Head and neck mucosal melanoma: The United Kingdom national guidelines. Eur. J. Cancer 2020, 138, 11–18.
36. Yura, Y. Presage of oncolytic virotherapy for oral cancer with herpes simplex virus. Jpn. Dent. Sci. Rev. 2017, 53, 53–60.
37. Kaufmann, J.K.; Nettelbeck, D.M. Virus chimeras for gene therapy, vaccination, and oncolysis: Adenoviruses and beyond. Trends Mol. Med. 2012, 18, 365–376.
38. Gryciuk, A.; Rogalska, M.; Baran, J.; Kuryk, L.; Staniszewska, M. Oncolytic Adenoviruses Armed with Co-Stimulatory Molecules for Cancer Treatment. Cancers 2023, 15, 1947.
39. Abudoureyimu, M.; Lai, Y.; Tian, C.; Wang, T.; Wang, R.; Chu, X. Oncolytic Adenovirus-A Nova for Gene-Targeted Oncolytic Viral Therapy in HCC. Front. Oncol. 2019, 9, 1182.
40. Bullard, B.L.; Corder, B.N.; Weaver, E.A. Species D adenoviruses as oncolytic viral vectors. Viruses 2020, 12, 1399.
41. Nemunaitis, J.; Ganly, I.; Khuri, F.; Arseneau, J.; Kuhn, J.; McCarty, T.; Landers, S.; Maples, P.; Romel, L.; Randlev, B.; et al. Selective replication and oncolysis in p53 mutant tumors with ONYX-015, an E1B-55kD gene-deleted adenovirus, in patients with advanced head and neck cancer: A phase II trial. Cancer Res. 2000, 60, 6359–6366.
42. Kondo, N.; Tsukuda, M.; Kimura, M.; Fujita, K.; Sakakibara, A.; Takahashi, H.; Ishiguro, Y.; Toth, G.; Matsuda, H. Antitumor effects of telomelysin in combination with paclitaxel or cisplatin on head and neck squamous cell carcinoma. Oncol. Rep. 2010, 23, 355–363.
43. Seiwert, T.Y.; Darga, T.; Haraf, D.; Blair, E.A.; Stenson, K.; Cohen, E.E.; Salama, J.K.; Villaflor, V.; Witt, M.E.; Lingen, M.W.; et al. A phase I dose escalation study of Ad GV.EGR.TNF.11D (TNFerade™ Biologic) with concurrent chemoradiotherapy in patients with recurrent head and neck cancer undergoing reirradiation. Ann. Oncol. 2013, 24, 769–776.
44. Chang, J.; Zhao, X.; Wu, X.; Guo, Y.; Guo, H.; Cao, J.; Guo, Y.; Lou, D.; Yu, D.; Li, J. A Phase I study of KH901, a conditionally replicating granulocyte-macrophage colony-stimulating factor: Armed oncolytic adenovirus for the treatment of head and neck cancers. Cancer Biol. Ther. 2009, 8, 676–682.

45. Ye, W.; Liu, R.; Pan, C.; Jiang, W.; Zhang, L.; Guan, Z.; Wu, J.; Ying, X.; Li, L.; Li, S.; et al. Multicenter randomized phase 2 clinical trial of a recombinant human endostatin adenovirus in patients with advanced head and neck carcinoma. Mol. Ther. 2014, 22, 1221–1229.

46. Oliveira, G.; Egloff, A.M.; Afeyan, A.B.; Wolff, J.O.; Zeng, Z.; Chernock, R.D.; Zhou, L.; Messier, C.; Lizotte, P.; Pfaff, K.L.; et al. Preexisting tumor-resident T cells with cytotoxic potential associate with response to neoadjuvant anti-PD-1 in head and neck cancer. Sci. Immunol. 2023, 8, eadf4968.

47. Hoffmann, F.; Franzen, A.; de Vos, L.; Wuest, L.; Kulcsár, Z.; Fietz, S.; Maas, A.P.; Hollick, S.; Diop, M.Y.; Gabrielpillai, J.; et al. CTLA4 DNA methylation is associated with CTLA-4 expression and predicts response to immunotherapy in head and neck squamous cell carcinoma. Clin. Epigenetics 2023, 15, 112.

48. Hwang, J.K.; Hong, J.; Yun, C.O. Oncolytic Viruses and Immune Checkpoint Inhibitors: Preclinical Developments to Clinical Trials. Int. J. Mol. Sci. 2020, 21, 8627.

49. Rodríguez-García, A.; Giménez-Alejandre, M.; Rojas, J.J.; Moreno, R.; Bazan-Peregrino, M.; Cascalló, M.; Alemany, R. Safety and efficacy of VCN-01, an oncolytic adenovirus combining fiber HSG-binding domain replacement with RGD and hyaluronidase expression. Clin. Cancer Res. 2015, 21, 1406–1418.

50. Larson, C.; Oronsky, B.; Reid, T. AdAPT-001, an oncolytic adenovirus armed with a TGF-β trap, overcomes in vivo resistance to PD-L1-immunotherapy. Am. J. Cancer Res. 2022, 12, 3141–3147.

51. Ottensmeier, C.; Evans, M.; King, E.; Emma, K.; Ioannis, K.; Tom, L.; David, K.; Jenny, L.; Matthew, T.; Kevin, H. 437 A multicentre phase 1b study of NG-641, a novel transgene-armed and tumour-selective adenoviral vector, and pembrolizumab as neoadjuvant treatment for squamous cell carcinoma of the head and neck. J. Immunother. Cancer 2021, 9, A1–A1054.

52. Rathbun, M.M.; Szpara, M.L. A holistic perspective on herpes simplex virus (HSV) ecology and evolution. Adv. Virus Res. 2021, 110, 27–57.

53. Epstein, A.L. HSV-1's contribution as a vector for gene therapy. Nat. Biotechnol. 2022, 40, 1316.

54. Pol, J.G.; Lévesque, S.; Workenhe, S.T.; Gujar, S.; Le Boeuf, F.; Clements, D.R.; Fahrner, J.E.; Fend, L.; Bell, J.C.; Mossman, K.L.; et al. Trial Watch: Oncolytic viro-immunotherapy of hematologic and solid tumors. Oncoimmunology 2018, 7, e1503032.

55. Harrington, K.J.; Hingorani, M.; Tanay, M.A.; Hickey, J.; Bhide, S.A.; Clarke, P.M.; Renouf, L.C.; Thway, K.; Sibtain, A.; McNeish, I.A.; et al. Phase I/II study of oncolytic HSV GM-CSF in combination with radiotherapy and cisplatin in untreated stage III/IV squamous cell cancer of the head and neck. Clin. Cancer Res. 2010, 16, 4005–4015.

56. Harrington, K.J.; Kong, A.; Mach, N.; Chesney, J.A.; Fernandez, B.C.; Rischin, D.; Cohen, E.E.W.; Radcliffe, H.S.; Gumuscu, B.; Cheng, J.; 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. Clin. Cancer Res. 2020, 26, 5153–5161.

57. Franke, V.; Stahlie, E.H.A.; Klop, W.M.C.; Zuur, C.L.; Berger, D.M.S.; van der Hiel, B.; van de Wiel, B.A.; Wouters, M.W.J.M.; van Houdt, W.J.; van Akkooi, A.C.J. Talimogene laherparepvec monotherapy for head and neck melanoma patients. Melanoma Res. 2023, 33, 66–70.

58. Kelly, C.M.; Antonescu, C.R.; Bowler, T.; Munhoz, R.; Chi, P.; Dickson, M.A.; Gounder, M.M.; Keohan, M.L.; Movva, S.; Dholakia, R.; 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 Oncol. 2020, 6, 402–408.

59. Kasuya, H.; Kodera, Y.; Nakao, A.; Yamamura, K.; Gewen, T.; Zhiwen, W.; Hotta, Y.; Yamada, S.; Fujii, T.; Fukuda, S.; et al. Phase I Dose-escalation Clinical Trial of HF10 Oncolytic Herpes Virus in 17 Japanese Patients with Advanced Cancer. Hepatogastroenterology 2014, 61, 599–605.

60. Esaki, S.; Goshima, F.; Ozaki, H.; Takano, G.; Hatano, Y.; Kawakita, D.; Ijichi, K.; Watanabe, T.; Sato, Y.; Murata, T.; et al. Oncolytic activity of HF10 in head and neck squamous cell carcinomas. Cancer Gene Ther. 2020, 27, 585–598.

61. Mace, A.T.; Ganly, I.; Soutar, D.S.; Brown, S.M. Potential for efficacy of the oncolytic Herpes simplex virus 1716 in patients with oral squamous cell carcinoma. Head Neck 2008, 30, 1045–1051.

62. Wang, Y.; Jin, J.; Li, Y.; Zhou, Q.; Yao, R.; Wu, Z.; Hu, H.; Fang, Z.; Dong, S.; Cai, Q.; et al. NK cell tumor therapy modulated by UV-inactivated oncolytic herpes simplex virus type 2 and checkpoint inhibitors. Transl. Res. 2022, 240, 64–86.

63. Bourhill, T.; Rohani, L.; Kumar, M.; Bose, P.; Rancourt, D.; Johnston, R.N. Modulation of Reoviral Cytolysis (II): Cellular Stemness. Viruses 2023, 15, 1473.

64. Gong, J.; Sachdev, E.; Mita, A.C.; Mita, M.M. Clinical development of reovirus for cancer therapy: An oncolytic virus with immune-mediated antitumor activity. World J. Methodol. 2016, 6, 25–42.
65. Chakrabarty, R.; Tran, H.; Selvaggi, G.; Hagerman, A.; Thompson, B.; Coffey, M. The oncolytic virus, pelareorep, as a novel anticancer agent: A review. Investig. New Drugs 2015, 33, 761–774.
66. Zhu, Z.; McGray, A.J.R.; Jiang, W.; Lu, B.; Kalinski, P.; Guo, Z.S. Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. Mol. Cancer 2022, 21, 196.
67. Karapanagiotou, E.M.; Roulstone, V.; Twigger, K.; Ball, M.; Tanay, M.; Nutting, C.; Newbold, K.; Gore, M.E.; Larkin, J.; Syrigos, K.N.; et al. Phase I/II trial of carboplatin and paclitaxel chemotherapy in combination with intravenous oncolytic reovirus in patients with advanced malignancies. Clin. Cancer Res. 2012, 18, 2080–2089.
68. Loewe, D.; Dieken, H.; Grein, T.A.; Weidner, T.; Salzig, D.; Czermak, P. Opportunities to debottleneck the downstream processing of the oncolytic measles virus. Crit. Rev. Biotechnol. 2020, 40, 247–264.
69. Riesco-Eizaguirre, G.; Santisteban, P.; De la Vieja, A. The complex regulation of NIS expression and activity in thyroid and extrathyroidal tissues. Endocr. Relat. Cancer 2021, 28, T141–T165.
70. Ling, Q.; Zheng, B.; Chen, X.; Ye, S.; Cheng, Q. The employment of vaccinia virus for colorectal cancer treatment: A review of preclinical and clinical studies. Hum. Vaccin Immunother. 2022, 18, 2143698.
71. Azad, T.; Rezaei, R.; Singaravelu, R.; Pelin, A.; Boulton, S.; Petryk, J.; Onsu, K.A.; Martin, N.T.; Hoskin, V.; Ghahremani, M.; et al. Synthetic virology approaches to improve the safety and efficacy of oncolytic virus therapies. Nat. Commun. 2023, 14, 3035.
72. Mell, L.K.; Brumund, K.T.; Daniels, G.A.; Advani, S.J.; Zakeri, K.; Wright, M.E.; Onyeama, S.J.; Weisman, R.A.; Sanghvi, P.R.; Martin, P.J.; et al. Phase I Trial of Intravenous Oncolytic Vaccinia Virus (GL-ONC1) with Cisplatin and Radiotherapy in Patients with Locoregionally Advanced Head and Neck Carcinoma. Clin. Cancer Res. 2017, 23, 5696–5702.
73. Breitbach, C.J.; Bell, J.C.; Hwang, T.H.; Kirn, D.H.; Burke, J. The emerging therapeutic potential of the oncolytic immunotherapeutic Pexa-Vec (JX-594). Oncolytic Virother. 2015, 4, 25–31.
74. Velazquez-Salinas, L.; Naik, S.; Pauszek, S.J.; Peng, K.W.; Russell, S.J.; Rodriguez, L.L. Oncolytic Recombinant Vesicular Stomatitis Virus (VSV) Is Nonpathogenic and Nontransmissible in Pigs, a Natural Host of VSV. Hum. Gene Ther. Clin. Dev. 2017, 28, 108–115.
75. Dy, G.; Davar, D.; Galanis, E.; Townsley, D.; Karanovic, D.; Schwaederle, M.; Kelly, B.; Zamarin, D.; Borad, M.; Harrington, K. Abstract CT244: A phase 1 study of IV MEDI5395, an oncolytic virus, in combination with durvalumab in patients with advanced solid tumors. Cancer Res. 2020, 80, CT244.