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REVIEW

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ABSTRACT

Oncolytic viruses selectively target and kill cancer cells in an immunogenic fashion, thus supporting the establishment of therapeutically relevant tumor-specific immune responses. In 2015, the US Food and Drug Administration (FDA) approved the oncolytic herpes simplex virus T-VEC for use in advanced melanoma patients. Since then, a plethora of trials has been initiated to assess the safety and efficacy of multiple oncolytic viruses in patients affected with various malignancies. Here, we summarize recent preclinical and clinical progress in the field of oncolytic virotherapy.

KEYWORDS

CAVATAK; DNX-2401; HF10; Maraba MG1; MV-NIS; Pexa-Vec; REOLYSIN; T-VEC

Introduction

Since immune checkpoint inhibitors (ICIs) have revolutionized the care of melanoma patients, the field of immunotherapy has diversified and extended to multiple malignant indications. Cancer immunotherapies currently approved by the US Food and Drug Administration (FDA) for clinical use include: a) six ICIs that bind either to programmed cell death 1 (PDCD1; best known as PD-1) (i.e., nivolumab, pembrolizumab), either to CD274 (best known as PD-L1) (i.e., avelumab, atezolizumab and durvalumab), or to cytotoxic T-lymphocyte associated protein 4 (CTLA4) (i.e., ipilimumab);[1–15] b) multiple monoclonal antibodies (mAb) targeting surface tumor-associated antigens (TAAs) (e.g., the anti-CD20 mAb rituximab, the anti-ERBB2 mAb trastuzumab);[15–17] c) two immunostimulatory cytokines (i.e., interferon [IFN]-α and interleukin [IL]-2);[18] d) several immunogenic cell death inducers (e.g., anthracyclines, cyclophosphamide [CPA], oxaliplatin),[19–28] e) adoptive chimeric antigen receptor [CAR] T-cell therapy (i.e., tisagenlecleucel and axicabtagene ciloleucel),[29–33] f) bacillus Calmette-Guérin (BCG) immunotherapy,[34,35] g) adoptive dendritic cell [DC]-based cancer vaccine (i.e., sipuleuceul-T)[31,36–39] and h) oncolytic viro-immunotherapy (i.e., talimogene laherparepvec [T-VEC]).[40–46]

Oncolytic viruses (OVs) are non-pathogenic replication-competent viruses that preferentially infect, replicate in and kill cancer cells while sparing their normal counterparts.[40,47–49] The list of viruses that demonstrate oncolytic activity keeps expanding and includes agents of animal (e.g., vaccinia virus [VV]) and human (e.g., serotype 3 reovirus, type 1 herpes simplex virus [HSV-1]) origin.[50–64] Tumor selectivity, referred to as 'oncotropism', requires that cancer cells i) express the virus entry receptor and ii) demonstrate permissiveness to virus life cycle completion.[65–69] Alongside, OVs should undergo abortive infection in most normal tissues to prevent side effects and toxicity, which is of particular concern when treating immunosuppressed patients.[70,71] Oncotropism can be natural or, more frequently, genetically acquired/restricted. Genetic engineering procedures implemented so far to OVs consisted of 1) modifying the OV attachment protein to redirect or strengthen its binding to a tumor-associated receptor,[72–81] 2) inserting cis-regulatory elements in the OV genome to guarantee a transcriptional and/or post-transcriptional

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control of its expression/replication in target rather than off-target tissues,[61,82–96] and/or 3) abolishing the activity of virulence factors in charge of hacking proliferation, survival and/or antiviral machineries of the host cell.[41,92,96–105] The latter strategy has been extensively applied in the development of most OVs currently evaluated into the clinic. Indeed, it generates viral strains with strongly attenuated infectivity in normal cells but with preserved replicative efficacy in cancer cells as the features of the malignant phenotype (e.g., defective/attenuated IFN response, sustained nucleotide and protein synthesis, resistance to cell death)[66,106–111] complement the activity of the mutated viral factors. For instance, the FDA-approved OV T-VEC (trade name Imlygic, formerly called OncoVex^{GM-CSF}, Amgen, Thousand Oaks, CA, USA) consists of an HSV-1 (JS1 strain) that underwent deletion of two neurovirulence factors, ICP34.5 and ICP47, responsible for counteracting innate and adaptive immunity, respectively.[41,112–114] OV-induced cancer cell killing, referred to as 'oncolysis', is consecutive to multimodal mechanisms of action. First, tumor cell elimination can result from direct oncolysis due to completion of a lytic viral cycle and/or induction of programmed cancer cell death upon virus replication.[19,20,47–49,112,115–118] Accordingly, some OVs have been armed with pro-apoptotic factors or combined with cytotoxic agents to enhance direct oncolysis.[77,87,88,92,98,118–139] Nevertheless, most of the efficacy of oncolytic virotherapy is attributed to indirect means. Indeed, OV replication within the tumor microenvironment (TME) remains limited in extent and transient due to the antiviral immune pressure, rendering direct oncolysis marginally efficient.[64,68,140–143] As an aside, multiple strategies have been introduced to favor OV targeting to, persistence and/or spread within the tumor by circumventing elimination from the host immune machinery. Genetic engineering, coating of the OV attachment protein,[59,144–146] cell carrier,[78,147–152] or biochemical/pharmacological immunosuppression[153-159] have proven efficient at limiting virus neutralization/clearing mediated by antibodies, the complement system or innate immune cells such as phagocytes. This is particularly important when OVs are administered systemically (rather than intralesionally) for the treatment of hardly accessible primary neoplasms or disseminated malignant tissues.[160–163] To facilitate the spread of OV progenies from one infected cell to uninfected neighbors, transgenes or agents affecting the cell junctions or the extracellular matrix have also been employed.[138,156,164–166] Of note, anti-angiogenic properties have also been ascribed to some OV strains for their ability to acutely disrupt the tumor neovasculature, thus inducing vast necrotic areas within infected neoplasms.[167–171] In line with this notion, several groups have equipped or associated OVs with genetic inserts or drugs impairing blood vessel development.[132,172,173] On the other hand, OVs demonstrate immunotherapeutic activity as viral infection profoundly reshapes the immunosuppressive TME in a way that supports the reinstatement of cancer immunosurveillance.[47,49,64,140,143,174,175] First, virus-induced cell stress and death produce pathogen/microbe-associated molecular patterns (PAMPs/MAMPs), release damage-associated molecular patterns (DAMPs) and favor tumor antigen spreading.[23,112,128,175–186] The immediate consequence of such pro-inflammatory environment consists of the recruitment of innate and adaptive actors of the intrinsically linked antiviral and antitumor immunities.[112,128,139,167,174,177,187–195] Such antitumor response plays a critical role in the overall efficacy of oncolytic virotherapy by eliminating spare malignant cells.[128,189,191,196] Additionally, the establishment of a tumor-specific immune memory contributes to prevent cancer recurrence.[191,196,197] Several strategies have been designed to support cancer immunosurveillance upon OV treatment. Pharmacological immunomodulators or transgenes expressing either immunomodulatory proteins (e.g., chemokines, cytokines, co-stimulatory molecules, antibodies), or shRNAs silencing mRNAs of immunoinhibitory factors, have been recurrently combined with/inserted into OVs.[112,119,126,132,192,194,197–220] For instance, T-VEC overexpresses colony stimulating factor 2 (CSF2, best known as GM-CSF), which drives chemotaxis and activation of antigen-presenting cells.[41,112] Alternatively, tumor-associated antigens or epitopes can be either coated on viral particules[221] or overexpressed from OVs to exacerbate their cancer vaccine potential.[222–231] Like prophylactic vaccines, the later strategy (referred as an 'oncolytic vaccine') authorizes prime-boost immunization protocols to further expand the adaptive arm of the antitumor response.[222–224,226,230,231] Finally, combinations of OV therapy with complementary immunotherapeutic approaches (e.g., ICIs or CAR T, DC and natural killer [NK] cell therapies), have demonstrated enhanced efficacy in preclinical models, and more recently into the clinic, and are actively investigated against multiple indications.[112,128,133,147,187,188,191,197–199,201,203,204,206,207,232–244] Not surprisingly, combinatorial regimens involving ICIs are predominant and have already confirmed synergistic effect with several strains of OVs.[112,128,147,187,188,191,197–199,239–245] Interestingly, OV therapy input can revert resistance to ICI treatment; a property that can be attributed, at least in part, to their ability to broaden neoantigenome-directed T-cell responses and to stimulate the expression of inhibitory checkpoints on both immune and tumor cells.[139,188,197,239,242,246,247]

Here, we provide an update on the preclinical and clinical progress achieved in the field of oncolytic viro-immunotherapy since the publication of the latest Trial Watch dealing with this topic (December 2015).[40]

Preclinical and translational advances

A plethora of preclinical and translational studies dealing with oncolytic viruses have been published during the past 2.5 years (source http://www.ncbi.nlm.nih.gov/pubmed). The following paragraphs provide a non-exhaustive compilation of recent original findings in the field.

Adenoviruses. **(1)** Eriksson et al. (Lokon Pharma AB, Uppsala, Sweden) introduced LOAd703, an oncolytic adenovirus (oAd) of chimeric serotype 5/35 armed with co-immunostimulatory CD40L and 4-1BBL. LOAd703 demonstrated oncolytic activity against pancreatic cell lines *in vitro*. In mice, LOAd703 given intratumorally (i.t.) was able to control the growth of a syngeneic pancreatic tumor model, particularly when combined with gemcitabine (an antimetabolite used as standard of care for pancreatic cancer patients).[248–251] LOAd703 infection was associated with DC maturation/activation which in turn increased the activation/expansion of NK and tumor-specific T cells. Following on these encouraging preclinical data, the safety and oncolytic viro-immunotherapeutic efficacy of LOAd703 will be investigated

clinically against pancreatic malignancy (for details, see "Recently initiated clinical trials" below).[200,252] **(2)** Delta-24-RGD, also referred to as DNX-2401 into the clinic (DNAtrix, Houston, TX, USA), is an oAd engineered to preferentially infect, replicate in and lyze tumor cells. Precisely, a RGD peptide motif has been introduced in the Ad fiber to favor interaction with tumor integrins and 24 base pairs have been deleted in the E1A gene to restrict replication to tumor cells with abnormality of the p16/RB/E2F pathway. DNX-2401 is currently evaluated in a Phase II clinical trial against various brain malignancies (see following sections on clinical trials).[97] In a preclinical study, i.t. Delta-24-RGD also demonstrated efficacy against human pancreatic tumor xenografts in mice. OV-mediated cytotoxicity was inducing phosphatidylserine exposure on the outer layer of the plasma membrane. Interestingly, the therapeutic efficacy was further enhanced when combining Delta-24-RGD to 1N11, a fully human phosphatidylserine antibody.[253] Following infection, several immune subsets involved in anticancer innate immunity (i.e., macrophages and NK cells) were infiltrating the tumor bed, particularly when the OV was accompanied with the 1N11-based immunotherapy. Among the mechanisms involved were cited the antibody-dependent cell-mediated cytotoxicity (ADCC) and an enhanced anticancer immune response, notably through an increased differentiation of pro-tumor M2 macrophages into anti-tumor M1 macrophages.[97] In this line, Delta-24-RGD was armed with the co-immunostimulator OX40L,[254,255] thus forming Delta-24-RGDOX. In an orthotopic model of glioma in immunocompetent syngeneic mice, Delta-24-RGDOX appeared to be more efficient than its precursor at recruiting $CD4^+$ and $CD8^+$ T lymphocytes in the tumor bed and exhibited superior ability to activate tumor-specific $CD8^+$ T cells. As a consequence, i.t. injection of Delta-24-RGDOX demonstrated a more potent immune-mediated antiglioma activity than Delta-24-RGD. Cured animals were also protected against tumor rechallenge thus validating the establishment of a protective immune memory. To further overcome the immune suppression mediated by PD-L1 expression at the surface of cancer cells, virotherapy was accompanied with a PD-L1 antibody. The combinatorial treatment showed synergistic inhibition of gliomas and significantly increased mouse survival. Altogether, these studies demonstrated that Delta-24-RGD and its armed derivatives could be promising agents for brain and pancreatic cancer therapy, particularly when combined with immunotherapies.[197] **(3)** VCN-01 (VCN Biosciences, Barcelona, Spain) is an engineered Ad5 with enhanced infectivity through RGD modification of the viral fiber, conditional-replication in retinoblastoma protein (Rb)-deficient cells through 24-bp deletion in the E1A gene and improved tissue distribution via transgene expression of the soluble hyaluronidase PH-20. It is currently undergoing Phase I clinical investigations against pancreatic cancer and retinoblastoma (see section "Recently initiated clinical trials"). Martinez-Velez and colleagues evaluated the efficacy of VCN-01 against relevant xenograft models of osteosarcoma in mice. The OV demonstrated remarkable anti-tumor activity against both orthotopic and lung metastatic osteosarcoma following i.t. or systemic delivery, respectively. These results motivated the authors to propel a Phase I/II study with VCN-01 in pediatric osteosarcoma.[146] **(4)** Two groups have armed oAds with bispecific T cell-engagers (BiTEs), some artificial proteins generated by the fusion of the single-chain variable fragments (scFv) of two different monoclonal antibodies, one binding to the T lymphocyte marker CD3 and the second one targeting a surface TAA.[256–259] By co-engaging T cell effectors and cancer cells, BiTEs can mediate immune-mediated tumor cell lysis. Fajardo and collaborators (Bellvitge Biomedical Research Institute/IDIBELL, L'Hospitalet de Llobregat, Spain) expressed a human epidermal growth factor receptor (EGFR)-targeting BiTE antibody from ICOVIR-15K, an oAd with RGD-modified fiber and truncated E1A protein.[260] The BiTE was potently secreted from ICOVIR-15K-cBiTE-infected cells and specifically bound to $CD3^+$ and $EGFR^+$ cells. Cocultures with human peripheral blood mononuclear cells (PBMCs) promoted the activation, proliferation and antitumor cytotoxicity of T cells. In immunodeficient mice bearing $EGFR^+$ tumor xenografts and transplanted with human PBMCs, i.t. treatment with ICOVIR-15K-cBiTE increased the accumulation and persistence of tumor-infiltrating lymphocytes (TILs) and enhanced antitumor efficacy in comparison to the parental strain ICOVIR-15K.[260] OV-mediated expression of BiTEs also benefited to CAR T cell therapy. Interestingly, the combinatorial strategy was unlocking activation and proliferation of tumor-infiltrating CAR T cells in the absence of the targeted antigen on cancer cells and improved outcome in mice bearing tumor xenografts. By bypassing limitations of CAR T cell monotherapy, clinical evaluation of such combination is encouraged.[261] Similarly, Freedman and colleagues introduced an EpCAM-targeting BiTE into EnAdenotucirev (EnAd), a chimeric Ad3/11p group B adenovirus (PsiOxus Therapeutics, Abingdon, UK).[208] The efficacy of EnAd-CMV-EpCAMBiTE was assessed on pleural effusions and peritoneal malignant ascites from patients with multiple indications of advanced carcinoma. Despite significant levels of immunosuppressive IL-10, EnAd-CMV-EpCAMBiTE adjunction appeared much more potent than its unarmed counterpart at activating endogenous T cells and eliminating endogenous cancer cells.[208] Translation into the clinic of this novel therapeutic is under consideration. **(5)** Ad5 is currently the benchmark oAd. However, high seroprevalence in the human population and known hepatotoxicity limits its delivery to localized and injectable malignant lesions.[262,263] In order to circumvent these downsides, Nguyen et al. (Translational Immunovirology and Biodefense Program, Rochester, MN, USA) introduced the lower seroprevalence Ad6. Following systemic injection, Ad6 appeared perfectly tolerated, without any signs of toxicity, and demonstrated efficacy against syngeneic and xenografted tumors in rodents.[59] **(6)** Villanueva and colleagues (IDIBAPS, Barcelona, Spain) developed a novel strategy to improve OV tumor-selectivity based on the recent discovery that mRNA translational control by cytoplasmic polyadenylation element (CPE)-binding proteins is reactivated in cancer. They inserted CPE regulatory sequences in the 3′-untranslated region of the adenoviral gene E1A. Following systemic delivery in mice, the resulting AdCPE conserved full potency against tumor xenografts with strongly attenuated replication

in normal tissues such as liver. This approach could be extended to other OV platforms.[83] **(7)** Capasso et al. (University of Helsinki, Helsinki, Finland) developed a versatile and rapid system to adsorb major histocompatibility complex class I (MHC-I)-restricted tumor peptides onto the virus surface to stimulate oAd treatment immunogenicity.[221] The peptide-coated oAd (PeptiCRAd) retained intact oncolytic activity and allowed cross-presentation of the exogenous epitope on MHC-I. When administered to mice bearing syngeneic melanoma, PeptiCRAd coated with melanoma-associated epitopes showed enhanced antitumor activity towards treated and distant untreated tumors.[221] This platform efficiently redirected the immunodominance of viral antigens towards tumor antigens, making PeptiCRAd a promising approach for clinical evaluation.[221] **(8)** Osteosarcoma is generally refractory to chemotherapy, hence of poor prognosis. Osaki and collaborators showed that OBP-301, a telomerase-specific oAd (also named Telomelysin, Oncolys BioPharma, Tokyo, Japan),[264] synergistically suppressed the viability of osteosarcoma cell line and xenograft tumor models in combination with chemotherapeutic agents (cisplatin and doxorubicin).[137] Mechanistically, OBP-301 infection was promoting the siRNA-mediated knockdown of anti-apoptotic myeloid cell leukemia 1 (MCL1), thus sensitizing cancer cells to chemotoxicity. OBP-301 would appear as a promising strategy to attenuate chemoresistance in osteosarcoma patients.[137] **(9)** Dey et al. (The Brain Tumor Center, The University of Chicago, Chicago, IL, USA) emphasized the ability of neural stem cells (NSCs) to cross the blood-brain barrier and reach orthotopic glioma tumors following non-invasive intranasal delivery. Once engineered to overexpress C-X-C Motif Chemokine Receptor 4 (CXCR4), then loaded with an oncolytic Ad, infected NSCs extended survival of experimental animals in the context of radiotherapy.[233] This approach deserves optimization for future applications against disorders of the central nervous system (CNS).

Flaviviruses. Two groups reported the oncolytic property of Zika virus (ZIKV), a neurotropic flavivirus. Zhu and colleagues (University of California School of Medicine, San Diego, CA, USA) showed that ZIKV infects and kills human glioblastoma stem-like cells (GSCs) at higher rates than differentiated glioma or normal neuronal cells. In vivo, intracranial injection of a mouse-adapted ZIKV substantially extended survival of immunocompetent mice bearing syngeneic orthotopic glioblastoma (GB).[50] Lately, Kaid et al. (University of São Paulo, São Paulo, SP, Brazil) validated the potent ZIKV oncolytic activity against orthotopic xenografts of human embryonic tumors of the CNS. Mechanistically, the sensitivity of CNS tumor cells to ZIKV was relying on the basal activation of the Wnt signaling, as the pharmacological inhibition or stimulation of this pathway was respectively reducing or enhancing viral replication and oncolysis.[265]

Herpesviruses. **(1)** In the clinic, the efficacy of poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) is limited to DNA repair-deficient cancers and still faces resistance.[266] Rabkin's team (Harvard Medical School, Boston, MA, USA) showed that two strains of oncolytic HSV-1 (oHSV-1), namely G47Δ (γ34.5Δ, ICP47-Us11 promoter Δ, ICP6^{-}, LacZ^{+}) and MG18L (Us3Δ, ICP6^{-}, LacZ^{+}), sensitized patient-derived GSCs to PARPi, irrespectively of their resistance status.[267] The synergistic effect resulted from the oHSV-mediated proteasomal degradation of the recombinase Rad51, a key protein of the DNA damage response.[268] It translated into an increased DNA damage and cell death in vitro and in vivo. The interaction between the approved PARPi olaparib and oHSVs significantly extended median survival of mice bearing PARPi-sensitive or -resistant GSC-derived brain tumors compared to either agent alone.[267] **(2)** The same group showed in a clinically relevant murine model of GB that combined application of G47Δ-mIL12, a G47Δ oHSV-1 expressing murine IL-12, with checkpoint inhibitors (anti-CTLA-4, -PD-1, -PD-L1) overcomes the highly immunosuppressive TME and eradicates tumors.[269] Mechanistically, the combination treatment promoted macrophage influx and M1-like macrophage polarization together with an increase of the effector/regulatory T cell ratio.[269] **(3)** Han & colleagues (The Ohio State University, Columbus, OH, USA) demonstrated that the immunosuppressive cytokine TGF-β could compromise NK cell-mediated cytotoxicity against oHSV-infected GB multiforme. Consequently, administration of TGF-β prior to oHSV treatment improved therapeutic efficacy against both xenograft and syngeneic GB multiforme mouse models.[158] In contrast, in GB multiforme refractory to temozolomide (TMZ, a standard-of-care alkylating agent) and typically enriched in cancer stem-like cells, Esaki and colleagues (Department of Neurosurgery, Harvard Medical School, Boston, MA, USA) showed that inhibition of the TGF-β signaling pathway benefited to oHSV therapy. Systemic administration of inhibitors of the TGF-β receptor together with i.t. injection of oHSV cured 60% of mice bearing orthotopic grafts of patient-derived recurrent GB multiforme. Mechanistically, the combination caused blockade of the mitogen-activated protein kinase (MAPK) pathways, thus affecting malignant cell clonogenicity, together with a boost of OV replication.[235] Similarly, Hutzen and co-workers (The Ohio State University, Columbus, OH, USA) also reported a benefit of TGF-β inhibition to oHSV therapy in murine models of rhabdomyosarcoma.[210] **(4)** Chen et al. (College of Medicine, Colombus, OH, USA) engineered NK cells to express last generation EGFR-CAR and demonstrated their cytotoxic activity against breast cancer cell lines expressing EGFR. Both *in vitro* and *in vivo* in a relevant model of breast cancer brain metastases, i.t. inoculation of both EGFR-CAR NK cells and oHSV1 demonstrated superior antitumor effectiveness than either therapy alone.[237] **(5)** In human breast cancer cell lines, using a genome-wide shRNA library, Workenhe et al. (McMaster Immunology Research Centre, Hamilton, Canada) observed that depleting serine/arginine-rich splicing factor 2 (SRSF2), or controlling its phosphorylation thanks to DNA topoisomerase I inhibitors, could enhance the oncolytic activity of the HSV-1 KM-100 (KOS strain, ICP0^{n212} VP16^{in1814}).[238,270] These results were confirmed *in vivo* as the combination of the approved topoisomerase inhibitor irinotecan[271] with KM-100 led to a synergistic antitumor activity against syngeneic murine breast cancer.[270] **(6)** A study by Oldfield and co-workers (The Johns Hopkins University, Baltimore, MD, USA) evaluated the potential of synthetic genome assembly methods for genome-wide

engineering of HSV-1.[272] The genome of wild-type KOS strain was cloned using yeast transformation- associated recombination. By using the overlapping sequences between the adjacent pieces, 11 fragments of the genome were assembled into a complete HSV-1 genome in yeast. The assembled genome was transferred into an *Escherichia coli* host for transfection into mammalian cells. This method of HSV-1 engineering allowed deletion of up to 5 combinatorial deletions of genes that encode virion structural proteins. This technology is a suitable platform to modify oncolytic HSV-1.[272] **(7)** To circumvent the obstacle of systemic delivery and enable access of the virus to metastases, Leoni and colleagues (University of Bologna, Bologna, Italy) infected mesenchymal stromal cells (MSCs) with HER2-retargeted oHSV. Following infusion of immunocompromised mice with oHSV-infected MSCs, the burden of xenografted models of ovarian cancer lung metastases and breast cancer brain metastases was significantly reduced.[78] Confirming the reliability of the approach, Du et al. (Harvard Medical School, Boston, MA, USA) efficiently treated syngeneic murine melanoma brain metastases with oHSV-armed MSCs. Moreover, combination with PD-L1 blockade increased tumor-infiltrating cytotoxic $CD8^+$ T lymphocytes (CTLs) and profoundly extended median survival of treated animals.[147]

Orthomyxoviruses. **(1)** Using Raf-BxB transgenic mice that spontaneously develop non-small cell lung cancer (NSCLC), Masemann and colleagues demonstrated that one single intranasal inoculation of 500 particles of influenza A virus (IAV) rapidly eliminated 70% of the initial tumor mass.[273] Interestingly, IAV infection caused a functional reversion of immunosuppressive tumor-associated lung macrophages into a M1-like pro-inflammatory phenotype that supports virus-induced oncolysis. This study demonstrated, for the first time in an immunocompetent in vivo model, that infection with oncolytic IAV reshapes the TME and instates an anti-NSCLC immunity.[273] **(2)** Recent works from Palese's team (Icahn School of Medicine, Mount Sinai, NY, USA) showed the feasibility to engineer an IAV that expresses an anti-CTLA-4 antibody. This recombinant virus significantly slowed tumor growth and extended overall survival of mice bearing aggressive melanoma. Importantly, the OV-mediated production of this immune checkpoint antibody successfully delayed the growth of distant, untreated, tumors thus supporting the induction of an abscopal effect.[198]

Paramyxoviruses. **(1)** Kazimirsky et al. (Mina & Everad Goodman Faculty of Life-Sciences, Bar-Ilan University, Ramat-Gan, Israel) demonstrated that glioma cells and glioma stem cells were more sensitive to the oncolytic effect of Newcastle disease virus (NDV) when the virus was delivered in MSCs. The therapeutic benefit was relying on the release of TNF-related apoptosis-inducing ligand (TRAIL) from infected MSCs.[152] **(2)** Ammayappan et al. (Mayo Clinic, Rochester, MN, USA) developed a reverse genetics system from a major isolate of the Urabe strain mumps virus (MuV) stock that allowed the construction and production of several recombinant strains. These recombinant MuVs demonstrated oncolytic activity against tumor cell lines in vitro and some efficacy against a syngeneic mouse model of colon carcinoma.[57] **(3)** Chen and colleagues (Laboratory of Molecular Medicine, Medical School, Nanjing University, Nanjing, China) demonstrated the therapeutic advantage of a local administration of a measle virus vaccine strain Edmonston (MV-Edm) in improving the adoptive transfer of $CD8^+$ $NKG2D^+$ cells in a hepatocellular carcinoma mouse model. Moreover, they showed that this combination could be further improved by the administration of fludarabine, an inhibitor of the therapy-induced immune suppressor enzyme IDO1.[232]

Picornaviruses. **(1)** PVSRIPO (Duke University, Durham, NC, USA), an engineered poliovirus Sabin type 1, is being evaluated clinically against recurrent grade IV glioma (see sections on clinical trials below). Recent preclinical studies investigated its efficacy against xenografted and syngeneic subcutaneous models of melanoma, breast and prostate cancers in mice. Following i.t. injection, PVSRIPO infection was stimulating the expression of numerous pro-inflammatory cytokines and chemokines within the tumor bed, primed the infiltration of innate immune cells (i.e., neutrophils, DCs) and the subsequent activation and recruitment of T lymphocytes including anticancer effectors. Ultimately, PVSRIPO viro-immunotherapy significantly slowed tumor growth and prolonged mouse survival.[142,274] **(2)** Bell and Pavenko (Mayo Clinic, Rochester, MN, USA) developed new hybrid strains of the picornavirus Theiler's murine encephalomyelitis virus (TMEV). In vitro, they identified one virus named GD7-KS1 as a potent oncolyic agent against melanoma cell lines. In melanoma-bearing immunocompetent mice, repeated i.t. injections of GD7-KS1 stimulated a strong infiltration of tumor-specific CTLs, delayed tumor outgrowth and promoted survival extension.[58]

Poxviruses. **(1)** Bartee and collaborators (Medical University of South Carolina, Charleston, SC, USA) developed an oncolytic myxomavirus (MYXV) that expresses a soluble PD-1 molecule allowing its secretion from infected cells. Interestingly, i.t. injection of the virus, referred to as vPD1, induced prolonged tumor-specific $CD8^+$ T lymphocyte response and demonstrated superior anticancer efficacy than the combination of the unmodified MYXV with PD-1 antibodies administered systemically.[202] **(2)** Liu and colleagues (University of Pittsburgh School of Medicine, Pittsburgh, PA, USA) demonstrated in preclinical murine colon and ovarian cancer models that oncolytic vvDD (a Western Reserve [WR] VV with a double-deletion of the genes encoding the thymidine kinase [TK] and the vaccinia growth factor [VGF]) attracts effector T cells and induces PD-L1 expression on both cancer and immune cells in the tumor.[242] Interestingly, the combination of poxvirus plus ICI reduced the count of $PD\text{-}L1^+$ cells and increased $CD8^+$ and $CD4^+$ T cell tumor infiltration as well as the expression of the activation/effector markers IFN-γ, Inducible T-cell COStimulator (ICOS), granzyme B and perforin. Overall, the treatment favored a sustained activation of effector T cells leading to extended survival.[242] In another study, a synergistic interaction between the ICIs anti-CTLA-4 or anti-PD-1 and the oncolytic VV-FCU1 has also been reported. VV-FCU1 (referred to as TG6002 into the clinic; Transgene, Illkirch-Graffenstaden, France) consists of a WR strain deleted of the TK and I4L/ribonucleotide reductase genes and armed with the fusion suicide gene FCU1 derived from the yeast cytosine deaminase (yCD) and uracil phosphoribosyltransferase genes.

Noteworthy, the combination with ICIs was also accompanied with regressions of distant untreated tumors (abscopal effect). The VV-FCU1-based treatment was particularly beneficial against cancer cells deficient for the interferon-α/β receptor (IFNAR) signaling pathway.[128,129] In the same way, Thorne's group (University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) had observed synergistic associations between the oncolytic vvDD and WR B18r$^{-/-}$ TK$^{-/-}$ and various immune checkpoint blockades (PD-1, PD-L1 or CTLA-4) against several preclinical murine tumor models. However, a particular concern was raised over the careful selection of the VV strain, antibody and timing of administration as some combinations actually produced antagonistic effects and loss of therapeutic activity.[275] Considering the variety of VV strains currently under clinical investigation (i.e., recombinant variants of WR, Lister, Copenhagen or Wyeth strains; for instance, see Table 1) and the anticipated introduction of ICIs, critical attention will have to be paid on identifying the correct settings of OV/ICI association to achieve best efficacy. **(3)** Thorne's group also identified myeloid-derived suppressor cells (MDSCs) as key mediators of resistance to immunotherapies, including OV therapy. Cumulative reports have identified cyclooxygenase (COX)-2-mediated production of prostaglandin E_2 (PGE_2) as a determinant of MDSC migration and maintenance of their immunosuppressive phenotype.[276–280] Therefore, their team aimed at targeting PGE_2 by engineering the VV WR.TK$^-$ strain to express the prostaglandin-inactivating enzyme 15-hydroxyprostaglandin dehydrogenase [NAD+] (HPGD). Treatment with the resultant VV WR.TK$^-$.HPGD$^+$ was reducing MDSC tumor infiltration, enhanced the immune response within and against the tumor and re-sensitized resistant neoplasms not only to virotherapy but also to other immunotherapies such as adoptive T cell-based cancer treatment.[281] **(4)** To selectively target cancer cells, Potts et al. (Faculty of Medicine and Dentistry, University of Alberta, Edmontion, Canada) constructed a VV strain that is deleted for the F4L gene which encodes a ribonucleotide reductase; an enzyme essential for virus replication and complemented in malignant cells.[282] The F4L-deleted VV demonstrated its safety and efficiency against syngeneic rat and xenografted human orthotopic bladder tumor models. Importantly, this treatment led to the establishment of a protective immune memory since tumor rechallenge of cured rats failed to reinstate a neoplasm. Thus, F4L-deleted VV could constitute a promising alternative against bladder cancers, particularly in patients that fail responding to standard intravesical BCG immunotherapy.-[34,282] **(5)** Hirvinen and colleagues (Laboratory of ImmunoViroTherapy, Faculty of Phamacy, University of Helsinki, Finland) experienced an original approach that consisted in overexpressing an intracellular pattern recognition receptor, the DNA-dependent activator of IFN-regulatory factors (DAI), from vvDD with the aim of enhancing the production of type I IFNs and the stimulation of both innate and adaptive arms of antitumor immunity. Compared to VV alone, local administration of vvDD-DAI resulted in an increase of tumor-infiltrating CD8$^+$ T-cells, which translated into better efficacy against melanoma in both syngeneic and humanized mouse models.[220] **(6)** In a model of syngeneic orthotopic glioma established from intracranial injection of brain tumor-initiating cells in mice, Pisklakova and colleagues (Moffitt Cancer Center, Tampa, FL, USA) demonstrated that removing the gene M011L, which encodes an anti-apoptotic Bcl2 homolog, from wild-type MYXV sensitizes brain tumor cells to virus-induced cell death and prolongs survival of tumor-bearing mice. Interestingly, the efficacy of vMyx-M011L-KO treatment was significantly enhanced in combination with the chemotherapeutic standard-of-care TMZ.[131] **(7)** Francis et al. (University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) reported on a novel combination regimen to improve OV immunotherapeutic activity. In a syngeneic peritoneal carcinomatosis model, oncolysis was first induced by a vvDD expressing the chemokine CXCL11 administered through i.p. injection. Subsequently, a chemokine modulating drug cocktail consisting of IFNα, plus the TLR3 agonist polyI:C, plus the COX-2 inhibitor celecoxib, was administered repeatedly. The dual treatment promoted the trafficking and supported the activity of OV-induced tumor-targeting CTLs and NK cells within the TME. Upon combination therapy, median and long-term survivals dramatically extended thus encouraging further evaluations of the approach.[194] **(8)** In a model of spontaneous pancreatic neuroendocrine tumors, Kim et al. (University of California, San Francisco, USA) showed that systemic mouse-prototype VV JX-594 (best referred to as pexastimogene devacirepvec/Pexa-Vec/TG6006 into the clinic – see sections below on clinical trials) targets and disrupts tumor blood vessels, sequentially spreads to malignant cells, and produces widespread CD8$^+$ T cell-dependent cancer cell killing in primary and metastatic lesions. Furthermore, these effects were amplified by concurrent or sequential administration of the multi-targeted receptor tyrosine kinase inhibitor (RTKi) Sunitinib.[167,283]

Reoviruses. **(1)** In a window-of-opportunity clinical trial, Melcher's group (University of Leeds, Leeds, UK) demonstrated that neoadjuvant reovirus successfully infected cancer cells within high-grade glioma and brain metastases following i.v. infusion in 9 patients.[188] OV administration enhanced infiltration of CTLs in the tumor bed and promoted the intra-tumoral expression of PD-L1 in a type I and II IFN-dependent manner. In mice affected with syngeneic brain tumors, sequential treatment using systemic reovirus followed by the blockade of the PD-1/PD-L1 axis improved survival. Altogether, these data support clinical investigation of viro-immunotherapeutic combinations against primary and disseminated neoplasms.[188] Additionally, the same team demonstrated that reovirus-induced proinflammatory antiviral immune responses can target hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) and also hamper HCV replication.[284] **(2)** Rajani and collaborators (Mayo Clinic, Rochester, Minnesota, USA) demonstrated that the timely combination of reovirus with anti-PD-1 antibody also enhanced the therapeutic efficacy against subcutaneous B16 melanoma in mice. This study showed that checkpoint inhibition potentiated both NK cell-mediated tumor cell killing and the CD8$^+$ T cell anti-tumor immune response while reducing regulatory T cell (Treg) activity.[285] **(3)** Ilett et al. (Mayo Clinic, Rochester, Minnesota, USA) utilized reovirus in a prime-boost vaccination approach in combination with anti-PD-1 therapy. Reovirus was applied as the immune primer and vesicular stomatitis viruses [VSV] expressing a cDNA library of melanoma antigens (VSV-ASMEL) were used as boosters.

Table 1. Clinical trials recently initiated to investigate the safety and efficacy of oncolytic viruses in cancer patients.

Virus family	Virus type	Virus name	Indication	Clinical phase	Status on ClinicalTrials.gov	Route of administration	Co-therapy	ClinicalTrials.gov identifier
Adenoviruses	Ad5	**Ad5-yCD/mutTKSR39rep-ADP**	NSCLC	I	Recruiting	IT	5-FC; Valganciclovir; Radiotehrapy	NCT03029871
			Pancreatic cancer	I	Recruiting	IT (?)	Chemotherapy	NCT02894944
		Ad5-yCD/mutTKSR39rep-hIL12	Pancreatic cancer	I	Recruiting	IT	5-FC; Chemotherapy	NCT03281382
		AdVince	Neuroendocrine cancers	I/IIa	Recruiting	IV	-	NCT02749331
		CRAd-Survivin-pk7	CNS cancer	I	Recruiting	IT	Neural stem cell carrier; Surgery; Chemotherapy; Radiotherapy	NCT03072134
		DNX-2401	CNS cancers	II	Recruiting	IT	Pembrolizumab	NCT02798406
			Pediatric CNS cancers	I	Recruiting	IT	-	NCT03178032
		OBP-301	Melanoma	IIa	Recruiting	IT	-	NCT03190824
			Solid tumors	I	Recruiting	IT	Pembrolizumab	NCT03172819
			Esophageal cancer	I	Recruiting	IT	Radiotherapy	NCT03213054
		VCN-01	Retinoblastoma	I	Recruiting	Intravitreal	-	NCT03284268
	Ad5/3	**ONCOS-102**	CRC; Ovarian cancers	I/II	Recruiting	IP	Durvalumab	NCT02963831
			Mesothelioma	Ib/II	Recruiting	IT	Cyclophosphamide; Pemetrexed; Cisplatin	NCT02879669
			Melanoma	I	Recruiting	IT	Cyclophosphamide; Pembrolizumab	NCT03003676
	Ad5/35	**LOAd703**	Pancreatic cancer; Biliary cancer; CRC; Ovarian cancer	I/II	Not yet recruiting	IT	Standard-of-care chemotherapy; Gemcitabine	NCT03225989
			Pancreatic cancer	I/II	Recruiting		Gemcitabine; Nab-paclitaxel	NCT02705196
	Ad3/11p	**EnAd**	CRC; NSCLC; Salivary gland cancer; SCCHN; UCC	I	Recruiting	IV	Pembrolizumab	NCT02636036
Herpesviruses	HSV-1 (CL1 strain)	**OrienX010**	Melanoma	Ic	Recruiting	IT	-	NCT03048253
	HSV-1 (JS1 strain)	**T-VEC**	Sarcoma	II	Recruiting	IT	Pembrolizumab	NCT03069378
			Sarcoma	II	Suspended	IT	Radiotherapy	NCT02923778
			Melanoma; Merkel Cell Carcinoma; Other solid tumors	II	Recruiting	IT	Radiotherapy	NCT02819843
			Melanoma	II	Recruiting	IT	Pembrolizumab	NCT02965716
			Melanoma	Prospective	Recruiting	IT	-	NCT02910557
			Melanoma	I	Recruiting	IT	-	NCT03064763
			Melanoma	Ib	Recruiting	IT	Dabrafenib; Trametinib	NCT03088176
			Non-melanoma skin cancers	I	Recruiting	IT	-	NCT03458117
			Non-melanoma skin cancers; Lymphomas	II	Recruiting	IT	Nivolumab	NCT02978625
			Breast cancer	II	Recruiting	IT	-	NCT02658812
			Breast Cancer	I/II	Recruiting	IT	Paclitaxel	NCT02779855
			Breast cancer; CRC	I	Not yet recruiting	IT	Atezolizumab	NCT03256344
			CRC	I	Recruiting	IT	Capecitabine; 5-FU; Oxaliplatin; Radiotherapy	NCT03300544
			Pancreatic cancer	I	Recruiting	IT	-	NCT03086642
			HNC	I	Recruiting	IT	Pembrolizumab	NCT02626000
			Pediatric non-CNS tumors	I	Recruiting	IT	-	NCT02756845
			UCC	I	Withdrawn	IT	-	NCT03430687
	HSV-1 (HF strain)	**TBI-1401 / HF10**	Melanoma	II	Recruiting	IT	Ipilimumab	NCT03153085
			Melanoma	II	Recruiting	IT	Nivolumab	NCT03259425
			Pancreatic cancer	I	Recruiting	IT	Gemcitabine; Nab-paclitaxel	NCT03252808
Paramyxoviruses	Measle virus (Edmonston strain)	**MV-NIS**	UCC	I	Not yet recruiting	Intravesical	Surgery	NCT03171493
			NSCLC	I	Recruiting	IT	Atezolizumab	NCT02919449
			CNS cancers	I	Recruiting	IT or intrathecal	Surgery	NCT02962167
			Non-CNS cancers	I	Suspended	IT	-	NCT02700230
Parvoviruses	Parvovirus H-1	**ParvOryx**	Pancreatic cancer	I/II	Recruiting	IV + IT	-	NCT02653313
Picornaviruses	Coxsackievirus 21	**CAVATAK**	NSCLC	I	Recruiting	IV	Pembrolizumab	NCT02824965
	Poliovirus type 1 (Sabin strain)	**PVSRIPO**	Pediatric CNS cancers	Ib	Recruiting	IT	-	NCT03043391
			CNS cancers	II	Recruiting	IT	Lomustine	NCT02986178

(*Continued*)

Table 1. (Continued).

Virus family	Virus type	Virus name	Indication	Clinical phase	Status on ClinicalTrials.gov	Route of administration	Co-therapy	ClinicalTrials.gov identifier
Poxviruses	Vaccinia virus (Lister strain)	**GL-ONC1**	Ovarian Cancer; Peritoneal carcinomatosis; Fallopian tube cancer	Ib/II	Recruiting	IP	-	NCT02759588
			Solid tumors	Ib	Active, not recruiting	IV	Surgery; Eculizumab	NCT02714374
	Vaccinia virus (Wyeth strain)	**Pexa-VEC / TG6006**	Solid tumors	I	Recruiting	IT	Ipilimumab	NCT02977156
			Renal Cell Carcinoma	I	Not yet recruiting	IT or IV	REGN2810	NCT03294083
			Hepatocellular carcinoma	I/IIa	Recruiting	IT	Nivolumab	NCT03071094
			Soft-tissue sarcoma; Breast cancer; Other solid tumors	Ib/II	Recruiting	IV	Cyclophosphamide	NCT02630368
			CRC	I/II	Recruiting	IV	Durvalumab; Tremelimumab	NCT03206073
	Vaccinia virus (Copenhagen strain)	**TG6002**	CNS cancers	I/II	Recruiting	IV	5-FC	NCT03294486
Reoviruses	Reovirus type 3 (Dearing strain)	**REOLYSIN**	Melanoma	I/II	Not yet recruiting	IV	GM-CSF	NCT03282188
			Pancreatic cancer	I	Active, not recruiting	IV	Gemcitabine; Irinotecan; Leucovorin; 5-FU; Pembrolizumab	NCT02620423
			Multiple myeloma	I	Recruiting	IV	Lenalidomide; Pomalidomide	NCT03015922
			Bladder carcinoma	I	Withdrawn	IT	Gemcitabine; Cisplatin	NCT02723838
Retroviruses	Moloney mouse leukemia virus	**Toca 511**	CNS cancer	I	Not yet recruiting	Intracranial	Toca FC; Surgery; Chemoradiotherapy; Temozolomide	NCT02598011
Rhabdoviruses	Maraba virus	**MG1MA3**	Melanoma	I/II	Recruiting	IV	AdMA3; Pembrolizumab	NCT02879760
	VSV (Indiana strain)	**VSV-IFNβ-NIS**	Multiple solid tumors	I	Recruiting	IT	-	NCT02923466
			Multiple myeloma; Leukemia; Lymphoma	I	Recruitment suspended	IV	-	NCT03017820
			Endometrial cancers	I	Recruitment suspended	IV	-	NCT03120624

The regimen formulated an effective systemic anti-tumor immuno-virotherapy that significantly enhanced survival of B16 melanoma-bearing mice, with long-term cures.[223] **(4)** Recent discoveries highlighted the ability of histone deacetylase (HDAC) inhibition to upregulate the reovirus entry receptor and junctional adhesion molecule 1 (JAM-1), thus facilitating reovirus infection and tumor cell killing both in vitro and in myeloma-bearing nude mice.[157] Jaime-Ramirez et al. investigated the anti-tumor efficacy of the pan-HDAC inhibitor suberoylanilide hydroxamic acid (SAHA, also known as Vorinostat) in conjunction with REOLYSIN®, a proprietary reovirus serotype 3-Dearing strain (also referred to as Pelareorep; Oncolytics Biotech Inc., Calgary, AB, Canada), in head and neck carcinoma (HNC). This combination therapy stimulated tumor infiltration by multiple immune cells, including macrophages, NK cells and $CD8^+$ T lymphocytes, and demonstrated improved anti-tumor efficacy, in comparison to either treatment alone, both against human tumor xenografts and syngeneic squamous tumors in mice.[156] **(5)** Finally, Sakurai et al. (Osaka University, Osaka, Japan) complexed reovirus with a cationic liposome transfection reagent and achieved enhanced tumor cell-killing in reovirus-resistant tumor cells by promoting endo-/lysosomal escape of the virus.[286]

Rhabdoviruses. **(1)** VSV-IFNβ-NIS (Mayo Clinic, Rochester, Minnesota, USA) is an oncolytic VSV that expresses IFN-β and the sodium/iodide symporter (NIS). IFN-β enhances VSV tumor-specificity by activating antiviral innate immunity in normal cells. Additionally, due to the enhanced iodine uptake by infected cells, administration of radioactive iodine ^{123I} allows non-invasive imaging of OV spread across tumor lesions and can utilize radiotherapy to enhance cancer killing.[119] Currently, VSV-IFNβ-NIS is being evaluated clinically against multiple solid malignancies following intralesional administration (see sections on clinical trials below). To support the clinical testing of intravenous (i.v.) VSV-IFNβ-NIS against hematologic malignancies, preclinical studies have been engaged in mouse models. Systemic VSV-IFNβ-NIS was well tolerated up to high dose of 5×10^{10} $TCID_{50}$. As expected, sequestration of the OV by macrophages was observed in the spleen and liver. Dose-limiting toxicities (DLT) included hepatic toxicity, thrombocytopenia and lymphopenia. Infectious viral particles were only detected in the tumor.[287] VSV-IFNβ-NIS delivered i.v. demonstrated noticeable therapeutic efficacy, prolonging survival of mice bearing subcutaneous syngeneic plasmacytomas or human myeloma xenografts.[287] Antitumor activity was also demonstrated against acute myeloid leukemia (AML), ex vivo on mononuclear cells collected from affected patients and in vivo against a syngeneic murine AML. In the latter model, therapeutic efficacy was improved when VSV-IFNβ-NIS was combined to PD-L1 blockade.[288] Lately, Naik et al. also demonstrated the tolerability and safety of i.v. VSV-IFNβ-NIS for the treatment of spontaneous advanced or metastatic cancers in dogs.[119] Altogether, the safety profile in mice and canine patients motivated the translation of systemic VSV-IFNβ-NIS therapy into humans. **(2)** Kim and collaborators demonstrated that the second mitochondrial-derived activator of caspases (Smac)-mimetic compound LCL161 synergizes with the oncolytic VSVΔM51 allowing to cure mice bearing syngeneic breast tumors. Tumor regression was depending on CTLs. LCL161 contribution consisted in creating an immunosupportive TME through the polarization of tumor-associated macrophages toward M1-like phenotype and in rescuing $CD8^+$ T-cell exhaustion within the TME. Moreover, the VSVΔM51 + SMC combination treatment was also synergizing with anti-PD-1 immunotherapy.[126] **(3)** Peritoneal carcinomatosis remains one of the most common causes of death from abdominal cancers. The Auer's group reported that intraperitoneal (i.p.) injection of an infected cell vaccine (ICV), consisting of autologous tumor cells infected ex vivo with an oncolytic Maraba MG1 virus expressing IL-12, promotes the migration of activated natural killer (NK) cells to the peritoneal cavity. As a consequence, MG1-IL12-ICV reduced tumor burden and remarkably improved survival in a murine colon cancer model of peritoneal carcinomatosis.[289] **(4)** Le Boeuf and colleagues evaluated the efficacy of MG1 Maraba virus against sarcoma, a poor prognosis cancer with limited therapeutic options. In comparison to four other clinically relevant OVs, namely the mutant VSVΔM51, HSV-1 N212, vvDD and type-3 reovirus, MG1 demonstrated the strongest cytotoxicity in vitro against human and canine cell lines. Ex vivo, MG1 was able to infect and replicate in human explants of sarcoma originating from diverse histotypes. In vivo, treatment of murine syngeneic sarcoma significantly prolonged survival and allowed complete regression. Efficacy was relying on immune effector activity and generated memory that protected against cancer rechallenge. Altogether, these results highlight the therapeutic potential of Maraba MG1 for the care of sarcoma, as a standalone intervention or in a combinatorial regimen.[290] **(5)** Bourgeois-Daigneault et al. investigated the efficacy of Maraba MG1 in a neoadjuvant setting against triple-negative breast cancer (TNBC). In patient-derived tumor xenografts, MG1 demonstrated direct oncolysis of infected malignant cells and minimized the metastatic burden. In immunocompetent animals, neoadjuvant MG1 induced a potent antitumor immunity that actively participated in controlling/protecting against outgrowth of rechallenged breast tumors. By microarray, the authors characterized the pro-inflammatory signature of Maraba-infected TNBC human cell lines and patient-derived xenografts. The intracellular virus sensors MyD88 and RIG-I appeared determinant in stimulating the production of IFNs and of the chemokines responsible for driving Th1/Tc1 effector cell migration (e.g., CXCL9 to 11, CCL2,5). MG1-induced inflammation was accompanied by an overexpression of PD-L1 in tumor cells and an increase of tumor-infiltrating Tregs. Based on this observation, immune checkpoint therapy with anti-PD-1 plus anti-CTLA-4 was introduced post-surgery and translated into a significant extension of long-term survival. This work describes MG1 as a promising neoadjuvant treatment against TNBC for its dual ability to induce potent antitumor immunity and to sensitize the TME to immune checkpoint blockade.[187] **(6)** Atherton and colleagues developed a heterologous prime-boost vaccine strategy to treat neoplasm positive for the human papillomavirus (HPV) E6/E7 antigens. A $CD8^+$ T cell antitumor response was primed through intramuscular injection of an Ad vaccine

expressing E6/E7 then boosted through systemic delivery of a Maraba MG1-based oncolytic vaccine expressing the same tumor antigens. This approach generated a weak response against the HPV-E6 antigen but an exceptionally robust reactivity against the E7 protein. Such strong anticancer immunity translated into curing 75% of mice bearing HPV E6/E7-positive syngeneic tumors.[222] Alternatively, the team reached similar efficacy by priming the anti-E6/E7 adaptive immunity with E6/E7-derived synthetic long peptides rather than the Ad vaccine.[291,292] Finally, the team extended this oncolytic immunotherapy to murine syngeneic prostate tumors using Ad and MG1 vaccines expressing the human six-transmembrane antigen of the prostate (STEAP) protein.[293] Therapeutic efficacy was remarkable. CTL responses against multiple STEAP epitopes were mounted and revealed a functional breach of tolerance. Activated TILs and MHC-I up-regulation were also detected.[293] Altogether, these preclinical studies provide rationale for the clinical evaluation of the Ad prime – MG1 boost oncolytic vaccination in patients affected with HPV-positive malignancies or against advanced prostate cancer.

Togaviruses. **(1)** Ramachandran et al. (Department of Immunology, Genetics and Pathology, Uppsala University, Sweden) successfully attenuated the neurovirulence of the Semliki Forest Virus-4 (SFV4). For this purpose, they inserted target sequences for miR124, miR125 and miR134 within the viral genome which prevented its replication within healthy cells of the central nervous system. The systemic delivery of the resulting SFV4miRT demonstrated a safety profile and potent oncolytic efficacy against experimental GB multiforme and neuroblastoma models. Thus, SFV4miRT constitutes a promising oncolytic candidate for the treatment of brain cancers.[82] **(2)** The alphavirus M1 is a Getah-like virus isolated from China whose natural oncolytic property has been reported in 2014. M1 preferentially kills cancer cells that are deficient in zinc-finger antiviral protein (ZAP).[62] Several compounds have since been described as potentiators of M1 oncolysis against human xenograft models in mice (e.g., CRC, HCC), including activators of the cyclic adenosine monophosphate (cAMP) signaling, an inhibitor of the valosin-containing protein (VCP) or else Smac mimetics, which each potentiates virus replication, induces prolonged endoplasmic reticulum stress and ultimately stimulates M1-induced apoptosis.[294–296] In non-human primates, Zhang and colleagues (Sun Yat-sen University, Guangzhou, China) validated the safety of repeated i.v. administrations of M1 opening the way to its clinical evaluation against malignant indications.[297]

Completed and advanced clinical studies

Since the submission of our latest Trial Watch dealing with OVs (December 2015),[40] preliminary or definitive results from about 50 clinical trials testing this immunotherapeutic approach in cancer patients have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed) or presented at the 2016–2018 meetings of the American Society of Clinical Oncology (ASCO) or the American Association for Cancer Research (AACR) (sources https://meetinglibrary.asco.org/ and http://aacrjournals.org/site/Meetings/, respectively).

Adenoviruses. **(1)** Alonso and colleagues evaluated the safety and efficacy of DNX-2401 into the clinic (DNAtrix, Houston, TX, USA), in 31 patients with glioma (NCT01956734).[298] All subjects were recruited upon first recurrence after ongoing surgery and standard care with radiotherapy and TMZ. DNX-2401 was injected into the brain parenchyma followed by several cycles of TMZ. The therapeutic regimen was well tolerated with no severe adverse events (AEs) associated with the virus observed. At the time of the report, objective responses (OR) were witnessed in 3 patients alive 30, 27 and 19 months post-combination therapy. Interestingly, the expression level of fibroblast growth factor 2 (FGF-2) in glioma biopsies appeared negatively correlating with IFN-γ production and positively correlating with overall survival (OS).[298] Of note, a complex interplay between FGF-2 and type I & III IFNs was uncovered the past years, with apparent antagonistic functions on cell proliferation, differentiation and antiviral response.[299–302] Along this line, FGF-2, which is mainly produced by cancer-associated fibroblasts in the TME, has been shown to enhance the susceptibility of malignant cells to infection and replication by multiple RNA and DNA oncolytic viruses.[299] Further investigations are encouraged to validate FGF-2 expression level as a prognostic biomarker for oncolytic virotherapy. **(2)** Ranki T et al. assessed the safety profile of ONCOS-102 (Targovax, Oslo, Norway), previously called CGTG-102 or Ad5/3-D24-GMCSF, in 12 patients affected with various solid tumors that failed standard therapeutic attempts (NCT01598129).[303] ONCOS-102 is an oncolytic Ad5/3 with a 24-bp deletion in the E1A gene and expressing GM-CSF. ONCOS-102 was injected topically following a 3 + 3 dose escalation design together with daily low-dose CPA to deplete immunosuppressive $CD4^+$ Tregs. The study did not reveal DLT or maximum tolerated dose (MTD). Forty percent of evaluable patients demonstrated stable disease (SD) at 3 months and median OS was 9.3 months. An acute increase in systemic pro-inflammatory cytokines/chemokines together with a marked increase of TILs was observed post-treatment in 11 out of the 12 patients. In 2 patients affected with pleural mesothelioma or ovarian cancer, tumor-infiltration of $CD8^+$ T cells was concomitant with the detection of circulating tumor-specific $CD8^+$ T cells targeting cancer-testis (CT) antigens such as melanoma antigen family A3 (MAGE-A3). Finally, ONCOS-102 was stimulating the expression of PD-L1, thus encouraging further combination with ICBs.[303] Along this line, one Stage IV treatment-refractory ovarian cancer patient was introduced to a FDA-approved compassionate program involving ONCOS-102. The protocol incorporates ONCOS-102 in a multi-therapeutic regimen with systemic administration of low-dose CPA together with dual ICB treatment with ipilimumab and nivolumab. In this patient, the ONCOS-102-containing therapeutic regimen appeared well tolerated with no virus-related AEs observed.[304] A similar combinatorial approach is being evaluated clinically against melanoma (see "Recently initiated clinical trials" below). **(3)** McNeish and colleagues are evaluating EnAd (PsiOxus Therapeutics, Abingdon, UK) in platinum-resistant epithelial ovarian cancers (NCT02028117). EnAd is injected i.p. either as a monotherapy or in association with paclitaxel. Preliminary analyses

indicate that the virus is reaching and replicating in the tumor with limited systemic exposure. Safety profile was acceptable at the dose tested. A dose escalation protocol will determine the MTD to be evaluated in Phase II.[305] **(4)** Hemminki's group (University of Helsinki, Helsinki, Finland) performed a retrospective analysis which incorporated clinical data from 290 patients into a Cox regression model to estimate prognostic factors significant in the context of oncolytic Ad therapy.[306] Subjects had solid tumors refractory to standard treatment prior enrollment in the Advanced Therapy Access Program (ATAP, a personalized therapy program ongoing 2007–2012)[307] where they received one oncolytic Ad, among Ad5-d24-GMCSF, Ad5/3-d24-GMCSF, Ad5-RGD-d24-GMCSF, Ad5/3-E2F-d24-GMCSF, Ad3-hTERT-E1, Ad5-d24-RGD, ICOVIR-7, Ad5/3-Cox2L-d24, Ad5/3-hTERT-CD40L, Ad5/3-d24-hNIS. Results highlighted that 1) absence of liver metastases correlated with an improved rate of disease control, 2) patients treated with viruses coding for GM-CSF tended to have better prognosis, as well as 3) women, regardless of the cancer type, 4) participants administered via i.p. injection were more likely to achieve disease control and 5) subjects with low neutrophil/lymphocyte ratio prior oAd therapy had significantly longer OS.[306] To uncover potential prognostic biomarkers, an additional study monitored mRNA and/or protein levels in tumor biopsies or fluid samples from cancer patients treated with oAd.[130] Significant modulations in several signaling pathways and genes associated with innate immunity appeared to be associated with poor prognosis. Conversely, lack of chronic innate inflammation at baseline may predict improved oAd therapy outcome.[130] Finally, the team provided preclinical evidences that low-dose CPA increases the efficacy of Ad5/3-D24-GMCSF against a TNBC model.[215] In the ATAP program, Ad5/3-D24-GMCSF treatment was administered to 16 patients with advanced breast cancer refractory to previous therapies; 13 of which received concomitant CPA including 3 TNBC. The combination treatment appeared safe and well-tolerated. Thirteen patients were evaluable according to modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria: 1 patient had a minor response, 2 had SD and 10 had progressive disease (PD). One patient was still alive at the end of the follow-up, 1771 days post-treatment. These preliminary data encourage further development of oAd against breast cancer, including TNBC.[215] **(5)** Ramirez et al. (Hospital Infantil Universitario Niño Jesús, Madrid, Spain) reported on the results of the first-in-man trial using Celyvir, a therapy consisting of autologous MSCs infected with the oAd ICOVIR5 (NCT01844661). Celyvir was well tolerated in the 9 patients affected with relapsed/refractory pediatric solid tumors that completed the treatment. Ad replication and antibodies were detected in 7 and 8 subjects, respectively. Rise in circulating effector $CD8^+$ T cells was observed. Two patients with neuroblastoma showed SD per RECIST, one of them continued on treatment for up to 6 additional weeks. Further evaluation in Phase II is warranted.[308]

Herpesviruses. **(1)** T-VEC (Amgen, Thousand Oaks, CA, USA) has been approved by the FDA for the treatment of melanoma.[41,44–46] A randomized, open-label, Phase II study evaluated neoadjuvant T-VEC + surgery (Arm 1, n = 76) versus surgery alone (Arm 2, n = 74) for resectable stage IIIB-IVM1a melanoma (NCT02211131).[309] At the interim analysis, the pathological complete response [CR] rate was 21% in patients of the Arm 1 that underwent scheduled surgery (15.8% when including the 19 patients that finally did not benefit from resection). Negative margin resection (R0) rates were 56.1% for Arm 1 and 40.6% for Arm 2. No unexpected toxicities were noticed. After 12 weeks of neoadjuvant T-VEC, the pathological CR rate was higher than observed by ORs (14.7%) and may account for the higher R0 margin in Arm 1. The primary analysis of relapse-free survival is ongoing.[309] Additional clinical trials investigated the efficacy of T-VEC along with the ICIs ipilimumab or pembrolizumab.[239,310–313] An initial multi-center open label Phase I study evaluated the combined application of T-VEC and ipilimumab in 19 patients harbouring a Stage IIIB-IVM1c melanoma that is not suitable for surgical resection but injectable (NCT01740297). The OV was injected directly into cutaneous, subcutaneous or nodal lesions that have not received systemic therapy, except a prior adjuvant therapy.[313] Dose escalation studies in the trial showed that the two monotherapies (either T-VEC or ipilimumab) can be administered at their full therapeutic doses without DLTs. Reported severe AEs consisted of Grade 3 nausea and a Grade 4 elevation of the lipase and amylase levels attributed to ipilimumab. Overall, the study concluded that T-VEC + ipilimumab combination was tolerable without unexpected AEs.[313] Subsequently, the efficacy of intralesional administration of T-VEC + ipilimumab versus ipilimumab alone (n ~ 100 patients per arm) has been evaluated in a Phase II trial in patients with advanced unresectable melanoma of stages IIIB to IV, with no more than one prior therapy if BRAF wild type, no more than two prior therapies if BRAF mutant, and that present measurable/injectable lesions and no symptomatic autoimmunity or clinically significant immunosuppression.[311] The primary end point was objective response rate (ORR) evaluated by investigators per immune-related (ir) response criteria (irRC). ORR was significantly higher for T-VEC + ipilimumab versus ipilimumab alone with 39% (38 patients) in the combination arm and 18% (18 patients) in the ipilimumab arm.[311] Responses were not limited to injected sites as decreases of visceral lesions were observed in 52% of patients in the combination arm and 23% of patients in the ipilimumab arm.[311] Finally, a Phase Ib clinical trial evaluated the ability of T-VEC to allow infiltration of CTLs within the tumor and its potential for synergy with pembrolizumab (NCT02263508).[239] Twenty-one patients harbouring advanced melanoma have been injected with T-VEC i.t. followed by systemic administration of pembrolizumab with baseline and on-therapy biopsies.[239] Seven of the 21 patients (33%) had received prior anticancer therapy (including adjuvant therapy) and four (19%) had received prior radiotherapy. Patient had a median follow-up time of 18.6 months. Overall, there was no DLT and serious AEs were solely related to pembrolizumab and included autoimmune hepatitis, meningitis and pneumonitis. Confirmed OR and CR rates were 62% and 33%, respectively.[239] Overall, the responses occurred across all substages of melanoma. Median progression-free

survival [PFS] and OS were not reached at the time of the last follow-up. A >50% reduction of the lesions has been observed with the combination treatment in: 82% of the injected non-visceral lesions, 43% of non-injected non-visceral ones, and 33% of non-injected visceral ones.[239] Patients who responded to combination therapy had increased $CD8^+$ T cells, elevated PD-L1 protein expression and IFN-γ gene expression on several tumor-infiltrating cell subsets following T-VEC administration. Response to combination therapy did not seem associated with baseline $CD8^+$ T cell infiltration or baseline IFN-γ signature.[239] In summary, this study showed that i.t. injection of T-VEC modifies the TME by attracting T cells and induces a systemic response in distant metastases after subsequent blockade of PD-1 with pembrolizumab (see also: [314–316]). On top of melanoma, intralesional T-VEC is being evaluated in a multicenter Phase Ib study against recurrent or metastatic HNC in combination with pembrolizumab (NCT02626000/MASTERKEY-232). Preliminary results have been disclosed at the 2018 ASCO meeting.[317] Thirty-six patients were treated. Overall, 66.7% participants had serious treatment-emergent AEs, among which pyrexia, dyspnea and fatigue were the most common. One DLT (fatal arterial hemorrhage) was reported. Seven deaths were recorded during the study, 1 of which was related to T-VEC (the DLT) and none to pembrolizumab. The ORR was 16.7% and the disease control rate (OR/SD) was 38.9%.[317] Preliminary results have also been revealed regarding the Phase II evaluation of T-VEC combined to pembrolizumab against metastatic and/or locally advanced sarcoma (NCT03069378).[318] Twenty patients were enrolled. Grade 3 treatment-related AEs occurred in 2 participants (10%): fever from T-VEC and one case of pneumonitis from pembrolizumab that led to treatment abortion. Among 19 evaluable patients, 4 PR (21%), 9 SD (47%) and 6 progressions (32%) were observed by RECIST 1.1.[318] **(2)** A Phase Ib study is evaluating the safety and efficacy of OrienX010, a recombinant CL1 strain of HSV-1 ($ICP34.5^{-/-}$ $ICP47^-$ $ICP6^-$) expressing human GM-CSF, in unresected Stage IIIC to IV acral melanoma, a main subtype of melanoma in Chinese patients.[319] Twelve patients received on average 10 intra-lesional injections. Overall, the OV was tolerated with no DLT. Grade 1/2 AEs included pyrexia, injection site pain, leucopenia, rash and nausea. ORR was 16.7% (2 partial responses [PR]) and SD rate was 41.7%.[319] Time to response was 6–12 weeks, median PFS of 12 weeks and duration of response was 24 weeks. OS was not reached. A related Phase Ic trial is testing the safety and efficacy of intralesional administration of OrienX010 in liver metastases of Stage IV melanoma patients that have undergone standard therapies (NCT03048253, Table 1).[320] The OV was tolerated with Grade 1/2 AEs that included pyrexia, fatigue, injection site pain, nausea/vomiting, hepatotoxicity and leucopenia. ORR was 8.3% (1 PR), disease control rate was 41.7% (1 PR, 4 SD).[320] OS was not reached. **(3)** Two Phase I clinical trials have been registered by the University of Alabama at Birmingham (Birmingham, AL, USA) in the past years to assess the safety and tolerability of two genetically-engineered HSV-1 strain F against brain tumors: G207 ($ICP34.5^{-/-}$ $ICP6^-$ $LacZ^+$) in children (NCT02457845) and M032 ($ICP34.5^{-/-}$ human $IL\text{-}12^+$) in adults (NCT02062827).[321,322] If no results have been disclosed yet, related reports have been published. In Phase I trials (including NCT00157703 and NCT00028158), Waters and colleagues validated the safety of G207 in adults suffering from recurrent/progressive high-grade gliomas.[321] No DLTs were seen in the patients and no MTD was reached. Approximately half of the 35 treated adults had radiographic or neuropathologic evidence of response at a minimum of one time point. These clinical observations support the current trial involving i.t. inoculation of G207 in pediatric recurrent or progressive supratentorial malignant tumors (NCT02457845). Additionally, Patel at al. validated the safety of intracerebral M032 in 30 HSV-hypersensitive non-human primates at a per-kilogram dose which far exceeds that intended to be injected in patients with recurrent and progressive GB multiforme, anaplastic astrocytoma, or gliosarcoma.[322] Finally, Ren and collaborators (Duke University Medical Center, Durham, NC, USA) evaluated the combination of local delivery of OrienX010 with adoptive immunotherapy based on the infusion of autologous dendritic cells and cytokine-induced killer cells (DC-CIK).[206] Nine patients with advanced malignancy were treated with OrienX010, of whom seven experienced SD. Five of the OV-treated patients underwent DC-CIK adoptive transfer, and two had SD, whereas three progressed. Overall, this treatment was well tolerated and long-term event-free and overall survivals were observed. Moreover, the combination allowed further systemic expansion of multiple T cell clone populations than with OV therapy alone.[206] **(4)** Steby et al. (The Ohio State University, Columbus, OH, USA) validated the safety and tolerability of i.t. HSV1716 in 9 pediatric patients with relapsed or refractory extracranial cancers.[323] Detection of HSV-1 genome in the blood of 6 patients and increases in metabolic activity on 18fluorine-deoxyglucose PET in 2 patients were consistent with de novo virus replication and inflammation, respectively. Such observations are encouraging further clinical investigations.[323] **(5)** Finally, two interesting clinical investigations have exploited oHSV-1 as a cancer diagnostic tool based on their oncotropism.[324,325] One clinical study involved NV1066, a replication-competent HSV-1 F strain with single-copy deletions of ICP0, ICP4 and ICP34.5 and which expresses the enhanced green fluorescent protein (GFP). The study evaluated NV1066 for the rapid detection of peritoneal dissemination of pancreatic cancer from peritoneal washings of 96 patients undergoing diagnostic laparoscopy for presumed or biopsy-proven pancreatic cancer. Cytology based on peritoneal fluid is the gold standard test owing to its clinical relevance and high specificity. In this trial, cytology assay detected any metastasis and peritoneal metastasis at rates of 44% and 89%, respectively. In contrast, HSV-GFP-based diagnosis of any metastasis or peritoneal metastasis demonstrated superior sensitivities with 94% and 100% detection rate, respectively.[324] The second clinical study involved a telomerase-specific replication-selective oHSV-1 that expresses GFP for the detection of circulating tumor cells (CTCs).[325] CTCs were detected in 59–100% of 326 blood samples from subjects affected with 6 different solid cancers (lung, colon, liver, gastric or pancreatic cancer and glioma) and lymphomas. Interestingly, CTC-positive rates increased remarkably with tumor progression in each of 5 tested cancers

and decreased in response to the treatment. In hematological malignancies, the monitoring of CTC values provided an efficient treatment response indicator. Compared to CellSearch (a commercialized test for detecting CTCs of epithelial origin), the oHSV-1-based method demonstrated higher sensitivity in 40 NSCLCs, regardless of the stage, and was less affected by chemotherapy.[325] Further investigations are encouraged to validate OV-based diagnostic assays as a new gold standard for the detection of advanced cancers. **(6)** In a single-arm Phase I dose-escalation trial (UMIN-CTR UMIN000010150), 10 patients affected with unresectable locally advanced pancreatic cancer received i.t. the HSV-1 TBI-1401, best referred to as HF10 (Takara Bio, Kusatsu, Japan), together with the RTKi erlotinib and gemcitabine.[326] The combination treatment was safe. Out of 9 subjects who completed the therapy, tumor responses were 3 PR, 4 SD and 2 PD. Two subjects ultimately achieved surgical CR. The median PFS and OS were of 6.3 and 15.5 months, respectively. The association of oncolytic HF10 with chemotherapy will deserve further prospective evaluations.[326] In a Phase II trial, HF10 has been evaluated in combination with ipilimumab in unresectable/unresected Stage IIIB-IV melanoma patients (NCT02272855).[327] HF10 AE profile appeared similar in combination with ipilimumab as in monotherapy. Twenty-eight percent of the patients had treatment-related ≥ Grade 3 AEs; the majority due to ipilimumab. Of the 44 evaluable participants, irRC best ORR at 24 weeks was 41% (18% irCR and 23% irPR); SD rate was 68% (27% irSD). As of February 2018, median PFS and OS were 19 and 26 months, respectively. Responding tumors exhibited an activation of the adaptive immune response with an increase of total TILs and $CD8^+$ T-cells together with a decrease of $CD4^+$ T-cells.[327]

Paramyxoviruses. MV-NIS (Vyriad, Rochester, MN, USA) is an attenuated oncolytic Edmonston strain of measles virus that expresses the sodium/iodide symporter (NIS). In a Phase I trial (NCT00450814), Dispenzieri et al. (Department of Hematology, Mayo Clinic, Rochester, MN, USA) demonstrated that systemic administration of MV-NIS, either alone (cohort 1) or following CPA treatment (cohort 2), was reasonably well tolerated in 29 patients with relapsed or refractory multiple myeloma.[328] Some severe AEs possibly related to therapy were reported in both cohorts at all dose levels and included leukocyte count decreased (n = 5), neutropenia (n = 9), thrombocytopenia (n = 2) or $CD4^+$ T lymphocytes decreased, anemia and lymphopenia (n = 1 each). ^{123}I SPECT/CT scan of malignant lesions and MV genome detection by RT-qPCR from gargle specimens, blood and urine body fluids up to one month post-infusion validated the ability of the virus to reach and amplify in the disseminated tumors. One patient achieved a CR and transient drops in serum free light chains (markers of disease progression) were seen in other patients. No DLT were observed and Phase II dose was determined.[328]

Parvoviruses. Systemic or local treatment with ParvOryx (ORYX GmbH & Co. KG, Baldham, Germany), a wild-type rat H-1 parvovirus (H-1PV), has been investigated in 18 patients with recurrent GB in a first Phase I/IIa clinical trial (NCT01301430/ParvOryx01). ParvOryx was administered before and after surgical resection. ParvOryx treatment appeared safe and well tolerated with no MTD reached. The OV succeeded to cross the blood-brain/tumor barrier and spread widely through the tumor. Markers of microglia/macrophage activation and CTL infiltration were detected in infected tumors, suggesting that ParvOryx may trigger an immunogenic stimulus with immunotherapeutic potential. Median survival was extended in comparison with recent meta-analyses. Based on these encouraging data, further clinical development of ParvOryx will follow (see section on "Recently initiated clinical tirals" below).[329]

Picornaviruses. **(1)** CAVATAK (Viralytics, Sydney, Australia), a proprietary formulation of the common cold coxsackievirus type A21 (CVA21), is being investigated against advanced malignancies in several clinical studies.[330–334] The completed Phase II CALM trial (NCT01227551) demonstrated the tolerability and efficacy of intralesional CVA21 monotherapy in 57 patients affected by late-stage melanoma.[334,335] The ORR assessed by irRECIST was 28.1% with a ≥ 6 months durable response rate (DRR) of 21.1%. Tumor responses were observed in both injected and non-injected, local and distant, lesions suggesting the generation of systemic antitumor immunity.[334,335] A CALM extension study was conducted in 13 patients and investigated CVA21-induced changes in immune cell infiltrates within the TME. In responders, increases in $CD8^+$ TILs and in the expression of PD-L1 were observed in injected lesions. Reconstitution of immune cell infiltrates was reported in some CVA21-treated lesions from patients that failed prior therapy with immune checkpoint blockers.[334] Along this line, the Phase Ib STORM trial (NCT02043665) was designed to evaluate the safety and efficacy of CVA21 administered systemically either as a standalone therapy (part A, n = 16) or in combination with the anti-PD-1 pembrolizumab (part B, still recruiting) against late-stage solid tumors.[330–332] Each arm includes 3 cohorts in a dose escalation design. In part A, no severe AEs were observed. Tumor targeting was confirmed in biopsies of melanoma, non-small cell lung cancer (NSCLC) and bladder cancer subjects. Thirteen patients were eligible for response assessment and demonstrated 8 SD, 1 PR and 4 PD. Out of the 6 patients enrolled in part B so far (cohorts 1 and 2 with the lowest doses), one Grade 3 virus-related hyponatremia with no DLT for the combination treatment was reported. Generally, systemic delivery of CVA21 appeared well tolerated and able to reach metastatic sites.[330–332] The latter observation is encouraging for a synergistic effect with pembrolizumab considering the ability of CVA21 tumor infection to restore immune cell infiltration and upregulate the expression of immune checkpoint molecules.[334] Finally, the Phase I/II CANON trial (NCT02316171) is investigating the safety and efficacy of escalating doses of neoadjuvant CVA21, delivered i.v. in 16 first-line patients with bladder cancer, either alone or in combination with low-dose mitomycin C.[333] Observations indicate general tolerance of i.v. CVA21. Evidences of complete tumor response, viral replication and signs of virus-induced tumor inflammation demonstrated clinical activity of CVA21, likely associated with the induction of local and systemic anti-tumor immunity.[333] **(2)** Two case reports suggested that oncolytic virotherapy with Rigvir, a wild-type enterovirus ECHO-7 (Riga Eastern Clinical University

Hospital, Riga, Latvia), could be applied for long-term treatment of patients with melanoma stage IV M1c (n = 2), small cell lung cancer stage IIIA (n = 1), and histiocytic sarcoma stage IV (n = 1). Prospective clinical studies are encouraged.[336,337]

Poxviruses. **(1)** Genelux (San Diego, CA, USA) developed a portfolio based on replicating VV Lister backbone flexible to express imaging genes, anti-tumor therapy genes and immune-modulator genes. Their lead candidate consists of GL-ONC1 (formerly named GLV-1h68), a genetically-engineered oncolytic VV encoding a Renilla luciferase-Aequorea GFP fusion protein as well as the β-galactosidase and β-glucuronidase. A Phase I clinical trial involving GL-ONC1 has been completed in 2015 and the results published recently (NCT01584284).[338] Primary outcome of the study was to determine the safety of GL-ONC1 when delivered i.v. with chemoradiotherapy to patients with HNC. An escalating dose of GL-ONC1 was given to 19 subjects with locoregionally advanced unresected, non-metastatic HNC. The MTD was not reached. Grade 3 hypotension, mucositis, nausea and vomiting were observed. Overall, systemic delivery of GL-ONC1 was considered safe and feasible in patients with locoregionally advanced HNC undergoing standard chemoradiotherapy. Interestingly, in several patients, viral presence in tumor was confirmed. With a median follow-up of 30 months, 1-year (2-year) PFS and OS were 74.4% (64.1%) and 84.6% (69.2%), respectively.[338] In a Phase Ib trial, 11 women with platinum-resistant/refractory recurrent ovarian cancer received repeated i.p. infusions of GL-ONC1 monotherapy (NCT02759588). Promising safety data, anti-tumor activity and immune activation mechanisms were documented. Disease control (PR+ CR≥ 15 weeks) was observed in 55% of patients. Extended PFS of 23, 35, 59 & 71 weeks were observed in 4 participants.[339] **(2)** Downs-Canner and collaborators (University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) published the results of a Phase I trial assessing the safety of systemic administration of vvDD in cancer patients (NCT00574977). The OV was infused in 11 patients with standard treatment-refractory advanced colorectal cancer (CRC) or other solid cancers. No DLT and severe AEs were observed. Interestingly, in two patients, prolonged virus replication was detected in malignant tissues but not in normal ones, with the exception of a healed injury site and an oral thrush. One patient showed a mixed response on PET-CT with resolution of some liver metastases and another patient with cutaneous melanoma demonstrated clinical regression of some lesions.[340]

Reoviruses. REOLYSIN® (Oncolytics Biotech Inc., Calgary, AB, Canada) has been investigated following i.v. delivery in combination with paclitaxel and/or carboplatin[341] in several Phase II trials: a) in 36 evaluable patients with metastatic pancreatic adenocarcinoma (NCT01280058),[342,343] b) in 14 subjects with advanced malignant melanoma (NCT00984464),[344] c) in 37 patients with NSCLC (NCT00861627),[345] d) in 52 women with recurrent ovarian, tubal, or peritoneal cancer (NCT01199263),[346] and e) in 36 subjects with metastatic breast cancer (NCT01656538).[347] Furthermore, REOLYSIN has been administered in combination with pemetrexed (a folate antimetabolite)[348] or docetaxel (an antimitotic drug that inhibits microtubule depolymerization)[349] in 152 randomized advanced stage refractory platinum doublet NSCLC participants (NCT01708993, Phase II)[350] and in 85 randomized metastatic castration resistant prostate cancer patients (NCT01619813/IND.209, Phase II). [351] Also, REOLYSIN has been combined with gemcitabine in 34 patients with advanced pancreatic ductal adenocarcinoma (NCT00998322, Phase II).[352] Lastly, it has been examined in combination with monoclonal antibodies: i) pembrolizumab plus either 5-fluorouracil[353] (5-FU; n = 3), gemcitabine (n = 6), or irinotecan (n = 2) in 11 patients with relapsed metastatic adenocarcinoma of the pancreas (NCT02620423, Phase I)[354] and ii) FOLFOX6/bevacizumab for 51 patients with metastatic CRC (NCT01622543, Phase II).[355] Of the abovementioned completed[344,345,350–352] or active[342,343,346,347,354,355] clinical trials, REOLYSIN was well tolerated with no major signs of toxicity/AEs for combinations with paclitaxel and/or carboplatin, pemetrexed, docetaxel, or with pembrolizumab and 5-FU, gemcitabine, and irinotecan combinations. Nonetheless, AEs can arise with REOLYSIN® combination therapy, as was observed in its combination regimen with FOLFOX6/bevacizumab, showing increased toxicity and decreased quality of life in metastatic CRC patients.[355] Regarding efficacy, REOLYSIN did not prove superiority in comparison to chemotherapy alone when combined with carboplatin/paclitaxel neither in metastatic pancreatic cancer (NCT01280058),[343] nor in recurrent ovarian, tubal, or peritoneal cancer (NCT01199263).[346] Detrimental consequences of the therapeutic association were even reported on OS or PFS with docetaxel in advanced castration resistant prostate cancer (NCT01619813/IND.209)[351] and with FOLFOX6/bevacizumab in metastatic CRC (NCT01622543/IND.210).[355] Mitigated results were reported in patients with advanced NSCLC. Indeed, no significant benefit of salvage REOLYSIN plus docetaxel/pemetrexed arms over standard salvage chemotherapy arms was observed. Nevertheless, PFS tended to improve in the female gender and in the subgroups with epidermal growth factor receptor (EGFR)-mutated and p53-mutated status (NCT01708993/IND.211).[350] In this line, in patients with advanced EGFR-mutated/amplified or KRAS-mutated NSCLC, an ORR of 31% (11 PR, 20 SD) suggested a benefit of the reovirus in combination with paclitaxel and carboplatin. The median PFS, median OS and 12-month OS rate were 4 months, 13.1 months and 57%, respectively. Seven patients were alive after a median follow-up of 34.2 months.[345] As interesting, the combination of REOLYSIN with paclitaxel in treatment-refractory breast cancer did not impact PFS or ORR but significantly extended OS (IND.213).[347] In patients with advanced melanoma, REOLYSIN combined with carboplatin and paclitaxel was potentially efficacious as the study met its efficacy goal for the first stage with an ORR of 21% (3 PR). The median PFS, median OS and 1-year OS were 5.2 months, 10.9 months, and 43%, respectively, with a disease control rate of 85%.[344] In the single-arm study combining i.v. REOLYSIN with gemcitabine against pancreatic adenocarcinoma, 1 PR, 23 SD and 5 PD were witnessed with a median OS of 10.2 months, and a 1- and 2-year survival rate of 45% and 24%, respectively. When considering the overall poor prognosis of pancreatic cancer (1 and 5-year survival rates of ~ 18% and 7%),[356] REOLYSIN appeared to

complement single agent gemcitabine against the disease. Moreover, upregulation of PD-L1 in the biopsy of a tumor treated with the combination therapy encourages future supplementation with PD-L1/PD-1 checkpoint inhibitors.[352]

Rhabdoviruses. The oncolytic rhabdovirus Maraba MG1 expressing the CT antigen MAGE-A3 (MG1MA3; Turnstone Biologics, Ottawa, ON, Canada) is currently being investigated in a Phase I/II trial against incurable advanced/metastatic MAGE-A3-positive solid tumors (NCT02285816/CCTG IND.214).[102,357] First results from Phase I have been disclosed at the 2017 ASCO meeting.[357] The oncolytic vaccine MG1MA3 was infused systemically either alone (arm A, n = 9 patients) or as a booster in a heterologous prime-boost vaccination strategy (arm C, n = 25). In the latter setting, a replication-deficient Ad vaccine expressing MAGE-A3 (AdMA3) was injected intramuscularly 14 days prior to MG1MA3 in order to prime MAGE-A3 immunity.[222,224,357,358] A third cohort received only AdMA3 (arm B, n = 6). A 3 + 3 escalating dose design in the arms A and C allowed to establish the recommended Phase II dose of MG1MA3. Acute AEs related to the Maraba virus in the arm C commonly included fatigue, flu-like symptoms, diarrhea, hypophosphatemia and hypotension. Interestingly, a pro-inflammatory gene signature was characterized in tumor biopsies, with markers of infiltration/activation of myeloid and lymphoid cell populations detected. Moreover, humoral and cellular immune responses specific to MAGE-A3 were observed in the blood of 3 out of 6 evaluable patients of the arm C. Remarkably, over 1% of the circulating $CD8^+$ T cells were reacting against MAGE-A3 in one patient. Overall, AdMA3 prime followed by the oncolytic MG1MA3 boost is applicable and able to induce potent antitumor immunity in cancer patients.

Recently initiated clinical trials

Since the submission of our latest Trial Watch on oncolytic virotherapy,[40] no less than 63 clinical studies have been initiated to evaluate this immunotherapeutic paradigm in cancer patients (Table1; source: https://www.clinicaltrials.gov/).

Adenoviruses. **(1)** A Phase I dose escalation study will determine the MTD of oncolytic Ad5-yCD/*mut*TK_{SR39}rep-ADP, also known as Theragene® (Henry Ford Health System, Detroit, MI, USA in partnership with Newgenpharm, Seoul, South Korea), in medically inoperable stage I/IIA NSCLC. The OV is a replication-competent Ad5 armed with a fusion gene expressing yCD and the mutant sr39 HSV TK (mutTKsr39) together with the 11.6 kDa adenoviral death protein (ADP) gene.[359–361] Following i.t. delivery of Ad5-yCD/*mut*TK_{SR39}rep-ADP, patients will be given 5-fluorocytosine (5-FC) and valganciclovir prodrugs, respectively metabolized by yCD and *mut*TK_{sr39}, along with stereotactic body radiotherapy (NCT03029871). Moreover, Ad5-yCD/*mut*TK_{SR39}rep-ADP and its IL-12-expressing derivative Ad5-yCD/*mut*TK_{SR39}rep-hIL12 are being evaluated in association to 5-FC and standard chemotherapy in patients suffering from metastatic pancreatic cancer (NCT02894944, NCT03281382). **(2)** AdVince (Uppsala University, Uppsala, Sweden), formerly named Ad5[CgA-E1A-miR122]PTD, is an oncolytic Ad that has been designed to treat liver metastases of neuroendocrine tumors (NETs).[362] A Phase I/IIa clinical trial is recruiting patients to determine the MTD and evaluate the safety of repeated infusions of AdVince into the hepatic artery of patients with metastatic NETs (NCT02749331/RADNET). **(3)** A Phase I study is assessing the tolerability and safety of neoadjuvant neural stem cell (NSC)-based virotherapy for patients with newly diagnosed malignant glioma. The strategy relies on the administration of NSCs loaded with oncolytic CRAd-Survivin-pk7; a conditionally replicative glioma-tropic Ad.[363–365] Patients undergo intracranial injection of NSC-CRAd-Survivin-pk7 together with standard chemoradiotherapy, after surgery if resection is feasible (NCT03072134; Northwestern Memorial Hospital, Chicago, IL, USA). **(4)** The efficacy, safety and immunological response of i.t. OBP-301 (Telomelysin, Oncolys BioPharma, Tokyo, Japan) are being assessed in an open-label, multi-center Phase IIa trial in patients with unresectable metastatic melanoma (NCT03190824). Two Phase I trials are recruiting participants to determine the safety and tolerability of OBP-301 in combination with pembrolizumab against advanced solid tumors (NCT03172819)[366] or with radiotherapy against esophageal cancer (NCT03213054). **(5)** A Phase I study investigates the safety and antitumor activity of the recently introduced VCN-01 (VCN Biosciences, Barcelona, Spain)[146,367] administered through intravitreal injection in 13 patients with refractory retinoblastoma (NCT03284268). **(6)** Up to 36 patients are currently recruited in a Phase II study to evaluate the efficacy of DNX-2401 (DNAtrix, Houston, TX, USA) against recurrent glioblastoma or gliosarcoma. The virus is delivered directly into the tumor followed by repeated i.v. administrations of the ICI pembrolizumab (NCT02798406/CAPTIVE). Additionally, the safety, tolerability and toxicity (hematologic and neurologic) of DNX-2401 as neoadjuvant therapy for diffuse intrinsic pontine glioma is being assessed in an unicentric non-randomized Phase I study. Administration of the OV is performed through injection in the cerebellar peduncle of newly diagnosed pediatric patients (NCT03178032).[368] **(7)** A Phase II trial will recruit a total of 30 patients with pleural mesothelioma to determine the safety, tolerability and efficacy of i.t. ONCOS-102 (Targovax, Oslo, Norway), preceded by CPA and followed by pemetrexed/cisplatin (NCT02879669). A Phase I/II study is investigating the safety, biologic and anti-tumor activities of i.p. ONCOS-102 in association with durvalumab (anti-PD-L1) in subjects with advanced CRC or platinum-resistant ovarian cancers (NCT02963831). A Phase I pilot study evaluates the safety of i.t. ONCOS-102, preceded by CPA and followed by pembrolizumab, in two cohorts of patients with advanced or unresectable melanoma progressing after ICB therapy. Cohort 1 regroups subjects that failed prior anti-PD-1 monotherapy while cohort 2 failed prior anti-PD-1 plus ipilimumab (NCT03003676). **(8)** Two Phase I/II trials have been registered to evaluate the safety and efficacy of LOAd703[200,252] (Lokon Pharma AB, Uppsala, Sweden) in patients with pancreatic, biliary, colorectal or ovarian cancers. LOAd703 will be co-administered i.t. together with the standard-of-care chemotherapy (NCT03225989; NCT02705196). **(9)** Harb WA and colleagues (PsiOxus Therapeutics, Abingdon, UK) have initiated a Phase I study (named SPICE; NCT02636036) to evaluate the safety profile of i.v. EnAd combined to pembrolizumab in patients with metastatic or advanced HNC, CRC, urothelial and salivary gland carcinomas.[369]

Herpesviruses. **(1)** The safety and efficacy of T-VEC (Amgen, Thousand Oaks, CA, USA) is being evaluated in various types of advanced and metastatic cancers.

Intralesional T-VEC monotherapy is undergoing testing in breast (NCT02658812), advanced and metastatic pancreatic cancer refractory to chemotherapy (NCT03086642), unresectable advanced Stage IIIB-IV malignant melanoma (NCT03064763) and advanced non-CNS pediatric tumors (NCT02756845). Moreover, T-VEC is being tested in combination with ICIs: i) pembrolizumab in patients with advanced sarcoma (NCT03069378),[318] melanoma (NCT02965716)[370] and recurrent metastatic HNC (NCT02626000/MASTERKEY232), ii) nivolumab in refractory lymphomas and metastatic non-melanoma skin cancers (NCT02978625) and iii) atezolizumab in patients harboring TNBC and metastatic CRC (NCT03256344). Additionally, T-VEC is being evaluated for efficacy in combination with a) standard chemotherapy against TNBC (NCT02779855) and CRC (NCT03300544), b) targeted therapies such as the BRAF and MEK inhibitors dabrafenib and trametinib, respectively, against BRAF-mutated advanced melanoma (NCT03088176) and c) radiotherapy in soft tissue sarcoma (NCT02923778), various forms of CRC (NCT03300544), and melanoma, Merkel cell carcinoma and other solid tumors (NCT02819843). One Phase I trial is recruiting participants to evaluate the mechanisms of action of T-VEC in patients with non-melanoma skin cancer through determination of local immune effects after repeated T-VEC injections (NCT03458117). Assays will include quantifying some local immune activation markers in skin biopsies of injected lesions (such as IFN, 2-prime, 5-prime oligoadenylate synthetase 1 [OAS1], Interferon-induced GTP-binding protein MxA [MXA] and C-X-C motif chemokine 11 [CXCL11]) as well as immune response markers in sera and peripheral blood mononuclear cells. Lastly, a prospective study is evaluating the risk of herpetic infection in melanoma patients that received T-VEC (NCT02910557). **(2)** Two single-arm open label Phase II studies, initiated by Takara Bio Inc, aim at determining the efficacy and saftey of i.t. injections of oncolytic HSV-1 HF10[371] in combination with ipilimumab in Japanese patients with Stage IIIb/C or IV unresectable or metastatic melanoma (NCT03153085) or in a neoadjuvant setting together with nivolumab against resectable Stage IIIB, IIIC, IVM1a melanoma (NCT03259425). Additionally, a Phase I dose trial is determining the recommended dose of HF10 in combination with chemotherapy (gemcitabine + Nab-paclitaxel) in Japanese patients with Stage III or IV unresectable pancreatic cancer (NCT03252808).

Paramyxoviruses. A Phase I trial, soon to be open for participant recruitment, will evaluate the safety and toxicity of MV-NIS (Vyriad, Rochester, MN, USA) in patients with urothelial carcinoma undergoing cystectomy. Antitumor efficacy of intravesical MV-NIS neoadjuvant therapy will be assessed as secondary outcome measures (NCT03171493). Safety of MV-NIS is being assessed in a Phase I study in children and young adults with recurrent medulloblastoma or atypical teratoid rhabdoid tumor. The OV is injected in the tumor bed for local recurrence (during surgical resection) or via lumbar puncture for disseminated recurrence (NCT02962167). I.t. MV-NIS monotherapy is also investigated against malignant unresectable or recurrent peripheral nerve sheath tumor (NCT02700230). A fourth Phase I trial aims at defining the MTD of i.t. MV-NIS in combination with atezolizumab, an anti-PD-L1, in patients with metastatic NSCLC (NCT02919449).

Parvoviruses. Safety and tolerability of ParvOryx (ORYX GmbH & Co. KG, Baldham, Germany) will be evaluated in a Phase I/II trial in subjects suffering from metastatic, inoperable pancreatic cancer. Parvovirus H-1 will be administered at three increasing dose levels with 40% of the total dose given i.v. and the remaining 60% given i.t. into a hepatic metastasis of the pancreatic cancer (NCT02653313/ParvOryx02)

Picornaviruses. **(1)** A Phase I study will evaluate the safety and efficacy of i.v. CAVATAK/CVA21 (Viralytics, Sydney, Australia) in combination with pembrolizumab in patients with advanced NSCLC (NCT02824965). **(2)** In a Phase Ib trial, the safety and toxicity of a single dose of i.t. PVSRIPO (Duke University, Durham, NC, USA) is evaluated in children affected with diverse brain cancers, including advanced glioma. A secondary objective will consist of estimating OS in this population (NCT03043391). A Phase II trial aims at evaluating the impact of PVSRIPO on the survival of adult patients with recurrent severe glioma, relative to the survival observed in a historical control group. PVSRIPO will be delivered i.t. either alone or with a single dose of lomustine, an alkylating nitrosourea compound used as standard-of-care chemotherapy. The safety of the latter combination treatment will also be assessed (NCT02986178).

Poxviruses. **(1)** Two Phase I/II trials have been initiated by Genelux (San Diego, CA, USA) involving their lead VV candidate, GL-ONC1. A Phase Ib trial (NCT02714374) enrolled 36 patients with solid organ cancers. The study will evaluate the tolerability of single or multiple doses of GL-ONC1 delivered i.v., with or without eculizumab (a humanized monoclonal antibody functioning as a terminal complement inhibitor), prior to surgery. A Phase Ib/II trial aims at recruiting 52 patients to investigate the safety and tolerability of repeated i.p. infusions of GL-ONC1 in women diagnosed with recurrent ovarian cancer, peritoneal carcinomatosis or fallopian tube cancer (NCT02759588/VIRO-15). PFS will also be assessed and tumor response to treatment evaluated by RECIST 1.1 and irRECIST 1.1. Results of the Phase Ib have been disclosed at the 2018 ASCO meeting and reported in the previous section on "advanced clinical trials".[339] **(2)** Pexa-Vec, also known as JX-594 or TG6006, is a TK^- $GM\text{-}CSF^+$ $LacZ^+$ variant of the VV Wyeth strain (SillaJen, San Francisco, CA, USA in partnership with Transgene, Illkirch-Graffenstaden, France; Green Cross, Kyoto, Japan; Lee's Pharmaceuticals, Hong Kong, China and Rex Medical, Conshohocken, PA, USA). Pexa-Vec is one of the most extensively investigated VV-based oncolytic biotherapeutic with no less than 19 clinical trials registered on the clinicaltrial.gov website. A multicenter, randomized, open-label, Phase 3 study has been initiated in 2015 and will enroll 600 patients to compare Pexa-Vec followed by sorafenib (a multikinase inhibitor) versus sorafenib alone in patients with advanced HCC without prior systemic therapy (NCT02562755/PHOCUS). During the past 2 years, 5 clinical trials involving Pexa-Vec have been initiated. A two-part Phase I clinical trial aims at assessing the DLT of escalating doses of ipilimumab (up to 5 injections given i.t.) in combination with a fixed dose of Pexa-Vec (up to

6 injections given i.t.) in 60 patients with advanced/metastatic solid tumors (NCT02977156/ISI-JX). The second part of the study will determine the ORR according to irRC. A second two-part Phase I trial will enroll up to 89 patients with renal cell carcinoma (NCT03294083). The first part will determine the MTD and maximum feasible dose (MFD) of Pexa-Vec administered by i.v. infusion in combination with REGN2810, an anti-PD-1 monoclonal antibody. The second part of the study will assess the safety of Pexa-Vec administered by i.v. infusions or i.t. injections in combination with i.v. REGN2810 and evaluate anti-tumor activity and efficacy with respect to ORR per RECIST 1.1. Secondary outcome evaluations will consist in measuring PFS and OS. A Phase I/IIa trial is recruiting 30 participants to evaluate the safety and efficacy of the combination of i.t. Pexa-Vec with Nivolumab as first-line therapy of advanced HCC (NCT03071094). Another clinical trial is determining the safety, tolerability and feasibility of Pexa-Vec in combination with immune checkpoint inhibitors in 35 patients with refractory metastatic CRC (NCT03206073). Precisely, two different doses of Pexa-Vec will be injected i.v. for 4 times together with repeated infusions of anti-PD-L1 durvalumab (cohort A) or durvalumab + anti-CTLA-4 tremelimumab (cohort B). Finally, a Phase Ib/II clinical trial is expecting to recruit 118 patients with advanced breast cancer, soft-tissue sarcoma or other solid tumors to assess the tolerability and antitumor efficacy of i.v. Pexa-Vec in combination with metronomic CPA (NCT02630368/METROmaJX). After determining the MTD in 14 subjects (Phase Ib), the antitumor activity of the combination therapy will be determined based on 6-month non-progression in soft-tissue sarcoma patients (48 receiving the dual therapy versus 24 ingesting CPA alone) or based on OR to treatment in the breast cancer cohort (single-arm, n = 32), following RECIST 1.1 criteria. **(3)** TG6002 (Transgene, Illkirch-Graffenstaden, France) is an engineered oncolytic vaccinia virus deleted from two genes expressing the viral TK and ribonucleotide reductase and outfitted with the suicide gene *FCU1*. *FCU1* gene encodes a bifunctional chimeric protein that catalyzes the conversion of the non-toxic 5-FC into the toxic 5-FU. A Phase I/II aims at evaluating the safety and efficacy of i.v. TG6002 plus oral 5-FC in recurrent GB patients (NCT03294486/ONCOVIRAC).[372]

Reoviruses. The safety and therapeutic efficacy of REOLYSIN® is being assessed in pancreatic adenocarcinoma patients, who are being treated with i.v. REOLYSIN® in combination with chemotherapy (gemcitabine, irinotecan, leucovorin, or 5-FU) and pembrolizumab (NCT02620423); in multiple myeloma patients, receiving REOLYSIN® with either lenalidomide or pomalidomide (NCT03015922/MUKeleven); as well as in individuals with skin melanoma in combination with GM-CSF (NCT03282188).

Retroviruses. Toca 511, also referred to as vocimagene amiretrorepvec (Tocagen, San Diego, CA, USA), is a replication-competent tumor-selective retrovirus that expresses an optimized yCD.[362] When combine to Toca FC, an extended-release formulation of the prodrug 5-FC, it locally generates toxic 5-FU. A Phase II study will establish the recommended dose of Toca FC to be used in combination with Toca 511, together with standard-of-care chemoradiation and TMZ, in subjects with newly diagnosed high grade glioma (HGG). Toca 511 will be administered by intracranial parenchymal injection into the cavity resulting from surgical resection (NCT02598011/Toca7).

Rhabdoviruses. **(1)** Three Phase I trials aim at determining the tolerability and safety of VSV-IFNβ-NIS (Vyriad, Rochester, MN, USA) administered either i.t. against refractory advanced/metastatic solid tumors (NCT02923466) or given i.v. against relapsed or refractory multiple myeloma, acute myeloid leukemia (AML) or T-cell lymphoma (NCT03017820) or against stage IV or recurrent endometrial cancers (NCT03120624). **(2)** A Phase I/II trial will determine the MTD and efficacy of the oncolytic vaccine Maraba MG1MA3 (Turnstone Biologics, Ottawa, ON, Canada) in patients with NSCLC who have completed a first standard therapy with a platinum-based chemotherapy. MG1MA3 will be given i.v. following an intramuscular delivery of the non-replicating AdMA3 vaccine and in association with pembrolizumab (NCT02879760).

Status changes

The following studies discussed in our previous Trial Watches related to oncolytic virotherapy [40,373,374] have changed status during the past 2.5 years: NCT02293850, NCT02457845, NCT02509507, NCT02068794, NCT02562755 and NCT02414165 which are currently "recruiting"; NCT02263508, NCT02365818, NCT02197169, NCT02045589, NCT02272855, NCT02366195, NCT02211131, NCT01491893, NCT01766739, NCT01274624, NCT01740297, which are now « active, not recruiting »; NCT00390299 which has been suspended; NCT02031965, NCT01438112 and NCT01017601, which have been terminated; NCT02028442, NCT01656538, NCT01844661, NCT01985256, NCT01156584, NCT02014441, NCT01864759, NCT01956734, NCT02053220, NCT02428036, NCT01721018, NCT01935453, NCT02316171, NCT01636882, NCT00794131, NCT01394939, NCT01469611, NCT01636284, NCT01171651, NCT01380600, NCT00602277, NCT01619813, NCT01708993 and NCT00861627 which are now completed.

Although their status is not completed, preliminary results are available for the trials NCT02263508 [228] (a Phase Ib/III study testing the combination of T-VEC with pembrolizumab in patients with unresected melanoma), NCT01740297 [297] (a Phase Ib/II trial evaluating the safety and efficacy of T-VEC in combination with ipilimumab in subjects with unresected melanoma) and NCT01656538 [325] (a Phase II trial investigating the benefit of REOLYSIN when given with Paclitaxel in subjects with advanced/metastatic breast cancer).

The results from the "completed" studies NCT02316171 [314] (a Phase I study assessing the safety and efficacy of CVA21 with or without sequencial combination with mitomycin C in individuals with bladder cancer), NCT01619813 [327] (a Phase II trial testing the efficacy of combining REOLYSIN with docetaxel and predisone in metastatic castration resistant prostate cancer patients), NCT01708993 [326] (a Phase II study evaluating the combination of REOLYSIN with docetaxel or pemetrexed in subjects with advanced or metastatic NSCLC), and NCT00861627 [323] (a Phase II trial combining REOLYSIN with paclitaxel and carboplatin in NSCLC patients) have been

considered in the *"completed and advanced clinical studies"* section above.

Finally, based on our investigations, the results from NCT02028442 (a Phase I/II trial testing EnAd in patients suffering from epithelial solid tumors or metastatic colorectal/bladder cancer), NCT01656538 (a Phase II study evaluating the safety of REOLYSIN in combination with the standard treatment Paclitaxel in metastatic or advanced breast cancer patients), NCT01985256 (a Phase I trial assessing the tolerability of the retroviral vector Toca 511 in patients undergoing brain tumor surgery), NCT01156584 (a Phase I study investigating the safety of Toca 511 in individuals that have undergone surgery of recurrent glioma), NCT02014441 (a Phase II study assessing the biodistribution of T-VEC after intralesional injection in subjects suffering from melanoma), NCT01864759 (a Phase I trial assessing the safety of ICOVIR-5 in subjects with locally advanced or metastatic melanoma), NCT01956734 (a Phase I study combining DNX-2401 with TMZ in glioblastoma patients), NCT02053220 (a Phase I trial determining the viral delivery and viral expression of ColoAd1 in tumor tissues of patients eligible for primary tumor resection), NCT02428036 (a Phase I trial testing the i.t. administration of HF10 in individuals with solid tumors comprising superficial lesions), NCT01721018 (a Phase I/IIa study assessing the safety and tolerability of HSV1716 inoculation into pleural cavity of subjects with inoperable malignant pleural mesothelioma), NCT01935453 (a Phase I trial investigating the safety of OrienX010 in patients with solid tumors), NCT01636882 (a Phase II extented use study aiming at continue the treatment with CAVATAK in individuals with stage IIIc and stage IV malignant melanoma), NCT00794131 (a Phase I trial evaluating the safety of GL-ONC1 i.v. administration in subjects with advanced solid tumors), NCT01394939 (a Phase I/IIa study of i.v. administration of Pexa-Vec with or without Irinotecan in patients with metastatic, refractory colorectal carcinoma), NCT01469611 (a Phase Ib trial designed to determine the MTD/MFD of Pexa-Vec and the safety of its biweekly i.v. infusion in individuals with advanced CRC), NCT01636284 (a Phase IIa study evaluating the efficacy of Pexa-Vec in HCC patients who had not formerly received sorafenib), NCT01171651 (a Phase II trial assessing the safety of Pexa-Vec i.v. and i.t. administration before standard therapy with sorafenib in subjects with unresectable primary HCC), NCT01380600 (a Phase Ib trial investigating the safety of Pexa-Vec biweekly i.v. administration in CRC individuals) and NCT00602277 (a Phase I study evaluating the REOLYSIN viral therapy in patients with ovarian, primary peritoneal and fallopian tube cancer who did not respond to platinum therapy), have not been disclosed yet even though their status is currently reported as "completed".

Concluding remarks

Based on the sizeable number of clinical trials reported, the attractiveness of oncolytic virotherapy has grown since the approval of T-VEC in 2015. The broad repertoire of OV strains allows their application for virtually any type of malignancy, whether hematological or solid, localized or disseminated. With that said, considerable efforts are being made on evaluating OVs against highly morbid cancers that keep resisting to the arsenal of approved drugs, such as brain and pancreatic tumors. OV therapeutic efficacy mostly relies on its ability to prime and adjuvantize both innate (NK cells, DCs, M1-like macrophages) and adaptive (CTLs) arms of antitumor immunity. For this reason, cumulative evidences evoke the use of oncolytic virotherapy in support of current standards of care. If, for instance, T-VEC can intervene as a first-line monotherapy, the OV platform seems adequately fitted for combinatory strategies and has already demonstrated promising benefits in association with surgery (in both neoadjuvant and adjuvant settings), chemotherapy, radiotherapy and immunotherapy. Regarding the latter, synergistic interaction between OVs and ICIs has been quasi systematically witnessed, regardless of the virus strain. Interestingly, antitumor activity was detected not only in the primary lesion but also at distant sites that were not necessarily targeted by the virus (abscopal effect). However, caution to the experimental design has been raised to prevent antagonistic interactions. If much of the focus has been dragged by anti-PD-1/CTLA-4, oncolytic virotherapy also appeared beneficial to other immunotherapeutic approaches, including CAR T cells and BiTE antibodies. The characterization of markers responsible for resistance to the various OV strains, as well as markers of good prognosis, will contribute to define and optimize the associations that best suit the therapeutic needs. Finally, OV application to the field of oncology could expand beyond treatment as their tumor selectivity can be exploited as a sensitive diagnostic tool, or for imaging tumor lesions, or for clearing residual malignant entities from cell preparations destined to autologous transfer.

Abbreviations

5-FC	5-fluorocytosine
5-FU	5-fluorouracil
Ad	adenovirus
AE	adverse event
BiTE	bispecific T cell-engager
CAR	chimeric antigen receptor
CNS	central nervous system
CPA	cyclophosphamide
CRC	colorectal cancer
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DLT	dose limiting toxicity
GB	glioblastoma
GSC	glioblastoma stem-like cell
HCC	hepatocellular carcinoma
HNC	head and neck cancer
HSV	herpes simplex virus
IAV	influenza A virus
ICI	immune checkpoint inhibitor
IFN	interferon
IL	interleukin
irRC	immune-related Response Criteria
MDSC	myeloid-derived suppressor cell
MSC	mesenchymal stem cell
MTD	maximum tolerated dose
MV	measle virus

MYXV	myxomavirus
NDV	Newcastle disease virus
NSCLC	non-small cell lung carcinoma
OR	objective response
ORR	overall response rate
OS	overall survival
OV	oncolytic virus
PFS	progression-free survival
SD	stable disease
TAA	tumor-associated antigen
TIL	tumor-infiltrating lymphocyte
TME	tumor microenvironment
TMZ	temozolomide
TNBC	triple-negative breast cancer
Treg	regulatory T cell
VV	vaccinia virus
yCD	yeast cytosine deaminase.

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