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Trial Watch
Oncolytic viruses for cancer therapy

Jonathan Pol[1,2,3,4,†], Norma Bloy[1,2,3,4,†], Florine Obrist[1,2,3,4], Alexander Eggermont[1], Jérôme Galon[5,6,7,8], Isabelle Cremer[5,6,7,9], Philippe Erbs[10], Jean-Marc Limacher[10], Xavier Preville[10], Laurence Zitvogel[1,11], Guido Kroemer[2,3,5,12,13,‡,*], and Lorenzo Galluzzi[1,3,5,‡,*]

[†]These authors contributed equally to this work.

[‡]These authors share senior co-authorship.

[1]Gustave Roussy; Villejuif, France; [2]INSERM, U848; Villejuif, France; [3]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers; Paris, France; [4]Université Paris-Sud/Paris XI; Paris, France; [5]Université Paris Descartes/Paris V, Sorbonne Paris Cité; Paris, France; [6]Université Pierre et Marie Curie/Paris VI; Paris, France; [7]INSERM, UMRS1138; Paris, France; [8]Laboratory of Integrative Cancer Immunology, Centre de Recherche des Cordeliers; Paris, France; [9]Equipe 13, Centre de Recherche des Cordeliers; Paris, France; [10]Transgene S.A.; Illkirch-Graffenstaden, France; [11]INSERM, U1015; CICBT507; Villejuif, France; [12]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP; Paris, France; [13]Metabolomics and Cell Biology Platforms; Gustave Roussy; Villejuif, France

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Abbreviations: CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; HR, hazard ratio; HSV, herpes simplex virus; ICD, immunogenic cell death; IL, interleukin; MPS, mononuclear phagocytic system; MSC, mesenchymal stem cell; T-vec, talimogene laherparepvec; TLR, Toll-like receptor

Oncolytic viruses are natural or genetically modified viral species that selectively infect and kill neoplastic cells. Such an innate or exogenously conferred specificity has generated considerable interest around the possibility to employ oncolytic viruses as highly targeted agents that would mediate cancer cell-autonomous anticancer effects. Accumulating evidence, however, suggests that the therapeutic potential of oncolytic virotherapy is not a simple consequence of the cytopathic effect, but strongly relies on the induction of an endogenous immune response against transformed cells. In line with this notion, superior anticancer effects are being observed when oncolytic viruses are engineered to express (or co-administered with) immunostimulatory molecules. Although multiple studies have shown that oncolytic viruses are well tolerated by cancer patients, the full-blown therapeutic potential of oncolytic virotherapy, especially when implemented in the absence of immunostimulatory interventions, remains unclear. Here, we cover the latest advances in this active area of translational investigation, summarizing high-impact studies that have been published during the last 12 months and discussing clinical trials that have been initiated in the same period to assess the therapeutic potential of oncolytic virotherapy in oncological indications.

*Correspondence to: Lorenzo Galluzzi; Email: deadoc@vodafone.it; Guido Kroemer; Email: kroemer@orange.fr
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Introduction

The term "oncolytic virus" is commonly employed to identify a non-pathogenic viral strain that selectively infects and kills neoplastic cells while leaving their normal counterparts virtually unaffected.[1] Thus, oncolytic viruses not only display a preferential tropism for transformed over non-transformed tissues, in thus far being oncotropic,[2-4] but also trigger the massive demise of infected cells.[5] Such a cytotoxic activity can be natural and simply reflect the so-called cytopathic effect, i.e., the lethal outcome of a replicative viral infection.[6,7] Alternatively, oncolytic viruses can mediate cytotoxic effects upon the expression of (endogenous or exogenous) gene products, irrespective of their ability to drive a productive infection.[1,5] Although the possibility to harness the lytic potential of viruses against cancer has been theorized as early as at the beginning of the 20th century, it is only with the advent of modern genetic engineering technologies in the late 1990s that the interest in oncolytic virotherapy has crystallized.[5,8-10] Since then, dozens of viruses have been tested for their natural oncolytic activity or genetically endowed with cancer-specific cytotoxic functions or immunostimulatory properties. A precise description of these viruses goes beyond the scope of this Trial Watch. For additional details on the viral species that have been harnessed so far for oncolytic virotherapy as well as on the advantages and pitfalls associated with their use please see Refs. 1,5 and 11.

Specificity is a critical requirement for the safety of oncolytic virotherapy and multiple strategies have been developed throughout the past 2 decades to improve the oncotropism of naturally occurring viruses or endow otherwise unspecific viral strains with a highly-targeted lytic potential.[1,5,12] Such a specificity can be obtained by conventional genetic engineering (1) at the transductional level, implying modifications of surface proteins

that allow for the infection of cells bearing one (or a few) tumor-specific markers on their surface;[13-17] (2) at the transcriptional level, based on the use of promoters that are active in neoplastic cells only to control the expression of essential viral genes;[18-25] (3) at the post-transcriptional/translational level, either based on the insertion of microRNA-binding elements in non-coding regions of essential viral genes, allowing productive infections to develop only in tissues that do not express such microRNAs;[26-32] or involving the cloning of genes that are absolutely required for the viral cycle downstream of internal ribosome entry sites that are inactive in selected tissues;[33-35] (4) at the post-translational level, either based on "destabilization domains" that render essential viral proteins unstable in tissues that are not artificially or naturally exposed to a specific stabilizing agent,[36-38] or based on viral protein precursors that can be processed only in cells expressing specific (cancer-associated) proteases;[39] and (5) at a cell-wide level, harnessing the ability of attenuated viral strains to productively replicate in neoplastic cells bearing peculiar genetic or epigenetic defects, such as the hyperactivation of Harvey rat sarcoma viral oncogene homolog (HRAS) or signal transducer and activator of transcription 3 (STAT3) as well as the inactivation of p53.[40-46] Among these strategies, the use of oxygen-dependent degradation domains (ODDs) stands out as a convenient approach to specifically direct the cytotoxicity of oncolytic viruses to solid tumors based on their limited oxygen supply.[38]

In addition, genetic engineering has been largely employed to endow oncolytic viruses with (at least hypothetically) desirable features, including (but not limited to) an increased cytotoxic potential and a superior ability to drive cell-mediated immune responses.[1,5,47] Thus, the viral genome has been integrated with sequences coding for (1) enzymes that convert non-toxic pro-drugs into a lethal cytotoxic agent;[48-55] (2) proteins that (at least on theoretical grounds) mediate tumor-specific lethal effects;[56-58] or (3) short-hairpin RNAs targeting proteins that are necessary for the survival of neoplastic cells, such as survivin.[59-61] All these approaches have been shown to improve the cytotoxic potential of oncolytic virotherapy, hence ameliorating its therapeutic profile (at least to some extent) in experimental settings.

Accumulating evidence indicates indeed that the antineoplastic effects of oncolytic virotherapy do not simply originate from cancer cell-autonomous mechanisms but involve the (re)activation of tumor-specific immune responses.[62-70] Thus, the administration of oncolytic viruses to cancer patients has been associated with the insurgence of cellular as well as humoral antitumor immune responses of potential therapeutic value.[71-74] Moreover, the clinical activity of oncolytic viruses seems to benefit from some extent of initial immunosuppression (which facilitates viral spread, see below) followed by the administration of immunostimulatory molecules (which exacerbate antitumor immunity).[1,5] In line with this notion, oncolytic viruses have also been engineered to express (1) tumor-associated antigens (generating so-called oncolytic vaccines);[75-79] (2) co-stimulatory molecules, such as CD40 ligand (CD40L) and CD80;[80-84] (3) immunostimulatory cytokines, including interleukin (IL)-2,[85-87] IL-12,[88-95] IL-15,[96-101] IL-23,[102] IL-24,[103-106] and granulocyte macrophage colony-stimulating factor (GM-CSF);[73,89,107-113] or (4) chemokines, such as chemokine (C-C motif) ligand 7 (CCL7)[114] and CCL19.[115]

The clinical profile of oncolytic virotherapy employed as a standalone therapeutic intervention is generally limited, for several reasons.[1,5,116] These include (but may be not limited to): (1) the heterogeneous and relatively incomplete diffusion of oncolytic viruses within neoplastic lesions;[117-127] (2) the equilibrium that is generally established between oncolytic viruses and continuously proliferating, non-infected cancer cells, which eventually shifts in favors of the latter owing to the insurgence of an antiviral immune response (at least in immunocompetent individuals);[128-130] (3) the propensity of malignant cells to become resistant to oncolytic virotherapy,[121,126,130-132] presumably reflecting their genomic instability;[133,134] (4) the elevated diffusion among the population of viral species that are employed to create therapeutic strains, resulting in a significant fraction of individuals who are insensitive to some oncolytic viruses owing to neutralizing humoral immunity;[135,136] (5) the elevated sensitivity of some oncolytic viruses to the complement system;[137,138] (6) the sequestration of intravenously administered oncolytic viruses by the mononuclear phagocytic system (MPS) of the liver and spleen,[139,140] limiting the availability of viral particles at the tumor site and (at least in some cases) causing driving serious, dose-limiting toxicities;[141-143] and (7) the threats that are intrinsically associated with the use of replicating viral particles in cancer patients, who are particularly weak and often immunodepressed.[144-150]

Consistent efforts have been dedicated at the development of strategies that would circumvent (at least in part) these issues. For instance, several oncolytic viruses have been genetically manipulated to express endogenous (or co-administered with exogenous) inhibitors of angiogenesis.[91,92,151-154] This approach may exert a dual benefit in that the inhibition of cancer-associated angiogenesis not only mediates direct antineoplastic effects,[155,156] but also causes a normalization of the tumor vasculature that improves the delivery/penetration of therapeutic agents, including oncolytic viruses themselves.[157-159] Along similar lines, tumor-infiltrating cells including macrophages,[160,161] myeloid-derived suppressor cells,[162-164] and mesenchymal stem cells (MSCs) have been harnessed as vehicles to selectively deliver oncolytic viruses to neoplastic lesions while shielding them from neutralizing antibodies and protecting them from sequestration by the MPS.[163,165-170] Finally, several laboratories worldwide have demonstrated that the therapeutic profile of oncolytic virotherapy can be remarkably boosted by the co-administration of several chemotherapeutics, including (but not limited to) gemcitabine (an immunostimulatory nucleoside analog),[171-173] paclitaxel (a microtubular inhibitor),[174-176] temozolomide and cyclophosphamide (two alkylating agents),[72,177-179] sunitinib (a relatively unspecific tyrosine kinase inhibitor),[180-182] cisplatin (a non-immunogenic DNA-damaging agent),[183-186] various histone deacetylase inhibitors,[187] and 13-*cis* retinoic acid (a retinoid employed for the treatment of high risk neuroblastoma).[188,189] Taken together, these findings indicate that oncolytic viruses can mediate therapeutically relevant anticancer effects in vivo. In line with this notion, clinical trials performed throughout the

2 past decades demonstrated that oncolytic virotherapy can be safely implemented in cancer patients and can exert substantial antineoplastic activity, at least in a fraction of individuals.

As it stands, no oncolytic virus is currently licensed by the US Food and Drug Administration and the European Medicines Agency for use in cancer patients (sources http://www.fda.gov/Drugs/default.htm and http://www.ema.europa.eu). Along similar lines, in spite of promising preclinical results,[190-194] oncolytic virotherapy has not yet been approved as part of veterinary protocols in the US and Europe. Conversely, the Chinese State Food and Drug Administration approved a recombinant adenovirus (H101, commercialized under the name of Oncorine®) for use together with chemotherapy in refractory head and neck cancer patients as early as in November 2005.[195-197]

One year ago, in the May issue of *OncoImmunology*, we presented the scientific background to the use of oncolytic viruses in oncological indications and discussed recent clinical trials evaluating the safety and efficacy of this immunotherapeutic regimen.[198] Along the lines of our monthly Trial Watch series,[199-201] here we summarize the latest developments in oncolytic virotherapy.

Literature Update

Since the submission of our previous Trial Watch on this topic (March 2013),[198] no less than 11 studies dealing with clinical aspects of oncolytic virotherapy have been published in peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed). Four of these studies tested a serotype-chimeric, infectivity-enhanced, conditionally-replicative adenovirus initially developed to specifically infect and kill ovarian cancer cells,[202,203] either in its pristine configuration (Ad5/3-Delta24)[204] or as a 2nd generation variant further modified to express GM-CSF (CGTG-102).[72,73,205] Kim and colleagues investigated the feasibility and efficacy of intraperitoneally administered Ad5/3-Delta24 in 10 recurrent ovarian cancer patients. Nine patients completed the therapeutic protocol and only manageable Grade I/II side effects were recorded. In spite of the development of neutralizing immunity in all individuals, 6 out of 8 patients that could be evaluated for response experienced disease stabilization.[204] Kanerva and coworkers tested multiple immunological and clinicopathological parameters in 115 cancer patients treated with CGTG-102, either as a single injection, either in a serial manner (3 injections over 10 wks), or in the context of a switch protocol involving the administration of viruses with modified capsid proteins to avoid neutralizing immunity. A good safety profile was recorded. Moreover, the serial regimen was associated with the induction of anticancer immune responses, with indirect indications of the mobilization of tumor-specific T cells to neoplastic lesions,[164,206,207] as well as with an improved overall survival (as compared with the single injection-based protocol).[73] Liikanen and collaborators assessed the clinical profile of CGTG-102 in combination with metronomic temozolomide and/or cyclophosphamide in 17 individuals affected by chemotherapy-refractory neoplasms. This chemoimmunotherapeutic regimen was well tolerated by all patients and elicited several signs of immunogenic cell death (ICD) in neoplastic cells, including the activation of autophagy and the release of high mobility group box 1 (HMGB1).[208-214] This was paralleled not only by the release of pro-inflammatory cytokines but also by the activation of tumor-specific immune responses, which were observed in 10 out of 15 patients. Clinical effects were evident in 67% of patients treated with CGTG-102 plus temozolomide and/or cyclophosphamide and these individuals exhibited a trend for improved survival as compared with subjects receiving CGTG-102 only.[72] Bramante et al. tested the clinical profile of CGTG-102 in 15 patients with treatment-refractory soft tissue (13/15) or primary bone (2/15) sarcoma. Of 12 patients who could be assessed for clinical outcome, 2 exhibited an objective (though minor) response, 6 stable disease, and 4 progressive disease. Median overall survival was 170 d, and 1 patient was still alive when the paper was published, approx. four years after oncolytic virotherapy.[205]

Different research groups investigated the clinical profile of Pexa-Vec (formerly known as JX-594), an oncolytic vaccinia virus engineered to selectively replicate in cells with alterations of the RAS pathway and to express GM-CSF.[109,215-217] Kim and colleagues reported that the administration of Pexa-Vec to 3 patients with diverse tumors (in the context of a Phase I clinical trial) resulted in the insurgence of a cancer cell-specific, antibody-mediated, complement-dependent cytotoxic response, whose intensity positively correlated with overall survival.[71] Breitbach and collaborators studied the effects of Pexa-Vec on the tumor vasculature in patients with treatment-refractory, histologically confirmed advanced/metastatic solid tumors (n = 18, from a Phase I clinical trial, NCT00625456) as well as in subjects with hepatic neoplasms of hepatocellular (n = 15) or colorectal (n = 1) origin (from Phase II clinical trials, NCT00554372 and NCT01171651). These authors demonstrated that Pexa-Vec infects not only neoplastic cells but also the tumor-associated (but not the normal) vasculature, resulting in its destruction and hence mediating antineoplastic effects.[155]

Markert and colleagues conducted a Phase I clinical trial to test the effects of the stereotactic intratumoral administration of G207, a conditionally replicating herpes simplex virus (HSV) Type 1 variant,[218-220] in 9 glioblastoma patients allocated to receive a single 5 Gy dose of radiation 24 h later. Oncolytic virotherapy was well tolerated and 6 out of 9 patients exhibited stable disease or a partial response at least at one evaluation time point.[221] Interestingly, interim overall survival data from a Phase III study comparing subcutaneous GM-CSF with intratumoral talimogene laherparepvec (T-vec), an oncolytic HSV variant manipulated to express GM-CSF,[222,223] in over 400 patients with unresected Stage IIIB, IIIC or IV melanoma (NCT00769704) have been released by Amgen at the 2013 meeting of the American Society of Clinical Oncology (ASCO), which was held in Chicago last June. In this setting, 26% of patients receiving T-vec developed serious adverse effects, including cellulitis and pyrexia, as compared with 13% of patients receiving GM-CSF. At a predetermined interim analysis, median overall survival among T-vec- and GM-CSF-treated patients was 23.3 and 19.9

mo, respectively (HR = 0.79, 95% CI 0.61–1.02; P = 0.0746). According to Amgen representatives, such a difference, which was slightly below the threshold for statistical significance, was "pronounced in the subset patients with Stage IIIB, IIIC or IV disease (HR = 0.56, 95% CI, 0.38-0.81) or who received T-vec as first-line treatment (HR = 0.49, 95% CI, 0.33-0.74), each comprising approximately 50% of the study population" (source http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1877950). Thus, although NCT00769704 met its primary endpoint of durable response rate, defined as the rate of complete or partial response lasting continuously for at least 6 mo (source http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1798143),[224] the actual clinical benefits of T-vec remains to be elucidated.

Morris and colleagues tested the clinical profile of percutaneously administered Reolysin®, a wild-type reovirus (serotype 3 Dearing),[225] in 19 patients with accessible solid tumors who failed to improve on standard therapeutic approaches. Common toxicities included Grade 1/2 local erythema and transient flu-like symptoms. Moreover, objective responses were recorded in 7/19 (37%) patients, with 1 individual exhibiting a complete response, 2 a partial response, and 4 stable disease.[226]

During the last 13 mo a few immunological and clinicopathological parameters have been suggested to have a prognostic or predictive value in patients treated with oncolytic virotherapy. Such parameters include polymorphisms in the gene coding for Fc fragment of IgG, low affinity IIIa, receptor (FCGR3A), perhaps because of their influence on natural killer (NK) cell antibody-dependent cellular cytotoxicity,[116,227] as well as a hypointense tumor core in T2-weighted magnetic resonance imaging, perhaps indicating ongoing coagulative necrosis,[228,229] Moreover, Koski and colleagues demonstrated that ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and computed tomography (CT) are equally reliable means to predict the long-term survival of cancer patients on oncolytic virotherapy.[230] These studies may have significant implications for oncolytic viruses to become a clinical reality, as they may allow for the identification of patients who are most likely to obtain actual benefits from therapy.

Among recent (i.e., published during the last 13 mo) preclinical studies investigating the safety and efficacy of oncolytic virotherapy in experimental settings we found of particular interest the work of (1) Beug and collaborators, from the Children's Hospital of Eastern Ontario Research Institute (Ottawa, Canada), who demonstrated that the therapeutic potential of SMAC mimetics is dramatically exacerbated by oncolytic viruses, as well as by Toll-like receptor (TLR) agonists, owing to their ability to stimulate the production of interferon β (IFNβ), tumor necrosis factor α (TNFα), and tumor necrosis factor (ligand) superfamily, member 10 (TNFSF10, best known as TRAIL);[231-236] (2) Zamarin and colleagues, from the Sloan Kettering Institute for Cancer Research (New York, NY, US), who proved that the intratumoral administration of oncolytic viruses can elicit tumor-specific immune reactions in distant, non-injected lesions, and that such an effect synergize with the systemic delivery of cytotoxic T lymphocyte-associated protein 4 (CTLA4)-blocking antibodies to achieve a superior antineoplastic activity;[237-240] and (3) Castleton et al., from the University College London (London, United Kingdom), who provided robust evidence in support of the notion that MSCs can be efficiently employed to deliver oncolytic viruses to neoplastic lesions even in the presence of high-titer neutralizing antibodies;[170] (4) Carew and coworkers, from the University of Texas Health Science Center (San Antonio, TX, US), who demonstrated that (at least some) oncolytic viruses promote the demise of transformed cells upon the establishment of endoplasmic reticulum stress, which is currently viewed as an absolute requirement for cell death to be perceived as immunogenic.[208,209,241] and (5) Donnelly and colleagues, from the Leeds Institute of Cancer and Pathology (Leeds, UK), who proved that the therapeutic activity of (at least some) oncolytic viruses is significantly enhanced in animals immunized against the same viruses and pre-administered with GM-CSF, but not IL-2 or granulocyte colony-stimulating factor (G-CSF).[242] This latter study has profound repercussions for the implementation of oncolytic virotherapy in patients who may be endowed with neutralizing immunity as a result of previous exposure to naturally occurring viruses.

Update on Ongoing Clinical Trials

When this Trial Watch was being prepared (March 2014), official sources listed no less than 16 clinical trials launched after March 1st, 2013 that would evaluate the efficacy and safety of oncolytic virotherapy in oncological indications (source http://www.clinicaltrials.gov).

In particular, (1) ColoAd1, a chimeric oncolytic virus developed by directed evolution,[243,244] is being tested as a standalone therapeutic intervention in patients with resectable colorectal carcinoma (NCT02053220), platinum-resistant ovarian carcinoma (NCT02028117) or various neoplasms of epithelial origin (NCT02028442); (2) the safety and efficacy of MV-NIS, a strain of measles virus genetically engineered to express human solute carrier family 5, member 5 (SCL5A5, best known as sodium/iodide symporter),[245-248] are being evaluated in ovarian cancer patients, receiving MV-NIS-loaded MSCs i.p. (NCT02068794), as well as in subjects with head and neck squamous cell carcinoma, who are treated with MV-NIS i.t. (NCT01846091); (3) the intratumoral or intravenous administration of VCN-01, a replication-competent adenovirus expressing human sperm adhesion molecule 1 (SPAM1, best known as PH20 hyaluronidase),[249] is being assessed in individuals affected by advanced pancreatic cancer (NCT02045589) or other solid neoplasms (NCT02045602), respectively; (4) the biodistribution and shedding of intratumorally administered T-vec are being evaluated in melanoma patients (NCT02014441); (5) the safety and efficacy of Toca 511, an amphotropic replication-competent retrovirus genetically modified to express cytosine deaminase,[250-252] given as a standalone therapeutic intervention are being assessed in patients undergoing surgery for recurrent brain tumors (NCT01985256); (6) a naturally occurring variant of coxsackievirus, namely, coxsackievirus

Table 1. Clinical trials recently launched to evaluate the safety and efficacy of oncolytic virotherapy in cancer patients*

Virus	Indication(s)	Phase	Status	Route	Notes	Ref.
CG0070	Bladder carcinoma	I	n.a.	Intravesical	As a single agent	NCT00109655
ColoAd1	Colorectal carcinoma	I	Recruiting	i.t. or i.v.	As a single agent	NCT02053220
	Ovarian carcinoma	I/II	Not yet recruiting	i.p.	As a single agent	NCT02028117
	Solid tumors	I/II	Recruiting	i.v.	As a single agent	NCT02028442
CVA21	Solid tumors	I	Not yet recruiting	i.v.	As a single agent	NCT02043665
DNX2401	Glioblastoma	I	Recruiting	i.t.	Combined with temozolomide and/or surgery	NCT01956734
HSV-1716	Glioma	I	Recruiting	Into the tumor resection cavity	Combined with dexamethasone and surgery	NCT02031965
ICOVIR-5	Melanoma	I	Recruiting	i.v.	As a single agent	NCT01864759
	Solid tumors	I/II	Recruiting	i.p. (via MSCs)	As a single agent	NCT01844661
MV-NIS	HNSCC	I	Recruiting	i.t.	As a single agent	NCT01846091
	Ovarian carcinoma	I/II	Not yet recruiting	i.p. (via MSCs)	As a single agent	NCT02068794
Pexa-Vec	Ovarian carcinoma	II	Not recruiting	i.v.	As a single agent	NCT02017678
T-vec	Melanoma	II	Not yet recruiting	i.t.	As a single agent	NCT02014441
Toca 511	Brain tumors	I	Recruiting	i.v.	Combined with 5-FC	NCT01985256
VCN-01	Pancreatic cancer	I	Recruiting	i.t.	Combined with gemcitabine	NCT02045589
	Solid tumors	I	Recruiting	i.v.	Combined with gemcitabine	NCT02045602

Abbreviations: 5-FC, 5-fluorocytosine; CVA21, coxsackievirus A21; i.a., intra arteriam; i.p., intra peritoneum; i.t., intra tumorem; i.v., intra venam; HNSCC, head and neck squamous cell carcinoma; MSC, mesenchymal stem cell; n.a., not available; T-vec, talimogene laherparepvec. *Between 2013, March 1st and the date of submission.

A21,[253-256] is being evaluated as a single agent for the systemic treatment of residual metastatic disease in subjects with NSCLC, melanoma, bladder carcinoma, and castration-resistant prostate cancer[257] (NCT02043665); (7) the intravesical instillation of CG0070, a conditionally replicating oncolytic adenovirus genetically modified to express GM-CSF,[108,258] is being investigated as a standalone therapeutic intervention in bladder carcinoma patients who failed Bacillus Calmette-Guérin (BCG)-based immunotherapy[259,260] (NCT00109655); (8) the clinical profile of ICOVIR-5 and DNX2401, 2 oncolytic adenoviruses engineered to replicate only in cells exhibiting alterations of the retinoblastoma 1 (RB1) signaling pathway,[261-266] is being assessed in subjects with advanced melanoma (NCT01864759) or other solid tumors (NCT01844661), in both scenarios as a standalone therapeutic intervention, as well as in patients with recurrent glioblastoma (in the context of temozolomide-based chemotherapy) (NCT01956734); (9) HSV-1716, a γ34.5-deficient variant of HSV,[267-270] is being tested in combination with dexamethasone (a glucocorticoid) in subjects with refractory or recurrent high-grade glioma that can be removed by surgery (NCT02031965); and (10) Pexa-Vec is being tested as a single therapeutic intervention in ovarian carcinoma patients (NCT02017678) (**Table 1**).

The following clinical studies discussed in our previous Trial Watch dealing with oncolytic virotherapy[198] have changed status during the last 12 mo. NCT00602277, NCT00805376, NCT00861627, NCT00984464, NCT00998192, NCT01240538, NCT01387555, NCT01394939, NCT01469611, NCT01533194, NCT01598129, and NCT0163628 are now listed as "Active, not recruiting"; NCT01017601, NCT01274624, and NCT01438112 now appear as "Recruiting"; NCT00651157, NCT01227551, and NCT01048892 are now indicated as "Completed"; NCT01437280 has been "Terminated"; and the status of NCT00753038 and NCT01443260 is now "Unknown" (source http://www.clinicaltrials.gov). In the context of NCT00651157, a Phase II study testing Reolysin® as a standalone therapeutic intervention in Stage IV melanoma patients,[225] serious adverse effects developed in a significant proportion of patients (50%) and no clinical activity was recorded (source http://clinicaltrials.gov/ct2/show/results/NCT00651157?term=NCT00651157&rank=1). Although both these trials have been completed, results are available neither for NCT01048892, a Phase I trial testing the Seneca Valley virus in

combination with metronomic cyclophosphamide in patients with neuroendocrine tumors, nor for NCT01227551,[271,272] a Phase II study testing coxsackievirus A21 as a standalone therapeutic intervention in patients with advanced melanoma.[253-256] NCT01437280, a Phase I trial testing the safety and efficacy of a GM-CSF-encoding oncolytic adenovirus (CGTG-102) in patients with advanced tumors has been terminated prior to enrollment for undisclosed reasons.[73,205]

Concluding Remarks

As discussed in this Trial Watch, oncolytic virotherapy has been shown to mediate robust, therapeutically relevant antineoplastic effects in both preclinical and clinical scenarios. It is now evident that such a therapeutic activity is not a mere consequence of the cytopathic effect, but rather involves the induction of a tumor-specific immune response. Oncolytic viruses appear indeed to specifically kill transformed cells, hence releasing elevated amounts of tumor-associated antigens, and deliver to the immune system robust stimulatory signals, de facto acting as therapeutic anticancer vaccines.[64] The elevated immunogenic potential of oncolytic virotherapy presumably reflects the ability of viral components to act as microbe-associated molecular patterns, hence activating multiple pattern recognition receptors,[273-279] as well as to promote the emission of endogenous danger-associated molecular patterns.[69,208,241,280] In line with this notion, oncolytic viruses have already been shown to improve the efficacy of multiple immunotherapeutic interventions against cancer, including peptide- as well as DNA-based vaccines.[75,77,281] Conversely, a large panel of immunostimulatory agents including multiple TLR agonists[259,282] and ICD inducers[174,283-286] appears to boost the antineoplastic activity of oncolytic virotherapy. We believe that precisely scheduled combinatorial regimens that initially allow for the replication and dissemination of viral particles thought neoplastic lesions, and then boost the ability of oncolytic viruses to induce tumor-specific immune responses may mediate optimal antineoplastic effects. Future will tell which, if any, of the immunochemotherapeutic regimens that may be devised[287] is best suited for this purpose.

Disclosure of Potential Conflicts of Interest

P.E., J.M.L., and X.P. are full-time employees of Transgene; L.Z. is part of the Board of Directors of Transgene.

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