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Trial watch
Oncolytic viruses for cancer therapy

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Abbreviations: CD40L, CD40 ligand; CRC, colorectal carcinoma; GM-CSF, granulocyte monocyte colony-stimulating factor; HNC, head and neck cancer; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; IRES, internal ribosome entry site; MPS, mononuclear phagocytic system; TK, thymidine kinase; TLR, Toll-like receptor; TNFα, tumor necrosis factor α

Oncolytic virotherapy is emerging as a promising approach for the treatment of several neoplasms. The term "oncolytic viruses" is generally employed to indicate naturally occurring or genetically engineered attenuated viral particles that cause the demise of malignant cells while sparing their non-transformed counterparts. From a conceptual standpoint, oncolytic viruses differ from so-called "oncotropic viruses" in that only the former are able to kill cancer cells, even though both display a preferential tropism for malignant tissues. Of note, such a specificity can originate at several different steps of the viral cycle, including the entry of virions (transductional specificity) as well as their intracellular survival and replication (post-transcriptional and transcriptional specificity). During the past two decades, a large array of replication-competent and replication-incompetent oncolytic viruses has been developed and engineered to express gene products that would specifically promote the death of infected (cancer) cells. However, contrarily to long-standing beliefs, the antineoplastic activity of oncolytic viruses is not a mere consequence of the cytopathic effect, i.e., the lethal outcome of an intense, productive viral infection, but rather involves the elicitation of an antitumor immune response. In line with this notion, oncolytic viruses genetically modified to drive the local production of immunostimulatory cytokines exert more robust therapeutic effects than their non-engineered counterparts. Moreover, the efficacy of oncolytic virotherapy is significantly improved by some extent of initial immunosuppression (facilitating viral replication and spread) followed by the administration of immunostimulatory molecules (boosting antitumor immune responses). In this Trial Watch, we will discuss the results of recent clinical trials that have evaluated/are evaluating the safety and antineoplastic potential of oncolytic virotherapy.

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Introduction

Oncolytic viruses. Using viruses against cancer is not a particularly new concept, as it was initially put forward at the beginning of the 20th century.[1] Still, it was not until the 1950s that the antineoplastic potential of (naturally occurring) viruses begun to be tested in preclinical settings as well as in patients, most often with deceiving results in terms of either safety or efficacy.[2–5] Throughout the following three decades, the clinical interest in viruses as antineoplastic agents declined, even though a few studies reported encouraging safety data and even anecdotic cases of tumor regression.[5–7] The possibility of using viruses as highly specific tumor-targeting tools came back under the limelight only in the late 1990s, along with the establishment of modern genetic engineering technologies.[8–10] Since then, the clinical interest in oncolytic (and oncotropic) viruses has never declined again.

The term "oncolytic viruses" is generally employed to indicate non-pathogenic viral particles that specifically infect cancer cells, and hence cause their demise, while leaving unaffected non-malignant tissues.[11] From a strict conceptual standpoint, oncolytic viruses differ from their oncotropic counterparts in that while the latter only exhibit a specific tropism for malignant cells, the former (be they replication-competent or not) kill their hosts upon infection (via several mechanisms, see below).[9] Thus, oncotropic viruses (e.g., baculovirus, canarypox virus and canine parvovirus) efficiently enter malignant cells (and hence can be used as vectors for anticancer gene therapy) but are unable to

complete the viral cycle and hence fail to exert major cytotoxic effects.[12–14] Conversely, bona fide oncolytic viruses selectively infect cancer cells and kill them, either as a mere consequence of viral replication (cytopathic effect, mediated by replication-competent viruses only) or following the expression of endogenous or exogenous cytotoxic gene products (suicide gene therapy, mediated by both replication-competent and replication-incompetent virions).[9,11] A detailed description of all the viral species that have been tested for their oncolytic potential or genetically engineered in this sense—each of which is associated with specific advantages and drawbacks—exceed the scope of the present Trial Watch and can be found in refs. 9 and 11.

Tropism and selectivity of oncolytic viruses. The specific targeting of malignant cells is an absolute requirement for the clinical success of oncolytic virotherapy. In line with this notion, during the past two decades several distinct strategies have been pursued to improve the oncotropism of naturally occurring viruses (some of which exhibit an inherent preference for malignant cells), as well as to increase their oncoselective cytotoxic potential.[9,11] The strategies that have been investigated to ameliorate the selectivity of oncolytic viruses include (1) the genetic manipulation of viral envelopes or capsids to provide viruses with a strict specificity for cells bearing a tumor-associated surface marker (*transductional targeting*);[15,16] (2) the expression of one or more genes that are essential for the viral cycle under the control of promoters that functions only in transformed cells, including tissue-specific and hypoxia-responsive promoters (*transcriptional targeting*);[17–20] (3) the insertion of essential viral genes downstream of internal ribosome entry sites (IRESs) that cannot be used as translational origins in specific tissues (*translational targeting*);[21] (4) the use of so-called "destabilization domains," rendering essential viral products inherently unstable unless a stabilizing chemical is administered (in a tissue-restricted manner) (*post-translational targeting*);[22,23] (5) the deletion of one or a few virulence factors, resulting in attenuated viral strains that are able to replicate only in cells bearing cancer-associated alterations in specific signal transduction pathways, such as the hyperactivation of RAS or the inactivation of p53 (*oncogenetic targeting*);[24–28] and (6) the insertion of tissue-specific microRNA-binding elements in the 3'-UTR of essential viral genes, allowing tissues that express such microRNAs to escape productive infection (*microRNA targeting*).[29–32]

Alongside, great efforts have been dedicated at rendering oncolytic viruses increasingly more toxic for cancer cells, well beyond the cytopathic effect normally mediated by replication-competent particles. Strategies that have been undertaken in this sense include the integration into the viral genome of sequences coding for: (1) enzymes that can transform a non-toxic pro-drug into a lethal cytotoxic chemical, such as the thymidine kinase (TK) of herpes simplex viruses (HSVs), converting ganciclovir into deoxyguanosine triphosphate;[33,34] or cytosine deaminase, catalyzing the conversion of 5-fluorocytosine into 5-fluorouracil;[35–37] (2) proteins that (at least potentially) exert tumor-restricted cytotoxic functions, such as wild-type p53 or death receptor ligands (e.g., FASL);[38,39] and (3) short-hairpin RNAs targeting proteins that are specifically required for the survival of malignant cells, such as survivin.[40] A detailed description of these approaches can be found in refs. 11 and 41. Of note, some viral particles are capable of inducing the demise of malignant (but not normal) cells upon uncoating even in the absence of viral gene expression.[42] The precise molecular mechanisms underlying this phenomenon remain obscure, yet its efficacy appears to be linked to the number of virions actually entering target cells and being uncoated. Along similar lines, a long list of viral proteins exerts bona fide tumor-selective pro-apoptotic functions.[43] For example, both apoptin, a 15 kDa protein encoded by the chicken anemia virus, and the polypeptide coded by the adenoviral E4 open reading frame have been shown to preferentially trigger the apoptotic demise of malignant, as opposed to non-transformed, cells.[44–46]

Immunogenic activity of oncolytic viruses. Contrarily to long-standing beliefs, the antineoplastic potential of oncolytic virotherapy is not a mere consequence of the cytopathic effect, but rather involves (at least in a majority of settings) the induction of a tumor-specific immune response.[9,11,47,48] In line with this notion, oncolytic viruses genetically engineered to drive the production of various immunostimulatory factors have been shown to mediate more robust therapeutic effects than their non-engineered counterparts. Proof-of-principle evidence in support of this concept has been generated for oncolytic viruses that express membrane-bound co-stimulatory molecules, such as CD40 ligand (CD40L) and CD80,[49–52] as well as multiple distinct immunostimulatory cytokines encompassing interleukin (IL)-2,[53] IL-12,[54–56] IL-15[57–59] and granulocyte macrophage colony-stimulating factor (GM-CSF).[55,60–62] In addition, the clinical efficacy of oncolytic virotherapy appears to be robustly ameliorated by some degree of initial immunosuppression (facilitating viral replication and spread) followed by the provision of immunostimulatory factor (boosting antitumor immunity).[9,11]

Obstacles against efficient oncolytic virotherapy. The administration of oncolytic viruses as a standalone therapeutic intervention has been shown to rarely induce the complete, long-term regression of established tumors in vivo, owing to several reasons.[9,11] First, preclinical and clinical evidence indicates that oncolytic viruses often infect neoplastic lesions in a rather heterogeneous and incomplete fashion, irrespective of administration route and whether viruses are replication-competent or not.[63–67] A prominent role in this context is played by tumor size[68] as well as physicochemical barriers to infection, including the layers of connective tissue,[69,70] the elevated interstitial pressure,[71] the poorly permissive vasculature[72] and the large areas of necrosis/calcification[73,74] that generally characterize solid tumors. Second, oncolytic viruses often establish a "dynamic equilibrium" with tumors, that is, a state in which viral infection affects a spatially-restricted population of malignant cells, rather than the entire lesion, and is continuously counterbalanced by the proliferation of non-infected cancer cells.[75,76] Of note, while in immunodeficient settings such an equilibrium may be relatively stable (and hence de facto impede tumor growth),[77] at some stage the immune system is expected to eradicate the viral infection in immunocompetent animals, thereby tilting the tip of the balance in favor of malignant cells. Third, similar to what commonly observed in the course of chemo- and radiotherapy, malignant cells are prone to become resistant to oncolytic virotherapy over

time,[67,72,77–79] presumably linked to their intrinsic genomic instability and propensity to accumulate mutations.[80,81] Interestingly, cancer cells that had been rendered resistant to the parvovirus H1 in vitro were found to be cross-protected against the cytotoxic effects of tumor necrosis factor α (TNFα),[82–84] an observation with profound implications for the development of combination chemoimmunotherapeutic regimens involving oncolytic viruses. Fourth, a large fraction of the population has previously been exposed to the naturally occurring viruses that are commonly employed to generate therapeutic strains, de facto being fully protected against their infectious potential by high levels of neutralizing antibodies.[85,86] Along similar lines, some viral particles, including HSV1- and murine leukemia virus-derived viruses, are particularly prone to inactivation by the complement system.[87,88] Fifth, unless specific preventive measures are undertaken, oncolytic viruses administered i.v. are massively sequestered (most often upon opsonization) by the mononuclear phagocytic system (MPS) of the liver and spleen.[89,90] On one hand, this significantly restricts the amount of infectious particles that are capable of reaching the tumor site, de facto compromising transduction efficiency and hence therapeutic effects.[91] On the other hand, the accumulation of viral particles into the liver and the spleen may trigger the release of pro-inflammatory cytokines, potentially driving serious, dose-limiting toxicities.[92,93] Sixth, although great progresses have already been made in this sense, the use of viruses remains intrinsically associated with some threats, in particular when cancer patients—who often exhibit some degree of immunosuppression—are concerned.[94–96] In this respect, one problematic issue relates to the fact that all viruses are potentially immunogenic and hence can cause—at the therapeutic doses of 10^{12} particles—unwarranted side effects including transient hepatic inflammation (see above) and low-grade disseminated intravascular coagulation.[97,98] In addition, great concerns have been raised by the case of three children who developed a leukemic syndrome following the reinfusion of retrovirally transduced T cells for the treatment of a severe monogenic immunodeficiency, most likely owing to the integration of the viral vector in the proximity of the *LMO2* oncogene.[99,100]

Taken together, these observations highlight an urgent need for the development of ever more refined oncolytic viruses and the design of combinatorial strategies by which the obstacles described above would be—at least in part—circumvented. Several approaches have already been conceived to ameliorate the therapeutic potential of oncolytic virotherapy, including (among several others) (1) the use of coating polymers to shield viral particles from the neutralizing effects of circulating antibodies and the complement system as well as from sequestration by the MPS;[101–103] (2) the pre-administration of molecules that selectively increase the permeability of tumor vessels (e.g., IL-2, TNFα, histamine, bradykinin analogs) or aggressive chemotherapy, to reduce interstitial pressure;[104,105] (3) the intratumoral administration of antifibrotic agents, such as the FDA-approved antihypertensive drug losartan, or enzymes that degrade components of the extracellular matrix, such as hyaluronidase;[106,107] (4) the development of oncolytic viruses that—in addition to cytotoxic factors—express extracellular matrix-degrading enzymes like hyaluronidase;[108] and (5) the careful modulation of the immune system (for instance with cyclophosphamide, which at high doses exerts potent immunosuppressive effects)[109–111] to avoid premature antiviral responses that would compromise viral spread (and hence therapeutic efficacy).[112]

The safety and preliminary antineoplastic effects of several naturally occurring and genetically modified viruses have been/are being tested in multiple distinct clinical trials (see below). As it stands, however, no oncolytic viruses are licensed by the U.S. FDA for use in cancer patients (source www.fda.gov). Conversely, gendicine, an oncotropic, recombinant adenovirus engineered to express wild-type p53, has been approved for the treatment of subjects affected by head and neck squamous cell carcinoma in China as early as in 2003.[113,114] Along the lines of our monthly Trial Watch series,[115–128] here we will briefly review the progress of recent clinical trials that have investigated/are investigating the antineoplastic potential of oncolytic viruses.

Clinical Development of Oncolytic Viruses

Literature. As mentioned above, the possibility of using viruses to specifically kill neoplastic cells begun to attract the attention of clinicians, and hence to be tested in patients, in the 1950s.[1] In this context, hundreds of patients bearing a wide array of distinct neoplasms received highly impure viral preparations (including infected body fluids and so-called "oncolysates," i.e., autologous malignant cells or established cancer cell lines killed by viruses ex vivo), via almost every conceivable route of administration.[3,11,129,130] Most often, these attempts failed to drive any therapeutic response as viruses were rapidly inactivated by the immune system. Nevertheless, sporadic cases of tumor regression were reported, in particular among immunodeficient patients, who however were at increased risk of death owing to the spread of the viral infection to healthy tissues.[3,11,129,130] Perhaps the most impressive results of this period were obtained by Asada and colleagues, who reported 37 tumor regressions among 90 terminal cancer patients treated with a non-attenuated strain of the mumps virus.[131]

In 1991, Martuza et al. were the first to demonstrate that a genetically manipulated variant of HSV lacking the TK-coding gene (and hence displaying attenuated virulence) could be successfully employed to treat glioblastoma in mice.[132] This report de facto paved the way to modern virotherapy and drove an intense wave of preclinical and clinical investigation that has not yet come to an end. Since then indeed, dozens—if not hundreds—of distinct oncolytic and oncotropic viruses have been developed and tested in preclinical models. An exhaustive discussion of the preclinical results obtained during the last two decades with oncolytic viruses can be found in refs. 9, 11, 133 and 134. Alongside, several oncolytic viruses entered the clinics and their safety and preliminary antineoplastic potential begun to be investigated in patients affected by a wide variety of (mostly solid) tumors.[11,135,136]

Adenoviruses and HSVs represent by far the oncolytic viruses most extensively investigated (at both the preclinical and clinical level) and developed so far.[137–139] Indeed, attenuated

adenoviral strains, most often lacking the genes coding for E3 or the anti-apoptotic protein E1B55K,[43] have already been used in patients affected by glioma,[140] sarcoma,[141] head and neck cancer (HNC),[97,142–145] pancreatic cancer,[146,147] colorectal carcinoma (CRC),[147–149] prostate carcinoma,[150–152] ovarian cancer,[153,154] bladder carcinoma[61] and multiple solid tumors.[155,156] Along similar lines, the safety and therapeutic potential of attenuated HSVs, near to invariably lacking the gene coding for the main neurovirulence factor γ34.5,[157] have been tested in subjects with glioma,[158–162] breast carcinoma,[163] HNC,[164–166] melanoma,[167–170] pancreatic carcinoma,[171] CRC hepatic metastases[172] and various solid malignancies.[173] Most of the remaining clinical trials that have been completed so far were designed to evaluated the safety and the oncolytic profile of stains of Newcastle disease virus (in subjects affected by glioma and other solid tumors),[174–176] parvovirus (in glioblastoma multiforme patients),[177] reovirus (in individuals bearing glioma, melanoma and other solid tumors)[178–181] and vaccinia virus (in hepatocellular carcinoma and melanoma patients).[62,182–184] The majority of these studies were Phase I/II trials, most often reporting reassuring safety data and sporadic antineoplastic activity, even when oncolytic viruses were employed as standalone therapeutic interventions. In this setting, the most encouraging results have surely been recorded with talimogene laherparepvec (developed by Amgen, also known as OncoVex), an oncolytic γ34.5-deficient variant of HSV genetically manipulated to drive the expression of GM-CSF by infected cells.[185] As a single agent administered i.t., talimogene laherparepvec induced the complete regression of both injected and distant lesions in 8 out of 50 metastatic melanoma patients.[170] A similar efficacy has been observed with JX954, an oncolytic vaccinia virus engineered to express GM-CSF that was shown to induce objective responses in a consistent percentage of hepatocellular carcinoma patients.[62,184] In addition, multiple studies have shown that combining oncolytic viruses with conventional radio- or chemotherapeutic is generally safe and improves (to some extent) the rates of clinical responses.[141,143,145,146,149–152,166,174,179] In summary, accumulating clinical data strongly support the development of oncolytic virotherapy.

Recent, ongoing clinical trials. Nowadays (April 2013), official sources list no less than 52 recent (started after January 1, 2008), ongoing (not withdrawn, terminated or completed at the day of submission), clinical trials assessing the safety and antineoplastic potential of oncolytic viruses in cancer patients (**Table 1**). One third (17) of these studies are investigating the activity of a wild-type reovirus (serotype 3 Dearing, developed by Oncolytics Biotech under the name of Reolysin®)[186] administered i.v. or (rarely) i.p., often in combination with conventional therapeutic regimens, to patients affected by multiple myeloma (NCT01533194), HNC (NCT00753038; NCT01166542), breast carcinoma (NCT01656538), melanoma (NCT00651157; NCT00984464), lung cancer (NCT00861627; NCT00998192; NCT01708993), pancreatic carcinoma (NCT00998322; NCT01280058), CRC (NCT01274624; NCT01622543), prostate cancer (NCT01619813), reproductive tract neoplasms (NCT00602277; NCT01199263) or pediatric solid tumors (NCT01240538). Eight clinical trials are assessing the safety and antineoplastic profile of JX594 (developed by Transgene as Pexa-Vec), administered i.v. most often as a standalone therapeutic intervention, in subjects bearing hepatocellular carcinoma (NCT01171651; NCT01387555; NCT01636284), CRC (NCT01380600, NCT01394939; NCT01469611) or chemorefractory solid tumors (NCT00625456; NCT01169584). The highly attenuated oncolytic vaccinia virus GL-ONC1 (developed by Genelux, also known as GLV-1h68)[187] is being tested in combination with chemoradiotherapy for the treatment of HNC patients (NCT01584284), as a standalone therapeutic intervention administered intrapleurally in lung cancer patients (NCT01766739), and upon intravenous or intraperitoneal delivery in subjects affected by advanced solid tumors or peritoneal carcinomatosis, respectively (NCT00794131; NCT01443260).

In addition, clinical trials are currently ongoing for investigating the safety and antineoplastic activity of: (1) talimogene laherparepvec,[62] administered i.t.—as a standalone intervention or combined with systemic ipilimumab[188,189]—to melanoma patients (NCT00769704; NCT01368276; NCT01740297); (2) naturally occurring coxsackievirus A21 (developed by Viralytics as Cavatak™),[190] administered i.t. as a single agent to melanoma patients (NCT01227551; NCT01636882); (3) CGTG-102 (an oncolytic adenovirus engineered to drive the local expression of GM-GSF, developed by Oncos),[191] administered i.t. or i.v.—alone or in combination with metronomic cyclophosphamide—to patients affected by advanced solid tumors (NCT01437280; NCT01598129); (4) DNX-2401 (a genetically manipulated replication-competent adenovirus developed by DNAtrix),[192,193] given i.t. as a standalone agent to glioblastoma and glioma patients (NCT00805376; NCT01582516); (5) HSV1716 (a γ34.5-deficient variant of HSV developed by Virttu as Seprehvir®),[169] administered intrapleurally or intratumorally to individuals affected by mesothelioma or solid tumors (NCT01721018; NCT00931931); (6) Toca511® (a retrovirus engineered to express cytosine deaminase, developed by Tocagen), given alone or in combination with 5-fluorocytosine to subjects affected by astrocytoma, glioblastoma, oligoastrocytoma and oligodendrocytoma (NCT01156584; NCT01470794); (7) the Seneca Valley virus (a replication-competent oncolytic picornavirus also known as NTX-010),[194] administered i.v. as a single agent or combined with metronomic cyclophosphamide to patients with lung cancer or neuroendocrine tumors, respectively (NCT01017601; NCT01048892); (8) PVSRIPO (an non-pathogenic recombinant poliovirus),[195] given i.t. as a standalone intervention to glioblastoma patients (NCT01491893); (9) the attenuated measles virus commonly used as a prophylactic vaccine,[75,196] given intrapleurally as a single therapeutic agent to mesothelioma patients (NCT01503177); (10) CG0070 (a conditionally replicating GM-CSF-armed oncolytic adenovirus),[61,197] instilled intravesically as a single agent to subjects with bladder carcinoma (NCT01438112); (11) HF10 (a spontaneous attenuated variant of HSV1),[198,199] administered i.t. as a standalone intervention to individuals affected by refractory HNC or other solid tumors (NCT01017185); (12) an attenuated lentogenic isolate of the Newcastle disease virus (known as NDV-HUJ),[174,200] given i.v. as a single agent to glioblastoma, neuroblastoma and sarcoma

Table 1. Recent clinical trials evaluating oncolytic virotherapy in cancer patients*

Virus	Indication(s)	Phase	Status	Route	Co-therapy	Ref.
CG0070	Bladder carcinoma	II/III	Not yet recruiting	Intravesical	As single agent	NCT01438112
CGTG-102	Solid tumors	I	Recruiting	i.t. and i.v.	Combined with cyclophosphamide	NCT01598129
			Not yet recruiting	i.t.	As single agent	NCT01437280
Coxsackievirus A21	Melanoma	II	Recruiting	i.t.	As single agent	NCT01227551 NCT01636882
DNX-2401	GBM	I/II	Recruiting	CED	As single agent	NCT01582516
	Glioma	I	Recruiting	i.t.	As single agent	NCT00805376
GL-ONC1	HNC	I	Recruiting	i.v.	Combined with cisplatin and RT	NCT01584284
	Lung cancer	I	Recruiting	Intrapleural	As single agent	NCT01766739
	Peritoneal carcinomatosis	I/II	Recruiting	i.p.	As single agent	NCT01443260
	Solid tumors	I	Recruiting	i.v.	As single agent	NCT00794131
HF10	HNC Solid tumors	I	Recruiting	i.t.	As single agent	NCT01017185
HSV1716	Mesothelioma	I/II	Recruiting	Intrapleural	As single agent	NCT01721018
	Non-CNS solid tumors	I	Recruiting	i.t.	As single agent	NCT00931931
JX594	HCC	II	Recruiting	i.v.	As single agent	NCT01636284
				n.a.	Combined with BSC	NCT01387555
			Active not recruiting	i.v. and i.t.	Followed by sorafenib	NCT01171651
	CRC	I	Active not recruiting	i.v.	As single agent	NCT01380600
			Recruiting	i.v.	As single agent	NCT01469611
		I/II	Recruiting	i.v. and i.t.	Combined with irinotecan	NCT01394939
	Solid tumors	I	Active not recruiting	i.t.	As single agent	NCT01169584
				i.v.	As single agent	NCT00625456
Measles virus	Mesothelioma	I	Recruiting	Intrapleural	As single agent	NCT01503177
NDV-HUJ	GBM NB Sarcoma	I/II	Not yet recruiting	i.v.	As single agent	NCT01174537
NTX-010	Lung cancer	II	Recruiting	i.v.	As single agent	NCT01017601
	Neuroendocrine tumors	I	Recruiting	i.v.	Combined with cyclophosphamide	NCT01048892
ParvOryx	GBM	I/II	Recruiting	i.t. or i.v.	As single agent	NCT01301430
PVSRIPO	GBM	I	Recruiting	i.t.	As single agent	NCT01491893

Abbreviations: BSC, best supportive care; CED, convection enhanced delivery; CNS, central nervous system; CRC, colorectal cancer; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HSV, herpes simplex virus; i.p., intra peritoneum; i.t., intra tumorem; i.v., intra venam; n.a., not available; NB, neuroblastoma; NDV, Newcastle disease virus; RT, radiotherapy. *Started after January 1, 2008, and not withdrawn, terminated or completed on the day of submission.

patients (NCT01174537); (13) parvovirus H1 (a naturally occurring parvoviral variant developed by Oryx Verwaltungs as ParvOryx®),[177,201] administered i.v. or i.t. as a standalone therapeutic intervention to glioblastoma patients (NCT01301430); and (14) a variant of the vesicular stomatitis virus engineered to drive the expression of interferon β (IFNβ),[202,203] given i.t. as a single agent to subjects affected by hepatocellular carcinoma (NCT01628640). The large majority of these studies are Phase I/II clinical trials, with the notable exceptions of NCT01438112 (assessing the antineoplastic activity of CG0070 in bladder carcinoma patients), NCT01166542 (evaluating the efficacy of Reolysin® in HNC patients) as well as NCT00769704 and

Table 1 (Continued). Recent clinical trials evaluating oncolytic virotherapy in cancer patients*

Virus	Indication(s)	Phase	Status	Route	Co-therapy	Ref.
Reolysin®	Breast carcinoma	II	Recruiting	n.a.	Combined with PTX	NCT01656538
	CRC	I	Active not recruiting	i.v.	Combined with FOLFIRI regimen	NCT01274624
		II	Recruiting	n.a.	Combined with BVC and FOLFOX regimen	NCT01622543
	HNC	II	Active not recruiting	i.v.	Combined with CBP and PTX	NCT00753038
		III	Active not recruiting	i.v.	Combined with CBP and PTX	NCT01166542
	Lung cancer	II	Recruiting	i.v.	Combined with CBP and PTX	NCT00861627
						NCT00998192
					Combined with DCX or pemetrexed	NCT01708993
	Melanoma	II	Active not recruiting	i.v.	As single agent	NCT00651157
			Recruiting	i.v.	Combined with CBP and PTX	NCT00984464
	Multiple myeloma	I	Recruiting	i.v.	As single agent	NCT01533194
	Pancreatic cancer	II	Recruiting	i.v.	Combined with CBP and PTX	NCT01280058
			Active not recruiting	i.v.	Combined with gemcitabine	NCT00998322
	Pediatric solid tumors	I	Recruiting	i.v.	Combined with cyclophosphamide	NCT01240538
	Prostate cancer	II	Recruiting	n.a.	Combined with DCX and prednisone	NCT01619813
	Reproductive tract tumors	I	Recruiting	i.v. + i.p.	As single agent	NCT00602277
		II	Recruiting	i.v.	Combined with PTX	NCT01199263
Talimogene laherparepvec	Melanoma	I/II	Recruiting	i.t.	Combined with ipilimumab	NCT01740297
		III	Active not recruiting	i.t.	As single agent	NCT00769704
			Enrolling by invitation	i.t.	As single agent	NCT01368276
Toca 511	Astrocytoma GBM Oligoastrocytoma Oligodendroglioma	I	Recruiting	Resection cavity	As single agent	NCT01470794
		I/II	Recruiting	i.t.	Combined with 5-FC	NCT01156584
VSV-IFN-β	HCC	I	Recruiting	i.t.	As single agent	NCT01628640

Abbreviations: 5-FC, 5-fluorocytosine; BVC, bevacizumab; CBP, carboplatin; CRC, colorectal cancer; DCX, docetaxel; FOLFIRI, folinic acid, 5-fluorouracil, irinotecan; FOLFOX, folinic acid, 5-flurouracil, oxaliplatin; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; HNC, head and neck cancer; IFN, interferon; i.p., intra peritoneum; i.t., intra tumorem; i.v., intra venam; n.a., not available; PTX, paclitaxel; VSV, vesicular stomatitis virus. *Started after January 1, 2008, and not withdrawn, terminated or completed on the day of submission.

NCT01368276 (both investigating the antineoplastic potential of talimogene laherparepvec in melanoma patients). Of note, Amgen representatives have very recently declared that NCT00769704 met its primary endpoint of durable response rate, defined as the rate of complete or partial response lasting continuously for at least six months (source www.amgen.com/media/media_pr_detail.jsp?releaseID=1798143). Thus, talimogene laherparepvec appears relatively close to being approved by FDA for use in melanoma patients.

Concluding Remarks

During the last two decades, great efforts have been dedicated at the development of viruses that would selectively and efficiently kill malignant cells while sparing their normal counterparts. Accumulating clinical evidence indicates that oncolytic virotherapy is generally well tolerated and, at least under specific circumstances, exerts durable antineoplastic effects. Importantly, although some degree of immunosuppression initially favors

transduction and viral spread, the antineoplastic potential of oncolytic viruses in fine appears to rely on the elicitation of tumor-specific immune responses.[9,11,47,48] This notion is best exemplified by the fact that oncolytic viruses engineered to drive the expression of immunostimulatory factors, such as GM-CSF and IFNβ, are usually more efficient at promoting tumor regression than their naturally occurring counterparts.[52,173,202,203]

As oncolytic virotherapy may soon move from the bench to the beside, future studies will have to elucidate to which extent, if any, the clinical efficacy of oncolytic viruses can be improved by combining them with appropriate immunomodulatory interventions. At least theoretically, both (pre-conditioning) immunosuppressive regimens and robust immunostimulatory interventions such as the local or systemic administration of recombinant cytokines,[118,204] Toll-like receptor (TLR) agonists,[119,120,205,206] or immune checkpoint-blocking antibodies,[115,124,188,207] may significantly boost the therapeutic effects of oncolytic virotherapy, yet optimal schedules and administration routes to achieve this objective will have to be carefully defined. Rommelfanger and colleagues have indeed demonstrated that the intratumoral administration of lipopolysaccharide (a natural TLR2/TLR4 agonist) significantly enhances the antineoplastic potential of an oncolytic vesicular stomatitis virus administered i.t. to melanoma-bearing mice, yet drives a lethal inflammatory syndrome in the majority of animals when viral particles are given i.v.[208] As several distinct oncolytic viruses delivered i.t. have been shown to induce clinical responses even in distant, non-injected lesions,[62,168,170] the local—as opposed to systemic—route of administration stands out as a safe and efficient alternative in this setting. Of note, encouraging results have also been obtained by combining oncolytic viruses with selected chemotherapeutics, such as the microtubular inhibitor paclitaxel.[209] It is tempting to speculate, yet remains to be formally demonstrated, that such an effect may originate from the capacity of some combinatorial antineoplastic regimens to elicit immunogenic cell death.[210,211] Irrespective of this unresolved issue, the rational combination of oncolytic virotherapy with immunotherapy and chemotherapy is expected to drive the development of ever more efficient clinical protocols for the treatment of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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