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REVIEW

Trial Watch—Oncolytic viruses and cancer therapy

Jonathan Pol[a,b,c,d,e,*], Aitziber Buqué[a,b,c,d,e,*], Fernando Aranda[f], Norma Bloy[a,b,c,d,e], Isabelle Cremer[a,b,c,g] Alexander Eggermont[e], Philippe Erbs[h], Jitka Fucikova[i,j], Jérôme Galon[a,b,c,k], Jean-Marc Limacher[h], Xavier Preville[h] Catherine Sautès-Fridman[a,b,c,g], Radek Spisek[i,j], Laurence Zitvogel[e,l], Guido Kroemer[a,b,c,d,m,n,o,**], and Lorenzo Galluzzi[a,b,c,d,e,**]

[a]INSERM, U1138, Paris, France; [b]Université Paris Descartes/Paris V, Sorbonne Paris Cité, Paris, France; [c]Université Pierre et Marie Curie/Paris VI, Paris, France; [d]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Center de Recherche des Cordeliers, Paris, France; [e]Gustave Roussy Cancer Campus, Villejuif, France; [f]Group of Immune receptors of the Innate and Adaptive System, Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [g]Equipe 13, Center de Recherche des Cordeliers, Paris, France; [h]Transgene S.A., Illkirch-Graffenstaden, France; [i]Sotio, Prague, Czech Republic; [j]Dept. of Immunology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, Prague, Czech Republic; [k]Laboratory of Integrative Cancer Immunology, Centre de Recherche des Cordeliers, Paris, France; [l]INSERM, U1015, CICBT507, Villejuif, France; [m]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [n]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; [o]Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Oncolytic virotherapy relies on the administration of non-pathogenic viral strains that selectively infect and kill malignant cells while favoring the elicitation of a therapeutically relevant tumor-targeting immune response. During the past few years, great efforts have been dedicated to the development of oncolytic viruses with improved specificity and potency. Such an intense wave of investigation has culminated this year in the regulatory approval by the US Food and Drug Administration (FDA) of a genetically engineered oncolytic viral strain for use in melanoma patients. Here, we summarize recent preclinical and clinical advances in oncolytic virotherapy.

Abbreviations: CFDA, China Food and Drug Administration; CI, confidence interval; CRC, colorectal carcinoma; DRR, durable response rate; FDA, Food and Drug Administration; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HSV-1, herpes simplex virus 1; IFN, interferon; MAGEA3, melanoma antigen family A3; ORR, overall response rate; OS, overall survival; TAA, tumor-associated antigen.

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Introduction

The term "oncolytic virus" generally refers to a non-pathogenic viral strain that selectively kills malignant cells, while sparing their non-malignant counterparts.[1-6] Such an oncotoxic activity (which can be natural or the result of precise genetic manipulations) generally reflect an elevated degree of oncotropism (*i.e.*, the ability of some viruses to preferentially enter neoplastic cells over normal cells of the same type),[7-9] and/or the pronounced susceptibility of some cancer cells to viral replication as such,[2,10-12] or to the expression of (endogenous or exogenous) cytotoxic gene products.[1,2,13] Importantly, preclinical and clinical observations accruing over the past decade indicate that the therapeutic activity of oncolytic viruses cannot be ascribed solely to oncolysis, but rather involves the activation of an adaptive, tumor-targeting immune response.[14-19] Conversely, antiviral immunity (be it innate or adaptive) often constitutes an obstacle against the efficacious implementation of oncolytic virotherapy in cancer patients, mostly because it sequesters or neutralizes viral particles before they reach malignant lesions.[20-30] Thus, considerable efforts have recently been dedicated at the development of oncolytic viral particles with improved features, including: (1) a refined oncotropism, based on the targeting of tumor-associated antigens (TAAs) exposed on the surface of malignant cells;[31-35] (2) an optimized selectivity of replication, based on various systems that allow for the expression of essential viral proteins only in cells of a predetermined tissue,[36-45] transformed cells,[46-57] cells exhibiting specific molecular defects,[58-65] or cells exposed to precise microenvironmental conditions (naturally or artificially);[66-68] (3) an exacerbated cytotoxicity, based on the expression of potentially lethal enzymes[69-76] or other tumor-targeting molecules;[13,46,77-84] (4) an enhanced capacity to boost tumor-targeting immune responses, based on the expression of TAAs (in the context of so-called "oncolytic vaccination"),[85-90] co-stimulatory molecules,[91-97] immunostimulatory cytokines,[16,98-126] or chemokines;[127,128] and (5) a limited standalone immunogenicity, based on coating/encapsulation strategies or changes of the viral surface that reduce the recognition of circulating viruses by the immune system and reticular phagocytes.[129-131]

CONTACT Lorenzo Galluzzi deadoc@vodafone.it ; Guido Kroemer kroemer@orange.fr
*Equally contributed to this work.
**Share senior co-authorship.

Additional issues may limit the clinical efficacy of oncolytic virotherapy, including common characteristics of solid neoplasms (*e.g.*, abnormal vascularization, high hydrostatic pressure), and several strategies are being conceived to circumvent these obstacles.[1,2,30] For instances, several populations of tumor-infiltrating cells have been engineered as vehicles to deliver viral particles within neoplastic lesions.[132-138] Oncolytic virotherapy has also been questioned owing to threats that are intrinsically associated with the use of replicating viral particles, especially in weak and sometimes immunosuppressed individuals like cancer patients.[139-145] Nevertheless, multiple oncolytic viruses have been associated with remarkable rates of objective and durable responses in clinical studies, especially when they were used in combination with other chemo- or immunotherapeutic agents.[146-152]

Although H101 (a recombinant adenovirus commercialized under the name of Oncorine®) had been licensed by the China Food and Drug Administration (CFDA) for use in combination with chemotherapy for the treatment of refractory head and neck cancer (HNC) as early as in November 2005,[153-155] no oncolytic virus was licensed by the US FDA and the European Medicine Agency (EMA) for use humans in the past decade (sources http://www.fda.gov/Drugs/default.htm and http://www.ema.europa.eu). Only earlier this year (on 2015, April 29th), the US FDA emitted the first formal recommendation supporting the approval of talimogene laherparepvec (also known as T-VEC or OncoVEX^{GM-CSF}), a granulocyte macrophage colony-stimulating factor (GM-CSF)-expressing variant of herpes simplex virus 1 (HSV-1), for use in melanoma patients.[156-160] A few days ago (on 2015, October 27th), the US FDA eventually granted Amgen, Inc. the approval to commercialize talimogene laherparepvec under the name of Imlygic® for the treatment of melanoma lesions in the skin and lymph nodes (source http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm469571.htm). Imlygic® represents therefore a first-of-its-kind in the US, and may soon enter the clinic in Europe as well, at least according to a recent statement from the EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002421.jsp&mid=WC0b01ac058004d5c1).

In this Trial Watch, we summarize recent preclinical and clinical progress in the development of oncolytic viruses.

Update on the development of oncolytic virotherapy

Completed clinical studies

Since the submission of our latest Trial Watch dealing with oncolytic virotherapy (March 2014), preliminary or definitive results from more than 30 clinical trials testing this immunotherapeutic paradigm in cancer patients have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed) or presented at the latest meetings of the American Society of Clinical Oncology (ASCO) or the American Association for Cancer Research (AACR) (sources http://meetinglibrary.asco.org/abstracts and http://cancerres.aacrjournals.org/content/75/15_Supplement.toc, respectively).

Intralesional Imlygic® has been compared to subcutaneous GM-CSF in a large, randomized clinical trial involving 436 individuals with injectable but not surgically resectable melanoma (NCT00769704, OPTiM).[161,162] Moreover, the clinical profile of Imlygic® combined with the FDA-approved cytotoxic T lymphocyte-associated 4 (CTLA4)-targeting monoclonal antibody ipilimumab[163,164] has been assessed in 18 patients with unresectable Stage IIIB-IV melanoma (NCT01740297).[165] Reolysin® (a proprietary variant of reovirus serotype 3 – Dearing strain)[166] has been tested either as standalone immunotherapeutic agent in 12 myeloma patients and in 15 subjects with recurrent malignant gliomas,[167,168] or combined with low-dose cyclophosphamide[169,170] in 29 children with relapsed or refractory extra-cranial solid tumors (NCT01240538),[171] and in 36 individuals affected by advanced neoplasms.[172] The safety and efficacy of Cavatak™ (a proprietary variant of Coxsackievirus A21)[173] administered intratumorally or intravenously as standalone immunotherapeutic agent have been evaluated in 57 subjects with unresectable Stage IIIC-IV melanoma (NCT01227551),[174,175] and in 30 individuals with other advanced solid malignancies (NCT02043665).[176] The clinical profile of ONCOS-102 (a GM-CSF-expressing human serotype 5 adenovirus optimized to replicate in malignant cells, also known as CGTG-102 or Ad5/3-D24-GMCSF)[177,178] has been investigated in nine subjects with melanoma, who received ONCOS-102 in combination with standard-of-care chemotherapy,[179] in two cohorts of 15 sarcoma patients and 90 subjects bearing GM-CSF-sensitive tumors, who were treated with ONCOS-102 as standalone immunotherapeutic intervention,[177,180] in 13 patients with solid tumors refractory to standard therapies, who received ONCOS-102 in combination with low-dose cyclophosphamide,[181] as well as in 12 patients with solid tumors, receiving ONCOS-102 *i.t.* and *i.v.* in combination with low-dose cyclophosphamide (NCT01598129).[182] Intravenous or intratumoral JX-594 (a GM-CSF-expressing oncolytic poxvirus engineered to replicate in cells with specific oncogenic defects, also known as pexastimogene devacirepvec, Pexavec)[183] has been tested as single therapeutic agent in 15 subjects with colorectal carcinoma (CRC) (NCT01469611)[184] as well as in 14 pediatric patients with chemorefractory solid malignancies (NCT01169584).[185] The safety and efficacy of GL-ONC1 (a genetically modified vaccinia virus also known as GLV-1h68)[186] have been evaluated in 14 individuals with malignant pleural effusion, who received intrapleural GL-ONC1 as standalone immunotherapeutic intervention (NCT01766739),[187] as well as in 19 subjects affected by HNC, who were treated with GL-ONC1 *i.v.* in combination with cisplatin-based chemoradiation[188,189] (NCT01584284).[190] Moreover, (1) G207 (a conditionally replicating HSV-1 strain)[191] has been tested in combination with radiation therapy in nine patients with progressive, recurrent glioblastoma (NCT00157703);[192] (2) the therapeutic profile of NTX-010 (a native, replication-competent variant of the Seneca Valley picornavirus, also known as SVV-001)[193] in combination with metronomic cyclophosphamide has been assessed in 22 children with neuroendocrine tumors (NCT01048892);[194] (3) Ad5-yCD/mutTKSR39rep-ADP (a replication competent adenoviral strain endowed with superior oncolytic potential)[195] has been tested in combination with intensity modulated radiation therapy[196,197] in 44 prostate carcinoma patients;[198] (4) the clinical activity of HF10 (a replicative HSV-1 strain)[199] has been investigated in 17 subjects

with advanced malignancies, who received HF10 intratumorally as standalone immunotherapeutic intervention;[200] (5) MV-NIS (a strain of oncolytic measles virus encoding the human thyroidal sodium iodide symporter),[201,202] has been tested as standalone immunotherapeutic intervention in two myeloma patients;[203] (6) the safety and efficacy of OBP-301 (an oncolytic adenovirus engineered to selectively target telomerase reverse transcriptase (TERT)-overexpressing cells, also known as telomelysin)[204] has been assessed in six elderly subjects with esophageal carcinoma, who received OBP-301 *i.t.* in combination with radiation therapy (UMIN000010158);[205] and (7) the clinical profile of an oncolytic variant Western Reserve vaccinia virus artificially endowed with improved specificity[206] has been evaluated in 16 individuals with advanced solid malignancies, who were treated with oncolytic virothapy *i.t.* as standalone immunotherapeutic intervention.[207]

Taken together, these studies demonstrate that the administration of oncolytic viruses to cancer patients is generally associated with a very low incidence of severe (Grade 3 or higher) side effects, and with (at least some degree of) clinical activity. Perhaps, the most remarkable findings in this respect have been obtained by Andtbacka and colleagues (University of Utah, Salt Lake City, UT, US) in the context of the OPTiM trial,[161] demonstrating that intralesional Imlygic® mediates superior clinical activity (in the absence of remarkable toxicity) in patients with injectable but non-resectable Stage IIIB-IV melanoma as compared to subcutaneous GM-CSF. Indeed, Imlygic®-based immunotherapy was associated with a durable response rate (DRR) of 16.3% (95% CI: 12.1–20.5%), an overall response rate (ORR) of 26.4% (95% CI: 21.4–31.5%) and median overall survival (OS) of 23.3 mo (95% CI: 19.5–29.6 mo), whereas subcutaneous GM-CSF was associated with a DRR of 2.1% (95% CI: 0–4.5%), an ORR of 5.7% (95% CI: 1.9–9.5%), and median OS of 18.9 mo (95% CI: 16.0–23.7 mo).[161] The findings of the OPTiM study constituted the clinical ground for the regulatory approval of Imlygic® by the US FDA (see above).

Preclinical and translational advances

A large number of preclinical and translational studies dealing with oncolytic virotherapy have been published during the last 21 mo (source http://www.ncbi.nlm.nih.gov/pubmed). Among this abundant literature, we found of especial interest the works of (1) Arulanandam and colleagues (Ottawa Hospital Research Institute, Ottawa, Canada), who discovered that a transcriptional modulator operating downstream of vascular endothelial growth factor receptors (VEGFRs)[208,209] suppresses Type I interferon (IFN) responses,[210] hence sensitizing the tumor vasculature to infection by oncolytic viruses,[211] and found that microtubule-destabilizing agents commonly employed in the clinic (e.g., paclitaxel)[212,213] synergize with oncolytic virotherapy by disrupting the translation of Type I IFN-coding mRNAs and by exacerbating the demise of cancer cells provoked by the cytopathic effect;[214] (2) Nishio and collaborators (Baylor College of Medicine, Houston, TX, US), who reported that an oncolytic adenovirus genetically engineered to express interleukin-15 (IL-15) and chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) improved the therapeutic potential of adoptively transferred T cells expressing a chimeric antigen receptor (CAR)[215,216] specific for ganglioside GD2;[217] (3) Yoo et al. (The Ohio State University, Columbus, OS, US), who identified in the unfolded protein response caused by the immunogenic proteasomal inhibitor bortezomib[218-222] a means to boost the replication (and hence the efficacy) of an oncolytic HSV-1 strain;[223] (4) Parrish and co-authors (St James's University Hospital, Leeds, UK), who discovered that an oncolytic reovirus enhances the capacity of the FDA-approved CD20-targeting monoclonal antibody rituximab[224,225] to stimulate antibody-dependent cellular cytotoxicity;[226] (5) Komatsu and colleagues (Memorial University of Newfoundland, St John's, Canada), who found that malignant cells expressing oncogenic variants of Harvey rat sarcoma viral oncogene homolog (HRAS)[227] may be particularly sensitive to oncolytic virotherapy because of low levels of interferon regulatory factor 1 (IRF1), resulting in blunted Type I IFN responses;[228] (6) Ilkow and collaborators (Ottawa Hospital Research Institute, Ottawa, Canada) who, characterized a transforming growth factor β1 (TGFβ1)- and fibroblast growth factor 2 (FGF2)-dependent cross-talk between cancer-associated fibroblasts and malignant cells that limits the ability of the latter to mount efficient Type I IFN responses, hence sensitizing them to oncolytic virotherapy;[229] (7) Gayral et al. (Université Toulouse III/Paul Sabatier, Toulouse, France), who engineered a HSV-1 strain for conditional replication in tissues overexpressing v-myb avian myeloblastosis viral oncogene homolog-like 2 (MYBL2), and demonstrated that this oncolytic virus can eradicate experimental pancreatic adenocarcinoma in mice when combined with standard-of-care chemotherapeutics;[230] (8) Gil and colleagues (Roswell Park Cancer Institute, Buffalo, NY, US), who found that an oncolytic vaccinia virus strain engineered to express a chemokine (C-X-C motif) receptor 4 (CXCR4) antagonist[231] exerts superior therapeutic effects against ovarian cancer as it limits tumor infiltration by immunosuppressive populations[232] of myeloid cells;[233] (9) Clements and collaborators (Dalhousie University, Halifax, Canada), who characterized the unexpected capacity of oncolytic reoviruses to promote the recruitment of immunosuppressive $CD11b^{+}GR\text{-}1^{+}Ly6C^{high}$ myeloid cells[234] to the tumor bed;[235] (10) Paglino et al. (Yale University School of Medicine, New Haven, CT, USA), who discovered that autonomous parvoviruses are endowed with a rather advantageous feature for the development of novel oncolytic virotherapies, namely, they neither trigger nor inhibit Type I IFN responses in normal and malignant cells;[236] (11) Zloza and co-authors (Rush University Medical Center, Chicago, IL, US), who suggested that the downregulation of leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1 (LILRB1, also known as ILT2) in peripheral blood mononuclear cells may constitute a reliable biomarker of therapeutic responses to oncolytic virotherapy in cancer patients;[237] (12) Liikanen and colleagues (University of Helsinki, Helsinki, Finland), who propose that the circulating levels of the damage-associated molecular pattern high mobility group box 1 (HMGB1)[238-241] at baseline may constitute a robust prognostic factor as well as a predictive indicator of disease control upon oncolytic adenoviral therapy;[242] and (13) Kuruppu and collaborators (Massachusetts General Hospital, Boston, MA, US), who developed an imaging platform based

on bioluminescence and positron emission tomography (PET) to monitor both viral replication and tumor responses to oncolytic virotherapy *in vivo*.[243]

Thus, recent findings from several independent laboratories demonstrate that the therapeutic efficacy of oncolytic virotherapy is blunted, at least to some extent, by Type I IFN responses, which is in line with the central role of Type I IFNs in innate antiviral immunity.[244,245] However, Type I IFN signaling in malignant cells appears to be crucial for their demise to trigger a therapeutically relevant adaptive immune response.[246] We therefore surmise that oncolytic virotherapy would benefit from the development of sequential strategies involving the initial inhibition of Type I IFN responses (allowing for efficient viral replication and dissemination), and their subsequent stimulation (facilitating the elicitation of tumor-targeting immune responses).

Recently initiated clinical trials

Since the submission of our latest Trial Watch on oncolytic virotherapy (March 2014),[247] no less than 28 clinical studies have been initiated to test this immunotherapeutic paradigm in cancer patients (source https://www.clinicaltrials.gov/). Eight of these trials involve Imlygic®, three Cavatak™, three Reolysin®, two HF10, two MV-NIS, two CG0070 (a conditionally replicating oncolytic adenovirus genetically modified to express GM-CSF),[121,248] two Toca 511 (an amphotropic replication-competent retrovirus genetically modified to express an enzyme that converts inactive 5-fluorocytosine into active 5-fluorouracil),[249-252] and the remaining six various oncolytic viruses including G207, JX-594, OBP-301, DNX-2401 (an oncolytic adenovirus engineered to replicate in cells exhibiting defects in cell cycle control, previously known as Delta-24-RGD or Delta-24-RGD-4C),[253-255] MG1-MA3 (an attenuated version of the Maraba rhabdovirus, further engineered to express the TAA melanoma antigen family A3, MAGEA3),[85,256,257] and Ad5-yCD/mutTKSR39rep-hIL12 (an oncolytic adenovirus endowed with an increased cytolytic potential and the ability to express human IL-12)[106,258,259] (Table 1).

Imlygic® is being tested in melanoma patients, who receive intratumoral Imlygic® either as standalone immunotherapeutic intervention (NCT02147951; NCT02173171; NCT02297529; NCT02366195) in combination with surgery (NCT02211131),[260] or together with the FDA-approved checkpoint blocker pembrolizumab[147,261,262] (NCT02263508); in individuals with hepatocellular carcinoma (HCC), who are treated with intratumoral Imlygic® alone (NCT025095079); and in subjects with soft tissue sarcoma, receiving Imlygic® *i.t.* in the context of neoadjuvant radiotherapy (NCT02453191). The safety and efficacy of Cavatak™ are being evaluated in advanced melanoma patients, who receive intralesional Cavatak™ together with ipilimumab (NCT02307149) or pembrolizumab (NCT02565992); and in individuals with bladder carcinoma, who are treated with intravesical Cavatak™ optionally combined with low-dose mitomycin C (NCT02316171). The clinical profile of Reolysin® is being assessed in multiple myeloma patients, who are treated with Reolysin® *i.v.* together with dexamethasone and a proteasomal inhibitor (NCT02101944; NCT02514382); as well as in individuals with brain malignancies, receiving intravenous Reolysin® in combination with subcutaneous GM-CSF (NCT02444546). Intratumoral HF10 is being tested as standalone immunotherapeutic intervention in subjects with advanced solid neoplasms (NCT02428036); or in combination with ipilimumab in metastatic melanoma patients (NCT02272855). The safety and efficacy of MV-NIS are being investigated in women with gynecological malignancies, receiving MV-NIS *i.p.* as single immunotherapeutic agent (NCT02364713); and in subjects with chemorefractory multiple myeloma, who are treated with intravenous MV-NIS in combination with cyclophosphamide (NCT02192775). The clinical activity of CG0070 is being evaluated in bladder carcinoma patients, who receive intravesical CG0070 as standalone immunotherapeutic intervention (NCT02143804; NCT02365818). Toca 511 is being tested in patients with resected glioblastoma multiforme or anaplastic astrocytoma, who receive Toca 511 in the surgical cavity plus systemic 5-fluorocytosine and standard-of-care chemotherapy (NCT02414165); and in subjects with advanced solid malignancies, who are treated with intravenous or intratumoral Toca 511 in combination with systemic 5-fluorocytosine (NCT02576665). Moreover, (1) the therapeutic profile of intratumoral G207 optionally combined with radiation therapy is being assessed in individuals with brain neoplasms (NCT02457845); (2) the safety and efficacy of JX-594 combined with the FDA-approved multikinase inhibitor sorafenib[263,264] are being investigated in HCC patients (NCT02562755);[265] (3) intratumoral OBP-301 is being tested as standalone immunotherapeutic intervention in subjects with HCC (NCT02293850); (4) the clinical profile of intratumoral DNX-2401 plus recombinant IFNγ is being evaluated in individuals with recurrent glioblastoma or gliosarcoma (NCT02197169); (5) the safety and efficacy of intravenous MG1-MA3 administered alone or in combination with a MAGEA3-encoding adenovirus are being assessed in patients with MAGEA3$^+$ advanced solid tumors (NCT02285816); and (6) intraprostatic Ad5-yCD/mutTKSR39rep-hIL12 is being tested as single immunotherapeutic agent in men with locally recurrent prostate carcinoma (NCT02555397).

Status change

The following studies discussed in our previous Trial Watches dealing with oncolytic virotherapy[247,266] have changed status during the last 21 mo: NCT01017601, NCT01199263, NCT01280058, NCT01438112, NCT01470794, NCT01619813, NCT01622543 NCT01636882, NCT01708993, NCT01844661, and NCT02068794, which are now listed as "Active, not recruiting;" NCT02028117, and NCT02043665, which are currently "Recruiting" participants; NCT00109655, and NCT01469611, whose status is nowadays "Unknown;" NCT01174537, NCT01437280, and NCT02017678, which have been "Withdrawn;" as well as NCT00625456, NCT00651157, NCT00753038, NCT00769704, NCT00805376, NCT00984464, NCT00998192, NCT00998322, NCT01017185, NCT01166542, NCT01169584, NCT01240538, NCT01301430, NCT01368276, NCT01387555, NCT01443260, NCT01533194, NCT01582516, NCT01584284, and NCT01598129, which have been

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

Agent	Indication	Phase	Status	Route	Notes	Ref.
Ad5-yCD/	mutTKSR39rep-hIL12	Prostate carcinoma	I	Recruiting	Intraprostatic	As single agent
NCT02555397						
Cavatak™	Bladder carcinoma	I	Recruiting	Intravesical	Optionally combined with low-dose mitomycin C	NCT02316171
	Melanoma	I	Recruiting	Intratumoral	Combined with ipilimumab	NCT02307149
	Combined with pembrolizumab	NCT02565992				
CG0070	Bladder carcinoma	II	No longer available	Intravesical	As single agent	NCT02143804
	Recruiting	Intravesical	As single agent	NCT02365818		
DNX-2401	Brain tumors	I	Recruiting	Intratumoral	Combined with IFNγ	NCT02197169
G207	Brain tumors	I	Not yet recruiting	Intratumoral	Optionally combined with radiation therapy	NCT02457845
HF10	Melanoma	II	Recruiting	Intratumoral	Combined with ipilimumab	NCT02272855
	Solid tumors	I	Recruiting	Intratumoral	As single agent	NCT02428036
Imlygic®	Hepatocellular carcinoma	I	Not yet recruiting	Intratumoral	As single agent	NCT02509507
	Melanoma	n.a.	Enrolling by invitation	Intratumoral	As single agent	NCT02173171
	II	Recruiting	Intratumoral	As single agent	NCT02366195	
	Combined with surgery	NCT02211131				
	III	Active, not recruiting	Intratumoral	Combined with pembrolizumab	NCT02263508	
	Available	Intratumoral	As single agent	NCT02147951		
	NCT02297529					
	Soft tissue sarcoma	I/II	Recruiting	Intratumoral	Combined with radiotherapy	NCT02453191
JX-594	Hepatocellular carcinoma	III	Not yet recruiting	Intratumoral	Combined with sorafenib	NCT02562755
MG1-MA3	Solid tumors	I/II	Recruiting	Intravenous	Combined with a MAGEA3-encoding adenovirus	NCT02285816
MV-NIS	Gynecological tumors	II	Recruiting	Intraperitoneal	As single agent	NCT02364713
	Multiple myeloma	II	Recruiting	Intravenous	Combined with cyclophosphamide	NCT02192775
OBP-301	Solid tumors	I	Not yet recruiting	Intratumoral	As single agent	NCT02293850
Reolysin®	Brain tumors	I	Recruiting	Intravenous	Combined with GM-CSF *s.c.*	NCT02444546
	Multiple myeloma	I	Recruiting	Intravenous	Combined with dexamethasone plus a proteasomal inhibitor	NCT02101944
	NCT02514382					
Toca 511	Brain tumors	II/III	Not yet recruiting	Intratumoral	Combined with 5-FC and standard chemotherapy	NCT02414165
	Solid tumors	I/II	Recruiting	Intratumoral Intravenous	Combined with 5-FC	NCT02576665

Abbreviations: 5-FC, 5-fluorocytosine; GM-CSF, granulocyte macrophage colony-stimulating factor; IFNγ, interferon γ; MAGEA3, melanoma antigen family A3; *s.c.*,*sub cutem*.*initiated between 2014, March 1st and 2015, October 31th.

"Completed" (source https://www.clinicaltrials.gov/). NCT01174537 (a Phase I/II trial testing Newcastle disease virus *i.v.* as standalone immunotherapeutic intervention in glioblastoma, sarcoma and neuroblastoma patients), NCT01437280 (a Phase I study investigating the therapeutic profile of ONCOS-102 in individuals with solid tumors), and NCT02017678 (a Phase II assessing the clinical potential of JX-594 in women with peritoneal carcinomatosis from ovarian carcinoma) have been withdrawn prior to patient enrollment for undisclosed reasons (source https://www.clinicaltrials.gov/).

Preliminary or definitive results from NCT00769704 (a Phase III study comparing intralesional Imlygic® to subcutaneous GM-CSF in subjects with unresectable Stage IIIb, IIIc and Stage IV melanoma), NCT01169584 (a Phase I trial assessing the safety of JX-594 in children with refractory solid tumors), NCT01240538 (a Phase I study testing Reolysin® plus low-dose cyclophosphamide in young patients with relapsed or refractory solid cancers), NCT01584284 (a Phase I trial investigating the clinical profile of GL-ONC1 plus cisplatin-based chemoradiation in HNC patients), NCT01598129 (a Phase I study testing the safety of ONCOS-102 combined with low-dose cyclophosphamide in individuals with advanced neoplasms), and NCT02043665 (a Phase I study assessing the safety of Cavatak™ in subjects with chemorefractory advanced malignancies) have been discussed above.[161,162,171,174-176,182,185,190,267] Although official sources indicate that the status of NCT01469611 (a Phase I testing the biweekly intravenous administration of JX-594 as standalone immunotherapeutic intervention in CRC patients) is "Unknown," preliminary findings have already been published (see above).[184] Results from NCT01048892 (a Phase I trial evaluating NTX-010 in combination with metronomic cyclophosphamide in children with neuroendocrine tumors), and NCT01227551 (a Phase II study testing Cavatak™ as standalone immunotherapeutic

intervention in subjects with advanced melanoma), both of which were "Completed" when we submitted our latest Trial Watch dealing with this topic,[247] are also available (see above),[175,194] and so are findings from NCT01740297 (a Phase I/II trial assessing the therapeutic profile of Imlygic® plus ipilimumab in melanoma patients), and NCT01766739 (a Phase I study testing intrapleural GL-ONC1 as single immunotherapeutic agent in individuals with malignant pleural effusion) (see above),[165,187] even though their status ("Recruiting") has not been updated during the last 21 mo.

NCT00651157 was a Phase II clinical trial testing Reolysin® as a standalone immunotherapeutic agent in subjects with metastatic melanoma. Twenty-three patients were enrolled in this study, 21 of whom completed oncolytic virotherapy. Fifty percent of these subjects manifested Grade 3–4 adverse effects, the most frequent of which were drops in serum albumin levels (in four patients), alterations in circulating electrolytes (in two patients), confusion (in two patients), a decreased neutrophil or lymphocyte counts (in two patients) and fatigue (in two patients). No objective responses were documented and the OS of the cohort was 5.42 mo (95% CI: 0.49–15.8) (source https://www.clinicaltrials.gov/). NCT01017185 was a Phase I study investigating the safety and efficacy of intratumoral HF10 in patients affected by refractory tumors with cutaneous or superficial lesions. Of more than 25 patients enrolled in this trial, six reported adverse effects related to oncolytic virotherapy including chills (two patients), as well as injection site discolorations (one patient), edema and pain (one patient), malaise (one patient), pruritus (one patient) and hypotension (one patient). Despite the rapid clearance of HF10 from blood, urine, and saliva, one patient manifested ulcers at both injected and non-injected lesions, involving malignant (but not normal) cells.[268]

To the best of our knowledge, clinical results from NCT00625456 (a Phase I, open-label, dose-escalation study testing the safety and efficacy of JX-594 in subjects with advanced or metastatic solid tumors refractory to standard therapy), NCT00753038 (a Phase II trial investigating the therapeutic profile of Reolysin® plus carboplatin and paclitaxel[269,270] in individuals with HNC), NCT00805376 (a Phase I study assessing the clinical profile of DNX-2401, alone or combined with surgical tumor resection, in individuals with brain neoplasms), NCT00984464, NCT00998192, and NCT01166542 (three Phase II trials testing Reolysin® plus carboplatin and paclitaxel in patients with metastatic melanoma, NSCLC and HNC, respectively), NCT00998322 (a Phase II study evaluating Reolysin® plus gemcitabine in subjects with pancreatic adenocarcinoma),[271] NCT01301430 (a Phase I/II clinical trial assessing the safety, tolerability and efficacy of H-1 parvovirus in subjects suffering from glioblastoma multiforme), NCT01368276 (a Phase III trial evaluating the safety and efficacy of the extended use of Imlygic® in melanoma patients), NCT01387555 (a Phase IIb study investigating JX-594 as standalone immunotherapeutic agent in subjects with advanced HCC who failed to respond to sorafenib), NCT01443260 (a Phase I/II trial assessing the safety of GL-ONC1 in patients with peritoneal carcinomatosis), NCT01533194 (a Phase I study testing Reolysin® as single immunotherapeutic agent in subjects with relapsed or refractory multiple myeloma), and NCT01582516 (a Phase I/II trial investigating the clinical profile of DNX-2401 in individuals with recurrent glioblastoma) have not yet been officially disclosed (source https://www.clinicaltrials.gov/).

Concluding remarks

As discussed above, oncolytic virotherapy has been extensively investigated in both preclinical and clinical settings throughout the past decade, with encouraging results in terms of both safety and efficacy. Nevertheless, no oncolytic virus was approved for cancer therapy in the US and Europe until very recently, at least in part because the clinical potential of oncolytic virotherapy was somehow shaded by the tremendous success of other immunotherapeutics, notably checkpoint blockers. Now that Imlygic® has been officially licensed in the US for use in melanoma patients as standalone immunotherapeutic intervention, we expect a remarkable boost in the number of clinical studies testing oncolytic virotherapy in cancer patients. It will indeed be interesting to see whether Imlygic® can be combined with other chemo- or immunotherapeutic agents, and if patients with GM-CSF-sensitive tumors other than melanoma may also benefit from intratumoral Imlygic®. The future will tell if the regulatory approval of Imlygic® will pave the way to a new era for oncolytic virotherapy.

Disclosure of potential conflicts of interest

PE, JML and XP are full-time employees of Transgene (Strasbourg, France); LZ is part of the Board of Directors of Transgene (Strasbourg, France).

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