Clinical trials using oncolytic viral therapy to treat adult glioblastoma: a progress report

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OBJECTIVE Adult glioblastoma (GBM) has proven refractory to decades of innovation. Oncolytic viral therapy represents a novel therapy that uses viral vectors as both a delivery and therapeutic mechanism to target GBM cells. Despite the growing body of basic science data supporting the feasibility of viral therapy to treat GBM, the reporting of clinical trial results is heterogeneous. Correspondingly, the aim of this study was to present a contemporary summary of the progress all clinical trials have made to date.

METHODS The ClinicalTrials.gov database was reviewed in August 2020 for all possible interventional clinical trials involving viral vector–based therapy to treat adult GBM. These were then screened against selection criteria to identify pertinent clinical trials.

RESULTS A total of 29 oncolytic viral therapy trials treating adult GBM were identified. The median start and expected completion years were 2014 and 2020, respectively. At the time of this writing, 10 (35%) trials were reported to have completed recruitment, whereas 7 (24%) were actively recruiting. The median target enrollment number was 36 (range 13–108), with the majority of trials being phase I ($n = 18$, 62%), and involving secondary GBM among other malignant glioma ($n = 19$, 66%). A total of 10 unique viral vectors were used across all trials, with the most common being adenovirus ($n = 16$, 55%). Only 2 (7%) phase I trials to date have reported outcomes on the ClinicalTrials.gov portal. Results of 12 additional clinical trials were found in academic publications, with median progression-free and overall survival times of 3 and 15 months, respectively, after the first viral dose at recurrence. The coordination of the large majority of trials originated from the US ($n = 21$, 72%), and the median number of testing sites per trial was 1 (range 1–15), via industry funding ($n = 18$ trials, 62%).

CONCLUSIONS There are multiple early-stage oncolytic viral therapy clinical trials for adult GBM currently active. To date, limited results and outcomes are promising but scarce. The authors expect this to change in the near future because many trials are scheduled to have either nearly or actually reached their expected recruitment completion time. How exactly oncolytic viral therapy will fit into the current treatment paradigms for primary and secondary GBM remains to be seen, and will not be known until safety and toxicity profiles are established by these clinical trials.

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KEYWORDS glioblastoma; viral therapy; adenovirus; clinical trial; oncolytic

THE prognosis of adult glioblastoma (GBM) has proven refractory to multiple decades of innovation since triple therapy involving maximal safe resection, chemotherapy, and radiation therapy was established in 2005.¹ Correspondingly, the need to consider novel therapies continues to grow.

Oncolytic viral therapy is one such option. It remains an experimental platform that takes advantage of a virus' biological ability to infiltrate, replicate, and lyse human

cells.² By means of advanced recombinant technologies, naturally occurring viruses can be genetically engineered to target specific tumor cells based on the proteins these cells express, and they become oncolytic in nature.³ There are many possible mechanisms by which these vectors can result in the death of tumor cells once delivered, and include direct tumor lysis, modification of tumor micro-environment, priming of immune responses, inhibiting tumorigenic vascularization, and promoting immunogenic

ABBREVIATIONS GBM = glioblastoma; HSV = herpes simplex virus; MoMLV = Moloney murine leukemia virus; NCDV = Newcastle disease virus; NCT = National Clinical Trial; OS = overall survival; PFS = progression-free survival.

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cell death.⁵ Indeed, *in vitro* glioma cells were one of the earliest tumor cells to validate this concept of a virus that was able to be engineered into an oncolytic virus with tumor cell-killing abilities.⁵ Since those early days, our biological understanding of viral therapy has grown exponentially, to the point where multiple clinical trials for multiple cancer types are active.⁶

Attention has turned to oncolytic viral therapy as a possible novel therapy that may confer a prognostic benefit to adult patients with GBM, particularly at recurrence. However, progress to date with respect to *in-human* clinical trials remains subject to highly heterogeneous reporting and result dissemination. Correspondingly, the aim of this study was to present a contemporary summary of the progress that all clinical trials have made to date.

Methods

Search Strategy

The search strategy was designed to capture all possible clinical trials with registration in both the US National Library of Medicine and ClinicalTrials.gov registry (<https://clinicaltrials.gov/>) investigating a viral therapy to treat GBM. The ClinicalTrials.gov site is a database of privately and publicly funded clinical trials on a wide range of diseases and conditions conducted around the world, providing information on more than 300,000 research studies conducted across all states of the US and in more than 200 countries worldwide.^{7,8} Databases were searched and screened in August 2020 using the following string of search terms for condition or disease: “glioblastoma” and “viral.” Synonyms used were “childhood anaplastic astrocytoma/childhood high-grade cerebral astrocytoma/grade IV astrocytoma/Grade IV Astrocytic Tumor/WHO Grade IV Glioma” and “virus,” respectively. For results of clinical trials, a combination of ClinicalTrials.gov, PubMed, and Google Scholar electronic academic search engines were used to look for viral vectors and National Clinical Trial (NCT) registration matching those described in the included studies.

Selection Criteria

For inclusion into our study, trials were required to investigate a brain tumor cohort with the following features: 1) intracranial GBM and/or malignant high-grade glioma as the only or major (> 80%) histological diagnosis, and 2) whose trial treatment involved a viral vector-based intervention designed to target and kill GBM cells as per the oncolytic viral therapy concept. This did not include interventions such as gene therapy that involved virus vectors for the purposes of white blood cell transformation. In the case of trials reporting outcomes that included gliomas of the spine, low-grade gliomas, or tumors of other organ systems outside the brain, these were not included due to lack of specificity and generalizability. Trials targeting the cytomegalovirus via dendritic cell therapy were not included because they did not use the virus as a therapeutic vector. Additionally, pediatric trials were also excluded to avoid biological confounding. There were no limitations set on age, nature of presentation (e.g., primary vs recurrence), or geographic location.

Assessment of clinical trials to satisfy these criteria was performed independently by two investigators (V.M.L. and F.A.V.), and any discrepancies were resolved by discussion.

Data Outcomes

The following outcomes were then extracted from the database: NCT number, title, institution of correspondence, country of origin of the corresponding institution, number of institutions involved, involvement of outside countries, recruitment status, availability of results, type of primary intervention, primary and secondary outcome measurements, gender enrollment, age of enrollment, number of patients enrolled, study phases, study type, funding source, start year, completion year, year of the first release of results, and last updated year.⁹ All missing data were reported as “not reported.” All data analyses, including the generation of figures and tables, were performed using STATA version 14.1 (StataCorp).

Results

Search Strategy

The initial search of the portal yielded 52 trials for screening. Eleven were excluded because their intervention did not involve a primary viral vector, 7 were excluded as they were pediatric trials, 3 describing dendritic cell therapy targeting cytomegalovirus were excluded, and 2 were excluded because they involved tumors in multiple organ systems. Ultimately, 29 trials were identified as appropriate for inclusion in this study, with parameters of the trials summarized in Table 1, and all individual details in Table 2.

Status

All trials reported start years between 2001 and 2020 (Fig. 1A), with a median start year of 2014. The period of 2017–2020 alone included 12 (41%) trials commencing recruitment. In terms of expected completion year, the median was 2020 (Fig. 1B). As of August 2020, 10 (35%) trials were reported to have completed recruitment; 7 (24%) are recruiting; 7 (24%) are declared as active, not recruiting; and 1 (3%) as not yet recruiting. A total of 4 (14%) trials had been terminated, suspended, or withdrawn since their commencement.

Cohort

The target number of patients to enroll across all trials ranged from 13 to 108, with the median number of patients being 36. There were 19 (66%) trials involving primary and secondary GBM and other malignant glioma, 5 (17%) trials involving primary and secondary GBM only, and 5 (17%) trials involving secondary GBM only. There were no trials involving primary GBM only.

Trial Design

The most common trials were 18 (62%) phase I trials, followed by 5 (17%) phase I and II trials, then 5 (17%) phase II trials, and 1 (3%) phase II and III trial (Fig. 2). Four trials reported a randomization process in their al-

location design, in 1 phase I trial, 2 phase II trials, and 1 phase II and III trial. Allocation in all other trials was nonrandomized. The most common primary outcome of interest was safety and toxicity in 24 (83%) trials, with progression-free survival (PFS), radiographic response, and immunological response the other outcomes reported.

Viral Therapy

Across all trials, 10 unique viral vectors were used (Fig. 3). The most common was adenovirus, used in 16 (55%) trials. With respect to standard-of-care treatment, 21 (72%) trials involved resection, 7 (24%) trials involved chemotherapy, and 4 (13%) trials involved radiation therapy.

Trial Outcomes

Only 2 (7%) trials to date have reported outcomes on the ClinicalTrials.gov portal. NCT00390299 was a phase I trial investigating carcinoembryonic antigen-expressing measles virus (MV-CEA) in recurrent GBM. For their primary outcome, they reported that 6/9 (67%) patients experienced a grade 3+ adverse event following viral therapy to a resection cavity versus 5/13 (39%) patients following intratumoral administration status after stereotactic biopsy. NCT01491893 was a phase I safety study of an oncolytic polio/rhinovirus recombinant in recurrent GBM. For their primary outcomes, they reported their maximum tolerable dose of 10^{10} median tissue culture infectious dose (TCID₅₀) based on dose-limiting toxicity events in 60 patients. They also noted that the median survival in their trial cohort was 6 years.

Survival Outcomes

A systematic review of electronic academic search engines revealed results for 12 clinical trials outside the ClinicalTrials.gov portal, with 7 studies that described adenovirus vectors (NCT03679754,¹⁰ NCT02026271,¹¹ NCT00031083,¹² NCT00589875,¹³ NCT00870181,¹⁴ NCT02798406,¹⁵ NCT04406272¹⁶), and then 1 study each describing outcomes of GBM using herpes simplex virus-1 (HSV-1; NCT00028158),¹⁷ Moloney murine leukemia virus (MoMLV; NCT02414165),¹⁸ Newcastle disease virus (NCDV; NCT01174537),¹⁹ parvovirus (NCT01301430),²⁰ and reovirus (NCT00528684)²¹ viral vectors (Fig. 4). The median PFS from first viral dose was 3 months (range 1–8 months) across 8 trial results. The median overall survival (OS) from first viral dose was 15 months (range 11–32 months) across all these reported outcomes.

Coordination and Funding

The median number of sites per trial was 1, with a range of 1–15 (Fig. 5A). A total of 7 countries are listed as the primary location for all included trials—the most common being the US with 21 (72%) trials—with 7 (33%) being coordinated from Massachusetts, 3 each from Texas and Alabama, 2 from Ohio, and 1 each from California, Illinois, Michigan, Minnesota, North Carolina, and Pennsylvania (Fig. 5B). Germany and Spain both had 2 (7%) trials, which was the next most common number at a country level, followed by China, France, Israel, and the

TABLE 1. Summary of 29 clinical trial characteristics

Parameter	Outcome*
Time	
Start yr	2014 (2001–2020)
Expected completion yr	2020 (2003–2030)
Results first posted	2018, 2020†
Last updated	2019 (2005–2020)
Status	
Current status as of August 2020	
Completed	10 (35%)
Recruiting	7 (24%)
Active, not recruiting	7 (24%)
Withdrawn	2 (7%)
Terminated	1 (3%)
Suspended	1 (3%)
Not yet recruiting	1 (3%)
Study results available	2 (7%)
Cohort	
Target no. of patients enrolled	36 (13–108)
GBM type	
GBM only, primary	0
GBM only, secondary	5 (17%)
GBM only, primary & secondary	5 (17%)
GBM & other malignant glioma	19 (66%)
Design	
Phase	
I	18 (62%)
I & II	5 (17%)
II	5 (17%)
II & III	1 (3%)
Primary outcome of interest	
Safety & toxicity	24 (83%)
PFS	3 (10%)
Radiographic response	2 (7%)
Location & funding	
Country of correspondence	
US	21 (72%)
Germany, Spain	2 (7% each)
China, France, Israel, Netherlands	1 (3% each)
No. of sites involved	1 (1–15)
Funding	
Industry	18 (62%)
NIH	7 (24%)

* Continuous data reported as median (range) and categorical data reported as no. (% total).

† Only 2 trials (NCT00390299 and NCT01491893) have reported results on the ClinicalTrials.gov portal.

Netherlands with 1 (3%) each. The majority of funding was through industry in the case of 18 (62%) trials, with only 7 (24%) trials reporting national funding via the National Institutes of Health (NIH).

TABLE 2. Individual characteristics of each clinical trial

Trial No.	NCT No.	Coordinating Country	Trial Sites (no.)	Phase(s)	Enrollment Target (no.)	Viral Vector	GBM Only	GBM Type	Start Yr	Expected Completion Yr	Status	Primary Outcome of Interest
1	NCT03294486	France	1	I & II	78	Poxvirus	Yes	Secondary	2017	2021	Recruiting	Toxicity
2	NCT01174537	Israel	1	I & II	NR	NCDV	No	Secondary	2011	2011	Withdrawn	PFS
3	NCT01956734	Spain	1	I	31	Adenovirus	Yes	Secondary	2013	2017	Completed	Toxicity
4	NCT00390299	US	1	I	23	Measles	No	Secondary	2006	2019	Completed	Toxicity
5	NCT04406272	US	2	II	45	Adenovirus	Yes	Both	2020	2023	Not yet recruiting	Toxicity
6	NCT03714334	Spain	1	I	24	Adenovirus	Yes	Secondary	2018	2022	Recruiting	Toxicity
7	NCT04105374	US	1	II & III	NR	MoMLV	No	Primary	2020	2030	Withdrawn	PFS
8	NCT00028158	Germany	1	I & II	65	HSV	No	Secondary	2001	2003	Completed	Toxicity
9	NCT01301430	Germany	1	I & II	18	Parvovirus	Yes	Both	2011	2015	Completed	Toxicity
10	NCT04327011	US	11	I	65	MoMLV	No	Both	2011	2019	Terminated	Toxicity
11	NCT01811992	US	1	I	19	Adenovirus	No	Primary	2014	2021	Active, not recruiting	Toxicity
12	NCT02197169	US	4	I	37	Adenovirus	No	Secondary	2014	2018	Completed	Radiographic
13	NCT01582516	Netherlands	1	I & II	20	Adenovirus	Yes	Secondary	2010	2014	Completed	Toxicity
14	NCT03657576	US	1	I	24	HSV	No	Secondary	2019	2024	Recruiting	Toxicity
15	NCT00870181	China	1	II	47	Adenovirus	No	Both	2008	2012	Completed	PFS
16	NCT02798406	US	15	II	49	Adenovirus	No	Secondary	2016	2021	Active, not recruiting	Radiographic
17	NCT02062827	US	1	I	36	HSV	No	Both	2014	2023	Recruiting	Toxicity
18	NCT03679754	US	4	I	36	Adenovirus	Yes	Both	2018	2021	Active, not recruiting	Toxicity
20	NCT03152318	US	2	I	108	HSV	No	Both	2017	2022	Recruiting	Toxicity
21	NCT02026271	US	6	I	48	Adenovirus	No	Both	2015	2019	Active, not recruiting	Toxicity
24	NCT04214392	US	1	I	36	Lentivirus	No	Both	2020	2023	Recruiting	Toxicity
25	NCT03636477	US	4	I	21	Adenovirus	Yes	Both	2018	2021	Active, not recruiting	Toxicity
26	NCT04006119	US	7	II	36	Adenovirus	Yes	Both	2019	2022	Active, not recruiting	Toxicity
27	NCT03896568	US	1	I	36	Adenovirus	No	Both	2019	2020	Recruiting	Toxicity
28	NCT01491893	US	1	I	61	Rhinovirus	Yes	Secondary	2012	2021	Active, not recruiting	Toxicity
29	NCT00589875	US	4	II	52	Adenovirus	No	Both	2007	2016	Completed	Toxicity
30	NCT00031083	US	5	I	35	Adenovirus	No	Both	2002	2004	Suspended	Toxicity
31	NCT03072134	US	2	I	13	Adenovirus	No	Primary	2017	2020	Completed	Toxicity
32	NCT00528684	US	3	I	18	Reovirus	No	Both	2006	2010	Completed	Toxicity

NR = not reported.

Discussion

Adult GBM is a devastating diagnosis with no cure despite decades of research and clinical trials. The emergence of oncolytic viral therapy has given new hope for discovering impactful interventions that can improve quality of life and survival in these patients. Our interrogation of the ClinicalTrials.gov portal reveals that there are many trials ongoing, and that most remain in the early safety and toxicity phases of investigation. Furthermore, the data would suggest that many trials are scheduled to

either have recently completed recruiting or will be completed within the coming years, stoking anticipation for meaningful results to emerge soon after. Then, the way in which oncolytic viral therapy could fit into the current treatment paradigm of triple therapy at initial diagnosis will need to be elucidated.

Clinical trials involving oncolytic viral therapy to target cancers have grown in number in recent years, with varying degrees of completion rates.²² Although the earliest reported trial for GBM in adults was listed to have

FIG. 1. Bar graphs showing the number of trials per start year (A) and the completion year or expected completed year of recruitment (B).

commenced recruitment in 2001, the majority of the trials we report started in 2013 or later. However, estimated dates for recruitment completion remain largely contemporary, with less than half of all trials having completion status. Furthermore, very few trials have posted results of their study. A reason for these lags may be intrinsic to trial design, development, and ethics approval needed to commence and continue viral therapy investigation in patients with GBM. Additionally, we note that 4 trials have been terminated, suspended, or withdrawn since their commencement. Although it is pure speculation as to the reasons why this occurred, it does speak to the technical difficulty and perseverance required to take this novel therapy from bench to bedside. Multiple practical features such as success, costs, and expertise are likely to be factors requiring constant attention and revision in order to take these trials to completion.²³

Although it is a novel treatment, emerging evidence in our review suggests that oncolytic viral therapy may confer a greater OS benefit compared to PFS benefit from

the start of the first dose. These findings are even more encouraging given that all studies incorporated patients with GBM who had recurrent disease, meaning overall time from initial diagnosis to recurrence must be added to these reported values for a true OS. It will be of great interest moving forward to see if these survival values extend as we accumulate more results and greater technical expertise.

Our results show that clinical trials of oncolytic viral therapy to treat adult patients with GBM are often single-site studies involving fewer than 50 patients. Although part of this could be attributed to the relatively rare incidence of GBM, there are other trials investigating other novel therapies that have completed higher enrollment goals. For example, tumor-treating field technology has emerged as another novel modality to treat GBM in adults, and already there have been randomized trials^{24,25} involving hundreds of patients, as well as many other phase II and III trials with enrollment targets greater than 50 that are currently ongoing.²⁶ In comparison, the majority of active clinical trials are phase I studies. Our findings then temper the expectation that novel therapies to treat GBM are directly comparable, in the sense that the biological variance of some treatments such as viral therapy demand

FIG. 2. Pie chart showing the distribution of clinical trials by phase.

FIG. 3. Summary of the viral vectors used in each trial.

FIG. 4. Reported median OS and PFS of pertinent clinical trials. The NCT identifier is included in parentheses following the viral vector. The academic reference is listed in square brackets.

greater time and titration than other novel treatments like the tumor-treating field modality.

There are a large number of different viral vectors currently being investigated in GBM clinical trials as an oncolytic virus medium, with the most common being adenovirus. This is not particularly surprising given that the adenovirus is the most common viral vector used across all cancers, and it was the first vector to be used in a trial in human patients.^{3,27} The next most common viral vector was that of HSV, the same vector used in the original in vitro experiments with glioma.⁵ We note that to date no clinical trial is directly comparing multiple different viral vectors against each other, which may be due to the prematurity of assessing clinical impact at this current stage of development. Nonetheless, this vast array of potential vector choices currently being investigated across all clinical trials demonstrates the large biological variance that viral therapy development faces in its optimization.²⁸

No clinical trial that we report was found to involve only primary GBM in its study cohort—rather, all trials in-

cluded patients with recurrent GBM, for which the optimal treatment sequence other than repeat surgery remains unclear.²⁹ The reason this could be an issue moving forward is that it will be difficult to discern efficacy potential from a recurrent GBM standpoint alone due to the large clinical heterogeneity in care at this point of diagnosis. Although the majority of trials involve repeat resection of recurrent GBM when evaluating viral therapy, only a minority included chemotherapy and radiation therapy. Direct comparability between active trials would therefore appear to be unwise. Even if modalities could be matched, however, viral therapies will face the challenge of how delivery affects their efficacy, with it being possible to deliver viral vectors to the tumor site via convection-enhanced delivery (NCT04214392), local injection at time of biopsy or resection (NCT01956734), or even systemically before or after surgery (NCT00870181).

There are limitations to this study. First, although the ClinicalTrials.gov portal is a comprehensive database, it is based in the US and is not an exhaustive list of every

FIG. 5. Summary of the coordination of trials from the number of sites per trial (A), and distribution of the coordination sites by US state (B) (n = 21).

single clinical trial being conducted in the world.³⁰ There will probably be some trials that have not been registered on this portal, and indeed, as our systematic search of electronic academic search engines shows, not all results are always reported on the portal itself, but rather in academic publications. However, we suspect that the proportions of trials complete and those with results reported are congruent with contemporary efforts worldwide. Second, granular details as to the motivation, direction, and rationale of each clinical trial cannot be abstracted based on the data provided at hand. Understanding the selection of oncolytic viral vector and the decision to pursue specific evaluations would greatly assist in the broader development and uptake of this novel therapy. Finally, the lack of posted results limits our ability to make inferences on how exactly viral therapy may clinically impact management of GBM in adults in the future. The distinct lack of trials involving primary GBM perhaps underestimates the clinical potential and significance of this novel therapy. This is because there are a number of other emerging novel therapies being tested in the sphere of secondary GBM, limiting the time and resources that we as a wider community can give to this specific therapy and to discovering its true efficacy.

Conclusions

Oncolytic viral therapy to treat adult patients with GBM is a novel concept. The basic science of using viral vectors to target GBM cells has been robustly developed over time, and we now find ourselves at the precipice of the advance to clinical translation into human patients. Our interrogation of a large clinical trials database reveals that a number of clinical trials are active and are investigating the safety and toxicity profile of a number of different viral vectors. Results are largely pending, and are expected to be complete and hopefully posted within the coming years. Understanding this will then arm clinicians and scientists around the world with sufficient data to design effective higher-phase trials to test efficacy. Ultimately, future clinical trials based on the outcomes of current trials are needed to validate the place oncolytic viral therapy warrants among current treatment regimens to improve the prognosis of this dire disease.

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Disclosures

Dr. Ivan is a consultant for Medtronic.

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Conception and design: Lu, Vallejo, Luther. Acquisition of data: Lu, AH Shah, Vallejo, Luther. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Lu, AH Shah, Vallejo, Eichberg, Luther, SS Shah, Komotar. Approved the final version of the manuscript on behalf of all authors: Lu. Statistical analysis: Lu. Study supervision: Ivan.

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