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# Combined cytotoxic and immune-stimulatory gene therapy for primary adult high-grade glioma: a phase 1, first-in-human trial

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## Abstract

**Background:** High-grade gliomas have a poor prognosis and do not respond well to treatment. Effective cancer immune responses depend on functional immune cells, which are typically absent from the brain. This study aimed to evaluate the safety and activity of two adenoviral vectors expressing HSV1-TK (Ad-hCMV-TK) and Flt3L (Ad-hCMV-Flt3L) in patients with high-grade glioma.

**Methods:** In this dose-finding, first-in-human trial, treatment-naive adults aged 18-75 years with newly identified high-grade glioma that was evaluated per immunotherapy response assessment in neuro-oncology criteria, and a Karnofsky Performance Status score of 70 or more, underwent maximal safe resection followed by injections of adenoviral vectors expressing HSV1-TK and Flt3L into the tumour bed. The study was conducted at the University of Michigan Medical School, Michigan Medicine (Ann Arbor, MI, USA). The study included six escalating doses of viral particles with starting doses of $1\times10^{10}$ Ad-hCMV-TK viral particles and $1\times10^{9}$ Ad-hCMV-Flt3L viral particles (cohort A), and then $1\times10^{11}$ Ad-hCMV-TK viral particles and $1\times10^{9}$ Ad-hCMV-Flt3L viral particles (cohort B), $1\times10^{10}$ Ad-hCMV-TK viral particles and $1\times10^{10}$ Ad-hCMV-Flt3L viral particles (cohort C), $1\times10^{11}$ Ad-hCMV-TK viral particles and $1\times10^{10}$ Ad-hCMV-Flt3L viral particles (cohort D), $1\times10^{10}$ Ad-hCMV-TK viral particles and $1\times10^{11}$ Ad-hCMV-Flt3L viral particles (cohort E), and $1\times10^{11}$ Ad-hCMV-TK viral particles and $1\times10^{11}$ Ad-hCMV-Flt3L viral particles (cohort F) following a 3+3 design. Two 1 mL tuberculin syringes were used to deliver freehand a mix of Ad-hCMV-TK and Ad-hCMV-Flt3L vectors into the walls of the resection cavity with a total injection of 2 mL distributed as 0·1 mL per site across 20 locations. Subsequently, patients received two 14-day courses of valacyclovir (2 g orally, three times per day) at 1-3 days and 10-12 weeks after vector administration and standad upfront chemoradiotherapy. The primary endpoint was the maximum tolerated dose of Ad-hCMV-Flt3L and Ad-hCMV-TK. Overall survival was a secondary endpoint. Recruitment is complete and the trial is finished. The trial is registered with ClinicalTrials.gov, NCT01811992.

**Findings:** Between April 8, 2014, and March 13, 2019, 21 patients were assessed for eligibility and 18

patients with high-grade glioma were enrolled and included in the analysis (three patients in each of the six dose cohorts); eight patients were female and ten were male. Neuropathological examination identified 14 (78%) patients with glioblastoma, three (17%) with gliosarcoma, and one (6%) with anaplastic ependymoma. The treatment was well-tolerated, and no dose-limiting toxicity was observed. The maximum tolerated dose was not reached. The most common serious grade 3-4 adverse events across all treatment groups were wound infection (four events in two patients) and thromboembolic events (five events in four patients). One death due to an adverse event (respiratory failure) occurred but was not related to study treatment. No treatment-related deaths occurred during the study. Median overall survival was 21·3 months (95% CI 11·1-26·1).

**Interpretation:** The combination of two adenoviral vectors demonstrated safety and feasibility in patients with high-grade glioma and warrants further investigation in a phase 1b/2 clinical trial.

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