Safety and efficacy of oncolytic virus therapy in malignant brain tumours: a meta-analysis

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Abstract

Introduction: Oncolytic virus (OV) therapy has been investigated as a treatment for malignant brain tumours due to its ability to directly induce tumour cell lysis and stimulate antitumor immunity, especially in malignant gliomas. Nonetheless, clinical evidence is primarily derived from small, early-phase trials. We conducted a meta-analysis to consolidate the safety profile and clinical outcomes of OV therapy in patients with malignant brain tumours.
Methods: We searched PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov up to 31 December 2025. The outcomes assessed were adverse events (AEs), serious adverse events (SAEs), objective response rate (ORR), disease control rate (DCR), 1-year overall survival (OS) rate, median progression-free survival (mPFS), and median overall survival (mOS). Pooled estimates were calculated using random effects models.
Results: A total of 24 studies comprising 26 cohorts were included, with glioma as the predominant tumour type. All studies were phase I/II single-arm trials. Commonly reported AEs included anaemia, lymphopaenia, fatigue, fever, gastrointestinal symptoms, headache, and seizures. The pooled incidence of SAEs was 16% (95% CI: 4–45%). The pooled ORR was 17% (95% CI: 11–26%), and the DCR was 66% (95% CI: 47–81%). The 1-year OS rate was 51% (95% CI: 33–67%). mPFS and mOS were 2.99 months (95% CI: 1.90–4.08 months) and 9.16 months (95% CI: 7.37–10.96 months), respectively. Leave-one-out analysis confirmed the stability of these estimates.
Conclusions: OV therapy appears feasible and generally tolerable in patients with malignant brain tumours. Although evidence remains non-confirmatory, pooled outcomes provide descriptive evidence of potential clinical activity, reflected by disease control and survival.

Key words: oncolytic virus, brain tumours, glioma, adverse events, survival outcomes.

Introduction

Primary brain tumours represent a diverse group of neoplasms associated with significant morbidity and mortality [1, 2]. Glioma, the most prevalent malignant primary brain tumour, constitutes about 81% of all cases. Among gliomas, glioblastoma (GBM) is the most common subtype, making up roughly 45% of these tumours. Notably, GBM is the most aggressive form, marked by rapid progression, diffuse infiltration, and resistance to conventional treatments. Despite multimodal therapy, the median overall survival is still around 15 months [3–5].

The standard treatment for high-grade glioma currently involves maximal safe surgical resection, followed by radiotherapy and temozolomide-based chemotherapy [6]. While this approach can provide temporary disease control, tumour recurrence is almost inevitable, and options for treating recurrence are limited [7]. The poor prognosis of high-grade gliomas is primarily due to significant intratumoural heterogeneity, infiltrative growth, and an immunosuppressive tumour microenvironment [8].

Immunotherapy has shown promise for several solid tumours, but progress in glioma remains discouraging [9]. Gliomas exhibit multiple mechanisms of immune evasion, such as low tumour mutational burden, limited antigen presentation, infiltration by immunosuppressive myeloid cells, and the functional exhaustion of effector T cells [8, 10]. These characteristics contribute to the disappointing outcomes observed in many immunotherapeutic approaches that have been effective in other solid tumours, including immune checkpoint inhibitors and cancer vaccines [11, 12]. Consequently, there is an increasing need to explore alternative immunotherapeutic strategies that can overcome the unique immune barriers of the central nervous system (CNS).

Oncolytic virus (OV) therapy has gained attention as an innovative strategy for treating malignant brain tumours. OVs are either genetically engineered or naturally occurring viruses that selectively target and replicate within tumour cells, causing direct oncolysis and triggering systemic antitumour immune responses [13–15]. In glioma, OV therapy presents several potential benefits, such as tumour-selective replication, the induction of immunogenic cell death, and modulation of the immunosuppressive tumour microenvironment [16].

Over the past two decades, various OVs have been developed and clinically evaluated for treating CNS tumours, including herpes simplex virus, adenovirus, poliovirus, reovirus, Newcastle disease virus, and parvovirus [17, 18]. Early-phase clinical trials indicate that OV therapy is generally well tolerated and may show promising clinical activity for certain patients. Notably, teserpaturev/G47Δ has been approved in Japan for treating GBM, supported by promising efficacy data [19]. Recently, there has been growing interest in combining OV therapy with other immunomodulatory strategies, such as immune checkpoint blockade, to boost therapeutic efficacy [20].

Despite the increasing number of clinical studies, most investigations into OV therapy for brain tumours are still in the early phases, typically single-arm trials with small sample sizes and varied study designs. As a result, the overall safety profile and clinical activity of OV therapy for malignant brain tumours have not yet been comprehensively quantified. Therefore, a systematic synthesis of the available evidence is essential to better characterise clinical outcomes across trials and guide future study designs.

In this study, we conducted a systematic review and meta-analysis of prospective clinical trials assessing OV therapy in patients with malignant brain tumours. By integrating data on reported adverse events, objective response rate (ORR), disease control rate (DCR), and survival outcomes, we aimed to offer an updated evaluation of the safety and efficacy of OV therapy and to elucidate its potential role in treating malignant brain tumours. To minimise the risk of overlooking relevant studies, we initially conducted a broad search across CNS tumours. Nonetheless, the eligible clinical evidence primarily concentrated on malignant gliomas, especially GBM.

Methods

Literature and search strategy

This meta-analysis followed the PRISMA reporting guidelines and was registered with PROSPERO (CRD420261286187). Two investigators (X.Y. and W.Z.) independently conducted searches in PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov, covering the period from inception to 31 December 2025. The search terms included combinations of “oncolytic virus”, “oncolytic virotherapy”, “central nervous system tumors”, “brain tumor”, “glioma”, and “glioblastoma”. The complete search strategy for each database is detailed in Supplementary Table SI. Conference abstracts indexed in the searched bibliographic databases were included and screened together with full-text articles. ClinicalTrials.gov records were reviewed individually, and trial records without sufficient extractable outcome data were excluded. No major deviations from the PROSPERO-registered protocol occurred.

Study selection

After eliminating duplicates, we screened titles and abstracts to exclude irrelevant records, followed by a full-text review for eligibility. We included prospective clinical trials that enrolled patients with CNS tumours and evaluated OV therapy, either as monotherapy or in combination with other treatments. The outcomes of interest were all-grade AEs, grade ≥ 3 AEs, events reported as serious adverse events (SAEs), ORR, DCR, 1-year overall survival (OS) rate, median progression-free survival (mPFS), and median overall survival (mOS). Preclinical experiments, case reports, reviews, editorials, and studies lacking extractable

outcome data were excluded. When multiple publications reported overlapping cohorts, the report that provided the most comprehensive clinical information was selected.

Data extraction and quality assessment

Two investigators (W.Z. and M.Z.) independently extracted the data, resolving any disagreements through discussion. The extracted data comprised basic study characteristics such as the first author, year, trial phase, age, viral platform, administration route, tumour type, and sample size, along with available patient characteristics. Efficacy endpoints included ORR, DCR, 1-year OS rate, mPFS, and mOS, while safety outcomes encompassed commonly reported AEs and SAEs. Quality assessment was independently conducted by two investigators (R.Z. and X.Y.) using the MINORS tool for single-arm clinical trials.

Statistical analysis

All analyses were conducted in R using the meta package. Because all included studies were single-arm trials, pooled estimates were calculated using random-effects models. Outcomes, including AEs, SAEs, ORR, DCR, 1-year OS rate, mPFS, and mOS, were synthesised. ORR was defined as the proportion of patients achieving complete response or partial response (CR + PR), while DCR included those achieving complete response, partial response, or stable disease (CR + PR + SD). The 1-year OS rate was the proportion of patients alive at 12 months. mPFS and mOS were extracted as reported in the original studies. AEs and SAEs were summarised according to the definitions used in the included studies. Statistical heterogeneity was assessed with the I^2 statistic and Cochran's Q test, with substantial heterogeneity defined as $I^2 > 50\%$ and $p < 0.10$. Leave-one-out sensitivity analyses were conducted to evaluate the influence of individual cohorts, especially on outcomes with substantial heterogeneity. Subgroup analyses for mOS were conducted by age group, virus species, viral platform, and treatment mode where data were available.

Results

Basic information of studies

A total of 3236 records were identified up to 31 December 2025. The study selection process is detailed in the PRISMA flow diagram (Figure 1). After duplicates were removed and titles and abstracts were screened for eligibility, 24 studies were included in the final analysis [21–41]. Two studies (NCT02986178 2025 and Qian 2025) reported outcomes for two independent treatment groups and were therefore analysed as separate cohorts, leading to a total of 26 cohorts included in the quantitative synthesis.

The 24 studies reviewed were phase I or II single-arm trials, with MINORS scores between 9 and 13 (Supplementary Table SII). Sample sizes varied from small to moderate, ranging from 6 to 121 participants. Of these studies, 18 trials enrolled

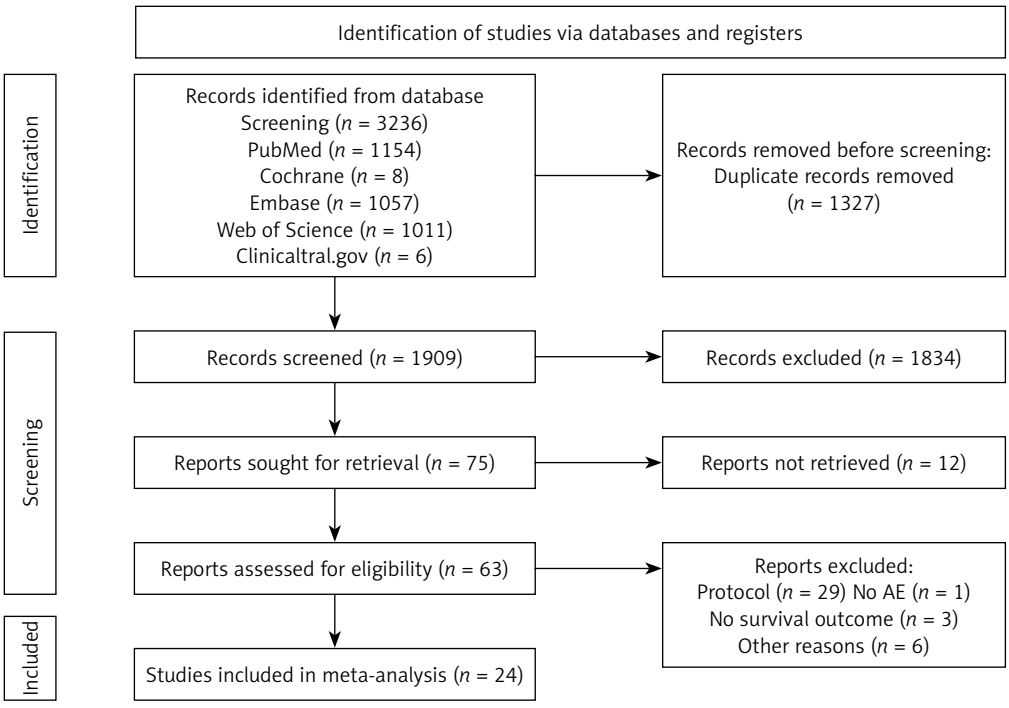


Figure 1. PRISMA flow diagram of study selection. A flow diagram illustrates the process of literature search, screening, eligibility assessment, and study inclusion in the meta-analysis, following the PRISMA guidelines

Table I. Main characteristics of included studies

Study	Study type	Phase	Median age	Viral type	Treatment	Number	Cancer type	Injection mode	MINORS score
Chiocca (2004)	Single-arm	I	52	Adenovirus	ONYX-015	24	Glioma	Intratumoural	9
Nassiri (2023)	Single-arm	I/II	53	Adenovirus	DNX-2401 + pembrolizumab	49	Glioblastoma	Intratumoural	13
Ning (2024)	Single-arm	I	54.9	Adenovirus	Ad-TD-nsIL12	8	Glioma	Intratumoural	11
Qian (2025)	Single-arm	I	6 (Group A) 6.5 (Group B)	Adenovirus	Ad-TD-nsIL12	15	Glioma	Intratumoural	10
Lang (2018)	Single-arm	I	52	Adenovirus	DNX-2401	37	Glioma	Intratumoural	12
Gállego (2022)	Single-arm	I	9	Adenovirus	DNX-2401 + radiotherapy	12	DIPG	Intratumoural	11
van Putten (2022)	Single-arm	I	53.5	Adenovirus	DNX-2401	19	Glioblastoma	CED	12
Fares (2021)	Single-arm	I	52	Adenovirus	NSC-CRAd-S-pk7	12	Glioma	Intratumoural	11
Kieran (2019)	Single-arm	I	12.5	Adenovirus	AdV-tk	8	Glioma/ ependymoma	Intratumoural	11
Markert (2000)	Single-arm	I	54.1	Herpes simplex virus	G207	21	Glioma	Intratumoural	10
Markert (2009)	Single-arm	Ib	54.5	Herpes simplex virus	G207	6	Glioblastoma	Intratumoural	9
Markert (2014)	Single-arm	I	50.2	Herpes simplex virus	G207 + radiotherapy	9	Glioblastoma	Intratumoural	12
Friedman (2021)	Single-arm	I	13.5	Herpes simplex virus	G207	12	Glioma	Intratumoural	11
Todo (2022)	Single-arm	II	51	Herpes simplex virus	G47Δ	19	Glioblastoma	Intratumoural	13
Todo (2022)	Single-arm	I/II	46	Herpes simplex virus	G47Δ	12	Glioblastoma	Intratumoural	12
Freeman (2006)	Single-arm	I/II	49.5	Newcastle disease virus	NDV-HUJ	11	Glioblastoma	Intravenous	10
Geletneky (2017)	Single-arm	I/IIa	57.8	Parvovirus	ParvOryx	18	Glioblastoma	Intratumoural or intravenous	11
NCT03043391 (Istari Oncology 2024)	Single-arm	Ib	16.5	Polio/rhinovirus recombinant	PVSRIPO	8	Glioma	Intratumoural	12
NCT02986178 (Istari Oncology 2025) Cohort A	Single-arm	II	54	Polio/rhinovirus recombinant	PVSRIPO ± lomustine	121	Glioma	Intratumoural	10
NCT04479241 (Istari Oncology 2025) Cohort B	Single-arm	II	55	Polio/rhinovirus recombinant	PVSRIPO + pembrolizumab	25	Glioblastoma	Intratumoural	10
Galanis (2024)	Single-arm	I	53.5	Measles virus	CEA-expressing oncolytic measles virus	22	Glioblastoma	Intratumoural	11
Schuelke (2022)	Single-arm	I	14.3	Reovirus	Pelareorep + sargramostim	6	Glioblastoma/DIPG/ medulloblastoma	Intravenous	13
Forsyth (2008)	Single-arm	I	53.5	Reovirus	Reovirus	12	Glioma	Intratumoural	9
Kicielinski (2014)	Single-arm	I	51.5	Reovirus	Reovirus	15	Glioblastoma	CED	13

DIPG – diffuse intrinsic pontine glioma, CED – convection-enhanced delivery, CEA – carcinoembryonic antigen. MINORS was assessed using the 8-item tool for non-comparative studies (total score 16).

adult patients, and 6 trials focused on paediatric populations.

Regarding tumour characteristics, gliomas constituted the predominant population, and GBM was the most frequently investigated subtype, although a small proportion of studies also enrolled patients with other brain tumours. The viruses investigated included herpes simplex virus, adenovirus, reovirus, parvovirus, measles virus, Newcastle disease virus, and recombinant polio/rhinovirus. Intratumoral administration was the most common injection approach, whereas a minority of studies utilised intravenous infusion. OV therapy was applied either as a monotherapy or combined with other treatment modalities. Study characteristics are detailed in Table I.

Adverse events (AEs)

AEs were common across the studies, but their reported incidence varied significantly. Among haematological toxicities, anaemia had a pooled incidence of 33% (95% CI: 16–55%, I^2 = 76.5%, p = 0.0003) (Figure 2 A), while lymphopaenia was observed at 30% (95% CI: 14–53%, I^2 = 77.4%, p < 0.0001) (Figure 2 B). For non-hematologic toxicities, fatigue was frequently reported, with

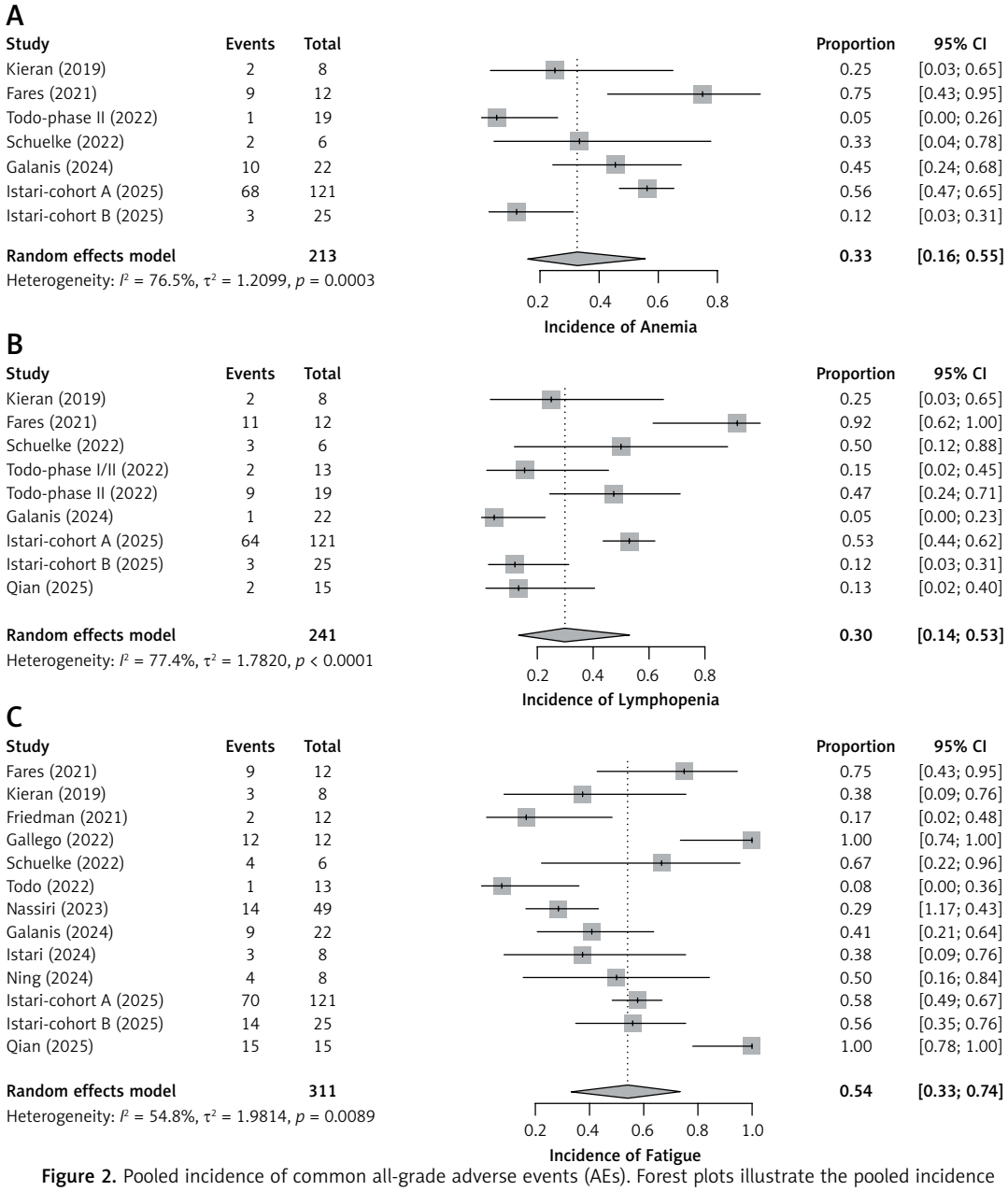
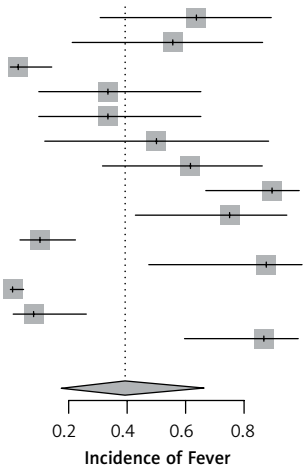


Figure 2. Pooled incidence of common all-grade adverse events (AEs). Forest plots illustrate the pooled incidence of commonly reported all-grade AEs following oncolytic virus (OV) therapy, using random-effects models: anaemia (**A**); lymphopaenia (**B**); fatigue (**C**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

D

Study	Events	Total	Proportion	95% CI
Freeman (2006)	7	11	0.64	[0.31; 0.89]
Markert (2014)	5	9	0.56	[0.21; 0.86]
Lang (2018)	1	37	0.03	[0.00; 0.14]
Fares (2021)	4	12	0.33	[0.10; 0.65]
Friedman (2021)	4	12	0.33	[0.10; 0.65]
Schuelke (2022)	3	6	0.50	[0.12; 0.88]
Todo-phase I/II (2022)	8	13	0.62	[0.32; 0.86]
Todo-phase II (2022)	17	19	0.89	[0.67; 0.99]
Gallego (2022)	9	12	0.75	[0.43; 0.95]
Nassiri (2023)	5	49	0.10	[0.03; 0.22]
Ning (2024)	7	8	0.88	[0.47; 1.00]
Istari-cohort A (2025)	1	121	0.01	[0.00; 0.05]
Istari-cohort B (2025)	2	25	0.08	[0.01; 0.26]
Qian (2025)	13	15	0.87	[0.60; 0.98]
Random effects model		**349**	**0.39**	**[0.17; 0.66]**

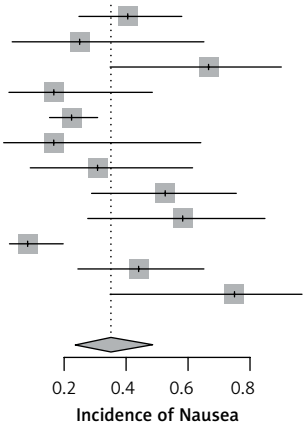
Heterogeneity: I^2 = 85.1%, τ^2 = 3.9888, p < 0.0001



E

Study	Events	Total	Proportion	95% CI
Lang (2018)	15	37	0.41	[0.25; 0.58]
Kieran (2019)	2	8	0.25	[0.03; 0.65]
Fares (2021)	8	12	0.67	[0.35; 0.90]
Friedman (2021)	2	12	0.17	[0.02; 0.48]
Istari-cohort A (2025)	27	121	0.22	[0.15; 0.31]
Schuelke (2022)	1	6	0.17	[0.00; 0.64]
Todo-phase I/II (2022)	4	13	0.31	[0.09; 0.61]
Todo-phase II (2022)	10	19	0.53	[0.29; 0.76]
Gallego (2022)	7	12	0.58	[0.28; 0.85]
Nassiri (2023)	4	49	0.08	[0.02; 0.20]
Istari-cohort B (2025)	11	25	0.44	[0.24; 0.65]
Ning (2024)	6	8	0.75	[0.35; 0.97]
Random effects model		**322**	**0.35**	**[0.24; 0.49]**

Heterogeneity: I^2 = 70.9%, τ^2 = 0.6635, p < 0.0001



F

Study	Events	Total	Proportion	95% CI
Lang (2018)	8	37	0.22	[0.10; 0.38]
Kieran (2019)	2	8	0.25	[0.03; 0.65]
Fares (2021)	4	12	0.33	[0.10; 0.65]
Friedman (2021)	2	12	0.17	[0.02; 0.48]
Schuelke (2022)	1	6	0.17	[0.00; 0.64]
Todo-phase I/II (2022)	6	13	0.46	[0.19; 0.75]
Todo-phase II (2022)	11	19	0.58	[0.33; 0.80]
Ning (2024)	3	8	0.38	[0.09; 0.76]
Istari (2024)	1	8	0.12	[0.00; 0.53]
Istari-cohort A (2025)	87	121	0.07	[0.03; 0.13]
Istari-cohort B (2025)	7	25	0.28	[0.12; 0.49]
Qian (2025)	13	15	0.87	[0.60; 0.98]
Random effects model		**284**	**0.29**	**[0.17; 0.45]**

Heterogeneity: I^2 = 77.0%, τ^2 = 1.0506, p < 0.0001

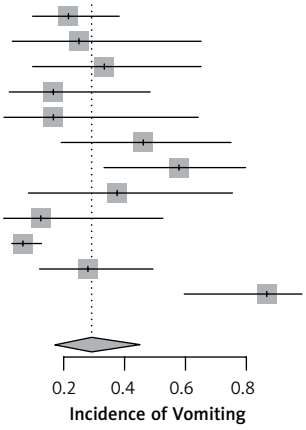


Figure 2. Cont. Fever (**D**); nausea (**E**); vomiting (**F**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

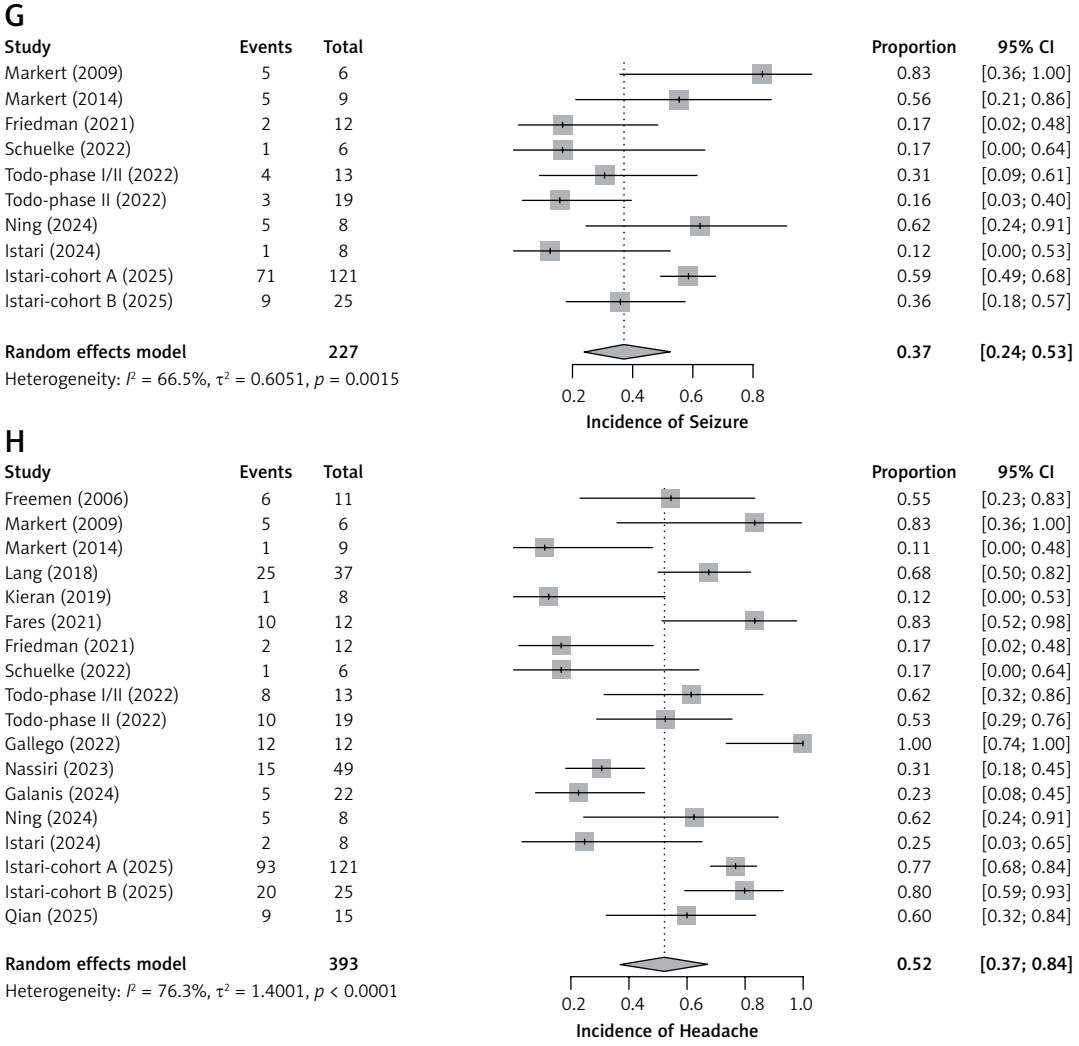


Figure 2. Cont. Seizures (**G**); headache (**H**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

a pooled incidence of 54% (95% CI: 33–74%, I^2 = 54.8%, p = 0.0089) (Figure 2 C). Fever had a pooled incidence of 39% (95% CI: 17–66%, I^2 = 85.1%, p < 0.0001) (Figure 2 D). Gastrointestinal issues were also prevalent, with a pooled incidence of 35% for nausea (95% CI: 24–49%, I^2 = 70.9%, p < 0.0001) (Figure 2 E) and 29% for vomiting (95% CI: 17–45%, I^2 = 77.0%, p < 0.0001) (Figure 2 F). Neurological events were also notable; seizures had a pooled incidence of 37% (95% CI: 24–53%, I^2 = 66.5%, p = 0.0015) (Figure 2 G), and headaches affected nearly half of the patients, with a pooled incidence of 52% (95% CI: 37–67%, I^2 = 76.3%, p < 0.0001) (Figure 2 H). These findings underscore that although the toxicity profile of oncolytic virus therapy is generally manageable, adverse events are common and vary widely across trials.

Leave-one-out sensitivity analyses were performed for each pooled adverse event, showing consistent results. For anaemia, the pooled estimates ranged from 27% to 40% (Supplementary Figure S1 A) and for lymphopaenia from 24% to 36% (Supplementary Figure S1 B), with overlapping confidence intervals. Similar stability was noted for fatigue (47–58%) (Supplementary Figure S1 C), fever (34–47%) (Supplementary Figure S1D), nausea (32–39%) (Supplementary Figure S1 E), vomiting (24–34%) (Supplementary Figure S1 F), seizures (33–41%) (Supplementary Figure S1 G), and headache (49–55%) (Supplementary Figure S1 H). These analyses indicate that no single study disproportionately influenced the pooled estimates, supporting the robustness of the overall safety findings.

Serious adverse events (SAEs)

We summarised grade ≥ 3 AEs and those reported as SAEs. Eight cohorts provided data on the overall incidence of SAEs, which were included in the quantitative analysis. The pooled incidence was 16% (95% CI: 4–45%, I^2 = 0.0%, p = 0.7021) (Figure 3 A). Among specific severe toxicities, headache as an SAE was reported in 10 cohorts, occurring in 7% (95% CI: 4–10%) of patients, with

no observed heterogeneity (I^2 = 0.0%, p = 0.9937) (Figure 3 B). Lymphopaenia as an SAE was noted in four studies, with a pooled incidence of 23% (95% CI: 14–36%, I^2 = 21.3%, p = 0.2826) (Figure 3 C). Vomiting, also reported as an SAE in four studies, was uncommon with a pooled incidence of 6% (95% CI: 2–16%, I^2 = 0.0%, p = 0.8575) (Figure 3 D).

Objective response rate (ORR)

The ORR meta-analysis included seven studies with a total of 135 patients (Figure 4 A). The pooled ORR was 17% (95% CI: 11–26%). A low between-study heterogeneity was observed (I^2 = 0.0%, p = 0.5570), indicating that the ORR estimates were relatively consistent across the studies. These findings suggest that OV therapy is associated with a modest objective response in early-phase clinical studies of malignant brain tumours.

Disease control rate (DCR)

The DCR analysis included 12 cohorts comprising 307 patients (Figure 4 B). The overall pooled DCR

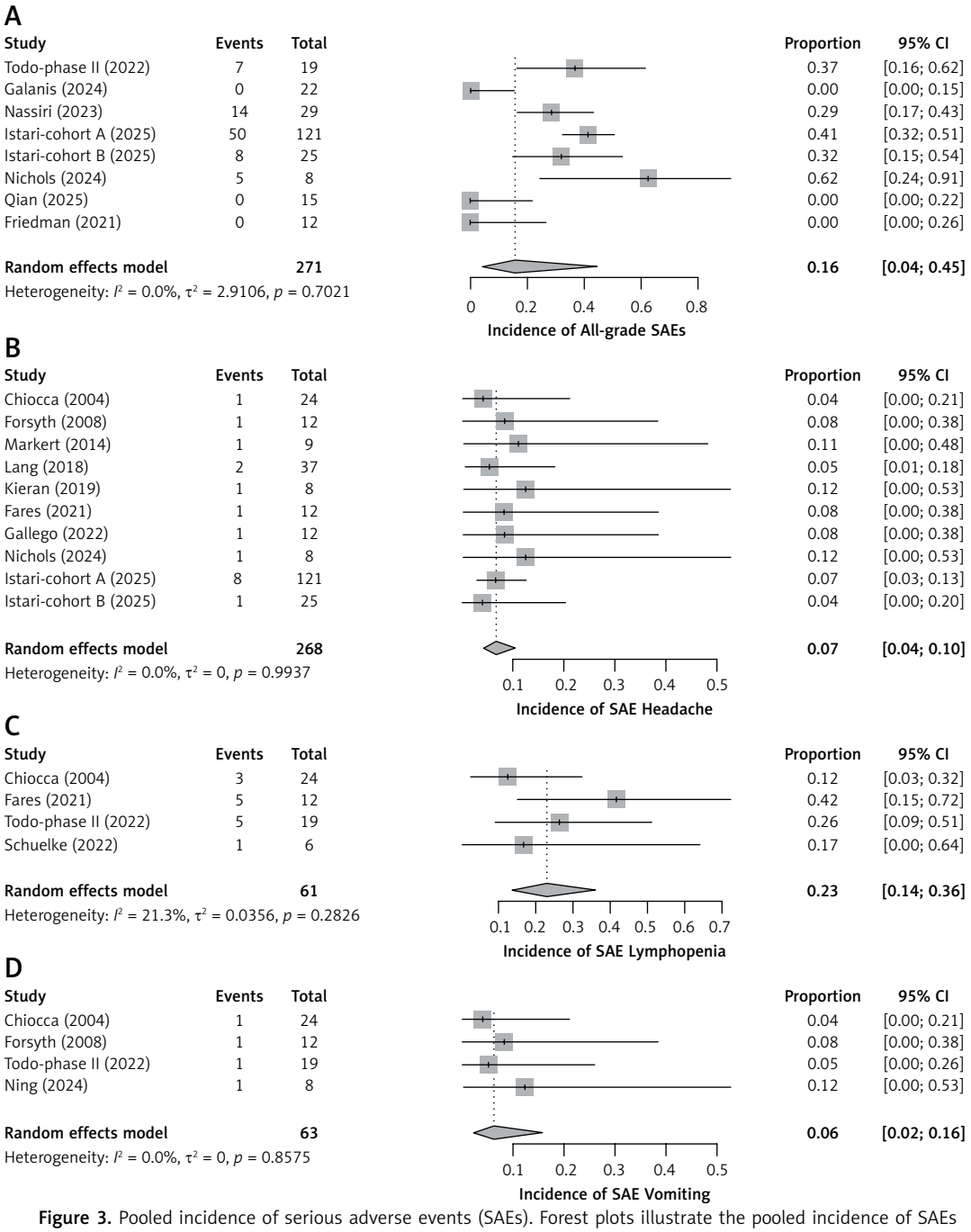


Figure 3. Pooled incidence of serious adverse events (SAEs). Forest plots illustrate the pooled incidence of SAEs across the included cohorts, utilising random-effects models: overall SAEs (**A**), headache (SAE) (**B**), lymphopaenia (SAE) (**C**), and vomiting (SAE) (**D**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

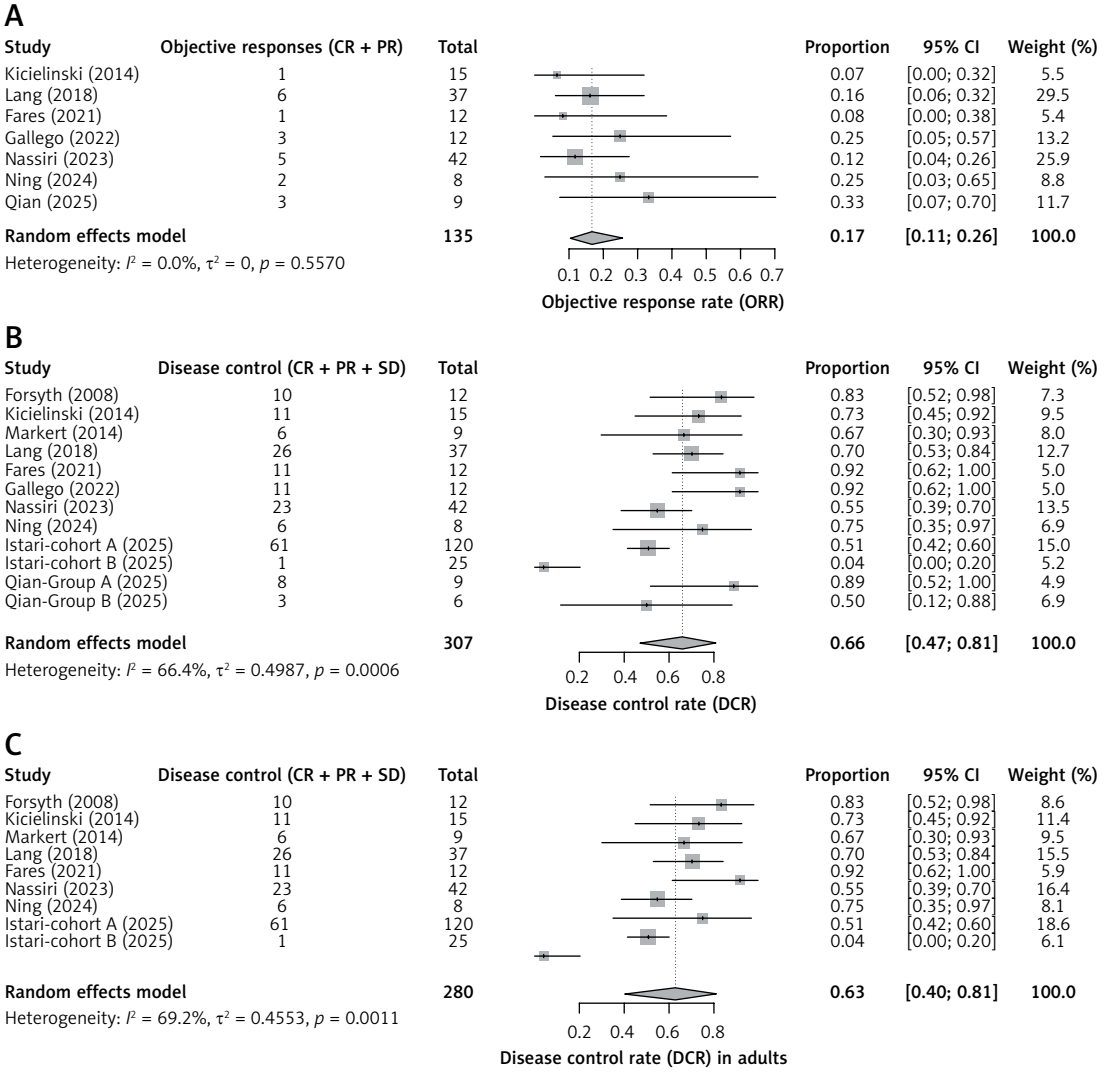


Figure 4. Pooled efficacy outcomes of OV therapy in brain tumours. Forest plots illustrate pooled estimates using random-effects models for three metrics: objective response rate (ORR) (**A**), disease control rate (DCR) (**B**), and DCR specifically in adults (**C**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

was 66% (95% CI: 47–81%), with significant heterogeneity detected between studies (I^2 = 66.4%, p = 0.0006). In the adult group, the pooled DCR was 63% (95% CI: 40–81%, I^2 = 69.2%, p = 0.0011) (Figure 4 C). These findings suggest that OV therapy was associated with disease control in a notable proportion of patients with malignant brain tumours during early-phase clinical trials. A leave-one-out sensitivity analysis was conducted. The sequential exclusion of each study resulted in pooled DCR estimates ranging from 64% to 69% (Supplementary Figure S2 A). No single study disproportionately influenced the pooled effect size or heterogeneity estimates, demonstrating that the results are robust and not dependent on any single study.

1-year OS rate

Five studies that reported 1-year OS were included in the meta-analysis. The pooled 1-year OS rate was 51% (95% CI: 33–67%) (Figure 5 A). There was significant heterogeneity among the studies (I^2 = 65.0%, p = 0.0222), probably due to variations in study design, patient populations, and oncolytic virus platforms. A leave-one-out sensitivity analysis was conducted, revealing that the pooled 1-year OS rate varied from 45% to 56% when each study was omitted in turn (Figure 5 B). No single study disproportionately influenced the pooled effect size. However, substantial between-study heterogeneity remained across iterations (I^2 approximately 15.4–73.2%, overall 65.0%), indicating underlying clinical and methodological differences among the studies.

Median progression-free survival (mPFS)

Ten single-arm clinical studies reporting the mPFS were analysed quantitatively. Using a random-effects model with Hartung–Knapp adjust-

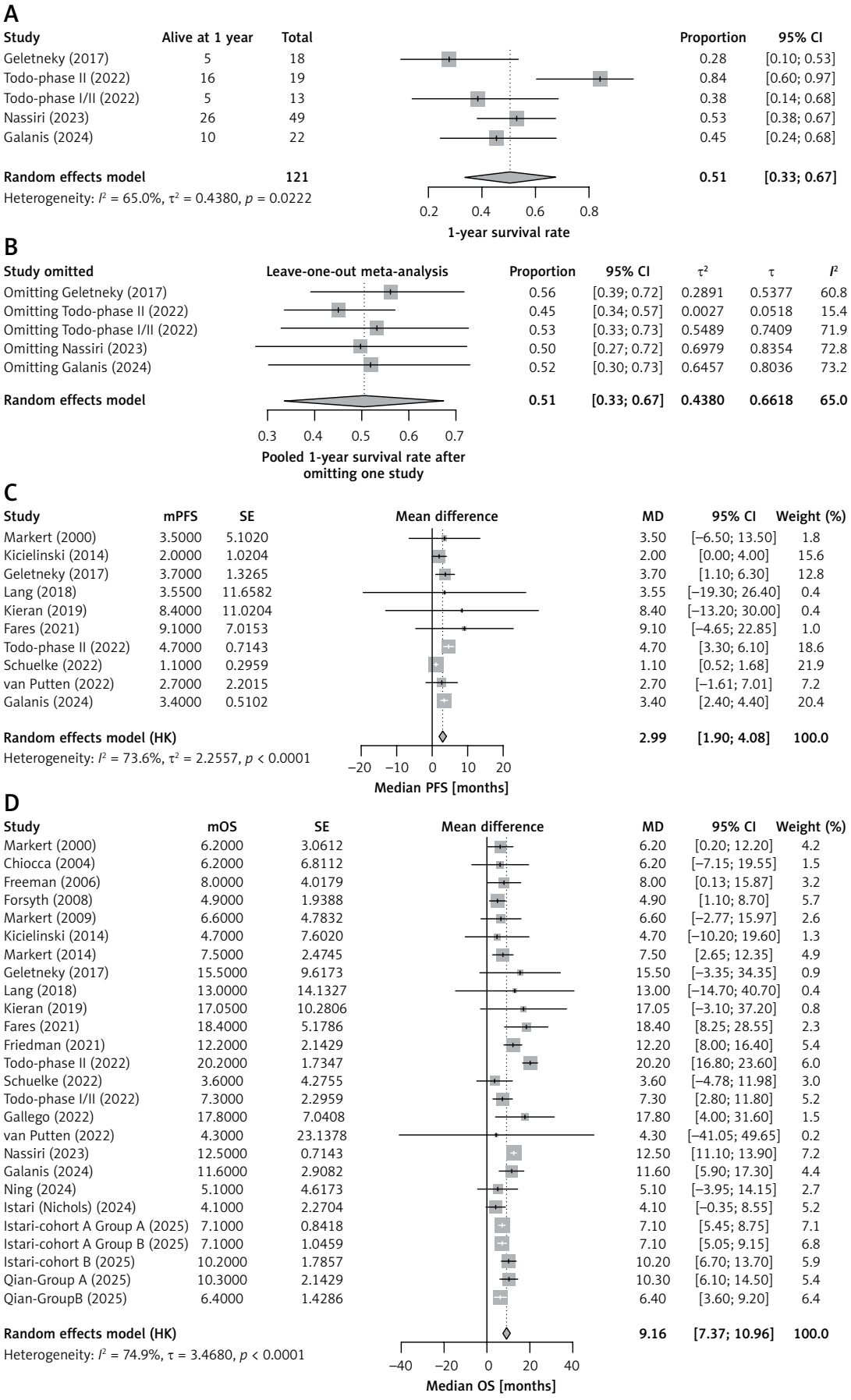


Figure 5. Pooled survival outcomes of OV therapy in brain tumours. **A** – The forest plot illustrates the pooled 1-year overall survival (OS) rate across the included cohorts, analysed using a random-effects model. **B** – A leave-one-out sensitivity analysis for the pooled 1-year OS rate, with each cohort sequentially omitted. **C** – The forest plot displays the pooled median progression-free survival (mPFS) using a random-effects model with Hartung–Knapp adjustment. **D** – The forest plot shows the pooled median overall survival (mOS) using a random-effects model with Hartung–Knapp adjustment. Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

ment, the pooled mPFS was 2.99 months (95% CI: 1.90–4.08 months) (Figure 5 C). Significant heterogeneity was observed among the included studies (I^2 = 73.6%, p < 0.0001), indicating substantial differences in patient populations, treatment regimens, and study designs. The mPFS values in individual studies varied from 1.1 to 9.1 months, with smaller studies showing wider confidence intervals and contributing less weight to the pooled estimate.

A leave-one-out sensitivity analysis was conducted (Supplementary Figure S2 B), revealing pooled mPFS estimates ranging from 2.50 to 3.58 months. The leave-one-out pooled mPFS values remained consistent with the overall result, as shown by overlapping confidence intervals. Exclusion of the study by Schuelke *et al.* significantly reduced heterogeneity, with I^2 dropping from 73.6% to 0%. The pooled mPFS increased to 3.58 months (95% CI: 2.86–4.30).

Median overall survival (mOS)

The pooled mOS across all eligible studies was 9.16 months (95% CI: 7.37–10.96 months, I^2 = 74.9%, p < 0.0001) (Figure 5 D). Exploratory subgroup analyses were conducted to identify potential sources of heterogeneity. In the age-stratified subgroup analysis, studies enrolling adult patients (≥ 18 years) showed a pooled mOS of 9.42 months (95% CI: 7.23–11.61 months, I^2 = 78.3%, p < 0.0001), whereas studies focusing on paediatric patients (< 18 years) yielded a pooled mOS of 8.35 months (95% CI: 4.39–12.32 months, I^2 = 53.7%; p = 0.0436). The test for subgroup differences did not achieve statistical significance (χ^2 = 0.31, df = 1, p = 0.5789) (Figure 6 A), suggesting no significant difference in mOS between adult and paediatric populations.

When stratified by virus species (DNA vs RNA), DNA virus-based therapies exhibited a pooled mOS of 9.76 months (95% CI: 7.37–12.15 months; I^2 = 73.1%), while RNA virus-based therapies had a pooled mOS of 7.57 months (95% CI: 5.46–9.68 months; I^2 = 27.4%). However, the difference between subgroups was not statistically significant (p = 0.1200) (Figure 6 B). Among viral platforms with sufficient data for subgroup analysis, the pooled mOS was 10.36 months for herpes simplex virus (95% CI: 4.47–16.26 months), 10.41 months (95% CI: 7.35–13.47 months) for adenovirus, and 7.27 months (95% CI: 4.36–10.18 months) for recombinant polio/rhinovirus. The test for subgroup differences did not reach statistical significance (p = 0.1076) (Figure 6 C). Additionally, subgroup analysis by treatment mode showed a pooled mOS of 9.13 months (95% CI: 6.86–11.40 months; I^2 = 72.6%) for OV monotherapy and 9.32 months (95% CI: 5.59–13.05 months; I^2 = 78.8%) for combination therapy, with no statistically significant difference between subgroups (p = 0.9147) (Figure 6 D). A leave-one-out sensitivity analysis did not significantly change the pooled estimate, with the recalculated mOS ranging from approximately 8.42 to 9.44 months (Supplementary Figure S2 C).

Discussion

This meta-analysis synthesised the available prospective evidence on OV therapy for malignant brain tumours, focusing on both safety and survival outcomes. The available literature predominantly consists of early-phase, single-arm studies in malignant gliomas. The pooled ORR was 17%, and the pooled DCR reached 66%, indicating that a substantial proportion of patients experienced disease stabilisation. Considering the limited treatment options for recurrence and the generally poor outcomes in high-grade glioma, these findings advocate for the ongoing clinical exploration of OV-based strategies in neuro-oncology [42, 43].

One notable finding was a pooled 1-year OS rate of 51% (95% CI: 33–67%). Despite substantial heterogeneity, this estimate may still suggest potential clinical activity in malignant brain tumours, especially GBM, where prognosis remains poor even with standard therapy [44, 45]. Previous studies of commonly used treatments for recurrent GBM, including lomustine, regorafenib, bevacizumab, and bevacizumab plus lomustine, have generally reported mOS values of approximately 5.6–10.0 months [46–49]. In this context, the pooled mOS of 9.16 months, 1-year OS rate of 51%, and DCR of 66% observed in the present meta-analysis suggest clinical activity of OV therapy in early-phase studies. However, given the single-arm design of the included studies and the heterogeneity in patient populations and treatment settings, this comparison is only contextual and should not be interpreted as evidence that OV therapy is superior to standard treatments.

In addition to directly lysing tumour cells, OV therapy can enhance antitumour immunity by inducing immunogenic cell death, boosting antigen presentation, and altering the immunosuppressive tumour microenvironment. These effects are particularly important in gliomas, where immune exclusion and suppressive myeloid populations often hinder the effectiveness of immunotherapy strategies [50]. These immunomodulatory mechanisms provide a biological rationale for OV-based combination strategies, particularly with immune checkpoint inhibitors. However, the present exploratory subgroup analysis showed broadly similar mOS between monotherapy and combination therapy. Given the limited number of heterogeneous and non-randomised combination cohorts, this result should not be interpreted as evidence

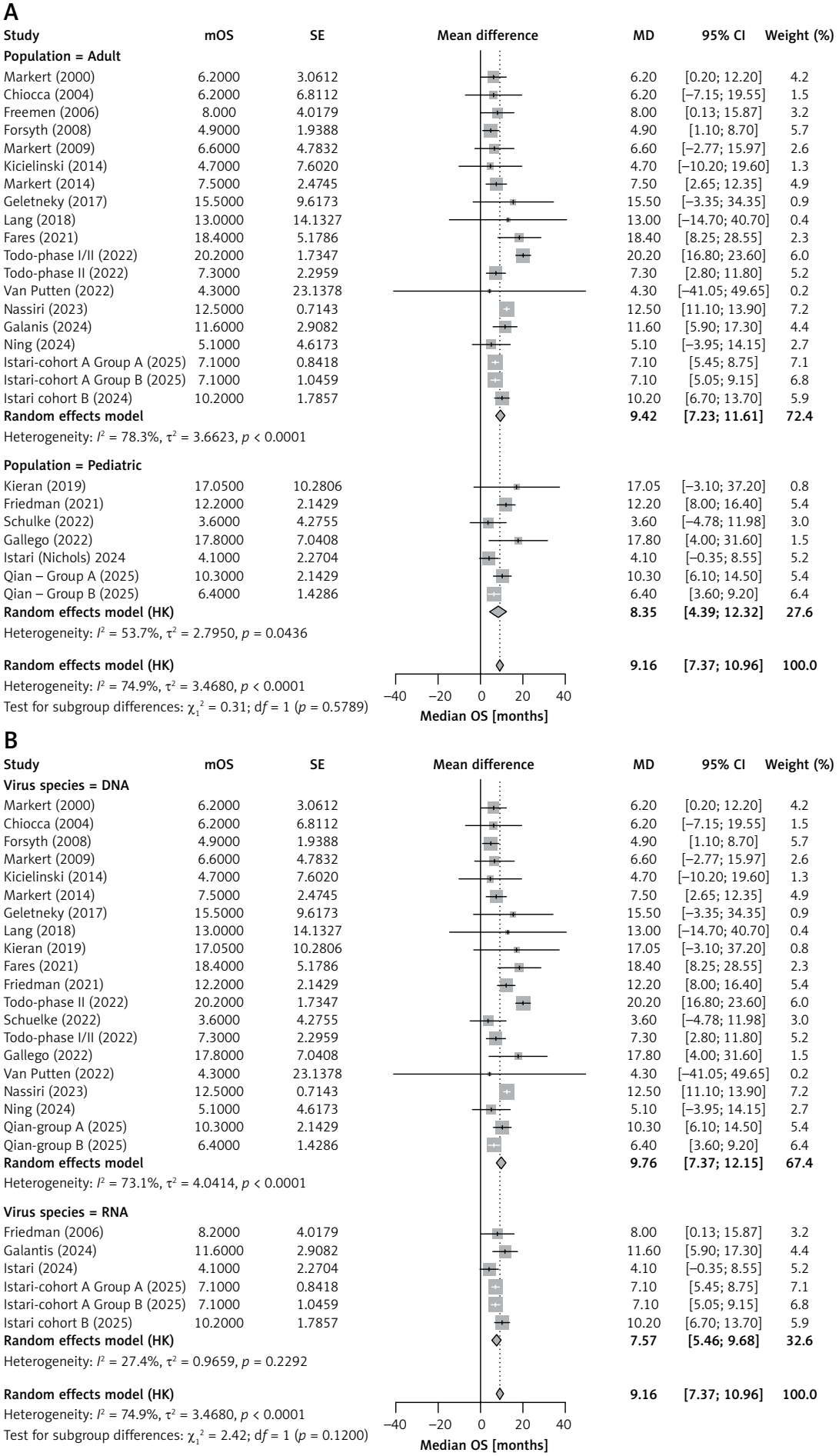
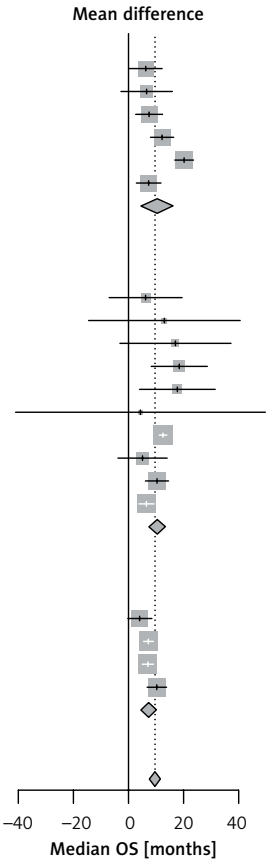


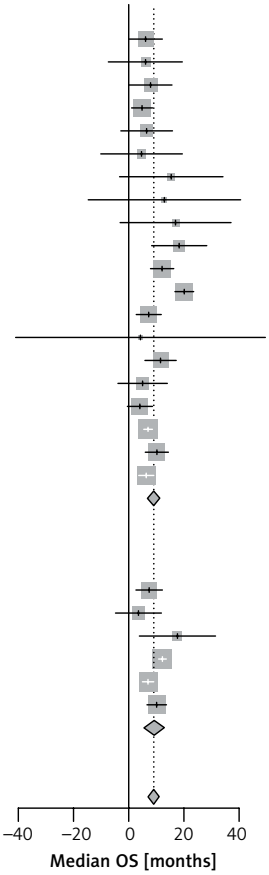
Figure 6. Subgroup analyses of pooled median overall survival (mOS). Forest plots showing subgroup analyses of pooled mOS stratified by age group (adult vs. paediatric) (**A**), virus species (DNA vs. RNA) (**B**). Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

C



Study	mOS	SE	MD	95% CI	Weight (%)
Virus species = Herpes simplex virus					
Markert (2000)	6.2000	3.0612	6.20	[0.20; 12.20]	5.2
Markert (2009)	6.6000	4.7832	6.60	[−2.77; 15.97]	3.2
Markert (2014)	7.5000	2.4745	7.50	[2.65; 12.35]	6.1
Friedman (2021)	12.2000	2.1429	12.20	[8.00; 16.40]	6.6
Todo-phase II (2022)	20.2000	1.7347	20.20	[16.80; 23.60]	7.3
Todo-phase I/II (2022)	7.3000	2.2959	7.30	[2.80; 11.80]	6.4
Random effects model			**10.36**	**[4.47; 16.26]**	**34.8**
Heterogeneity: I^2 = 85.6%, τ^2 = 5.9699, p < 0.0001					
Virus species = Adenovirus					
Chiocca (2004)	6.2000	6.8112	6.20	[−7.15; 19.55]	1.9
Lang (2018)	13.0000	14.1327	13.00	[−14.70; 40.70]	0.5
Kieran (2019)	17.0500	10.2806	17.05	[−3.10; 37.20]	1.0
Fares (2021)	18.4000	5.1786	18.40	[8.25; 28.55]	2.9
Gallego (2022)	17.8000	7.0408	17.80	[4.00; 31.60]	1.8
Van Putten (2022)	4.3000	23.1378	4.30	[−41.05; 49.65]	0.2
Nassiri (2023)	12.5000	0.7143	12.50	[11.10; 13.90]	8.7
Ning (2024)	5.1000	4.6173	5.10	[−3.95; 14.15]	3.4
Qian-group A (2025)	10.3000	2.1429	10.30	[6.10; 14.50]	6.6
Qian-group B (2025)	6.4000	1.4286	6.40	[3.60; 9.20]	7.8
Random effects model			**10.41**	**[7.35; 13.47]**	**34.8**
Heterogeneity: I^2 = 55.7%, τ^2 = 2.9053, p = 0.0161					
Virus species = Recomninant polio/rhinovirus					
Istari (Nichols) (2024)	4.1000	2.2704	4.10	[−0.35; 8.55]	6.4
Istari-cohort A Group A (2025)	7.1000	0.8418	7.10	[5.45; 8.75]	8.5
Istari-cohort A Group B (2025)	7.1000	1.0459	7.10	[5.05; 9.15]	8.3
Istari cohort B (2025)	10.2000	1.7857	10.20	[6.70; 13.70]	7.2
Random effects model (HK)			**7.27**	**[4.36; 10.18]**	**30.4**
Heterogeneity: I^2 = 36.3%, τ^2 = 0.9771, p = 0.1946					
Random effects model (HK)			**9.58**	**[7.45; 11.72]**	**100.0**
Heterogeneity: I^2 = 79.0%, τ^2 = 3.5675, p < 0.0001					
Test for subgroup differences: χ_2^2 = 4.46; df = 2 (p = 0.1076)					

D



Study	mOS	SE	MD	95% CI	Weight (%)
Treatment mode = Single					
Markert (2000)	6.2000	3.0612	6.20	[0.20; 12.20]	4.2
Chiocca (2004)	6.2000	6.8112	6.20	[−7.15; 19.55]	1.5
Freeman (2006)	8.0000	4.0179	8.00	[0.13; 15.87]	3.2
Forsyth (2008)	4.9000	1.9388	4.90	[1.10; 8.70]	5.7
Markert (2009)	6.6000	4.7832	6.60	[−2.77; 15.97]	2.6
Kicielinski (2014)	4.7000	7.6020	4.70	[−10.20; 19.60]	1.3
Geletneky (2017)	15.5000	9.6173	15.50	[−3.35; 34.35]	0.9
Lang (2018)	13.0000	14.1327	13.00	[−14.70; 40.70]	0.4
Kieran (2019)	17.0500	10.2806	17.05	[−3.10; 37.20]	0.8
Fares (2021)	18.4000	5.1786	18.40	[8.25; 28.55]	2.3
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Todo-phase II (2022)	20.2000	1.7347	20.20	[16.80; 23.60]	6.0
Todo-phase I/II (2022)	7.3000	2.2959	7.30	[2.80; 11.80]	5.2
Van Putten (2022)	4.3000	23.1378	4.30	[−41.05; 49.65]	0.2
Galanis (2024)	11.6000	2.9082	11.60	[5.90; 17.30]	4.4
Ning (2024)	5.1000	4.6173	5.10	[−3.95; 14.15]	2.7
Istari (Nichols) (2024)	4.1000	2.2704	4.10	[−0.35; 8.55]	5.2
Istari – cohort A Group A (2025)	7.1000	0.8418	7.10	[5.45; 8.75]	7.1
Qian-group A (2025)	10.3000	2.1429	10.30	[6.10; 14.50]	5.4
Qian-group B (2025)	6.4000	1.4286	6.40	[3.60; 9.20]	6.4
Random effects model			**9.13**	**[6.86; 11.40]**	**70.7**
Heterogeneity: I^2 = 72.6%, τ^2 = 4.0230, p < 0.0001					
Treatment mode = Combination					
Markert (2014)	7.5000	2.4745	7.50	[2.65; 12.35]	4.9
Schuelke (2022)	3.6000	4.2755	3.60	[−4.78; 11.98]	3.0
Gallego (2022)	17.8000	7.0408	17.80	[4.00; 31.60]	1.5
Nassiri (2023)	12.5000	0.7143	12.50	[11.10; 13.90]	7.2
Istari-cohort A Group B (2025)	7.1000	1.0459	7.10	[5.05; 9.15]	6.8
Istari cohort B (2025)	10.2000	1.7857	10.20	[6.70; 13.70]	5.9
Random effects model (HK)			**9.32**	**[5.59; 13.05]**	**29.3**
Heterogeneity: I^2 = 78.8%, τ^2 = 3.0308, p = 0.0003					
Random effects model (HK)			**9.16**	**[7.37; 10.96]**	**100.0**
Heterogeneity: I^2 = 74.9%, τ^2 = 3.4680, p < 0.0001					
Test for subgroup differences: χ_1^2 = 0.01; df = 1 (p = 0.9147)					

Figure 6. Cont. Viral platform (herpes simplex virus, adenovirus, and recombinant polio/rhinovirus) (**C**), treatment mode (monotherapy vs. combination therapy) (**D**), using random-effects models with Hartung–Knapp adjustment. Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test

against combination approaches. Further controlled and biomarker-driven studies are needed to determine whether OV-based combinations provide additional clinical benefit.

AEs were prevalent but generally manageable. The most frequently reported haematological issues were anaemia and lymphopaenia, while common non-haematological toxicities included fatigue, fever, nausea, vomiting, headache, and seizures. It is important to note that the attribution of adverse events was inconsistently reported across the included studies. As a result, some pooled estimates of adverse events may represent a mix of treatment-related toxicity and manifestations of the underlying disease or tumour progression. Therefore, these pooled AE estimates should be interpreted as reported adverse-event incidences rather than definitive treatment-related toxicity rates. This issue is particularly relevant for neurological events such as headache and seizures, which may also be influenced by the underlying tumour, tumour progression, prior treatments, peritumoral oedema, or local administration procedures. Notably, severe toxicity was less common, with a pooled SAE incidence of 16% and minimal heterogeneity, suggesting relatively consistent reporting across trials. The most frequently reported SAEs were headache, lymphopaenia, and vomiting. Overall, this pattern aligns with recent studies, suggesting that OV therapy is generally tolerable and may have a toxicity profile different from that of conventional cytotoxic chemotherapy [51].

Significant heterogeneity was observed across the analyses, especially regarding AEs and survival outcomes. To investigate potential sources of heterogeneity, we conducted additional exploratory subgroup analyses for mOS based on age group, virus species, viral platform, and treatment mode. Although some numerical differences were observed across subgroups, no statistically significant subgroup effects were identified. Specifically, mOS appeared somewhat higher in DNA virus-based therapies than in RNA virus-based therapies. Among viral platforms with sufficient data, HSV and adenovirus showed similar pooled mOS estimates, both of which were numerically higher than that of recombinant polio/rhinovirus. Broadly similar estimates were observed between monotherapy and combination therapy.

Although the observed heterogeneity may be related to differences in viral platforms, administration routes (intratumoural versus intravenous), prior treatments, treatment settings, tumour characteristics, and patient selection criteria, the limited number of included cohorts and small sample sizes may have reduced the statistical power of subgroup analyses. This may partly explain the absence of statistically significant subgroup effects in the mOS analysis, and it limited the feasibility of further stratified analyses for other outcomes, such as AEs, DCR, and mPFS. Despite the observed heterogeneity, leave-one-out analyses indicated that most pooled estimates were not disproportionately influenced by any single study. Notably, the sensitivity analysis suggested that the study by Schuelke was an important contributor to the heterogeneity in mPFS. A plausible explanation is the very small sample size (n = 6) and the use of intravenous rather than intratumoural administration, which may have limited intratumoural exposure due to systemic clearance and barriers to effective CNS penetration [52].

This study has several important limitations. First, substantial heterogeneity exists across various endpoints, reflecting both clinical and methodological diversity among the studies. As more data become available, more extensive subgroup analyses across additional endpoints will be crucial. Second, the majority of the evidence comes from phase I/II single-arm trials, with no randomised phase III studies available for inclusion. These early-phase studies are prone to selection bias, often enrolling highly selected patients with relatively favourable performance status. As a result, the pooled analysis relies on non-comparative data, limiting the ability to draw definitive conclusions about treatment efficacy. Additionally, publication bias could not be reliably assessed for several endpoints because of the limited number of included studies, and the possibility of selective publication of positive findings cannot be excluded. Third, the pooled analyses of mPFS and mOS should be interpreted cautiously because median survival outcomes do not account for censoring distributions and may not be directly comparable across studies with varying follow-up durations. In addition, differences in response criteria and assessment timing across trials may have limited the comparability of pooled ORR and DCR estimates. Finally, most included studies focused on malignant gliomas, particularly glioblastomas, with limited evidence for other brain tumour subtypes. Due to the insufficient number of studies and small sample sizes in non-glioma tumours, meaningful subgroup analyses by tumour subtype were not possible. Therefore, our findings are largely driven by glioma populations, and their generalisability to other brain tumour types should be interpreted with caution.

In conclusion, this meta-analysis suggests that OV therapy is feasible and generally tolerable in patients with malignant brain tumours, with manageable toxicity and a relatively low incidence of SAEs. Although the available evidence is derived mainly from early-phase, single-arm studies and

remains non-confirmatory, the pooled outcomes provide descriptive evidence compatible with potential clinical activity, mainly reflected by observable disease control and survival outcomes despite modest objective responses. However, these findings should be interpreted cautiously given the non-comparative nature of the available evidence. Future well-designed and large-scale trials are essential to better define efficacy, optimise treatment strategies, and evaluate the safety and efficacy of OV therapy across various brain tumour subtypes.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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