ScienceDirect

Critical Reviews in Oncology/Hematology

Volume 222, June 2026, 105279

Immunotherapy failure in glioblastoma: A systematic review and meta-analysis of randomized controlled trials

Tomasz Tykocki [a] [b]

[a] Department of Paediatric Neurosurgery, Children's Hospital named after prof. dr med. Jan Bogdanowicz in Warsaw, Poland

[b] Faculty of Medicine, Lazarski Medical University in Warsaw, Poland

Received 17 February 2026, Revised 2 March 2026, Accepted 12 March 2026, Available online 14 March 2026, Version of Record 24 March 2026.

What do these dates mean?

Check for updates

Show less

Share Cite

https://doi.org/10.1016/j.critrevonc.2026.105279 ↗ Get rights and content ↗

Highlights

- Immunotherapy fails to improve overall survival in randomized glioblastoma trials.
- Pooled OS shows a consistent unfavorable effect with low between-study heterogeneity.
- Apparent PFS and ORR benefits are driven by small, early-phase studies.
- Phase III trial status predicts worse survival outcomes with immunotherapy.

- Findings indicate systematic translational failure in glioblastoma immunotherapy.

Abstract

Background

Immunotherapy has transformed outcomes in several solid tumors but has repeatedly failed to demonstrate benefit in glioblastoma. Early-phase signals of activity have not translated into improved survival in randomized trials, creating uncertainty regarding its true clinical value.

Methods

A systematic review and random-effects meta-analysis of randomized controlled trials (RCTs) evaluating immunotherapy in adult glioblastoma was conducted in accordance with PRISMA 2020. PubMed, Embase, and Scopus were searched through December 2025. Overall survival (OS) was the primary outcome; progression-free survival (PFS) and objective response rate (ORR) were secondary outcomes. Hazard ratios (HRs) and odds ratios (ORs) were pooled using random-effects models. Heterogeneity, publication bias, and meta-regression were assessed.

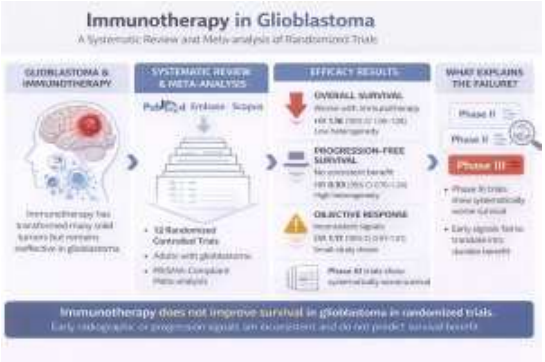
Results

Twelve RCTs were included. Immunotherapy was associated with significantly worse OS compared with control (pooled HR = 1.16, 95% CI 1.06–1.28; I^2 = 14.2%). No OS benefit was observed in any individual trial. PFS (11 trials) showed no consistent improvement (pooled HR = 0.93, 95% CI 0.70–1.24; $I^2 \approx 78\%$), and ORR (OR = 1.17, 95% CI 0.91–1.51) demonstrated heterogeneous, non–survival-concordant signals driven by small studies. Meta-regression identified phase III trial status as the dominant predictor of unfavorable OS effects.

Conclusions

Randomized trials demonstrate no improvement in overall survival with immunotherapy in glioblastoma, while signals in progression-free survival and objective response remain inconsistent and biased, with no survival concordance.

Graphical Abstract



Download: Download high-res image (225KB)

Download: Download full-size image

Introduction

Glioblastoma remains emblematic of therapeutic resistance in solid oncology. Despite maximal multimodal treatment incorporating surgery, radiotherapy, and alkylating chemotherapy, survival expectations remain tightly constrained within a narrow temporal window that has shown little population-level shift since the introduction of temozolomide-based chemoradiotherapy (Stupp et al., 2005, Stupp et al., 2017) The absence of meaningful survival extension despite successive waves of systemic therapeutic development highlights not merely a lack of effective agents, but a deeper failure of prevailing treatment paradigms to disrupt the underlying biology of the disease.

In this context of therapeutic stagnation, immunotherapy emerged as a particularly compelling strategy. Immune checkpoint blockade and related immune-based approaches have transformed outcomes in multiple solid tumours, producing durable responses and long-term surviva (Borghaei et al., 2015, Hodi et al., 2010, Topalian et al., 2012). Parallel advances in tumour immunology challenged the view of glioblastoma as immunologically inert, identifying tumour-associated antigens, immune cell infiltration, and mechanisms of immune evasion within a profoundly immunosuppressive microenvironment (Dunn et al., 2012, Quail and Joyce, 2017, Woroniecka et al., 2018). Together, these observations provided a strong biological rationale for the rapid clinical translation of immunotherapy in glioblastoma.

Over the past decade, this rationale drove an unprecedented expansion of clinical trials evaluating diverse immunotherapeutic platforms. Immune checkpoint inhibitors were tested alone and in combination with radiotherapy, temozolomide, or anti-angiogenic therapy; vaccine-based strategies targeted tumour-associated or neoantigenic epitopes; oncolytic and gene-modified viral therapies sought to couple direct cytotoxicity with immune activation; and adoptive cellular approaches aimed to overcome local immune suppression (Lim et al., 2022, Omuro et al., 2022, Reardon et al., 2020a). Early-phase studies frequently demonstrated biological activity, including immune activation and radiographic tumour regression, fostering optimism regarding clinical translation.

However, this optimism has not been borne out in randomized testing. Large randomized controlled trials of immune checkpoint blockade in both newly diagnosed and recurrent glioblastoma have consistently failed to improve overall survival (Cloughesy et al., 2020, Weller et al., 2017, Wen et al., 2019). Similarly, vaccine-based and viral immunotherapies that generated early-phase enthusiasm have not translated into durable benefit in later-phase trials. Notably, several studies reported discordant secondary signals—such as improvements in progression-free survival or objective response rate—without corresponding survival benefit (Cloughesy et al., 2019, Desjardins et al., 2018).

In glioblastoma, such discordance is particularly consequential. Surrogate endpoints are vulnerable to bias from pseudoprogression, corticosteroid exposure, evolving imaging criteria, and treatment-related inflammatory effects, limiting their reliability as indicators of true clinical benefit (Brandsma and van den Bent, 2009, Ellingson et al., 2017, Okada et al., 2015). The repeated emergence of early efficacy signals that fail to translate into survival improvement suggests a pattern of translational failure rather than isolated trial-specific limitations.

A systematic review and meta-analysis of randomized controlled trials was conducted to evaluate immunotherapy in glioblastoma, focusing on overall survival and key secondary outcomes to determine whether randomized evidence supports therapeutic benefit or consistent failure.

Section snippets

Study design and selection

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive search of PubMed/MEDLINE, Embase, and Scopus was performed to identify English-language studies published from January 2005 through December 2025 evaluating immunotherapeutic interventions in adult patients with glioblastoma. The meta-analysis was registered in PROSPERO database.

The combined search string applied across databases (with database-specific syntax adaptations) was:

…

Results

A systematic literature search was performed in PubMed, Embase, and the Cochrane Central Register of Controlled Trials from database inception to the final search date. The search identified 1243 records. After removal of 312 duplicates, 931 unique records were screened at the title and abstract level.

Of these, 881 records were excluded for irrelevance, non-glioblastoma populations, non-immunotherapeutic interventions, or non-comparative study designs. Fifty full-text articles were assessed for …

Discussion

This review deliberately prioritized trial-level causal inference by restricting inclusion to randomized controlled trials with extractable overall survival effects. Of 50 full-text studies screened, only 12 met these criteria, reflecting a literature base dominated by single-arm and early-phase studies that cannot resolve efficacy in a disease where historical controls are unstable and radiographic endpoints are confounded. This RCT-only selection is clinically consequential because most …

Limitations

This analysis has several limitations. First, although restricted to randomized trials, included studies were heterogeneous with respect to immunotherapy modality, line of therapy, and control regimens, which may limit generalisability of pooled estimates. Second, progression-free survival and objective response rate were subject to variable assessment criteria, open-label designs, and small-study effects, increasing susceptibility to bias and imprecision. Third, several effect estimates were …

Conclusions

In this systematic review and random-effects meta-analysis restricted to randomized controlled trials, immunotherapy did not improve overall survival in patients with glioblastoma. Across 12 trials spanning multiple immunotherapeutic classes and disease settings, pooled estimates showed a consistent and statistically significant association with worse survival in experimental arms compared with standard therapy, with low between-study heterogeneity. These findings indicate that, despite a …

Ethical approval

This study is a systematic review and meta-analysis of previously published research. Ethical approval was not required. …

Funding

This research received no specific grant from any funding agency in the public, commercial, or

not-for-profit sectors. ...

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ...

Recommended articles

References (42)

M.E. Barish *et al.*
Spatial organization of heterogeneous immunotherapy target antigen expression in high-grade glioma
Neoplasia N. Y N. (2022)

D.Y. Cho *et al.*
Adjuvant immunotherapy with whole-cell lysate dendritic cells vaccine for glioblastoma multiforme: a phase II clinical trial
World Neurosurg. (2012)

B.M. Ellingson *et al.*
Modified criteria for radiographic response assessment in glioblastoma clinical trials
Neurother. J. Am. Soc. Exp. Neurother. (2017)

H. Okada *et al.*
Immunotherapy response assessment in neuro-oncology: a report of the RANO working group
Lancet Oncol. (2015)

D.F. Quail *et al.*
The microenvironmental landscape of brain tumors
Cancer Cell (2017)

M. Weller *et al.*
Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial
Lancet Oncol. (2017)

J. Yang *et al.*
Targeting EGFRvIII for glioblastoma multiforme
Cancer Lett. (2017)

K.C. Arbour *et al.*
Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer
J. Clin. Oncol. J. Am. Soc. Clin. Oncol. (2018)

H. Borghaei *et al.*
Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer
N. Engl. J. Med. (2015)

D. Brandsma *et al.*
Pseudoprogression and pseudoresponse in the treatment of gliomas
Curr. Opin. Neurol. (2009)

View more references

Cited by (1)

HOXD9 affecting glioma proliferation and invasion ↗
2026, Cytotechnology

View full text