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RESEARCH ARTICLE

Advances and challenges in glioblastoma immunotherapy: a meta-analysis of immune checkpoint inhibitors

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Abstract

Introduction Glioblastoma (GBM) remains the most aggressive primary brain tumor, with poor prognosis and limited therapeutic options. Immune checkpoint inhibitors have shown promising results in solid tumors, but their role in GBM remains uncertain.

Methods A PRISMA-based systematic review and meta-analysis including studies evaluating checkpoint inhibitors in newly diagnosed and recurrent GBM. Random-effects models calculated pooled hazard ratios for OS and PFS.

Results Eleven studies were included, six ($n = 2{,}019$) incorporated into pooled survival analyses. No significant OS benefit was observed (HR = 1.12; 95% CI: 0.97–1.29; $I^2 = 0\%$; $p = 0.138$). PFS showed significant differences (HR = 1.34; 95% CI: 1.06–1.68; $I^2 = 74.3\%$; $p = 0.013$). Grade ≥ 3 toxicity occurred in 32.1% of patients.

Conclusion Checkpoint inhibitors did not significantly improve OS or PFS in GBM patients and were associated with substantial toxicity and inter-study heterogeneity.

Keywords Glioblastoma · Immunotherapy · Nivolumab · Ipilimumab · Overall survival · Progression-free survival

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant tumor of the central nervous system, classified as grade IV by the World Health Organization (WHO) [1–3]. This type of tumor originates from astrocytes and presents high cellular heterogeneity, rapid growth, and diffuse invasiveness, making its complete removal difficult [1, 4]. GBM can arise from the malignant progression of a pre-existing lower-grade astrocytoma (10% of cases), or develop directly as a grade 4 tumor (90% of cases). Epidemiologically, GBM occurs most frequently in adults between 55 and 65 years of age, being slightly more prevalent in males [5, 6]. The median overall survival rate of patients, even with adequate treatment, ranges between 12 and 15 months, while the five-year survival rate is below 5% [2, 7].

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The risk factors for the development of this tumor are poorly understood. Despite medical advances, GBM still has an unknown etiology and no means that could have influenced its emergence have been discovered. Thus, it accounts for 14.5% of all CNS tumors and is the most aggressive diffuse glioma of the astrocytic lineage, remaining an incurable tumor [1, 2, 5]. Since 2021, the WHO recognizes molecular subtypes of gliomas: Glioblastoma IDH wildtype, IDH-mutant astrocytoma, IDH-mutant oligodendroglioma with 1p/19q codeletion[8].

Conventional treatment follows a multimodal approach, which includes maximum surgical resection, radiotherapy, and chemotherapy with temozolomide [4]. Surgery aims to reduce the tumor burden and relieve neurological symptoms caused by the mass effect [8]. However, due to the infiltrative nature of the tumor, it is nearly impossible to remove all neoplastic cells, making adjuvant treatment essential. Radiotherapy is applied to eliminate residual tumor cells and is frequently combined with temozolomide, an alkylating agent that promotes DNA damage in tumor cells, potentiating the cytotoxic effect [8, 9].

Bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), was introduced in

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GBM treatment to reduce tumor angiogenesis and cerebral edema [10, 11]. However, despite improving quality of life and reducing the need for corticosteroids, bevacizumab did not demonstrate a significant impact on overall survival. Furthermore, its toxicity profile, including an increased risk of thrombotic events and arterial hypertension, led to a reduction in its recommendation as first-line therapy [11].

Treatment depends on multiple factors, including age, functional status (Karnofsky scale), molecular tumor profile (such as MGMT promoter methylation and IDH1/2 mutation), and extent of surgical resection [12]. Younger patients with better functional performance are generally candidates for aggressive combined therapy, which includes maximum possible surgical resection, followed by fractioned concomitant radiotherapy with daily temozolomide chemotherapy, plus adjuvant cycles of temozolomide after radiotherapy [13]. On the other hand, older individuals or those with significant comorbidities may receive less intensive therapeutic regimens, such as hypofractionated radiotherapy, with or without temozolomide, depending on the molecular status of the tumor and the patient's clinical conditions [14].

Due to glioblastoma's resistance to conventional treatments, new therapeutic targets and therapy combination strategies are being researched with the aim of improving efficacy in treating this type of tumor. In recent years, innovative therapies have been investigated for GBM treatment. CAR-T cell therapy, which has demonstrated success in hematological neoplasms, involves genetic modification of T lymphocytes to recognize specific tumor antigens. However, its application in GBM faces significant challenges, such as tumor heterogeneity, low expression of specific targets, and the presence of the blood–brain barrier, which limits the penetration of modified cells into the brain. Even so, this approach continues to be explored as a possibility for the future [15–17].

Beyond checkpoint inhibitors and CAR-T cell therapy, other immunotherapeutic strategies, including tumor vaccines, oncolytic viruses, and bispecific antibodies, have been investigated in glioblastoma, yet all face significant limitations. Tumor vaccines and oncolytic viruses are hindered by the tumor's low immunogenicity, antigenic heterogeneity, and antiviral host responses. Bispecific antibodies, while promising in hematologic malignancies, are undermined in glioblastoma by the blood–brain barrier, poor T-cell infiltration, and heterogeneous target expression. Collectively, these challenges reflect glioblastoma's intrinsically immunosuppressive microenvironment, low mutational burden, and robust immune evasion mechanisms, which impair the generation of durable antitumor immune responses. [18–20]

Immunotherapy has established itself as a promising alternative in cancer treatment and is one of the focuses of this study. Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, tislelizumab (anti-PD-1), and atezolizumab (anti-PD-L1), act by blocking mechanisms that inhibit T cell activation, allowing a more efficient immune response against tumor cells [21]. Additionally, ipilimumab, an anti-CTLA-4 antibody, is also being explored as part of combined strategies, seeking to further stimulate the immune system [22]. However, GBM presents an immunosuppressive microenvironment, characterized by the presence of immunoregulatory cells, low T lymphocyte infiltration, and production of pro-immunosuppressive factors, which reduces the efficacy of these therapies. Clinical trials are evaluating the impact of these approaches, alone and in combination, in an attempt to overcome these barriers and improve immune responses in GBM [9].

Given the aggressiveness of GBM and the limitations of conventional therapies, immunotherapy emerges as an innovative alternative that can significantly impact patient prognosis [15]. Despite the challenges, advances in understanding the tumor microenvironment and the development of new immunotherapeutic strategies make this approach a promising field of study. Deepening investigations into its efficacy in GBM can open new perspectives for treating the disease, broadening therapeutic possibilities and potentially improving patient survival [23]. Thus, obtaining results from this study is crucial to verify whether it is possible to overcome the limitations of conventional treatments, improving not only survival rates but also quality of life.

This study aims to analyze the current perspective on advances and challenges in glioblastoma treatment, with an emphasis on immunotherapy as a promising intervention. It seeks to identify the most effective modality, discuss its main approaches and challenges, and recognize risks, side effects, and possible complications. It also intends to evaluate the impact on patients' quality of life and survival, relating these factors to the development of the intervention and its prognosis.

Methods

Research type

We conducted a systematic review in accordance with the protocols established by the Cochrane Collaboration and following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [24]. The study protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identification number CRD420251126758.

Eligibility criteria

Two reviewers (AGSB, CSRP) independently examined articles for inclusion. Any conflicts were resolved by a third

author (EHID). Inclusion in this systematic review was restricted to studies meeting all of the following eligibility criteria: (1) randomized clinical trials; (2) observational studies; (3) cohort studies; (4) studies in humans; (5) patients with glioblastoma who have already undergone conventional treatments; (6) inoperable patients; (7) direct comparisons between conventional treatments with or without the use of immunotherapy; (8) studies with outcomes analyzing survival rates and intervention effects; (9) studies demonstrating the effects of immunotherapy for glioblastoma.

Exclusion criteria included: (1) studies that do not explicitly specify the use of immunotherapy, such as nivolumab, pembrolizumab, tislelizumab, atezolizumab, and ipilimumab; (2) unpublished or incomplete clinical trials; (3) studies that do not directly compare the outcome of conventional treatment (radiotherapy, temozolomide, and surgical resection) with the use of immunotherapy; and (4) duplicate publications.

Search strategy and data extraction

The systematic search encompassed the PubMed, Embase, and Cochrane Library databases. The final search was performed on February 27, 2025, establishing the cutoff date for study inclusion in this systematic review. The search strategy employed was: ("Glioblastoma") AND ("Immunotherapy" OR "nivolumab" OR "pembrolizumab" OR "tislelizumab" OR "atezolizumab" OR "ipilimumab") AND ("chemotherapy" OR "temozolomide" OR "bevacizumab").

After removing duplicates, the titles and abstracts of the remaining studies were screened in Rayyan. Titles and abstracts were reviewed based on eligibility criteria. Subsequently, selected articles were submitted to detailed analysis through full reading. These processes were performed independently by two reviewers (A.G.S.B. and C.S.R.P.) to minimize bias. Discrepancies were resolved by a third reviewer (E.H.I.D.) and consensus was reached among all three reviewers.

Two authors (AGSB, CSRP) independently extracted data to obtain the following information from each study: author names, year of publication, country of origin, inclusion criteria, number of patients, patient age, patient sex, previously used treatments, follow-up, immunotherapeutic interventions used, main findings for quality of life, survival, and adverse effects. Any discrepancies were resolved by a third author (EHID).

Quality assessment

Data analysis followed the same systematic approach, with double independent assessment and conflict resolution by a third reviewer. The most relevant effects of immunotherapy on quality of life and survival, compared to conventional or isolated alternative therapies, were highlighted. Methodological quality of studies was assessed using the RoB 2 tool from the Cochrane Collaboration for randomized clinical trials [25], the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies for non-randomized clinical trials [26], and the Newcastle–Ottawa Scale (NOS) for cohort studies [27].

Additionally, the overall quality of the evidence was assessed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines. Studies were categorized into four certainty levels (very low, low, moderate, or high), considering factors such as risk of bias, inconsistency of results, imprecision, and publication bias [28]. The outcomes analyzed encompassed overall survival, progression-free survival, toxicity, and safety, evaluated according to the time horizon defined in each study.

Compliance with ethical standards

This study is a systematic review based exclusively on previously published data and does not involve direct experimentation with human subjects or animals. Therefore, ethical approval was not required.

Statistical analysis

Pooled estimates were calculated using a random-effects model with the inverse variance method. For single-arm analyses, proportion meta-analyses were performed using a random-effects model with inverse variance weighting and logit transformation (PLOGIT). For time-to-event outcomes, hazard ratios (HRs) and corresponding 95% confidence intervals were converted to the logarithmic scale, and standard errors were calculated from confidence interval widths before pooling. Additionally, leave-one-out sensitivity analyses were conducted to assess the robustness of the findings. All analyses and plots were performed using RStudio 4.5.1 [29].

Results

Study selection

As illustrated in Fig. 1, our search identified 4,356 results: 944 from PubMed, 4,320 from Embase, and 187 from the Cochrane Library. Of these, 1,095 were identified as duplicates and 4,247 were excluded based on their title and/or abstract for not meeting the inclusion criteria. Subsequently, 109 studies were submitted to full-text review, of which 11 met the eligibility criteria and were included in this systematic review. The included studies comprised 7 randomized

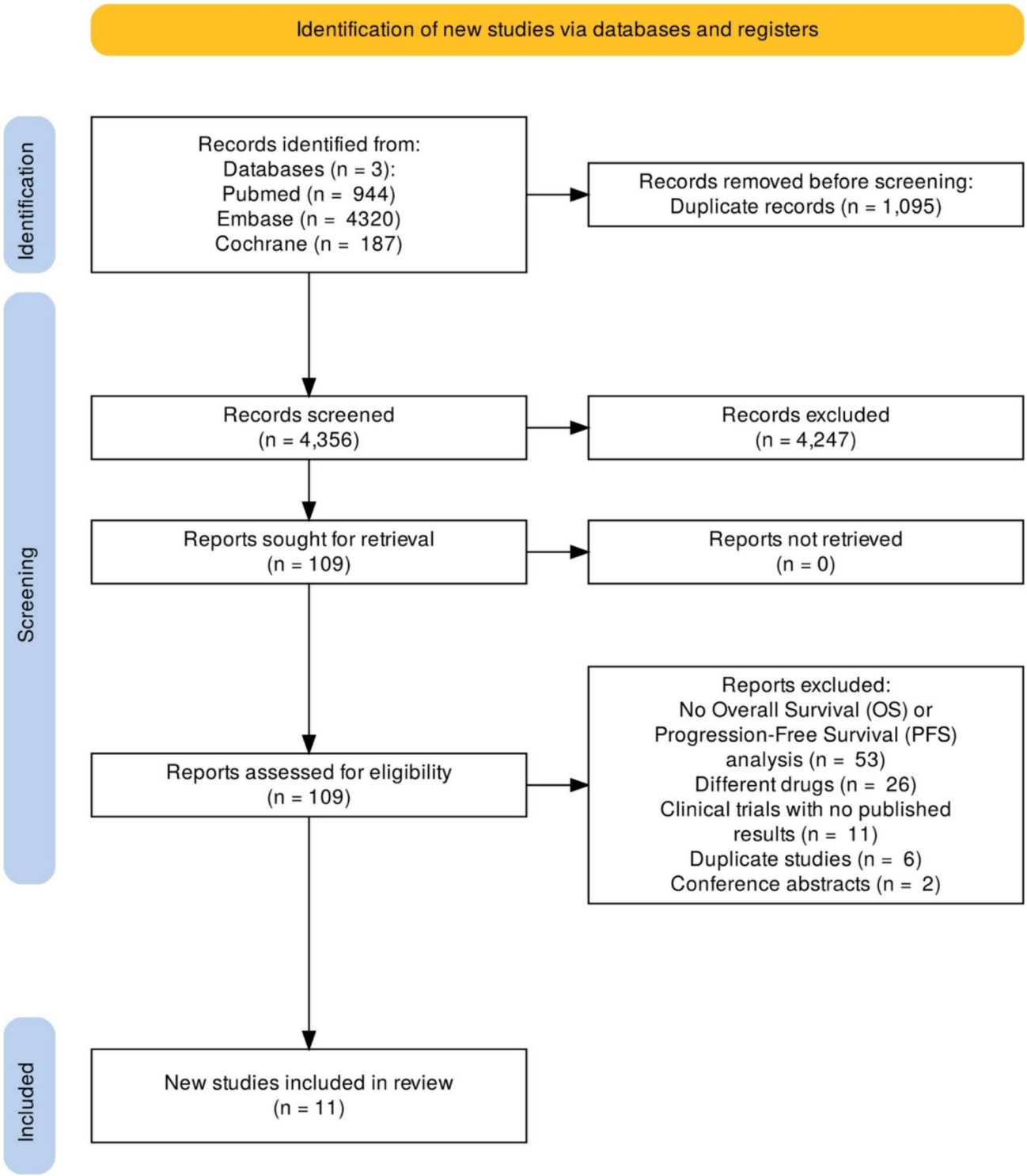

Fig 1. PRISMA flow diagram of study selection

clinical trials, 1 retrospective cohort, and 3 non-randomized clinical trials. A total of 2,270 patients were included; across the analyzed studies, treatments involved Nivolumab, Bevacizumab, and Ipilimumab.

Of the 11 articles, 10 used nivolumab as intervention or control [30, 32–40], 3 used ipilimumab as intervention [31, 33, 40] and 2 used bevacizumab as a comparator to nivolumab [35, 38]. In addition, patients underwent standard

treatments with surgical resection, radiotherapy (RT), and temozolomide (TMZ), according to the specific inclusion criteria of each study.

Participant ages ranged from 18 to 84 years, all diagnosed with glioblastoma, encompassing both newly diagnosed cases and recurrent tumors. The characteristics of the studies are presented in Table 1 and summarized in Table 2.

Population and study characteristics

Among the 11 studies, 3 were conducted with recurrent glioblastoma patients [30, 35, 38] and 8 with newly diagnosed patients [31–34, 36, 38–40]. The most common inclusion criteria in recurrent tumor studies involved patients previously submitted to surgical resection, RT, and TMZ, in most cases at first relapse. In newly diagnosed studies, patients received standard treatment prior to or concomitant with immunotherapy. In all 11 studies, all patients underwent surgical resection, either partial or total. All data used in this meta-analysis are available in the supplementary information.

Overall survival (OS) outcomes

The overall survival meta-analysis included six studies totaling 2,019 patients and is presented in Fig. 2a. Of these, five studies involved patients with newly diagnosed disease ($n = 1{,}650$) and one study included patients with recurrent disease ($n = 369$). In the subgroup of newly diagnosed patients, the pooled hazard ratio was 1.14 (95% confidence interval: 0.96 to 1.36; $I^2 = 0\%$), indicating no heterogeneity among studies. In the study with recurrent patients, the HR was 1.04 (95% CI: 0.83 to 1.30). The combined overall hazard ratio was 1.12 (95% CI: 0.97 to 1.29; $I^2 = 0\%$), with no statistically significant effect observed ($p = 0.138$). These results indicate that, for the outcome of overall survival, combination therapy did not demonstrate superior benefit compared to the control, either in the general population or in the subgroups analyzed.

Progression-free survival (PFS) outcomes

Six studies, with the same total of 2,019 patients, were included in the progression-free survival analysis and are presented in Fig. 2b. In the newly diagnosed patient group, the pooled HR was 1.22 (95% CI: 1.04 to 1.44; $I^2 = 36.4\%$), suggesting low-to-moderate heterogeneity. In the recurrent patient group, the HR was 1.97 (95% CI: 1.57 to 2.48), indicating a substantially larger effect. The combined overall effect was 1.34 (95% CI: 1.06 to 1.68; $I^2 = 74.3\%$), reaching statistical significance ($p = 0.013$), demonstrating that combination therapy significantly reduced the risk of disease progression relative to the control group. Furthermore, the difference between subgroups was highly significant ($p = 0.0008$), indicating that the observed benefit was more pronounced among patients with recurrent disease.

Treatment discontinuation

Ten studies, encompassing 1,183 patients, were analyzed with respect to treatment discontinuation rates and are presented in Fig. 2c. Among newly diagnosed patients, the pooled discontinuation rate was 19.1% (95% CI: 6.9% to 43.1%; $I^2 = 94.8\%$), while among recurrent patients the rate was 27.1% (95% CI: 2.6% to 84.0%; $I^2 = 97.8\%$). The overall discontinuation rate was 21.2% (95% CI: 8.4% to 44.0%; $I^2 = 96.5\%$). Despite the numerical difference between subgroups, the test for subgroup differences was not statistically significant ($p = 0.7596$). The extremely high heterogeneity in both subgroups and in the overall analysis suggests that study-specific factors — such as differences in therapeutic protocols, patient profiles, and discontinuation criteria — substantially influenced the observed rates.

Grade ≥ 3 toxicity

Eleven studies, totaling 1,194 patients, provided data on grade 3 or higher adverse events and are presented in Fig. 2d. In the subgroup of newly diagnosed patients, the pooled proportion of severe toxicity was 41.1% (95% CI: 31.0% to 52.0%; $I^2 = 90.1\%$). Among recurrent patients, the proportion was significantly lower, at 16.7% (95% CI: 12.7% to 21.6%; $I^2 = 0\%$). The combined overall rate was 32.1% (95% CI: 22.2% to 44.1%; $I^2 = 92.0\%$). The difference between subgroups was highly significant ($p < 0.0001$), indicating that newly diagnosed patients faced a substantially higher risk of serious adverse events when undergoing combination therapy. The high heterogeneity in the newly diagnosed subgroup suggests considerable variation across studies, while the complete homogeneity in the recurrent subgroup ($I^2 = 0\%$) indicates consistency in results among the three studies that comprised this analysis.

Sensitivity analyses

To investigate the sources of heterogeneity observed across the different outcomes, leave-one-out analyses were performed and Baujat plots were constructed for all outcomes, presented in Figs. 3, 4. Regarding overall survival, the study by Omuro et al. was identified as the primary contributor to heterogeneity in the Baujat plot; however, its exclusion did not meaningfully alter the pooled hazard ratio nor reduce heterogeneity, which remained at $I^2 = 0\%$.

For progression-free survival, the studies by Omuro et al. and Sim et al. were identified as the main sources of heterogeneity. The simultaneous removal of these two studies

Table 1. Characteristics of included studies and main outcomes

Author/Year	Study Title	Intervention and Control	Eligibility Criteria	Median Overall Survival (OS)	Median Progression-Free Survival (PFS)	Main Side Effects/Toxicity
Aoki et al. 2021 [30]	Efficacy and safety of nivolumab in Japanese patients with first recurrence of glioblastoma: an open-label, non-comparative study	Nivolumab (3 mg/kg, IV, every 2 weeks) (N = 50)	Tumor type: recurrent – 1 st relapse Prior Treatment: Temozolomide and radiotherapy KPS ≥ 70, Life expectancy ≥ 12 weeks	13,1 months (10,4–17,7)	1,5 months (1,4–1,5)	Fatigue, pruritus, anorexia, skin rash Grade 3 events: skin rash, elevated lipase, anorexia, pruritus One patient died (due to disease progression)
Brown et al. 2025 [31]	A Phase II, open label, randomised study of ipilimumab with temozolomide versus temozolomide alone after surgery and chemoradiotherapy in patients with recently diagnosed glioblastoma (IPI-GLIO)	Intervention: Ipilimumab (3 mg/kg, IV, every 3 weeks × 4 doses) + Temozolomide (TMZ) Control: Temozolomide (TMZ) (N = 119)	Tumor type:newly diagnosed Prior Treatment – Surgery and radical radiotherapy with concomitant temozolomide	18,2 months (16-23,9 months) (Intervention) vs 23 months (17,3 a 26,4 months) (Control)	10,8 months vs 12,5 months	Most common adverse events in both groups: fatigue, headache, nausea Seizures (9%), thrombocytopenia (8%), diarrhea (6%), autoimmune colitis (5%), skin rash (5%) in the Ipilimumab + TMZ group
Kesari et al. 2024 [32]	Pre-radiation Nivolumab plus ipilimumab in patients with newly diagnosed high-grade gliomas	Nivolumab (300 mg, IV, every 2 weeks) + Ipilimumab (1 mg/kg, IV, every 6 weeks) (N = 15)	Tumor type – newly diagnosed Prior Treatment – Planned surgical resection or already submitted to surgery, KPS ≥ 60	19,3 months	1,3 months	Grade 1/2 adverse events. One death due to disease progression. Most common adverse events in both groups: fatigue, pruritus, anorexia, skin rash, nausea. One grade 4 cerebral edema. No grade 5 dose-limiting events occurred
Lassman et al. 2025 [33]	A Randomized Phase II/III Open-Label Study of Ipilimumab and Nivolumab Versus Temozolomide in Patients With Newly Diagnosed MGMT (Tumor O-6-Methylguanine DNA Methyltransferase) Unmethylated Glioblastoma	Intervention: Ipilimumab (1 mg every 4 weeks, max 4 doses) + Nivolumab (3 mg/kg every 2 weeks or fixed 240 mg after ipilimumab completion) until disease progression + RT (6 adjuvant cycles of 28 days with up to 12 cycles). Control: Radiotherapy combined with TMZ (N = 159)	Tumor type – newly diagnosed, MGMT unmethylated Prior Prior Treatment – Surgical resection	Insufficient final data for analysis	7,7 months (Intervention) vs 8,5 months (Control)	Grade 3/4 adverse events. Reported in 26 (33.3%) and 4 (5.1%) in the immunotherapy arm. 2 treatment-related deaths in the immunotherapy arm. 9 patients (11.5%) with gastrointestinal disorders ≥ 3. Reported in 22 (29.7%) and six (8.1%) patients in the TMZ arm

Table 1. (continued)

Author/Year	Study Title	Intervention and Control	Eligibility Criteria	Median Overall Survival (OS)	Median Progression-Free Survival (PFS)	Main Side Effects/Toxicity
Lim et al. 2022 [34]	Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter	Intervention: NIVO (240 mg every 2 weeks, then 480 mg every 4 weeks) + Radiotherapy (RT) + Temozolomide (TMZ) Control: Placebo + RT + TMZ (N = 709)	Tumor type – newly diagnosed, MGMT methylated Prior treatment – Surgical resection	28,9 months (24,4–31,6) (Intervention) vs 32,1 months (29,4—33,8) (Control)	10,6 months (NIVO + TMZ + RT) vs 10,3 months (Placebo + TMZ + RT)	TRAEs of any grade in 92.4% (NIVO + RT + TMZ) vs 83.6% (PBO + RT + TMZ) Grade 3/4 TRAEs: 52.4% vs 33.6% Nausea (34.1%), fatigue (32.8%). 141 (Intervention) and 52 (Control) discontinued
Mantica et al. 2018 [35]	Retrospective study of nivolumab for patients with recurrent high grade gliomas	Intervention: NIVOLUMAB IV (3 mg/kg, with 60-min infusion, once every 2 weeks). Each therapeutic cycle lasted 14 days, with nivolumab administered on day 1 of each cycle. + BEVACIZUMAB Control: NIVOLUMAB IV (3 mg/kg, with 60-min infusion, once every 2 weeks) (N = 50)	Tumor type – Recurrent, refractory to bevacizumab or extensively pre-treated. Prior treatment – Total/partial surgical resection, RT, TMZ or Bevacizumab	6,5 months (intervention and control)	4,3 months (intervention and control)	Treatment adverse events were: fatigue, constipation 4 patients had grade 3 and 4 events Peripheral neuropathies, autoimmune retinopathy, myopathy or internuclear ophthalmoplegia
Omuro et al. 2022 [36]	Nivolumab plus radiotherapy with or without temozolomide in newly diagnosed glioblastoma: Results from exploratory phase I cohorts of CheckMate 143	NIVO + RT + TMZ or NIVO + RT. Nivolumab (3 mg/kg, IV, every 2 weeks); RT (60 Gy); TMZ (concomitant and adjuvant) Part A: (NIVO + RT + TMZ) and (NIVO + RT) Part B: (NIVO + RT + TMZ) and (NIVO + RT) (N = 117)	Tumor type – newly diagnosed Prior treatment – surgical resection	Part A: MGMT met/unk: 33.38 months; MGMT unmet: 16.49 (N + R + T)/14.41 (N + R) Part B: MGMT unmet: 14.75 (N + R + T)/13.96 (N + R)	Part A: MGMT met/unk: 15.47 months; MGMT unmet: 6.47 (N + R + T)/5.59 (N + R) Part B: MGMT unmet: 6.47 (N + R + T)/6.01 (N + R)	Grade 3/4 TRAEs higher with TMZ (46.4–51.6% vs 28.6–30%). Lymphopenia (most common). Discontinuation due to TRAEs: 12.9–17.9%

Table 1. (continued)

Author/Year	Study Title	Intervention and Control	Eligibility Criteria	Median Overall Survival (OS)	Median Progression-Free Survival (PFS)	Main Side Effects/Toxicity
Omuro et al. 2023 [37]	A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor 06-methylguanine DNA methyltransferase)	Intervention: NIVO (240 mg every 2 weeks for 8 doses, then NIVO 480 mg every 4 weeks until toxicity or disease progression) + RT (60 Gy in 2 Gy fractions) Control: TMZ + RT (N = 560)	Tumor type – newly diagnosed, MGMT unmethylated Prior treatment – Complete and partial surgical resection	13,4 months (NIVO + RT) vs 14,9 months (TMZ + RT)	6,0 months (NIVO + RT) vs 6,2 months (TMZ + RT)	Nausea (NIVO + RT) vs Fatigue (TMZ + RT) Grade 3/4 TRAEs: 25.1% (TMZ + RT) Neurological TRAEs in 9.5% (TMZ + RT)
Reardon et al. 2020 [38]	Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial	Intervention: Nivolumab (3 mg/kg, IV, every 2 weeks) Control: Bevacizumab (10 mg/kg, IV, every 2 weeks) (N = 369)	Tumor type – Recurrent Prior treatment – Previous surgery, previous radiotherapy (≥ 12 weeks), without previous surgery (≥ 28 days) KPS ≥ 70	9,8 months (intervention) vs 10 months (control)	1,5 months (intervention) vs 3,5 months (control)	Fatigue (Nivolumab). Hypertension (Bevacizumab) Grade 3/4 TRAEs: 18.1% (Nivo) vs 15.2% (Bevac) 175 (Nivo) and 158 (Bevac) discontinued
Sim et al. 2023 [39]	NUTMEG: A randomized phase II study of nivolumab and temozolomide versus temozolomide alone in newly diagnosed older patients with glioblastoma	Intervention: Hypofractionated chemoradiation + Adjuvant Nivolumab + Adjuvant TMZ Control: Hypofractionated chemoradiation + Adjuvant TMZ (N = 103)	Tumor type – newly diagnosed, elderly patients Prior treatment – Total/partial surgical resection	11,6 months (Intervention) vs 11,8 months (Control)	7,4 months (Intervention) vs 5,9 months (Control)	Fatigue, nausea, thrombocytopenia, headache Grade 3 + : pulmonary infection, sepsis, gait disorder 31 discontinuations (disease progression and patient and investigator preference)
Sloan et al. 2024 [40]	NRG-BN002: Phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma	Intervention: Ipilimumab (1 mg/kg every 4 weeks × 4 cycles) + Nivolumab (3 mg/kg every 2 weeks × 16 cycles) Control: Nivolumab (3 mg/kg every 2 weeks × 16 cycles) (N = 19)	Tumor type – newly diagnosed Prior treatment – Chemoradiotherapy with TMZ. Total/partial surgical resection KPS ≥ 70	20,7 months vs 11,1 months	16,1 months vs 5,3 months	Skin disorders (Grade 3), Grade 4 events (15.4%), elevated lipase (Grade 4) Dexamethasone impacted efficacy

Table 2. Main outcomes of included studies

Author/Year	Population	MGMT Status	OS (months)	PFS (months)	Main Toxicity
Aoki et al. 2021 [30]	Recurrent	Not reported	13,1 months (10,4–17,7)	1,5 months (1,4–1,5)	Fatigue, pruritus, anorexia, skin rash. Grade 3 events
Brown et al. 2025 [31]	Newly diagnosed	Not reported	18,2 vs 23 months	10,8 vs 12.5 months	Fatigue, nausea, autoimmune colitis, seizures
Kesari et al. 2024 [32]	Newly diagnosed	Not reported	19,3 months	1,3 months	Fatigue, pruritus, cerebral edema (G4)
Lassman et al. 2025 [33]	Newly diagnosed	Unmethylated	Not available	7,7 vs 8,5 months	Grade ¾ eventos, treatment- related deaths
Lim et al. 2022 [34]	Newly diagnosed	Methylated	28,9 vs 32,1 months	10,6 vs 10,3 months	High rate of adverse events (UP to 52,4% G3/4)
Mantica et al. 2018 [35]	Recurrent	Not reported	6,5 months	4,3 months	Neuropathy, retinopathy, grade ¾ events
Omuro et al. 2022 [36]	Newly diagnosed	Methylated/Unmethylated	33,38 (meth)/˜14–16 (unmeth)	15,47 (meth)/˜5 6 (unmeth)	Lymphopenia, high Grade ¾ event rate
Omuro et al. 2023 [37]	Newly diagnosed	Unmethylated	13,4 vs 14,9 months	6 vs 6,2 months	Nausea, neurological events
Reardon et al. 2020 [38]	Recurrent	Not reported	9,8 vs 10 months	1,5 vs 3,5 months	Fatigue, hypertension
Sim et al. 2023 [39]	Recurrent	Not reported	11,6 vs 11,8 months	7,4 vs 5,9 months	Pulmonary infection, sepsis
Sloan et al. 2024	Newly diagnosed	Not reported	20,7 vs 11,1 months	16,1 vs 5,3 months	Grade ¾ eventos, skin toxicity

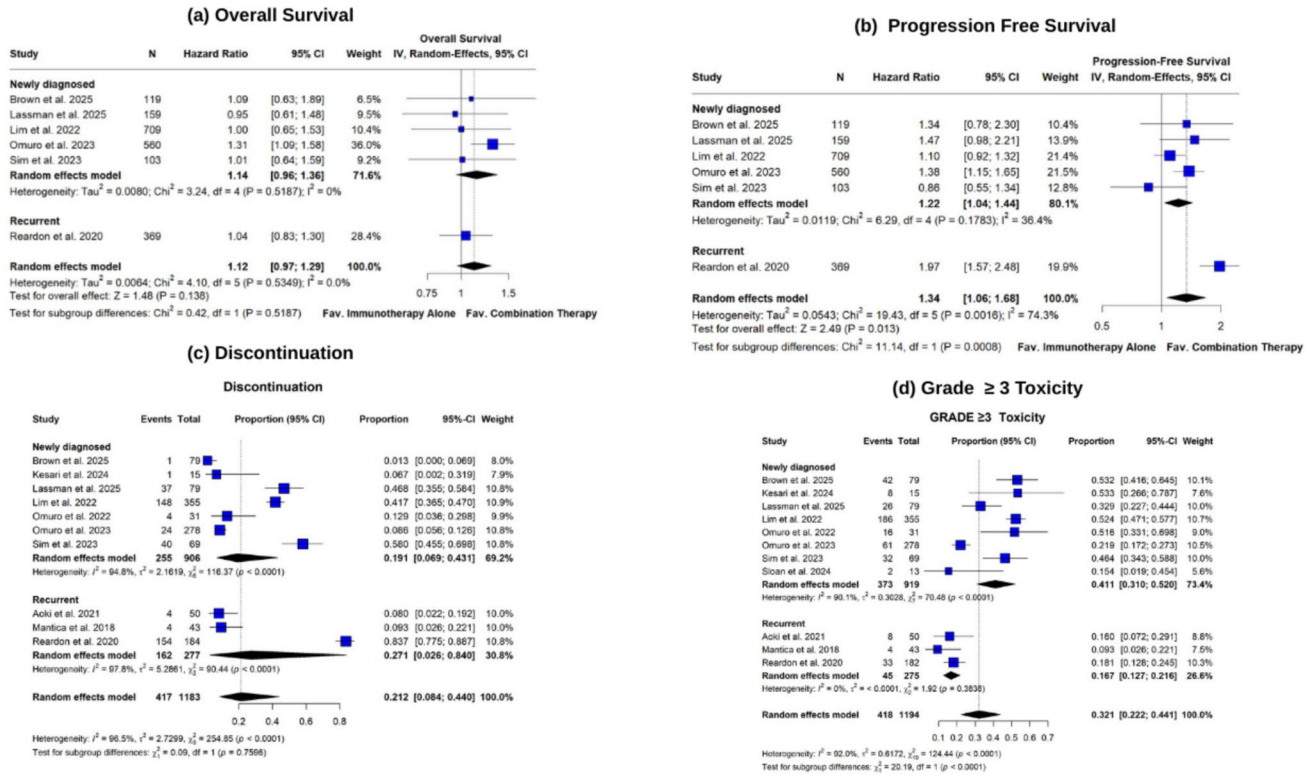

Fig 2. **a** Overall Survival. **b** Progression Free Survival. **c** Discontinuation. **d** Grade ≥ 3 Toxicity

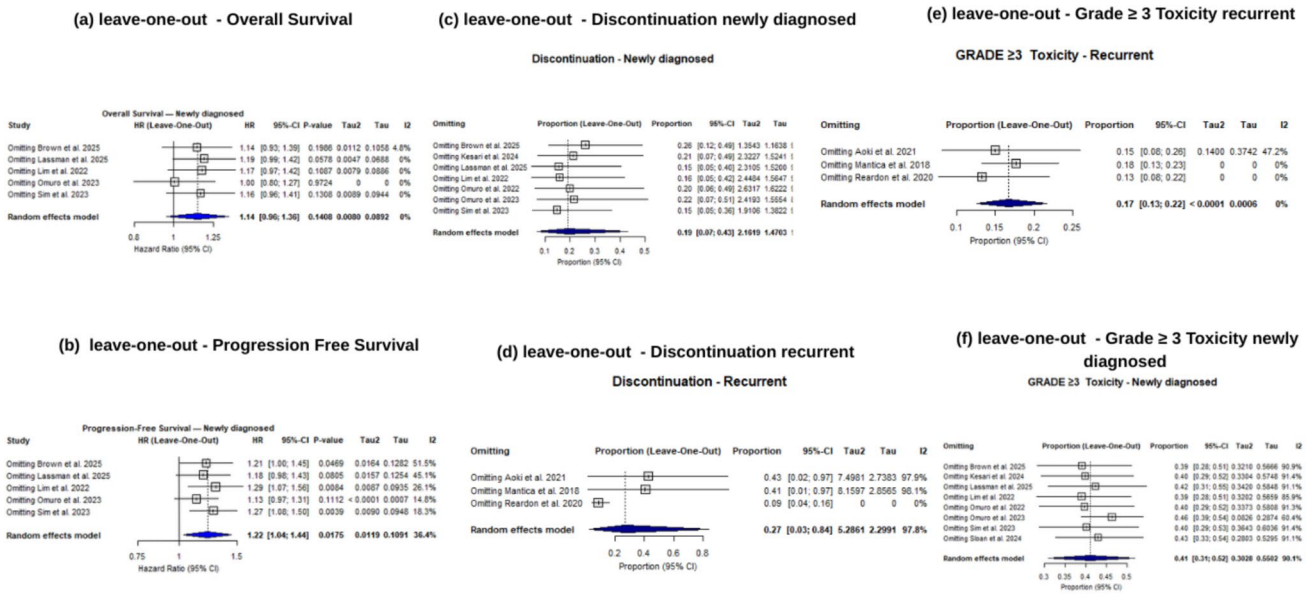

Fig 3 Sensitivity analyses/leave-one-out. **a** Leave-one-out—Overall Survival. **b** Leave-one-out—Progression Free Survival. **c** Leave-one-out—Discontinuation newly diagnosed. **d** Leave-one-out—Discontinuation recurrent. **e** Leave-one-out—Grade ≥ 3 Toxicity recurrent. **f** Leave-one-out—Grade ≥ 3 Toxicity newly diagnosed

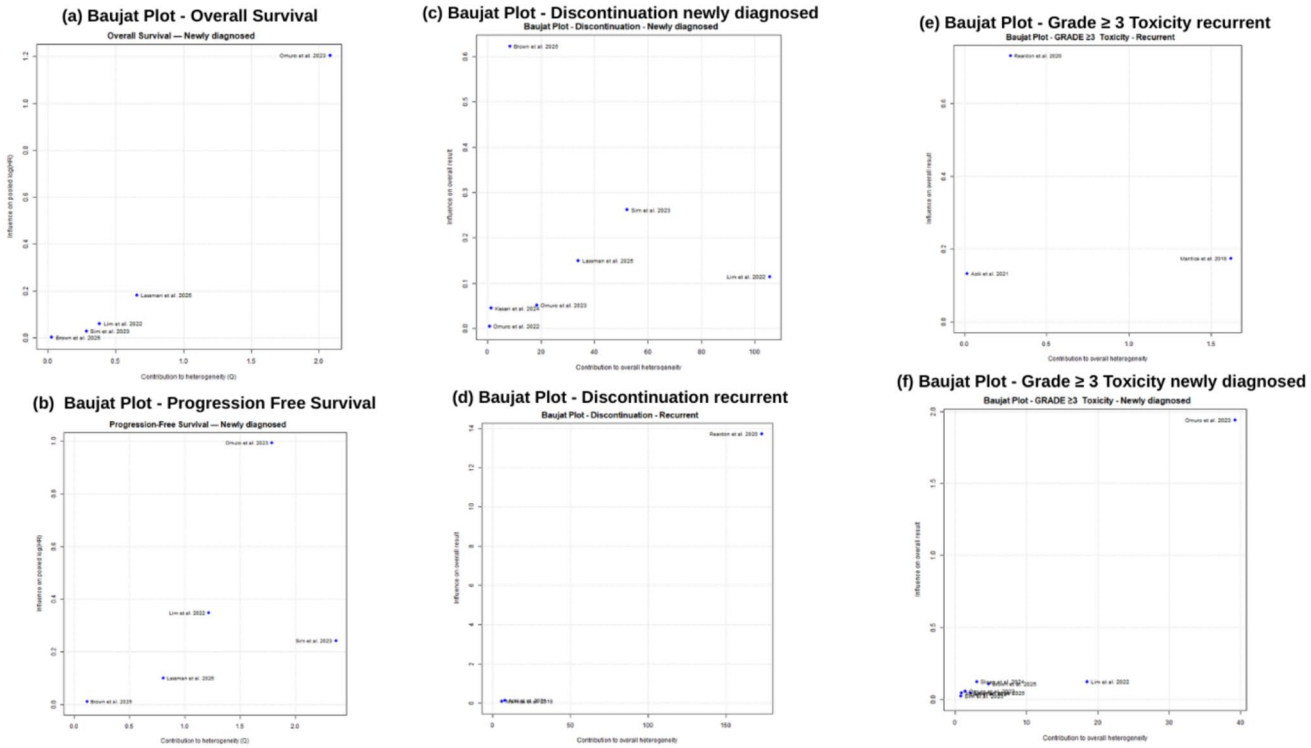

Fig 4 Sensitivity analyses/Baujat Plot. **a** Baujat Plot—Overall Survival. **b** Baujat Plot—Progression Free Survival. **c** Baujat Plot—Discontinuation newly diagnosed. **d** Baujat Plot—Discontinuation recurrent. **e** Baujat Plot—Grade ≥ 3 Toxicity recurrent. **f** Baujat Plot—Grade ≥ 3 Toxicity newly diagnosed

reduced the I^2 from approximately 50% to 15%, indicating that they were the primary drivers of the variation observed among studies for this outcome.

Regarding treatment discontinuation, the study by Lim et al. was the main contributor to heterogeneity in the newly diagnosed patient subgroup, while the study by Reardon et al. was the primary contributor in the recurrent patient subgroup. The exclusion of the Reardon et al. study was the only scenario that completely eliminated heterogeneity in the recurrent subgroup ($I^2 = 0\%$), demonstrating that this study was the principal source of inconsistency observed in that subgroup.

For the outcome of grade ≥ 3 toxicity, the study by Omuro et al. was identified as the main driver of heterogeneity in the newly diagnosed patient subgroup, while the study by Mantica et al. was responsible for the majority of heterogeneity in the recurrent patient subgroup, as identified in the Baujat plot.

It should be noted that, even after the exclusions carried out in the sensitivity analyses, residual clinical and methodological heterogeneity remains and must be taken into account when interpreting the findings.

Additional findings and modulating factors

MGMT promoter methylation status proved to be a consistently relevant prognostic factor. Patients with methylated MGMT showed superior OS and PFS compared to unmethylated patients [31, 33, 34, 36]. Subgroup analyses suggested a possible greater benefit of immunotherapy in this molecular profile [36, 38].

The use of corticosteroids at the start of treatment was identified as a possible negative predictive factor of response to immunotherapy. Reardon et al. [38] and Sloan et al. [40] observed that the need for corticosteroids, either as a marker of more aggressive disease or due to their direct immunosuppressive effects, may compromise the efficacy of immune checkpoint inhibitors.

Additionally, complete macroscopic surgical resection was associated with better OS and PFS outcomes, reinforcing the importance of locoregional disease control even in the context of systemic therapies [31, 34].

Quality and evidence assessment

Individual assessments of randomized clinical trials, performed using the RoB 2 tool [25], are presented in Fig. 5. The majority of studies were classified as "low risk of bias." Only one study presented "high risk of bias," due to insufficient data for overall survival analysis, resulting from a high dropout and mortality rate during treatment (Fig. 5).

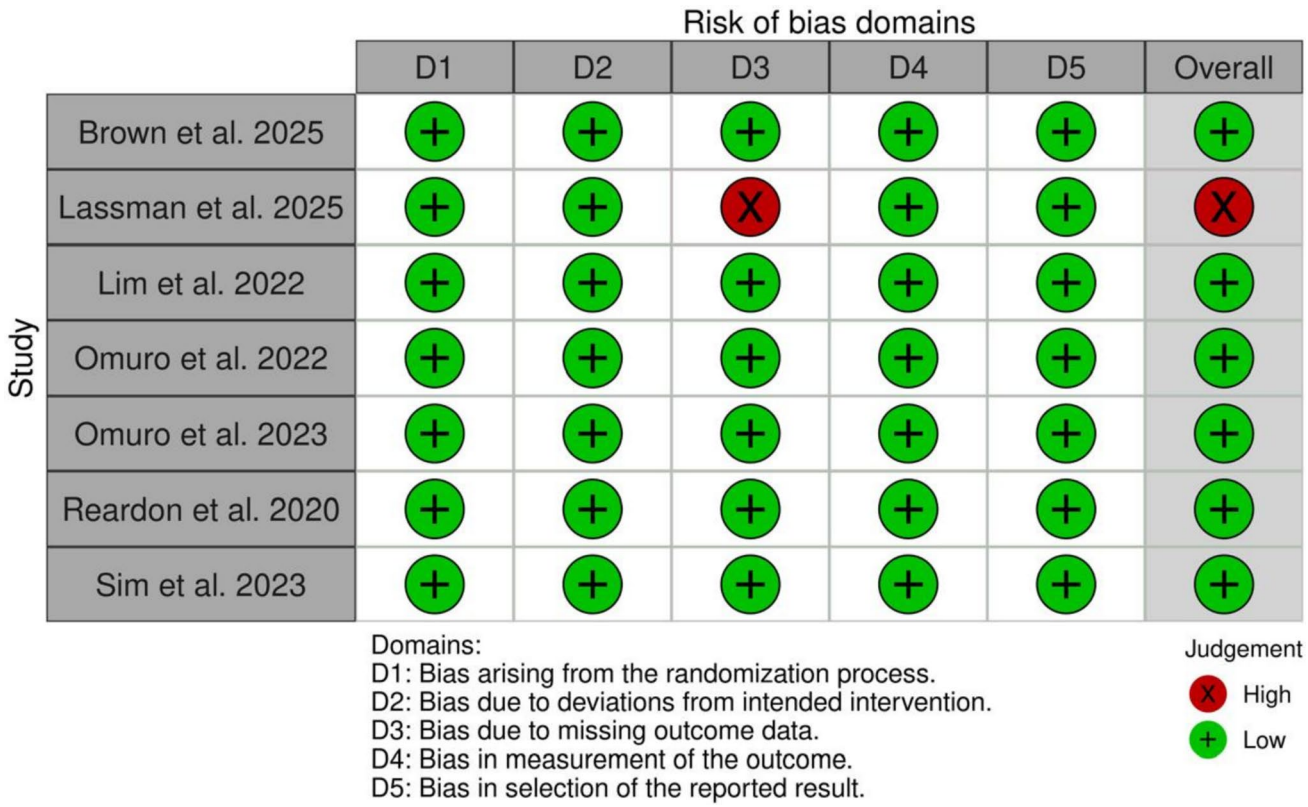

Fig 5. Risk of bias assessment of the included randomized clinical trials

Table 3. Joanna Briggs Institute (JBI) Checklist for quasi-experimental studies (Non-randomized experimental studies)

Study/Question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Risk of bias
Aoki et al. 2021	Yes	Yes	N/A	No	Yes	Yes	N/A	Yes	Yes	Low
Kesari et al. 2024	Yes	Yes	N/A	No	Yes	Yes	N/A	Yes	Yes	Low
Sloan et al. 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

N/A: Not applicable.

Q1: Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?

Q2: Were the participants included in any comparisons similar?

Q3:Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?

Q4: Was there a control group?

Q5: Were there multiple measurements of the outcome both pre and post the intervention/exposure?

Q6: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?

Q7: Were the outcomes of participants included in any comparisons measured in the same way?

Q8: Were outcomes measured in a reliable way?

Q9: Was appropriate statistical analysis used?

Individual assessments of non-randomized clinical trials, performed using the JBI tool [26] are presented in Table 3. All studies were classified as "low risk of bias."

Regarding the cohort study, the assessment performed using the NOS [27] tool is presented in Table 4. The analysis of this study also classified it as "low risk of bias."

The quality of evidence according to the GRADE [28] results (Table 5) revealed important differences in evidence certainty between randomized and non-randomized studies. For overall survival (OS), randomized clinical trials provided high-quality evidence, although pooled analyses did not demonstrate a statistically significant benefit associated with immunotherapy-based strategies (HR = 1.12; 95% CI: 0.97–1.29). In contrast, non-randomized studies were rated as very low-quality evidence due to serious risk of bias related to the absence of randomization, lack of control groups, and potential selection bias.

For progression-free survival (PFS), randomized studies also demonstrated high-quality evidence and showed a statistically significant improvement favoring immunotherapy-based approaches (HR = 1.34; 95% CI: 1.06–1.68). However, evidence from non-randomized studies was rated as very low quality due to small sample sizes, phase I study designs, and imprecision of effect estimates.

Regarding toxicity outcomes, evidence from randomized studies was rated as high quality, supporting the consistency of observed grade ≥ 3 adverse event rates across studies.

Table 4 - Risk of bias Newcastle–Ottawa Scale (NOS) of cohort studies

Study	Selection	Comparability	Outcomes	Total
Mantica et al. 2018	★★★★	★★	★★★	9★

Non-randomized studies presented low-quality evidence for safety outcomes. Overall, the GRADE analysis reinforced the robustness of findings from randomized trials while highlighting the limitations and the need for caution in interpreting non-randomized evidence.

Discussion

General synthesis

The findings of this systematic review and meta-analysis demonstrate that combination therapy was associated with statistically significant improvement in progression-free survival, with a particularly pronounced effect among patients with recurrent disease. However, no statistically significant benefit in overall survival was observed, suggesting that improved disease control did not translate into increased overall survival in the studied population.

Rates of severe toxicity were considerable, especially among newly diagnosed patients, in whom more than 40% experienced grade 3 or higher adverse events. This finding has important clinical implications, indicating that the potential benefit in progression control may be counterbalanced by an unfavorable toxicity profile in specific subgroups.

The substantial heterogeneity observed in outcomes such as treatment discontinuation and toxicity, even after sensitivity analyses, suggests that unmeasured factors — including differences in therapeutic regimens, baseline patient characteristics, and study eligibility criteria — may have influenced the results. Therefore, caution is warranted when generalizing these findings and

Table 5 GRADE assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunotherapy	standard treatment (surgical resection and chemoradiotherapy)	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (follow-up: median 24 months; assessed with: Kaplan–Meier.)												
4	non-randomised studies	serious[a]	serious[a]	not serious	not serious	none	121 participants -	13 participants 0.0%	**HR 1.12** (0.97 to 1.29) [Overall Survival (Time from diagnosis or start of treatment until the patient's death)]	**– per 1.000** (from – to –) **– per 1.000** (from – to –)	⨁◯◯◯ Very low[a]	IMPORTANT
Overall Survival (follow-up: median 24 months; assessed with: Kaplan–Meier.)												
7	randomised trials	not serious	not serious	not serious	not serious	none	1107 participants -	1029 participants 0.0%	**HR 1.12** (0.97 to 1.29) [Overall Survival (Time from diagnosis or start of treatment until the patient's death)]	**– per 1.000** (from – to –) **– per 1.000** (from – to –)	⨁⨁⨁⨁ High	CRITICAL
Progression-free survival (follow-up: median 18 months; assessed with: Kaplan–Meier.)												
4	non-randomised studies	serious[b]	serious[b]	not serious	not serious	none	63 participants -	6 participants 0.0%	**HR 1.34** (1.06 to 1.68) [Progression-free survival (time from randomization until progression)]	**– per 1.000** (from – to –) **– per 1.000** (from – to –)	⨁◯◯◯ Very low[b]	IMPORTANT

Table 5 (continued)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunotherapy	standard treatment (surgical resection and chemoradiotherapy)	Relative (95% CI)	Absolute (95% CI)		
Progression-free survival (follow-up: median 18 months; assessed with: Kaplan–Meier.)												
7	randomised trials	not serious	not serious	not serious	not serious	none	184 participants -	185 participants 0.0%	**HR 1.34** (1.06 to 1.68) [Progression-free survival (time from randomization until progression)]	**– per 1.000** (from – to –) **– per 1.000** (from – to –)	⨁⨁⨁⨁ High	CRITICAL
Toxicity/safety profile (Adverse Events) (follow-up: median 36 months; assessed with: CTCAE v4.03)												
7	randomised trials	not serious	not serious	not serious	not serious	none	1052/1107 (95.0%)	967/1029 (94.0%) 94.0%	not estimable	 **– per 1.000** (from – to –)	⨁⨁⨁⨁ High	CRITICAL
Toxicity/safety profile (Adverse Events) (follow-up: median 36 months; assessed with: CTCAE v4.03))												
4	non-randomised studies	not serious	not serious	not serious	not serious	none	115/121 (95.0%)	12/13 (92.3%)	not estimable		⨁⨁◯◯ Low	CRITICAL

CI confidence interval, *HR* hazard ratio

[a]Is a retrospective study with no randomization, no control group, and no blinding. Patient selection was based on physician's discretion rather than predefined criteria, introducing significant convenience sampling bias

[b]The available body of evidence consists of a single non-randomized phase I trial, whose primary design objective is safety assessment and dose determination, and which was not powered to estimate efficacy with adequate statistical precision. Although the observed result was markedly positive, the small sample size yields wide confidence intervals, which compromises the stability and reproducibility of the effect estimate

interpreting pooled effects, particularly for outcomes demonstrating substantial heterogeneity.

Overall survival

The most relevant finding of this meta-analysis was the absence of statistically significant benefit in overall survival (HR = 1.12; 95% CI: 0.97–1.29; $p = 0.138$), both in the general population and in the analyzed subgroups. This result is aligned with data from previous clinical trials, particularly CheckMate 143, which evaluated nivolumab in recurrent glioblastoma and demonstrated no improvement in overall survival [38, 41].

The lack of benefit in OS can be attributed to multiple biological and clinical factors. This absence of benefit in OS is consistent with the pattern described in the literature [18, 19]. Glioblastoma presents a profoundly immunosuppressive tumor microenvironment, characterized by high infiltration of bone marrow-derived myeloid cells (MDSCs) and tumor-associated macrophages (TAMs) with an M2 phenotype, which secrete immunosuppressive cytokines such as IL-10 [18, 19, 42]. Furthermore, the blood–brain barrier (BBB) limits the penetration of monoclonal antibodies, reducing the efficacy of ICIs in the cerebral parenchyma [18, 19, 43].

Progression-free survival

In contrast to OS results, the progression-free survival (PFS) analysis revealed a statistically significant benefit of combination therapy (HR = 1.34; 95% CI: 1.06–1.68; $p = 0.013$). More importantly, there was a highly significant difference between subgroups ($p = 0.0008$), with a substantially larger effect in patients with recurrent disease (HR = 1.97; 95% CI: 1.57–2.48) compared to patients with newly diagnosed disease (HR = 1.22; 95% CI: 1.04–1.44).

This finding suggests that immunotherapy may be more effective in delaying disease progression in patients with recurrent glioblastoma, possibly because these patients have already been exposed to standard treatment (surgery, radiotherapy, and temozolomide) and may have developed a more robust immunological response. Furthermore, patients with recurrent disease may have tumors with higher mutational burden, which is associated with better response to ICIs [44, 45].

Treatment discontinuation

The overall treatment discontinuation rate was 21.2% (95% CI: 8.4%–44.0%), with extremely high heterogeneity ($I^2 = 96.5\%$). Although there was no statistically significant difference between subgroups (p = 0.7596), the numerical rates were higher in patients with recurrent disease (27.1%) compared to patients with newly diagnosed disease (19.1%).

The extremely high heterogeneity in this result suggests that study-specific factors, such as differences in therapeutic protocols, discontinuation criteria, and patient profiles, substantially influenced the observed rates. Some studies may have discontinued treatment due to toxicity, while others may have discontinued due to disease progression or administrative reasons. This is consistent with the existing literature, which widely reports a vast range of events leading to treatment interruption in patients with GBM [46, 47]. This variability highlights the importance of standardizing discontinuation criteria in future investigations.

Grade ≥ 3 toxicity

A clinically relevant finding was the significant difference in severe toxicity rates between subgroups ($p < 0.0001$). Newly diagnosed patients presented a proportion of severe toxicity of 41.1% (95% CI: 31.0%–52.0%), while patients with recurrent disease presented a significantly lower rate of 16.7% (95% CI: 12.7%–21.6%).

This difference can be explained by several factors. First, newly diagnosed patients receive combined treatment with radiotherapy and temozolomide concomitantly with immunotherapy, which may increase cumulative toxicity. Second, patients with recurrent disease may have better performance status or lower comorbidity burden, resulting in better treatment tolerance. Third, the complete homogeneity in recurrent disease studies ($I^2 = 0\%$) suggests consistency in results, while the high heterogeneity in newly diagnosed disease studies ($I^2 = 90.1\%$) indicates variability in protocols and studied populations.

Compared to other studies, recent analyses of combined multimodal therapy in glioblastoma have demonstrated that, although toxicity rates are elevated in newly diagnosed patients receiving concurrent chemoradiotherapy with immunotherapy, the additional toxicity burden from ICIs alone is minimal [48].

Sensitivity analyses

The sensitivity analyses (leave-one-out and Baujat plots) identified specific studies as major contributors to the observed heterogeneity. For PFS, the studies by Omuro et al. and Sim et al. were identified as the main drivers of variation, and their exclusion reduced the I^2 from approximately 50% to 15%. For toxicity, the study by Omuro et al. was the main contributor in the newly diagnosed patient subgroup.

Although these analyses identified sources of heterogeneity, the exclusion of these studies did not substantially alter the overall conclusions, suggesting that the findings are robust. However, residual heterogeneity remains and must be considered when interpreting the results.

The MGMT predictive factor and the tumor microenvironment

MGMT promoter methylation emerged as the most prominent biomarker in this review, consistently associated with better OS and PFS outcomes in Brown et al. (2025) [31], Lassman et al. (2025) [33], and Lim et al. (2022) [34], regardless of the treatment arm. Subgroup analyses from Omuro et al. (2022) [36] and Reardon et al. (2020) [38] further suggested a possible greater benefit of immunotherapy in this molecular profile.

This pattern converges with what is broadly documented in the literature. MGMT methylation silences the DNA repair gene through an epigenetic pathway, sensitizing tumor cells to temozolomide; patients with unmethylated MGMT consistently show inferior survival [49]. Beyond the classic prognostic role, applied studies demonstrated that MGMT methylation correlates with a distinct immunogenic signature, higher expression of cytotoxic T lymphocyte markers and lower density of immunosuppressive TAMs, which may make these tumors relatively more responsive to ICIs [50, 51].

However, even in the methylated-MGMT subgroup, immunotherapy did not demonstrate consistent benefit, as evidenced by CheckMate 548 [33]. This confirms that the immunosuppressive microenvironment of GBM is multifaceted and cannot be overcome simply by selection based on MGMT status. TAMs, MDSCs, and Tregs create a suppressive environment that blocks lymphocyte activation through multiple simultaneous pathways, including PD-L1 expression by TAMs themselves, depletion of essential amino acids, and metabolic acidification of the microenvironment, imposing barriers that current ICIs cannot overcome in isolation [19, 20].

The impact of corticosteroids

The use of corticosteroids as a complicating factor was identified in this review in the studies of Reardon et al. (2020) [38] and Sloan et al. (2024) [40], who observed that the need for corticosteroids, as a marker of more aggressive disease or due to their direct immunosuppressive effects, may compromise ICI efficacy.

This finding has robust support in the literature. It was demonstrated, in an analysis of 181 patients with IDH-wildtype GBM treated with PD-(L)1 blockade, that concomitant use of dexamethasone reduced survival in a dose-dependent manner, with baseline dexamethasone use being the strongest negative risk factor for OS in multivariate analysis [52]. Subanalyses of CheckMate 143 itself confirmed that patients on baseline dexamethasone had worse prognosis in the nivolumab arm than in bevacizumab [52].

A systematic review published in Neuro-Oncology Advances evaluated the effects of dexamethasone on the tumor microenvironment and ICI efficacy, demonstrating that dexamethasone significantly reduces microglia, macrophages, and T lymphocytes in the tumor and periphery, abolishing the antitumor effects of ICIs on T lymphocyte populations, mechanisms that directly antagonize the action of checkpoint blockade [53]. Even more compelling data were published by Gani et al. (2024) [54], demonstrating that a subanalysis of a phase 2 checkpoint blockade trial revealed that 90% of effective responses occurred exclusively in patients who did not receive dexamethasone, reinforcing the magnitude of this deleterious effect [54].

Study limitations

This review presents significant methodological limitations that compromise the comparability of findings. Heterogeneity in study design (distinct phases, varying arms), populations (newly diagnosed vs. recurrent; MGMT-methylated vs. unmethylated), and therapeutic regimens (monotherapy vs. combinations) hinder direct comparisons. Additionally, small sample sizes in phase 1 studies and the retrospective nature of some studies introduce biases that limit the generalizability of the conclusions.

Clinical implications and future directions

The findings of this review indicate that immunotherapy alone, in its current form, does not constitute standard treatment for GBM. The absence of consistent overall survival benefit, combined with a high toxicity profile, warrants cautious interpretation prior to clinical implementation. However, signals of activity in specific subgroups — particularly in MGMT-methylated patients undergoing combination regimens — justify more targeted and mechanistically grounded investigations.

Investigative priorities for future studies include: identification of predictive biomarkers beyond MGMT (tumor mutational burden, inflammatory signatures, immune infiltration profile); rational development of combinations with stronger biological rationale, integrating data on mechanisms of action and resistance; and optimization of the management of immune-mediated and neurological adverse events, preserving therapeutic adherence and patients' quality of life.

Several considerations regarding the quality of evidence are warranted: phase 1 studies, while essential for establishing proof of concept and safety profiles, involve small sample sizes (Kesari et al., 2024; Sloan et al., 2024) [32, 40] whose promising results should be interpreted as preliminary until validation in adequately powered phase 2/3 trials, since the small sample size compromises the generalizability of the findings and

may have overestimated the effect estimates. The retrospective nature of some studies (Mantica et al., 2018)[35] introduces selection and measurement biases that reduce the strength of the evidence. Furthermore, the rapidly evolving landscape of glioblastoma research implies that new data may emerge soon, potentially reshaping the current therapeutic scenario.

Conclusion

This systematic review and meta-analysis demonstrated that immune checkpoint inhibitor-based therapies have not demonstrated consistent improvement in overall survival among patients with glioblastoma, despite the promising biological rationale and encouraging findings observed in selected subgroups. Although progression-free survival demonstrated statistically significant differences in pooled analyses, the substantial heterogeneity observed across studies limits the interpretation and generalizability of these findings.

The results also demonstrated that immunotherapy-containing regimens are associated with considerable toxicity, particularly among newly diagnosed patients undergoing combined therapeutic approaches involving radiotherapy and temozolomide. High rates of grade ≥ 3 adverse events and treatment discontinuation emphasize the importance of carefully balancing potential therapeutic benefits against treatment-related risks.

The substantial clinical and methodological heterogeneity identified in this review reflects the biological complexity of glioblastoma and the variability of currently available immunotherapeutic strategies. Factors such as MGMT methylation status, corticosteroid use, tumor microenvironment characteristics, prior treatments, and differences in therapeutic combinations likely influence treatment response and may partially explain the inconsistent findings observed across studies.

Therefore, immune checkpoint inhibitors should not yet be considered standard therapy for glioblastoma outside specific clinical contexts. Future research should prioritize biomarker-guided molecular selection, reduction of corticosteroid exposure whenever clinically feasible, development of rationally designed combination therapies, and strategies capable of overcoming the profoundly immunosuppressive glioblastoma microenvironment. High-quality randomized clinical trials with improved molecular stratification remain necessary to better define the true clinical role of immunotherapy in glioblastoma management.

Non-financial interests

The authors declare that they have no personal, academic, institutional, or other relationships that could partially influence the results or interpretation of this work.

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Authors' contributions All authors contributed equally to the conception and planning of the study. ACPV was responsible for the bibliographic search. AGSB and CSRP performed data collection and analysis. AGSB, CSRP, and EHID interpreted the data from the systematic review and meta-analysis and drafted the manuscript. AGSB, CSRP, EHID, and HJFJ critically reviewed the manuscript for relevant intellectual content. AGSB supervised the study. All authors approved the final version for submission.

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Data Availability All data used in this meta-analysis are derived from previously published studies and are available in the respective original publications cited in this manuscript.

Declarations

Conflicts of interest The authors have no conflicts of interest that are directly relevant to the content of this article.
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