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Assessment of the clinical effectiveness and safety of immune checkpoint inhibitors for glioblastoma: A systematic review

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ABSTRACT

Glioblastoma (GBM) is a malignant primary brain tumor which is commonly found in humans. Conventional therapeutic approaches for GBM offer only a short median overall survival (MOS), thereby accentuating its poor clinical outcome. Despite the promising potential shown by use of immune checkpoint inhibitor (ICI) in animal models to treat GBM, human trials result remains inconclusive. This systematic review evaluated the safety and clinical efficacy of ICIs in GBM patients. A literature search from Embase and MEDLINE (Ovid) was completed in October 2023. A total of 10 suitable articles, which encompass 168 patients (164 recurrent and 4 newly-diagnosed GBM), are taken into account. 3 studies assessed the OS, 7 studies assessed the PFS and/or response assessment in neuro-oncology (RANO) criteria and 8 studies assessed the safety, tolerability and/or adverse events. These studies show that the range of MOS of ICI treatments was between 2.6-10.4 months (MOS using current standard treatment for recurrent GBM = 3.5-12.5 months). The median PFS and the median period until patients reach partial response score based on RANO criteria are ranging from 1.5 months to 4.6 months (PFS using current standard treatment is 5.5 months). In conclusion, ICIs are safe in patients with GBM. Reported adverse effects only include mild fatigue, headache, hyperglycemia, and diarrhea. However, ICIs display suboptimal clinical efficacy compared to conventional GBM treatments. Therefore, further research is needed in order to improve the clinical efficacy of ICIs.

Keywords: glioblastoma, immune checkpoint inhibitors, overall survival, progression free survival, safety

INTRODUCTION

Glioblastoma (GBM) is a primary brain tumor in humans which happens to be the most malignant and most commonly found. It is hypothesized that the tumor originates from pluripotent stem cells located within the central nervous system vascular niches [1,2]. A multicenter analysis conducted by Dobes et al. in Australian teaching hospitals found that GBM makes up almost 30% of all primary brain tumors [3]. In 2005, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) recommended the first-line therapy regimen for newly diagnosed GBM: maximal safe tumor resection followed by concurrent temozolomide (TMZ) and conventional fractionated radiotherapy (RT) and subsequent adjuvant TMZ. However, due to its ability to develop its own blood supply, GBM is characterized by poor prognosis; patients only have a median overall survival (MOS) of 12-18 months following these conventional therapies and tend to succumb to relapses [1-2,4,5]. Thus, in order to improve the clinical outcome of GBM patients, a novel therapeutic strategy against GBM is desperately needed.

A growing number of studies have started evaluating immunotherapy as a novel therapeutic approach against GBM. The notion of using immunotherapy in GBM treatment lies upon its ability to modulate the body's immune system to target and effectively kill cancerous cells [2]. There are different types of immunotherapy, but one that might be effective against GBM is immune checkpoint inhibitor (ICI) therapy. Previous studies have shown that tumor cells can evade killing by our immune system by

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stimulating certain immune checkpoints located on the surface of immune cells like T cells. These activated immune checkpoints will inhibit regulatory pathways which eventually dampen immune response towards the tumor cell, leading to its survival. ICI drugs are able to block immune checkpoints such as PD-MRI1/PD-L1 and CTLA-4/CD-80/CD-86 [6].

Although administration of ICIs into animal models has proven to be safe and effective [7-9], such evidence is still limited in human trials [10-13]. Hence, this systematic review attempts to evaluate the safety and clinical efficacy of ICIs in human patients in line with evidence-based medicine. To the best of our knowledge, this is the first analysis conducted to thoroughly evaluate the use of ICIs in treating patients with GBM.

METHODS

Review design

The protocol of this review was prepared before the review was started and it is used as a strict guideline throughout the review. The reporting of this review was conducted in accordance to PRISMA guideline [14].

Data sources and search strategy

A literature search of two databases; Embase and MEDLINE (Ovid), was completed in October 2023. The keywords used were "glioblastoma" in conjunction with "immune checkpoint inhibitors" and were not restricted to "clinical efficacy" nor "safety" for more extensive findings. The search was limited to the studies in English, yet there were no boundaries on the year of publication. Secondary literatures were excluded. Both randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSIs) were included in the study for a more extensive finding. Studies which have no available full-text report were not to be looked further. The established articles from the two databases were then evaluated upon the title and abstract. Articles that failed to fulfil all the eligibility criteria will be excluded. Suitable study reports that fulfil the criteria were taken into deeper analysis. Supplementary Table 1 will exhibit the full search strategy.

Inclusion and exclusion criteria

Table 1 underneath epitomized the inclusion and exclusion criteria. The inclusion and exclusion criteria are made based on PICO components. However, because majority of cancer-related clinical trial phase I and II were done in single-arm approach, no comparator group will be included in these eligibility criteria.

TABLE 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Primary literature	Secondary literature
Human studies, adult only	Pediatric subjects
English language studies	Animal studies
Subjects had GBM and have undergone the treatment with ICIs	Non-English language studies
Study measured the clinical efficacy and/or safety of ICIs	
Full-text article available	

Data extraction and data analysis

Articles were obtained from Embase and MEDLINE (Ovid) and were exported directly to a reference management software, EndNote X9.2. Data extraction was completed by one author and then reviewed by a second author. If there was disagreement between authors, it was resolved by consensus. Duplicates were removed automatically, using the "Remove Duplicate" function, and also manually. Titles and abstracts were then screened to retrieve articles that fulfilled all eligibility criteria. Data to be included in the systematic review was then extracted and recorded in Microsoft Excel 2011; recorded data was: first author, year of study, study type, study's setting, population, number of subjects, intervention, outcome results and conclusion.

Quality and risk of bias assessments

Study quality assessments were done using standardized critical appraisal tools and risk of bias tools. Quality and risk of bias assessments were completed independently by two reviewers. If there was disagreement between reviewers, all reviewers will inspect and discuss the disagreements thoroughly. There were constant agreements in the final discussion. RCT studies were appraised using the PEDro scale, NRSIs were assessed using the Newcastle-Ottawa scale (NOS) checklist and case reports were assessed using the JBI critical appraisal tool checklist for case reports [15-17]. Furthermore, Cochrane risk of bias in non-randomized studies – of intervention (ROBINS-I) and risk of bias tool for randomized trials (RoB 2) were used to assess NRSIs and RCTs, respectively [18,19].

Assessment of heterogeneity

Assessment of heterogeneity was conducted using the quantitative comparison of the length of MOS and PFS; and qualitative comparison between the types and number of adverse events, between ICIs and current standard treatment for GBM. Assessment of heterogeneity is described using narrative approach.

RESULTS

Search findings

Initial electronic search was run on MEDLINE (Ovid) and Embase, which resulted in a total of 182 articles. Following duplicates removal, 166 unique articles were found. Based on title and abstract screening, 138 of these articles were excluded. The remaining 28 records were further assessed for eligibility. Of these, only 10 studies fulfilled the inclusion and exclusion criteria and were included in qualitative synthesis. For the full list of included and excluded studies, please refer to Supplementary Table 3. The complete PRISMA flowchart is shown in Figure 1.

Study characteristics

A total of 168 subjects were part of these 10 studies: 101 males (60.12%) and 67 females (39.89%) aged between 27-75 years of age, with median age of 51 years [2,21-29]. The study designs consisted of 6 cohort studies (2 retrospective and 4 prospective), 2 case reports, and 2 RCTs [2,21-29]. All the studies had some or all of their participants with GBM with 164 patients with recurrent GBM and 4 newly diagnosed GBM patients [2,21-29]. Detailed study characteristics are as summarized in Supplementary Tables 4 to 6.

Quality and risk of bias assessments of included studies

Three critical appraisal tools were utilized to perform the methodological quality assessments. 2 retrospective and 4 prospective cohort studies were critically appraised using Newcastle Ottawa Scale (NOS); 2 case reports were critically appraised using JBI critical appraisal tool for case reports; 2 RCTs were critically appraised using PEDro scale. Risk of Bias was calculated using ROBINS-I for 8 studies and RoB 2 for 2 studies. The result of quality and risk of bias assessment are fully displayed in Supplementary Table 7-11. Following thorough examination, 9 included studies have low risk of bias and 1 NRSI study has moderate risk of bias with moderate risk in 'measurement of outcome' and 'missing data' domain.

Summary of measured outcomes

Overall Survival: There are four studies that assessed the OS of patients treated with ICIs. Blumenthal et al. and Cloughesy et al. studied pembrolizumab, Schalper et al. studied nivolumab, while Omuro et al. studied nivolumab and its combination with ipilimumab [2,21-23]. The MOS from these studies range from as low as 2.6 months to as high as 10.4

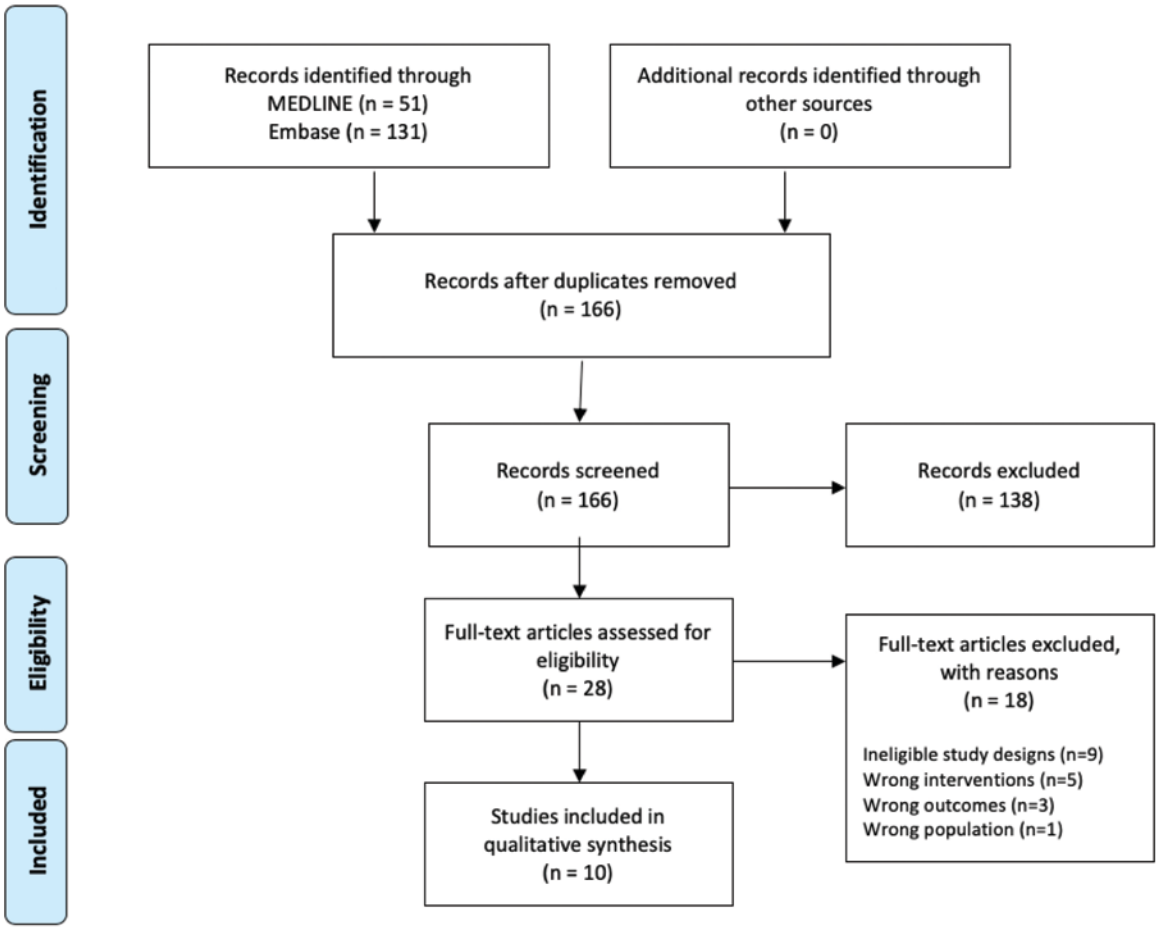

FIGURE 1. PRISMA flowchart. 182 records were obtained from Embase and MEDLINE (Ovid). 10 studies were included in the qualitative synthesis

months. The usual MOS survival for patients with recurrent GBM using current standard first-line therapy (surgery, radiation and chemotherapy) ranges from 3.5 to 12.5 months. Therefore, it can be deduced that the number is slightly lower for patients with ICI drugs [2,21-23].

Tumor Progression: Tumor progression could be reported based on PFS itself or based on the radiological criteria of Response Assessment in Neuro-Oncology (RANO) criteria. There were 7 studies that reported median PFS and/or RANO criteria. 6 of which reported PFS, while 3 reported the tumor progression based on RANO criteria. The median PFS and the median period until patients reach 'partial response' score based on RANO criteria are between 1.5 months and 4.6 months [2,22-29]. However, if only studies with low risk of bias were included, the median PFS ranges from 1.5 months to 4.1 months [2,22-27,29].

Safety: Safety was analyzed in 8 studies by Blumenthal et al., Carter et al., Cloughesy et al., Lukas et al., Omuro et al., Schalper et al., Ranjan et al. and Tay et al. Overall, most ICIs are safe and well tolerated with the most common side effects of fatigue, diarrhea, headache, muscle weakness, and hyperglycemia [2,21-23,25-27,29].

DISCUSSION

ICIs are proven to be effective in animal models with GBM [7-9], but remain inconclusive based on human clinical trials [10-13]. This review aims to give a conclusive evidence on the clinical efficacy and safety of ICIs in GBM patients [10]. Studies were included with 9 deemed to have low risk of bias [2,21-29].This review summarized the clinical efficacy and safety of ICIs; clinical efficacy were measured with the length of OS, PFS and RANO criteria. The discussion of this review compared ICIs with current standard first-line treatment for GBM patients. Further plausible explanation of the results and impact on clinical practice were also made.

Current standard therapy for GBM includes multidisciplinary approach with maximal tumor resection, radiotherapy and adjuvant TMZ. Most patients would eventually experience tumor progression and passed away. The length of MOS of patients with recurrent GBM are reported to be 3.5 to 12.5 months [30]. Combination therapy of standard treatment with the addition of bevacizumab are reported to be able to prolong the PFS, but its correlation with prolonged MOS remain to be inconclusive [30].

Clinical efficacy

Overall survival (OS)

Based on the included studies, the length of MOS of patients with ICI treatment ranges from 2.6 to 10.4 months [2,21-23,30]. Blumenthal et al. reported the MOS of recurrent patient to be 2.6 months (0.4-11.6 months) after the regimen started [21]. The result of the study shows that the MOS of ICI are comparatively the same with a slight tendency to be on the lower side. Before ICI regimen, the participants have previously had previous regimens, with the mean number of 2 regimens (1-6). The conclusion of the study shows that most patients experienced no significant response to pembrolizumab [21]. Interestingly, Cloughesy et al. found that neoadjuvant treatment of pembrolizumab before surgery had a statistically significant greater MOS compared to adjuvant treatment or treatment after surgery (HR 0.39 [95% CI= 0.17-9.94, p= 0.04, log-ranked test). The MOS of participants with adjuvant pembrolizumab were 228 days (7.6 months), meanwhile participants in neoadjuvant arm had the MOS of 417 days (13.9 months) [22].

Schalper et al. reported the MOS of patients using nivolumab to be 7.3 months (5.4-7.9 months) [2]. Based on the study, an intriguing discovery was found on newly-diagnosed GBM patients. There were 2 newly-diagnosed GBM patients and they were alive after a long-term follow up of 28.5 and 33 months [2]. Therefore, further investigations of nivolumab on newly-diagnosed GBM are highly recommended [2]. Omuro et al. measured 3 different dosage of the combination therapy of nivolumab and ipilimumab and found out that the patient group that had the longest MOS had the dosage of 3mg/kg every 2 weeks of nivolumab with no administration of ipilimumab [23].

After analysis, it can be concluded that the MOS of ICI are not satisfying. All of the included studies reported a slightly lower MOS than the current standard treatment. The results among studies were deemed to be homogenous; that is lower than the standard treatment.

Tumor progression

Based on the included studies, the median PFS reported is ranging between 1.5 and 4.6 months [2, 22-29]. However, van Linde et al. reported that the median PFS of recurrent GBM patients using current standard therapy is 5.5 months [31].

Byron et al. examined the PFS of nivolumab and found out to be 195 days (using radiological screening) and 100 days (without radiological screening) [24]. Another study that compared the neoadjuvant and adjuvant treatment of pembrolizumab shows that neoadjuvant pembrolizumab has longer PFS of 99.5 days compared to adjuvant with 72.5 days [22]. Omuro et al. reported that combination therapy of nivolumab and ipilimumab has the median PFS of between 1.5 and 2.1 months [23]. Furthermore, Blumenthal et al. reported the median PFS of patients using nivolumab at 4.1 months (2.8-5.5 months) [2].

Moreover, Qin et al. reported the median PFS of nivolumab + pembroliumab at 4.6 months. Qin et al. divided the participants into two arms; the first group was deemed to have potential beneficial biomarkers through MRI lived up to 6.5 months, while those who did not have potential beneficial biomarfers lived up to 2.7 months [28]. However, the study done by Qin was observed to have moderate risk of bias due to bias in missing data and measurement of outcome.

A case series done by Ranjan et al. reported 4 recurrent GBM patients that were treated with ICI [27]. One patient with tumor located at left frontal region was treated with combination therapy of nivolumab and TMZ. Patients had no tumor progression until 2 months, before the tumor started to regrow on her left frontal lobe near the left ventricle. Clinical deteriorations started to occur at 3.5 months but can be managed with the administration of dexamethasone. The tumor remains stable on the twelfth month [27]. Second patient had GBM in right temporal region; he was treated with nivoumab + TMZ and had PFS of 8 weeks; before a new tumor started to progress in the right sylvian fissure. At 10 months, progression started to be seen through radiological imaging, but it turns out to be immunotherapy-related pseudo progression [27]. Third patient had the tumor at the right temporal region and was treated with ipilimumab + TMZ. The patient had disease progression at 8.5 months and remains stable up until 19 months after the initiation of the regimen [17]. Fourth patient had GBM located in the left temporal lobe. He was given a combination therapy of ipilimumab + TMZ. Tumor did not progress up until the ninth month; clinically manifested with focal seizures. Maximal tumor resection then conducted 2 weeks later with adjuvant therapy of low-dose bevacizumab and nivolumab. Patients remain stable 21 months after the diagnosis of recurrent GBM [27].

Carter et al. assessed recurrent GBM patients that underwent combination therapy of ipilimumab + bevacizumab with RANO criteria. The results show us that, after 12 weeks, 31% of participants were stable, 31% had partial progression and 38% had disease progression [25].

Lukas et al. examined the length of progression free in patients that underwent the therapy of IV atezolizumab 1200mg every 3 weeks. The study found out that the PFS is 1.2 months (0.7-10.7 months) [26].

All of the included studies reported the PFS of ICI medications were lower than the PFS of current standard treatment (5.5 months). Therefore, it can be concluded that the progression free survival of ICIs were lower than current standard treatment; and the results of studies were deemed to be homogenous.

Plausible factors that lead to suboptimal efficacy

We found that the vast majority of studies exploring the effect of ICI on GBM patients showed suboptimal clinical efficacy. It is suggested that ICI are not yet applicable to be used in patients with GBM. There are a number of plausible factors that may explain this phenomenon. One of the reasons includes the poor ability of ICI to penetrate the blood-brain barrier (BBB), thus affecting drug delivery. Aside from the BBB, it is known that GBM may induce an immunosuppressive environment of the brain, which is indicated by low number of tumor-infiltrating lymphocytes (TILs) and low neoantigen burden. Hence, new strategies of treatment that may increase immune and antitumor response in the tumor microenvironment are needed. Some examples include molecular screening prior to ICI treatment and combination therapy with other types of treatment.

Safety

A single study declared that the ipilimumab and bevacizumab combination was well tolerated [25], with fatigue (40%) and diarrhea (30%) as the most common adverse effect. An intracerebral hemorrhage was reported in one patient and two patients had pulmonary emboli that were associated with the disease. ICIs were discontinued due to presence of grade 2 rash in one patient and grade 2 arthritis in another single patient. 6 patients experienced diarrhea which was well controlled using corticosteroid [21-23,25-27,29].

One study reported muscle weakness, headache, and hyperglycemia as the most common treatment-related adverse events (TRAEs) on pembrolizumab [22]. However, the study stated that pembrolizumab was predominantly well tolerated. 10 out of 16 patients in the neoadjuvant arm experienced grade 3-4 adverse events that may or may not be attributable to the treatment, with treatment discontinued in two patients due to grade 3 pneumocystis and grade 4 elevations in alanine transferase. Another study on nivolumab also suggested it to be safe and well tolerated, with a low incidence of TRAEs. In addition, out of 3 newly diagnosed GBM patients treated with nivolumab, 2 patients survive for 28 and 33 months [2].

In comparison to nivolumab + ipilimumab, nivolumab alone is better tolerated, as its tolerability is impacted by the ipilimumab dose. With diarrhea and fatigue as the most usual adverse reactions; TRAEs shown in 10% of patients with nivolumab treatment, while 23% in patients treated with nivolumab and ipilimumab combination [23].

Another research with recurrent GBM patients stated that atezolizumab was safe and well tolerated. Treatment-related events occurred in 10 patients

(63%) but without any grade 4-5 TRAEs. Each of the patients that died in this study was due to GBM, irrelevant to drug-related events [26].

All of the studies reported similar findings that most ICIs are well tolerated and have milder adverse events in comparison to standard treatment.

Limitations of the study and future recommendations

A number of limitations are attributed to this systematic review. Firstly, there is a limited amount of studies regarding GBM patients with ICIs treatment. Moreover, the majority of published studies are phase I and II clinical trials, which only have a relatively small number of participants with no comparison arm. Thirdly, most of patients recruited in the studies have recurrent GBM (164/168), which may yield different outcomes compared to patients with newly diagnosed GBM. Fourthly, meta-analysis was not done due to reasons. Consequently, the conclusion from this analysis cannot be overstated and on further investigation, the conclusion from this analysis could be substantially altered. In order to completely understand the clinical efficacy and safety of ICI drugs in the medical field, Author highly suggests having additional research with regards to the clinical efficacy and safety of ICI drugs in patients with GBM.

CONCLUSION

To conclude, this review presents that ICIs can be safely applied in GBM patients, with fatigue and diarrhea as the most frequent adverse events. However, ICI drugs have a moderately lower clinical efficacy in comparison to the current standard treatment, marked by lower MOS and PFS in all included studies.

Therefore, ICI drugs can be an alternative treatment for GBM patients who display severe adverse reactions to conventional therapeutic approaches (chemotherapy, radiation, and surgery).

Future research should also assess the influence on newly diagnosed GBM patients, since the majority of the participants in these studies are recurrent GBM patients. Following administration of ICIs, patients with newly diagnosed GBM may exhibit different outcomes, compared to those with recurrent GBM. Moreover, further research is needed in order to improve the clinical efficacy of ICIs.

Conflict of interest: none declared
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APPENDICES

SUPPLIMENTARY TABLE 1. Full search strategy on Embase and MEDLINE (Ovid)

Date	#	Search Keywords
October 2023	1	(glioblastoma* or GBM* or glioblastoma multiforme or giant cell* glioblastoma* or giant-cell* glioblastoma)
	2	(immune checkpoint inhibitor* or immune check-point inhibitor* or nivolumab or pembrolizumab or ipilimumab or tremelimumab or atezolizumab or durvalumab or cemiplimab or avelumab)
	3	(trial*)
	4	1 and 2 and 3
	5	Limit 4 to (human and English language)

SUPPLIMENTARY TABLE 2. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2-3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	-
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3

Section/topic	#	Checklist item	Reported on page #
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	20-21
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	3-5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	6

SUPPLIMENTARY TABLE 3. List of included and excluded studies with full-text available

Author	Title	Title and Abstract screening (include/exclude)	Full-text screening (include/exclude)	Justifications of exclusion
Blumenthal et al.[21] (2016)	Pembrolizumab: first experience with recurrent primary central nervous system (CNS) tumors	Include	Include	-
Byron et al.[24] (2017)	Prospective feasibility trial for genomics-informed treatment in recurrent and progressive glioblastoma	Include	Include	-
Carter et al.[25] (2016)	Ipilimumab and bevacizumab in glioblastoma	Include	Include	-
Cloughesy et al.[22] (2019)	Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma	Include	Include	-
Lukas et al.[26] (2018)	Clinical activity and safety of atezolizumab in patients with recurrent glioblastoma	Include	Include	-
Omuro et al.[23] (2018)	Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase 1 cohorts of CheckMate 143	Include	Include	-
Qin et al.[28] (2017)	Advanced MRI assessment to predict benefit of anti-programmed cell death 1 protein immunotherapy response in patients with recurrent glioblastoma	Include	Include	-
Ranjan et al.[27] (2018)	Clinical decision making in the era of immunotherapy for high grade-glioma: Report of four cases	Include	Include	-
Schalper et al.[2] (2019)	Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma	Include	Include	-
Tay et al. [29] (2017)	Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy	Include	Include	-
Choi et al.[32] (2018)	Temozolomide-associated hypermutation in gliomas	Include	Exclude	Wrong intervention: temozolomide (TMZ))
Filley et al.[13] (2017)	Recurrent glioma clinical trial, CheckMate-143: the game is not over yet	Include	Exclude	Ineligible study design: review

Author	Title	Title and Abstract screening (include/exclude)	Full-text screening (include/exclude)	Justifications of exclusion
Gomes et al.[33] (2018)	Characterization of the selective indoleamine 2,3-dioxygenase-1 (IDO1) catalytic inhibitor EOS200271/PF-06840003 supports IDO1 as a critical resistance mechanism to PD-(L)1 blockade therapy	Include	Exclude	Wrong intervention: indoleamine 2,3-dioxygenase-1 (IDO1)
Kalbasi et al.[34] (2013)	Radiation and immunotherapy: a synergistic combination	Include	Exclude	Ineligible study design: review
Hodges et al.[35] (2017)	Mutational burden, immune checkpoint expression, and mismatch repair in glioma: Implications for immune checkpoint immunotherapy	Include	Exclude	Wrong outcome: biomarker phenotypes
Kiesewetter et al.[36] (2017)	The European Society for Medical Oncology 'magnitude of clinical benefit scale' field-tested in infrequent tumour entities: an extended analysis of its feasibility at the Medical University of Vienna	Include	Exclude	Wrong intervention: The European Society for medical Oncology 'magnitude of clinical benefit scale' (ESMO-MCBS)
Ladomersky et al.[37] (2018)	IDO1 inhibition synergizes with radiation and PD-1 Blockade to durably increase survival against advanced glioblastoma	Include	Exclude	Wrong population: preclinical study design on mouse models
Lawler et al.[38] (2017)	Shifting the balance of power? The combination of oncolytic virotherapy and immune checkpoint blockade for glioblastoma treatment	Include	Exclude	Wrong intervention: oncolytic virotherapy
Lynes et al.[39] (2019)	Cytokine microdialysis for real-time immune monitoring in glioblastoma patients undergoing checkpoint blockade	Include	Exclude	Ineligible study design: review
Maxwell et al.[40] (2017)	Clinical trials investigating immune checkpoint blockade in glioblastoma	Include	Exclude	Ineligible study design: review
Modjtahedi et al.[41] (2012)	Therapeutic application of monoclonal antibodies in cancer: advances and challenges	Include	Exclude	Wrong intervention: monoclonal antibodies
Naidoo et al.[42] (2015)	Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies	Include	Exclude	Wrong outcome: interferon gamma level
Novotny et al.[43] (2016)	Establishing a complementary diagnostic for anti-PD-1 immune checkpoint inhibitor therapy	Include	Exclude	Wrong outcome: complementary diagnostic
Pardoll et al.[44] (2012)	Immunotherapy earns its spot in the ranks of cancer therapy	Include	Exclude	Ineligible study design: review
Rangel-Sosa et al.[45] (2017)	Immunotherapy and gene therapy as novel treatments for cancer	Include	Exclude	Ineligible study design: review
Sahebjam et al.[46] (2017)	Assessing response of high-grade gliomas to immune checkpoint inhibitors	Include	Exclude	Ineligible study design: review
Silver et al.[47] (2016)	The intersection of cancer, cancer stem cells, and the immune system: therapeutic opportunities	Include	Exclude	Ineligible study design: review
Wick et al.[48] (2018)	Drug repositioning meets precision in glioblastoma	Include	Exclude	Ineligible study design: review

SUPPLIMENTARY TABLE 4. Main study characteristics of cohort studies

Studies (n=6)	Study Design	Study's Setting	WHO Tumor Grade and Characteristics	Clinical Trial Phase	Patients (n)	Year of Study	Regimen	Measured End-points	Results	Conclusion
Blumenthal et al.[21] (2016)	Retrospective	Four Israeli brain tumor centers	IV (GBM), recurrent	-	10	N/R	Pembrolizumab 150 mg every 3 weeks. Some patients had adjuvant steroids and/or bevacizumab	AE OS	No significant adverse event was found 2.6 months (0.4-11.6)	Pembrolizumab was well tolerated No patients showed significant response to pembrolizumab
Byron et al.[24] (2017)	Prospective	University of California, San Fransisco, USA	IV (GBM), recurrent and newly diagnosed	II	2	September 2014 -August 2015	Nivolumab	PFS	195 and 100 days	The clinical efficacy of nivolumab remain inconclusive
Carter et al.[25] (2016)	Prospective	University College Hospital /University College London, London, UK	IV (GBM), recurrent 1 patient had a recurrent grade II astrocytoma (radiologically consistent with GBM)	II	20	January 2014-April 2015	Ipilimumab 3mg/ kgBW 4 times every 3 weeks (followed by maintenance therapy every 12 weeks) and Bevacizumab 10mg/ kgBW every 2 weeks	RANO AE	6 weeks-assessment stable:9 patients partial response:6 progression:5 12 weeks assessment stable:11 partial response:2 progression:4 Well tolerated in 18 patients. 2 patients had immune-related toxicities, but manageable with corticosteroids.	The clinical efficacy remains inconclusive Ipilimumab + bevacizumab is well tolerated
Lukas et al.[26] (2018)	Prospective	N/R	IV (GBM), recurrent	I	16	May 2015-December 2016	IV atezolizumab 1200mg every 3 weeks (until disease progression and/or intolerable toxicities)	PFS AE / TRAE	PFS = 1.2 months (0.7-10.7) 16 patients had ≥ 1 AE with 10 patients had treatment-related adverse events (TRAE)	The clinical efficacy remains inconclusive Atezolimumab was well tolerated
Qin et al.[28] (2017)	Retrospective	New Jersey, USA	IV (GBM), recurrent	-	10	N/R	Nivolumab + pembrolizumab with/without ipilimumab (after RT and TMZ)	PFS	PFS = 4.6 months (Deemed to have therapeutic benefit= 6.5 months; to not have benefit= 2.7 months)	The clinical efficacy remains inconclusive
Schalper et al.[2] (2019)	Prospective	Yale School of Medicine, New Haven, Connecticut, USA Clinica Universidad de Navarra, Pamplona, Spain	IV (GBM), recurrent and newly diagnosed	II	30	N/R	Nivolumab (given before or after surgery)	AE PFS OS	2 patients had adverse eve nts - 1 liver impairment (▲AST, ▲ALT) - 1 grade 2 hyperthyroidism PFS = 4.1 months OS = 7.3 months	Nivolumab was well tolerated The clinical efficacy remains inconclusive, especially for recurrent glioblastoma Nivolumab was effective in 2/2 newly diagnosed GBM, with OS=28.5 and 33 months

**N/R, not reported; AE, adverse events; GBM, glioblastoma; OS, overall survival; PFS, progression free survival; RANO, response assessment in neuro-oncology; TRAE, treatment-related adverse events*

SUPPLIMENTARY TABLE 5. Main study characteristics of randomized controlled trials

Studies (n=2)	Study's Setting	WHO Tumor Grade and Characteristics	Clinical Trial Phase	Patients (n)	Year of Study	Regimen			Measured End-points	Results	Conclusion
						1st Arm	2nd Arm	3rd Arm			
Cloughesy et al.[22] (2019)	Seven brain institutions in the USA	IV (GBM), recurrent	II	35	October 2016-July 2018	Neoadjuvant pembrolizumab	Adjuvant pembrolizumab	-	AE OS PFS	No significant adverse event was found OS = 417 days (neoadjuvant), 228 (adjuvant) PFS = 99.5 days (neoadjuvant), 72.5 (adjuvant)	Pembrolizumab was well tolerated. Pembrolizumab had better clinical efficacy when administered in neoadjuvant setting
Omuro et al.[23] (2018)	Nine institutions in the USA	IV (GBM), recurrent and newly diagnosed	I	40	September 2014-August 2015	Nivolumab 3 mg/kgBW every 2 weeks (NIVO3; Q2W)	Nivolumab 1 mg/kgBW and ipilimumab 3 mg/kgBW every 3 weeks (NIVO1+IPI3; Q3W)	Nivolumab 3 mg/kgBW and ipilimumab 1 mg/kgBW every 3 weeks (NIVO3+IPI1; Q3W)	AE	The most common adverse events are fatigue (30%, 80%, 55%) and diarrhea (10%, 70%, 30%)	Nivolumab monotherapy was better tolerated (1st arm)

**AE, adverse events; GBM, glioblastoma; OS, overall survival; PFS, progression free survival*

SUPPLIMENTARY TABLE 6. Main study characteristics of case reports

Studies (n=2)	WHO Tumor Grade and Characteristics	Patients (n)	Study's Setting	Year of Study	Tumor Location	Regimen	Results	Conclusion
Ranjan et al.[27] (2018)	IV (GBM), recurrent	4	Bethesda, USA	N/R	Left frontal	Maximal tumor resection, radiation, TMZ, nivolumab Dexamethasone was administered at 7 months	At 7 months, there is disease progression, worsened aphasia, right-sided weakness and headache. Dexamethasone was administered afterward. Tumor is still stable at 12 months	-
					Right temporal	Maximal tumor resection, radiation, TMZ, nivolumab	No significant disease progression. Immunotherapy-related pseudo progression was found at 10 months	-
					Right temporal	Maximal tumor resection, radiation, TMZ, ipilimumab At 8.5 months, due to disease progression, ipilimumab was discontinued and continued by nivolumab	Disease progression at 8.5 months Disease is stable at 19 months	-
					Left temporal	Maximal tumor resection, radiation, TMZ, ipilimumab After 9 months, due to disease progression, patient had salvage surgery, re-irradiation, nivolumab and low-dose bevacizumab	Disease progression at 9 months Disease is stable at 21 months	-
Tay et al.[29] (2017)	IV (GBM), recurrent and newly diagnosed	1	Alfred Health, Melbourne, Australia	N/R	Right temporo-parietal		8 days after administration of nivolumab, patient developed malignant arrythmias	Immune-mediated cardiotoxicity may occur in a small proportion of population as an AE of nivolumab

**AE, adverse events; GBM, glioblastoma; TMZ, temozolomide*

SUPPLIMENTARY TABLE 7. Methodological quality assessment of the included cohort studies using Newcastle Ottawa Scale

Cohort Studies	Selection			Comparability	Assessment of Outcome		Total Quality Score
Studies (n=6)	Representativeness of treated arm	Selection of the comparative treatment arm	Ascertainment of the treatment regimen	Demonstration that outcome of interest was not present at start of study	Comparability between patients in different treatment arms – main factor: GBM	Assessment of outcome with independency	Adequacy of follow up length (to assess outcome) OS:13.5m PFS:7m	Lost to follow up acceptable (less than 10% and reported)	
Blumenthal et al.[21] (2016)	*		*	*		*	*	*	6/9
Byron et al.[24] (2018)	*		*	*		*	*		4/9
Carter et al.[25] (2016)	*		*	*		*		*	4/9
Lukas et al.[26] (2018)	*		*	*		*	*	*	5/9
Qin, et al.[28] (2017)	*		*	*		*	*		4/9
Schalper et al.[2] (2019)	*		*	*		*	*	*	5/9

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SUPPLIMENTARY TABLE 8. Methodological quality assessment of the included RCTs using PEDro scale

RCTs Studies (n=2)	PEDro scores											Total Quality Score
Studies (n=6)	1	2	3	4	5	6	7	8	9	10	11	
Cloughesy et al.[22] (2019)	V	V		V				V	V	V	V	7/11
Omuro, et al.23 (2018)	V			V				V	V		V	5/11

SUPPLIMENTARY TABLE 9. Methodological quality assessment of the included case reports using JBI

Case Reports	JBI Scores							
Studies	1	2	3	4	5	6	7	8
Ranjan, et al.[27] (2018)	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes
Tay, et al.[29] (2017)	Yes	No	Yes	Yes	Yes	Yes	No	Yes

SUPPLIMENTARY TABLE 10. Results of risk of bias assessment for non-randomized studies of interventions (ROBINS-I)

		Pre-intervention		At intervention	Post-intervention				Overall risk of bias judgment
Author	**Study Type**	**Confounding bias**	**Selection bias**	**Classification bias**	**Deviation bias**	**Missing data bias**	**Measurement of outcome bias**	**Selective reporting bias**	
Blumenthal, 2016 [21]	**RC**	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**
Byron, 2018 [24]	PC	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk	Low Risk	Low Risk	Low Risk
Carter, 2016[25]	PC	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Lukas, 2018[26]	PC	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk	Low Risk	Low Risk
Qin, 2017[2]	RC	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk	Moderate Risk	Low Risk	Moderate Risk
Schalper, 2019 [2]	PC	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

RC= Retrospective cohort studies; PC= Prospective cohort studies

SUPPLIMENTARY TABLE 11. Results of risk of bias assessment for randomized controlled trials (RoB 2)

	Random sequence generation	Deviation from the intended interventions	Incomplete outcome data	Measurement of outcome	Selective reporting
Cloughesy, 2019[22]	+	+	+	+	+
Omuro, 2018[23]	+	+	?	+	+

x = High Risk	? = Some concerns	+ = Low Risk

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