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Review Article

A systematic review of immunotherapies in combination with temozolomide as treatment for glioblastoma

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ABSTRACT

Glioblastomas comprise a significant percentage of malignant adult central nervous system tumor cases and patients typically do not survive longer than a year after diagnosis. There are few treatment options for patients which meaningfully prolong survival other than chemotherapy, radiotherapy, and surgery. There are many clinical trials examining immunotherapy-chemotherapy combination treatments. This systematic review uses database research of clinical trials to identify randomized controlled immunotherapy-temozolomide combination trials which evaluate the median overall and progression-free survival in adult patients. The review also assesses the study design of selected trials for risk of bias. The desired outcomes are presented as they are reported in the selected studies and are evaluated based on reported statistical significance. We included 10 studies in the final selection and found five studies focused on bevacizumab as an immunotherapy in combination with temozolomide while five used unique interventions. Of those studies, only bevacizumab and autologous dendritic cell vaccination reported an improvement in desired outcomes compared to the control. The risk of bias analysis identified only one study with high risk of bias and five studies with unclear risk of bias in blinding. Our study identifies promising treatments and recommends further examination of those interventions but does not make any recommendations on changes to current glioblastoma treatments. The authors have no funding or conflict of interests to declare. The authors followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for writing this review.

1. Introduction

1.1. Challenges of treating glioblastoma

Glioblastomas are highly malignant, incurable tumors comprising 45.2% of malignant Central Nervous System (CNS) tumor cases in adults [1]. Glioblastomas are categorized by the World Health Organization (WHO) as a Grade 4 CNS Tumor: highly malignant and predisposed to necrosis. The pace of tumor growth exceeds blood delivery to cells resulting in a large necrotic center to the tumor. Symptoms include headache, seizures, nausea, blurry vision, cognitive deficiencies, and symptoms associated with incident brain region [2]. Patients younger than 50 years of age have a median survival of 13.7 months while older patients have an overall survival of less than 12 months [2].

Temozolomide (TMZ), shelf name Temodar, is a synthetic DNA alkylating agent approved by the FDA in 1999 for treating anaplastic astrocytomas and glioblastomas [3]. Its half-life is 1.8 h fexxt. It spontaneously converts to methyl triazeno imidazole carboxamide (MTIC) within cells and can methylate guanine nitrogenous bases [3]. Failure of DNA repair pathways to undo this modification results in cell apoptosis. Thus, TMZ particularly affects highly proliferating cells and especially those that have deficiencies in DNA repair mechanisms." [1]. TMZ alone extends post-diagnosis survival by an additional 10 months which is a relatively minimal increase. Research must continue to find new methods to prolong survival post-diagnosis even more.

Another approach to treating glioblastomas is immunotherapy. Immunotherapies are anti-cancer treatments which seek to stimulate the body's immune system into attacking cancer cells. Current FDA-approved immunotherapies for treating glioblastoma are bevacizumab and naxitamab: both are monoclonal antibody treatments [3]. With

Abbreviations: TMZ, temozolomide; ACNU, [Drug with an] additional condition for nonprescription use; BEV, bevacizumab; DC, dendritic cell; GM-CSF, granulocyte macrophage colony stimulating factor; IFN-β, interferon-beta; IRI, irinotecan; mOS, median overall survival; mPFS, median progression free survival; PBMC, peripheral blood mononuclear cells; PBO, placebo.

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immunotherapies still the target of many clinical trials, it is worth evaluating this method in combination with proven TMZ. Combining promising immunotherapy treatments with proven TMZ may significantly improve patient survival over one treatment alone.

This systematic review evaluated current literature on the efficacy of TMZ and immunotherapy combination treatments to identify interventions which may increase the median overall survival and median progression free survival of primary glioblastoma.

2. Materials and methods

2.1. Inclusion criteria

We followed the 2020 iteration of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards in searching and selecting appropriate trials for this systematic review [4]. The selected Patient, Intervention, Comparison and Outcome (PICO) established the first parameters for determining trial eligibility. The patient subjects must have presented with a diagnosed primary glioblastoma at the start of the trial and were not previously treated for glioblastoma prior to trial participation. The intervention selected was temozolomide plus a variable immunotherapy intervention administered concomitantly with the intention to treat the glioblastoma. The comparison was temozolomide alone, administered to treat the glioblastoma. The outcomes measured were median overall survival (mOS), median progression-free survival (mPFS), and adverse event rate in months post-treatment. All records were written in English. All clinical trials had to be phase III/IV, randomized, controlled, include data, and provide full text if published.

2.2. Exclusion criteria

Non-primary research articles, non-clinical trials, trials which were listed as open-label, papers published prior to 2014, papers using data from a previously published study, and duplicated papers were excluded.

2.3. Search methods

Our systematic literature search utilized PubMed and Embase and Cochrane Reviews Databases to identify worthy clinical trials. This search occurred on 30 November 2022 followed by update searches on 12 March 2023 and 28 September 2023. We used keywords: “Temozolomide”, “Temozolomide combination”, “Astrocytoma”, “Randomized controlled trial”, “RCT”, “combined modality therapy”, and “Glioblastoma”. All records were written in English. All clinical trials had to be randomized, controlled, include data, published in 2014 or later, and provide full text if published. Our search strategy for Pubmed is provided below.

("Astrocytoma"[Mesh] OR astrocytoma[tiab] OR "Glioblastoma"[Mesh] OR Glioblastoma[tiab]) AND ((("Temozolomide"[Mesh] OR temozolomide[tiab]) AND "Combined Modality Therapy"[Mesh]) OR (Temozolomide Combination) OR "temozolomide combin*"[tiab] OR temozolomide OR Temodar OR (temozolomide alone) AND (randomized controlled trial OR RCT))

2.4. Data selection

The papers gathered from the literature search were screened first at the title and abstract level. We used Rayyan to search for keywords and to label papers appropriately for inclusion. Here we excluded papers which were not randomized controlled trials, did not have an immunotherapy as an intervention, was a review article, was open-label, was a retrospective analysis, or did not meet our PICO criteria. At the full text level, we removed papers which were open label, used the same patient data from a primary research study, or was ongoing at time of literature search. This process was conducted independently by two authors, differences in selection results were resolved by discussion between the two authors. Fig. 1 provides a visualization of the data selection effect on the number of papers we eventually included.

2.5. Data collection

Information about the study design, results, and analyses was collected independently by two authors using copies of a single spreadsheet. Data of interest included: number of patients who proceeded to randomization, inclusion and exclusion criteria, intervention, and control group treatment standards, mOS and mPFS for both intervention and control groups. Any missing data was treated as nonexistent, and the paper was omitted from consideration for the missing data category.

2.6. Risk of bias assessment

The risk of bias assessment was modeled after the Cochrane Bias Checklist and used the same six criteria with modified definitions [5]. The assessment evaluated (1) participant randomization methods, (2) allocation concealment from participants and staff, (3) assignment blinding of participants and staff, (4) outcome blinding, (5) data availability for all participants regardless of outcome status, and (6) alignment of study execution and analyses with original study design. We defined low risk as the criteria having a near-zero influence on the study outcomes. We interpreted an unclear risk of bias as a suspicion of risk influencing the outcome and would agree with a repeat of the study under more controlled rigor. A high-risk mark meant the study outcomes were very likely being influenced by the flagged criteria.

3. Results

3.1. Study inclusion

We used several criteria to select papers from databases to use in this review. A total of 444 articles (PubMed: 156, Embase: 178 Cochrane Library: 110) were identified using the keyword search. 128 articles were removed due to being published outside the specified time frame. 94 articles were identified as duplicates and removed. This resulted in 222 randomized, clinical trials being screened for eligibility. Fig. 1 shows 10 randomized controlled clinical trials were included in this systematic review for analysis.

3.2. Evaluating study design

To identify promising treatments, we evaluated the study design to determine if the treatment results were reasonably valid. It is important to consider the sample size used in each study. Four of the studies, Chinot et al. 2014, Gilbert et al. 2014, Liau et al. 2018, and Lim et al. 2022 had results from more than 300 participants [6, 7l, 8, 9]. Chinot 2014 estimated 80% would need 683 participants [6]. Gilbert 2014 sought a 25% reduction in the risk of death, at a power of 80%, they gathered 612 participants [7]. Lim et al. 2022 did not make any power or sample size calculations [9]. Liau et al. 2018 recruited 331 participants but did not report any power or sample size calculations [8].

The other studies had data for fewer than 200 participants. Chauffert et al. 2014 had 80% power sample size calculations of 60 participants [10]. Wakabayashi had 80% power sample size calculation of 120 participant [11]. Wen et al. 2019 calculated 70 deaths for 83% power [12]. Herrlinger et al. 2016 reported 80% power for a 2:1 assignment required 156 total participants [13]. Balana et al. reported 80% power required 90 total participants [14]. Yang et al. 2022 recruited 92 participants but did not report any power or sample size calculations [15].

Larger sample sizes indicate greater accuracy for reported results. Therefore, the trials with more than 300 participants have results with

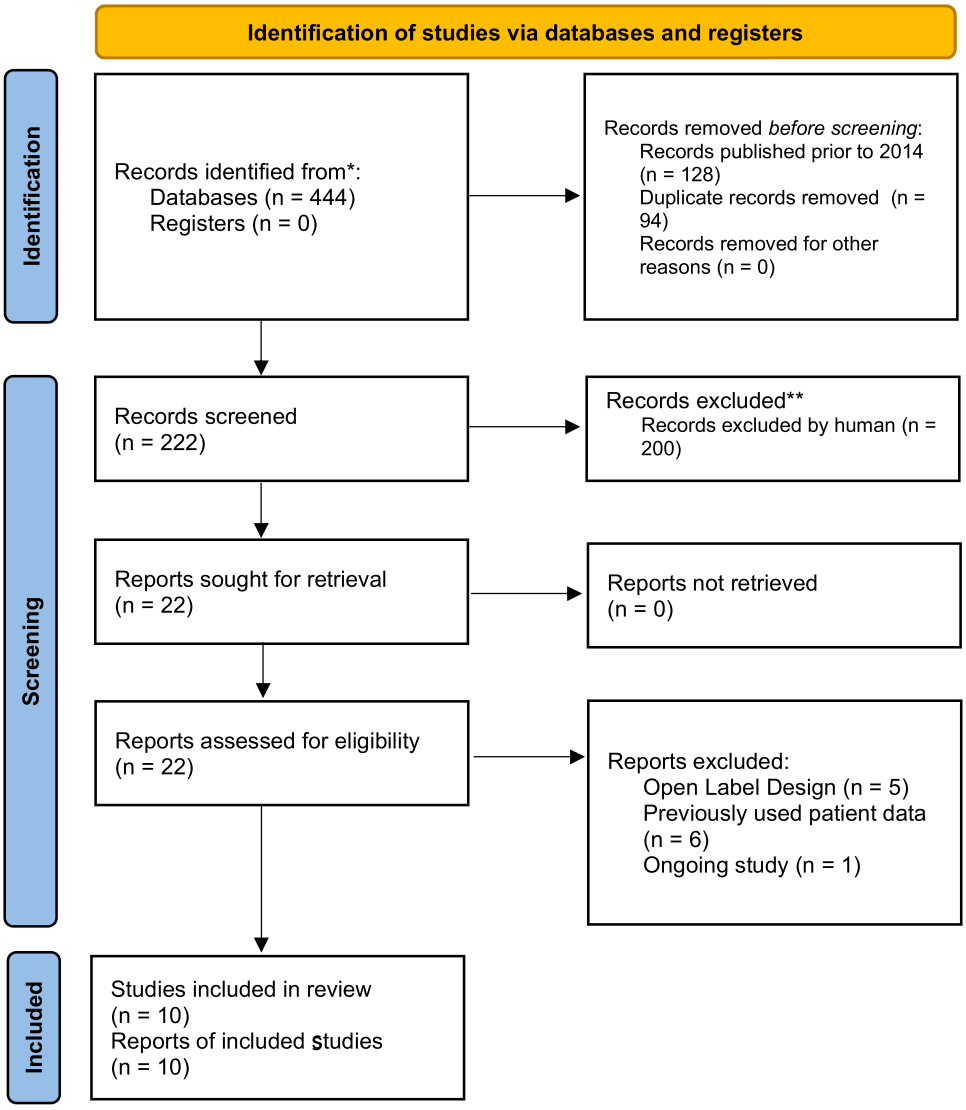

Fig. 1. PRISMA Flowchart of study identification, screening, and inclusion process.

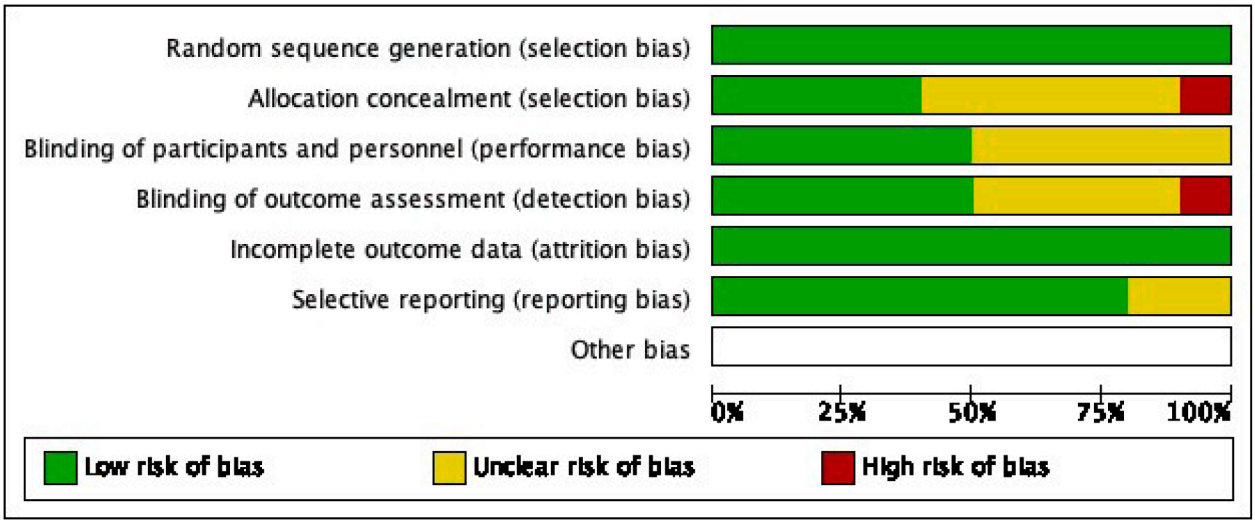

Fig. 2. Each risk of bias item presented as percentages across all included studies.

reduced error margins and more representative of the wider population. Conclusions from those results are more likely to be accurate. Trials with less than 200 participants, and especially those with fewer than 100 participants, are likely to have larger error margins and be less representative of the population, thus increasing the likelihood of drawing inaccurate conclusions from the results.

In evaluating the risk of bias for each study, we found that 9 of the 10 papers had minimal bias in the methodology and data reporting (Figs. 2 and 3). Herrlinger et al. 2016 openly stated there was no blinding of any party during the study [13]. Our analysis of study design heavily focused on the statistically determined sample size, participant distribution between treatment arms, and the risk of bias analysis.

3.3. Literature findings

In our examinations of our selected 10 papers, we identified 7 unique immunotherapies (Table 1). These were bevacizumab, irinotecan, autologous dendritic cell (DC) vaccine, nivolumab, interferon-beta (β), ICT-107 vaccine, and granulocyte macrophage colony stimulating factor (GM-CSF).

It is important to note that not all studies reported p-values or confidence intervals for either mOS or mPFS. Therefore, we conducted two separate analyses, one for p-value and one for confidence intervals, to appropriately analyze the data presented.

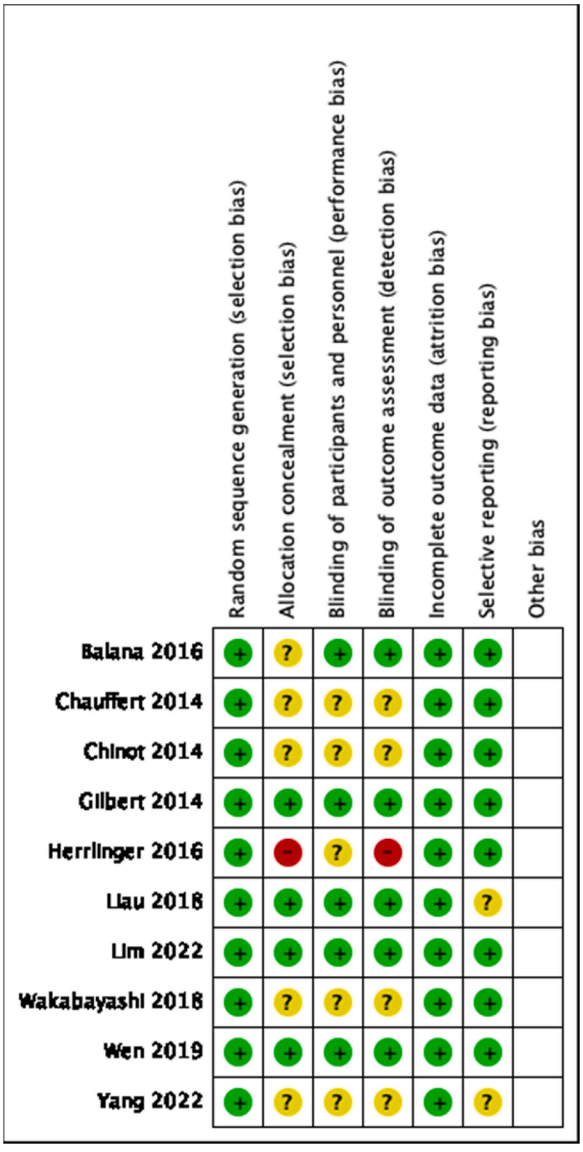

Fig. 3. Review of authors' judgement about each risk of bias item for each included study.

Based on P-value analysis, Yang et al. 2022 reports Granulocyte Macrophage Colony Treatment in combination with TMZ improves the median overall survival of its patients as well as the median progression free survival [15] (Tables 2 and 3). Chinot et al. 2014, Herrlinger et al. 2016, Wen et al. 2019, report an improvement only in progression free survival for Bevacizumab, irinotecan with bevacizumab, and dendritic cell vaccine ICT-107 [6,12,13] (Table 3).

Based on analysis of confidence intervals, Balana et al. 2016, Gilbert et al. 2014, and Herrlinger et al. 2016, report Bevacizumab, and irinotecan and bevacizumab only improve progression free survival [7,13,14]. These findings informed us of the quality of the treatments which met our search criteria.

3.4. Bevacizumab as a treatment

Five studies utilized bevacizumab as part of the intervention combined with TMZ and all five studies presented different results for the measured outcomes. Those studies were Balana et al. 2016, Chauffert et al. 2014, Chinot et al. 2014, Gilbert et al. 2014, and Herrlinger et al. 2016 [6,7,10,13,14]. The two studies which used irinotecan presented dissimilar results although one study used TMZ in the intervention while the other presented irinotecan with bevacizumab against TMZ alone. Those studies were Chauffert et al. 2014 and Herrlinger et al. 2016 [10,13]. We looked to heterogeneity in study designs as possible sources of differences in outcomes.

With half of our selected papers focusing on bevacizumab with TMZ, we evaluated all the papers to create a single outcome for bevacizumab with TMZ as a treatment. All five studies administered Bevacizumab treatments at the same dosage (10mg/kg) with the same amount of TMZ (75 mg/mˆ2/day) with differing regimens. Chinot et al. 2014 administered bevacizumab every 2 weeks immediately post-surgery, every 2 weeks for the 24-week maintenance phase, and then every 3 weeks until progression or unacceptable toxic effects during the monotherapy phase [6] . On the other hand, Gilbert et al. 2014 administered its treatments for 24 doses over 12 cycles where 1 dose was administered every 2 weeks [9]. Chauffert et al. 2014 administered its intervention before radiotherapy biweekly for 4 cycles and then biweekly for 6 months during radiotherapy [10].

We also found it notable that Chinot et al. 2014 used an investigator to calculate mPFS and hired an independent analyst to calculate the mPFS. Both calculations were included in the final reporting [6] (Table 3).

The risk of bias analysis flags only one paper with high risk but all five of the bevacizumab studies also have low risk in select criteria. Fig. 2 presents the percentage of the total studies which present low, high, and unclear risk for the six categories we used to evaluate each study. Fig. 3 presents the results each trial's risk of bias analysis. The papers with unclear risk of bias in blinding do not present any information on blinding. We interpreted the absence of a low risk of bias as minimal influence negatively impacting the validity and accuracy of the results. Low risk of bias is preferred because it allows our conclusions to be more accurate.

We find there to be significant heterogeneity in the study designs which could be associated with the differences in results.

Chinot et al. 2014 and Gilbert et al. 2014 both report a p-value less than 0.05 and both have sample sizes greater than 500 participants [6,7]. Both studies do not have a high risk of bias. These studies show Bevacizumab with TMZ has a statistically significant effect on mPFS favoring the combination therapy over TMZ alone.

3.5. Other treatments

Each of these five trials: Liau et al. 2018, Lim et al. 2022,

Table 1
Presentation of each selected study's important design characteristics.

Study	Total Patients (N)	Intervention	Intervention Participants	Control	Control Participants
Balana et al. 2016	102	TMZ + Bev	44	TMZ alone	43
Chauffert et al. 2014	120	TMZ + Neoadjuvant BEV/IRI	51	RT + TMZ	45
Chinot et al. 2014	921	TMZ+Bev	452	Placebo + TMZ	459
Gilbert et al. 2014	637	TMZ+Bev	309	Placebo + TMZ	312
Herrlinger et al. 2016	182	Bev + IRI	116	TMZ	54
Liau et al. 2018	331	Autologous DC vaccine (DCVax-L) +TMZ	232	Placebo (PBMC for placebo) + TMZ	99
Lim et al. 2022	716	NIVO+RT+TMZ	358	PBO+RT+TMZ	358
Wakabayashi et al. 2018	122	TMZ + IFNβ + RT	44	TMZ+RT	55
Wen et al. 2019	124	ICT-107 + TMZ	75	Placebo + TMZ	42
Yang et al. 2022	92	RT + TMZ + GM-CSF	46	RT + ACNU + TMZ	46

Table 2
Summary presentation of reported median overall survival calculations (mOS) from each paper.

Study	Intervention	Intervention Median (months)	CI	Control Median (months)	CI	P-Value
Balana et al. 2016	TMZ + Bev	10.6	(6.9,14.3)	7.7	(5.4,10)	0.07
Chauffert et al. 2014	TMZ + Neoadjuvant BEV/IRI	11.1	(9.0,15.0)	11.1	(9.0,15.0)	N/A
Chinot et al. 2014	TMZ+Bev	16.8	N/A	16.7	N/A	0.1
Gilbert et al. 2014	TMZ+Bev	15.	(14.2,16.8)	16.1	(14.8,18.7)	0.21
Herrlinger et al. 2016	Bev + IRI	16.6	(15.4,18.4)	17.5	(15.5,20.5)	0.55
Liau et al. 2018	Autologous DC vaccine (DCVax-L) +TMZ	19.3	(17.5,21.3)	16.5	(16.0,17.5)	N/A
Lim et al. 2022	NIVO+RT+TMZ	28.9	(24.4,31.6)	32.1	(29.4,33.8)	N/A
Wakabayashi 2018	TMZ + IFNβ + RT	24.0	(18.8,27.4)	20.3	(15.4,26.9)	0.51
Wen et al. 2019	ICT-107 + TMZ	17.0	(13.7,20.6)	15.0	(12.3,23.0)	0.58
Yang et al. 2022	RT + TMZ + GM-CSF	19.2	(15.7,21.0)	17.1	(14.6,18.3)	0.045

Table 3
Summary presentation of reported median progression free survival calculations (mPFS) from each paper.

Study	Intervention	Intervention Median	CI	Control Median	CI	P-Value
Balana et al. 2016	TMZ + Bev	4.8	(4.0,5.6)	2.2	(2.0,2.5)	0.1
Chauffert et al. 2014	TMZ + Neoadjuvant BEV/IRI	7.5	(5.5,9.2)	5.2	(4.3,6.8)	N/A
Chinot et al. 2014	TMZ+Bev	10.6 (investigator), 8.4 (independent)	N/A	6.2(investigator), 4.3 (independent)	N/A	<0.001
Gilbert et al. 2014	TMZ+Bev	10.7	(10.0,12.2)	7.5	(5.9,7.9)	0.007
Herrlinger et al. 2016	Bev + IRI	9.7	(8.7,10.8)	6.0	(2.7,7.3)	<0.001
Liau et al. 2018	Autologous DC vaccine (DCVax-L) +TMZ	6.2	(5.7,7.4)	7.6	(5.6,10.9)	N/A
Lim et al. 2022	NIVO+RT+TMZ	10.6	(8.9,11.8)	10.3	(9.7,12.5)	N/A
Wakabayashi et al. 2018	TMZ + IFNβ + RT	8.5	(6.6,11.9)	10.1	(7.5,11.8)	0.25
Wen et al. 2019	ICT-107 + TMZ	11.2	(8.2,13.1)	9.0	(5.5,10.3)	0.011
Yang et al. 2022	RT + TMZ + GM-CSF	7.8	(7.3,8.3)	6.9	(6.5,7.4)	0.016

Wakabayashi et al. 2018, Wen et al. 2019, and Yang et al. 2022, were unique in the treatments they tested in combination with TMZ [8,9,11,12,15]. Therefore, we evaluated each treatment individually and considered heterogeneity in both the treatment itself as well as the study design.

Liau et al. 2018 used an autologous tumor lysate-pulsed dendritic cell vaccine, dendritic cells with pulsed tumor lysates to stimulate an immune response in patients. Patients were injected intradermally in alternating arms for each injection [8]. The injection schedule resulted in one injection on days 0, 10, and 20, then 2, 3 and 8, and then at 6-month intervals starting a month 12 [8].The risk of bias analysis produced low risk in all categories except selective reporting where unclear risk was marked due to no reporting of power calculations and representation of survival numbers as percentages instead of number of patients. We believe the results are valid and accurate based on our analysis. In addition, the large number of participants does give us confidence in saying the results are representative of the wider population.

However, Tables 2 and 3 shows the overlap of mOS confidence intervals, absence of p-value in both mOS and mPFS, and mPFS favoring the control treatment. This provides strong evidence against autologous tumor lysate-pulsed dendritic cell vaccine with TMZ as a potential combination treatment.

Lim et al. 2022 used nivolumab, an IgG4 monoclonal antibody which targets the programmed cell death-1 (PD-1) receptor [9]. This treatment is approved for other cancers and has recorded anti-tumor activity in melanoma patients [9]. The paper does not indicate the method of delivery for the intervention but does state patients received 8 biweekly doses followed by one dose every 4 weeks. The risk of bias analysis showed the paper had minimal risk of bias in all categories, the only paper to achieve such a scoring. Therefore, we believe the paper's results are valid and accurate.

The reported results in Tables 2 and 3 shows the mOS results favoring the control, absence of p-value, and overlap of confidence intervals in the mPFS. This provides strong evidence against IgG4 with TMZ as a potential combination treatment.

Wakabayashi et al. 2018 studied interferon beta (IFNβ), a type 1 interferon that is a cytokine with known control of cell proliferation

[16]. IFNβ enhances chemosensitivity to TMZ and has been used to treat gliomas in Japan [11]. Patients received 3 MU/body IFNβ intravenously 3 times during the RT concomitant period and every 4 weeks during the maintenance period. The authors did not report any blinding or lack thereof, introducing uncertain risk of bias. As a result, we cannot be fully confident in labeling the results as valid.

This study reported 122 participants in Table 1, thus making the sample less likely to be representative of the wider population. In Tables 2 and 3, there is overlap of the confidence intervals and the p-values are greater than 0.05 and the mPFS favors the control over the intervention. This provides strong evidence against IFNβ with TMZ as a potential combination treatment.

Wen et al. 2019 studied ICT-107 vaccination, pulsed autologous dendritic cells HLA-A1–restricted, melanoma- associated antigen-1 (MAGE-1) and antigen isolated from immunoselected melanoma-2 (AIM-2), and the HLA-A2–restricted, human EGFR-2 (HER2/neu), tyrosinase-related protein-2 (TRP-2), glycoprotein 100 (gp100), and IL13 receptor alpha 2 (IL13Rα2) [12]. Patients were administered treatment intradermally. The risk of bias analysis showed low risk of bias in all categories; therefore, we believe the paper's results are valid and accurate.

This study reported 124 participants in Table 1, like Wakabayashi et al. 2018, the small sample size makes it difficult to assume the data is representative of the population. In Table 2, the mOS confidence interval overlap and $p > 0.05$. However, Table 3 shows a confidence interval overlap and $p < 0.05$ for the mPFS. This data suggests some effect on the mPFS but the small sample size and lack of impact on mOS challenge ICT-107 vaccination with TMZ as a potential combination treatment.

Yang et al. 2022 used granulocyte-macrophage colony stimulating factor (GM-CSF) in its trial [15]. GM-CSF regulates hematopoietic differentiation, particularly the production of granulocytes, macrophages, and B cells [15]. Patients received the treatment in 3ug/kg/d intranasal drops on days 1 and 3 of each chemotherapy cycle. The paper did not report any blinding or lack thereof, introducing uncertain risk of bias in our analysis. We cannot be confident in describing the results as valid. The results for mOS and mPFS both favor this intervention with TMZ over TMZ and placebo alone.

This study reported the smallest sample size of 92 total participants which makes it difficult to assume the data is representative of the population (Table 1). However, Tables 2 and 3 show confidence intervals overlap and $p < 0.05$ for both mOS and mPFS. The data reported in this study is the strongest supporting the intervention, but the small sample size is limiting.

Of all the presented trials, Yang et al. 2022 data strongly supports the intervention of GM-CSF + TMZ over TMZ + placebo. This makes it the most promising treatment based on data alone but the study design analysis showing possible bias and limitations of data does indicate further trialing is necessary to highlight the validity and accuracy of the data.

General Study Design Information (Item + TMZ) mOS mPFS

4. Discussion

4.1. In ten selected studies, we identified seven unique immunotherapies

Of those selected, five trials focused on combinations of bevacizumab with irinotecan and TMZ. Autologous dendritic cell (DC) vaccine, nivolumab, interferon-beta (β), ICT-107 vaccine, and granulocyte macrophage colony stimulating factor (GM-CSF) were the subject of their own trials. Of these selected studies, our analysis highlighted several methods to study bevacizumab with TMZ. The results overall pointing to this combination treatment producing results favoring extended progression-free survival over TMZ alone. This highlights this immunotherapy combination intervention as a treatment which may be able to slow the progression of glioblastoma or mitigate the symptoms of a growing tumor in the brain. Of the other five treatments, GM-CSF with TMZ showed improvement in both median overall survival and median progression free survival. However, reporting the smallest number of participants of all the selected papers and unclear risk of bias does mean the results may not be truly representative of the general population and future studies should focus on including more participants to be a part of the trial.

4.2. Overall outcomes from bevacizumab plus temozolomide

Since some papers used the same treatments, it is worth considering how that mitigates the individual heterogeneity of study designs. Three papers used bevacizumab in conjunction with temozolomide. The bevacizumab papers had similar participant allocation and did not have high risk of bias. These additional similarities should add to the likelihood of consistency between studies. We hypothesize that the difference in mPFS between Balana et al. 2016 and Chinot et al. 2014 and Gilbert et al. 2014 may be associated with the difference in sample size of 102, 921 and 637 participants respectively. More participants mean more datapoints which can change the median value of a single dataset.

Two papers used bevacizumab and irinotecan although one paper also adds temozolomide to the intervention. However, the differences in participant allocation and sample size, as well as Herrlinger 2016 having a high risk of bias in two categories leads us to reason that it is much more difficult to compare the two studies. For now, we find no evidence indicating bevacizumab should be discontinued as an approved treatment for glioblastoma.

Based on our risk of bias analysis we are confident in Gilbert et al. 2014 results being accurate and valid using the same study design. In contrast, we do not believe Herrlinger et al. 2016 results would be accurate or valid.

Based on the data presented, we conclude that studies show that TMZ is favored for improvements in mOS while bevacizumab plus TMZ is favored for improvements in mPFS.

4.3. Other treatments to consider

The positive results from Liau 2018 in combination with the minimal risk of bias does raise the potential for GM-CSF in combination with TMZ to be considered for additional study as a treatment for glioblastoma.

Therefore, we find that the evidence does not change TMZ, and bevacizumab's validity as glioblastoma treatments and the evidence highlights GM-CSF may be worthy of additional investigation as a potential glioblastoma treatment.

4.3.1. Limitations

We found fewer studies conducted post-2020 than post-2015 in our literature search. This could mean a decrease in interest in studying immunotherapies for glioblastoma. Furthermore, our selected studies from 2014 to 2016 used bevacizumab whereas 2016-present did not use that treatment. We do not know if there is an explanation which motivated this trend or if this is the result of our search strategies. If future reviews also note a chronological difference in the types of immunotherapies trialed, there should be an effort to investigate why certain treatments were studied during a specific timeframe.

We focused on median overall survival and median progression free survival. We did not consider other measured outcomes such as adverse events which may impact a patient's quality of life. This is significant because patient wellbeing also affects the worthiness of the treatment: a patient may not take a treatment which extends survival but also causes unnecessary daily pain.

We did not consider patient demographics and given the different countries where our reported studies were conducted, there may be significant differences in social determinants of health which may have affected patient wellbeing.

We selected papers from three databases, which limited the total

number of papers we gathered. Limiting the number of papers limits the immunotherapy combination treatments that we can analyze in a single review and make conclusions about. Our three databases do not represent the exhaustive list of possible immunotherapy combination treatments and future reviews using other databases can present equally viable combination treatments.

Despite these limitations, our review brought to light several interventions that were trialed to be treatments for glioblastoma and identified two immunotherapies that hold promise as meaningful enhancers of post-diagnosis survival compared to TMZ alone. Bevacizumab with TMZ stands out because its improvements to mPFS are statistically significant, either in p-value or confidence intervals) for five studies. Autologous dendritic cell vaccine with TMZ is notable because it shows statistical significance in a 95% confidence interval and is relatively free from bias.

5. Conclusion

We conclude that bevacizumab with TMZ is a better intervention than TMZ alone to extend progression-free survival in patients. GM–CSF with TMZ is worth further study as a treatment to extend overall survival in patients comp.

Nivolumab, interferon-beta (β), ICT-107 vaccine, and Autologous dendritic cell (DC) vaccine did not show sufficient evidence with TMZ to warrant future investigation.

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Protocol

The protocol for this study is available on PROSPERO (ID: CRD42023481916)

Ethical statement

IRB review requirements did not apply to this paper due to the paper being a systematic review of non-identifiable data.

CRediT authorship contribution statement

Brendan Chen: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Janet Alder:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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

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Data availability

All data presented in this study is available on Mendeley Data and is also available upon request.

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