BMJ Open

Efficacy of cell-based immunotherapies on patients with glioma: an umbrella review of systematic reviews and meta-analysis protocol

Mehdi Nikoobakht,[1,2] Parisa Shamshiripour,[3,4,5] Seyed Mostafa Mostafavi Zadeh,[6,7] Mehrana Rahnama,[8] Fahime Hajiahmadi,[9] Aghdas Ramezani,[4] Vahideh Farzam Rad,[4,10] Elaheh Nazari,[10] Ali-Reza Moradi,[4,10] Mahzad Akbarpour,[11] Davoud Ahmadvand[4]

To cite: Nikoobakht M, Shamshiripour P, Mostafavi Zadeh SM, *et al*. Efficacy of cell-based immunotherapies on patients with glioma: an umbrella review of systematic reviews and meta-analysis protocol. *BMJ Open* 2023;**13**:e072484. doi:10.1136/bmjopen-2023-072484

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072484).

MN, PS and SMMZ contributed equally.

Received 03 February 2023
Accepted 25 October 2023

For numbered affiliations see end of article.

Correspondence to
Dr Davoud Ahmadvand; d.ahmadvand@iums.ac.ir

ABSTRACT

Introduction Glial brain tumours are highly mortal and are noted as major neurosurgical challenges due to frequent recurrence or progression. Despite standard-of-care treatment for gliomas, the prognosis of patients with higher-grade glial tumours is still poor, and hence empowering antitumour immunity against glioma is a potential future oncological prospect. This review is designed to improve our understanding of the efficacy of cell-based immunotherapies for glioma.

Methods and analysis This systematic review will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of main electronic databases: PubMed/MEDLINE, Scopus, ISI Web of Science EMBASE and ProQuest will be done on original articles, followed by a manual review of review articles. Only records in English and only clinical trials will be encountered for full-text review. All the appropriate studies that encountered the inclusion criteria will be screened, selected and then will undergo data extraction step by two independent authors. For meta-analyses, data heterogeneity for each parameter will be first evaluated by Cochran's Q and I2 statistics. In case of possible heterogeneity, a random-effects meta-analysis will be performed and for homogenous data, fixed-effects models will be selected for reporting the results of the proportional meta-analysis. Bias risk will be assessed through Begg's and Egger's tests and will also be visualised by Funnel plots.

Ethics and dissemination As this study will be a systematic review without human participants' involvement, no ethical registration is required and meta-analysis will be presented at a peer-reviewed journal.

PROSPERO registration number CRD42022373297

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review is the first umbrella review of systematic reviews and meta-analyses evaluating the efficacy of cell-based immunotherapies on patients with glioma.
- ⇒ Meta-analysis of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.
- ⇒ A comprehensive literature search from multiple databases was conducted.
- ⇒ The search was restricted to English-language articles only.
- ⇒ A limited number of studies will meet the inclusion criteria.

INTRODUCTION

Gliomas are among highly mortal neoplastic lesions that remain a major neuro-oncological concern due to their frequent recurrence/progression despite standard treatments.[1] Up to the present, numerous attempts have been devoted to improving the efficacy of the current standard-of-care treatment for gliomas that comprise concurrent chemoradiation and surgical interventions.[2] The major challenges limiting the efficacy of the standard-of-care treatments for gliomas comprise the infiltrative nature of high-grade gliomas, which limits the efficacy of total aggressive surgery due to residues remaining and also tumour heterogeneity. Another main concern is the mesenchymal-transformed cells referred to as cancer stem cells in the glioma tumour microenvironment (TME), which are resistant to chemoradiation. This piece of evidence proves the ultimate need for designing treatment strategies with precision to individual characteristics of the tumour in each patient.

A key feature in the glioma pathogenesis is its immune-suppressed microenvironment due to the pauci nature of the brain as an immune-privileged site and also the overproduction of angiogenic signals in the glioma TME produced in the hypoxic central niche of highly proliferating glioma cells, which

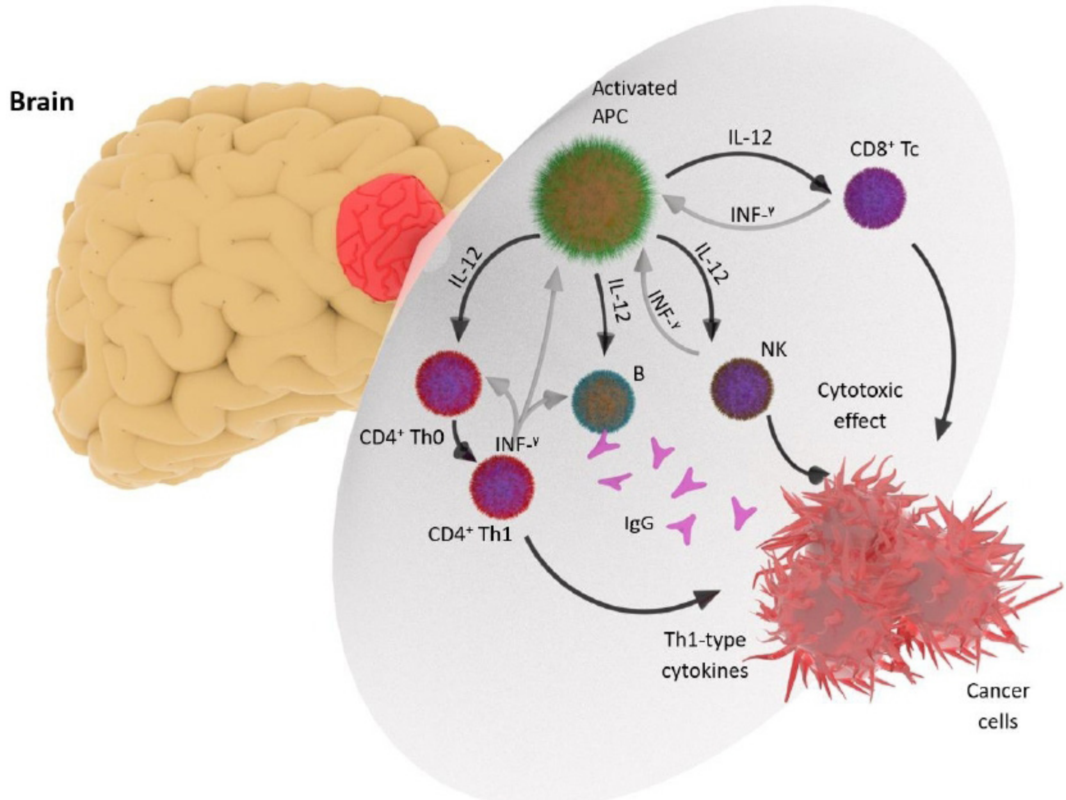

Figure 1 A schema of different cell-based immunotherapy strategies to combat glioma growth.

induces generation of tolerogenic dendritic cells (DCs) and impairs the antigen presentation process.[3] The glioma TME comprises a low density of immune cells making it a 'cold tumour' with limited immune contexture. Hence, re-empowering the immune system components (ie, NK cells, cytotoxic T cells and DC cells) against gliomas in a coordinated fashion and also transferring autologous/allogeneic immune cells (ie, adoptive immunotherapy) to the tumour site to combat tumorous cells has been of particular interest as a highly precise therapy in the past decades.[4] Standing at the first and foremost stages of interest for such attempts in the previous literature are cellular immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Cellular immunotherapies can comprise both innate and adoptive immune cells (figure 1). NK cells, granulocytic lymphocytes acting as powerful armamentaria of the innate immune system, are capable of eliminating abnormally transformed cells without any need for prior sensitisation. NK cells recruit to their action site in a chemokine-mediated manner. Some NK cells act as empowered soldiers able to kill numerous and diverse cells named 'serial killers', which are noted as potent antitumour cells.[5] Moreover, the introduction of chimeric antigen receptor (CAR) NK cells also represented a step forward towards more efficient NK products[6] and efforts are underway to further clinically translate such immune products from benches to bedsides.

DCs are also key players in the immune system referred to as linkers of adaptive and innate immune responses. DCs enhance NK cell migration and recruitment to the tumour site by the production of numerous chemokines (eg, CXCL8, CXCL9 and CXCL11).[7] Furthermore, DCs act as regulators of adaptive/cellular immune responses against tumorous cells mediated by CD8+cytotoxic T cells by cross-presenting the tumorous antigens via major histocompatibility complex II (MHCII)-antigen complexes.[8] DCs are also responsible for coordinating the immune contexture in the TME by producing chemokines and cytokines responsible for an orchestrated migration of immune cells to the tumour site. DC therapy for gliomas has long been studied in clinical settings, yielding acceptable results[9] and has introduced a paradigm shift toward more precise glioma management.

Furthermore, the advent of adaptive T-cell generation and clinical testing of such immune cell products has yielded promises towards glioma therapy. Early reports have suggested alloreactive T cells for glioma therapy.[10] Testing the autologous lymphocyte transfer has also opened a new avenue toward more precision.[11] Such T cells were activated by several strategies against tumorous cells *ex vivo* such as total tumour RNA pulsing. Furthermore, mounting the previous literature, earlier attempts generating antigen-specific T cells have been of particular interest (eg, CMV-specific T cells).[12] Recently, the advent of CAR T cells has revolutionised the advent of T-cell therapy for gliomas as well as other neoplastic lesions.[13–15] Genetically engineered T cells that express CARs can recognise tumour-associated antigens (TAAs) or tumour-specific antigens (TSAs) presented by the MHCs resulting in a powerful antitumour immune response. Despite the potential limitations of CAR T cells for solid tumours, in gliomas, promises have been obtained in early attempts possibly due to the cold nature of the glioma immune context.[16] CARs can be engineered to target various highly expressed tumour antigens and can serve as next-generation adoptive cell therapies for gliomas[17] (online supplemental table 1). As future prospects, using combination therapy regimens may yield substantial improvements in the field of glioma immunotherapy. Furthermore, using adjuvants is also a potential proposed strategy to improve the efficacy of adoptive immune cell therapy for gliomas.[18–21]

Summarising the results of the efficacy and limitations of the previous attempts on glioma immunotherapies opens the door to the discovery of novel techniques and yields insight into the treatment failure causes and ways to overcome them. Here, we aimed to discuss the main methods that will be applied in a comprehensive meta-analysis for assessing the response efficacy and survival of cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma. The meta-analysis on cell-based immunotherapies aims to provide a hierarchical summary on the road to clinical translation of adoptive immunotherapies for gliomas and also discusses the technical limitations introducing variability in generating GMP-grade immune cell products. The review will also highlight the potential need for standardised protocols for more reproducible and scalable production techniques. Furthermore, the review will discuss the potential strategies to enhance the efficacy of adoptive immunotherapies for gliomas. For instance, using adjuvants and also combination therapy.

Objectives

This systematic review and meta-analysis aims to summarise the results of previous clinical trials on (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma patients regarding the number of patients, administered doses, adjuvants, antigens/targets, phases, submission dates, completion dates and allocation. Furthermore, this study aims to investigate the immunological efficacy of cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) for glioma. Also, this compares the administered dose of each therapy (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) and the survival outcome of the patients enrolled in treatment groups or control groups for each treatment. Moreover, the survival of the patients enrolled in different treatment groups will also be compared. Furthermore, the immunological response will be compared among the patients receiving each treatment and control groups for each therapy. Furthermore, standardisation of the protocols used to harvest cells and produce and scale up the manufacturing process will hugely revolutionise the results obtained from each trial. There is a substantial need to improve guidelines for the GMP-level products moving from benches to bedsides to let the process be more reproducible and reliable. Additionally, standardising the strategies to assess treatment efficacy will also hugely impact the results of trial pipelines (eg, immunological response assessment, radiological response assessment criteria such as AVA Glio, RESICT, RANO or iRANO). In the current meta-analyses, we will discuss the limitations on the way of clinical translation of the GMP-level products in the trial pipelines for better outcome management and standardised results reporting.

METHODS AND ANALYSIS

Eligibility criteria

This study follows the Population, Intervention, Comparison, Outcomes and Study (PICOS)-type format for conducting systematic reviews and meta-analyses.[22] According to PICO parts, the eligibility criteria will be as follows.

Participants/population

Inclusion criteria

This umbrella review will consider systematic reviews that include the population for the current work consisting of adult patients and controls enrolled in clinical trials for glioma cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Exclusion criteria

Studies reporting patients with other cancers will be excluded.

Intervention(s), exposure(s)

The intervention (exposure) of this study will be cell-based immunotherapies (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells).

Comparator(s)/control

Administered doses, percentage of clinical trials targeting each tumorous antigen, immunological efficacy and survival.

Main outcome(s)

The standardised mean difference for administered doses, the pooled effect size for each antigen for glioma immunotherapy, the pooled effect size of significant immunological responses for each therapy and the overall survival benefit for each immunotherapy as an indicator of treatment efficacy.

Studies design

Inclusion criteria

Only systematic reviews and systematic review and meta-analysis studies will be included.

Exclusion criteria

Narrative reviews, commentaries, letters, case reports, case series, experimental studies and research works in any other language rather than English are excluded from this review. Furthermore, studies suggesting a controversial result will be excluded with no time limits. Controversies are among the unavoidable issues while collecting huge clinical data from diverse clinical centres worldwide testing a specific therapy in trial pipelines. To cope with this issue in the systematic reviews, several strategies have been proposed such as removing the controversial reports. Here, when meeting a controversy, the two independent authors reviewing the selected manuscripts will discuss the potential differences and diversities in the cell production process or obtain the efficacy results and will draw a certain conclusion by getting in touch with the corresponding authors. If the conflicting answer is due to inappropriate methodology, it will not be considered in the meta-analysis stage. For instance, if the lack of adequate cell count to start the treatment is the reason for the trial failure, that study will not be considered in the meta-analysis stage but will be discussed in a separate section. For instance, if the lack of adequate cell count to start the treatment is the reason for the trial failure, that study will not be considered in the meta-analysis stage but will be discussed in a separate section summarising the failure reasons for each cell-based therapy and solutions to overcome will further be discussed.

Information sources

The current work includes a comprehensive search of main electronic databases (PubMed, Scopus, ISI Web of Science, EMBASE and Clinicaltrial.gov) and is also followed by a manual search of the reference lists of the previously published review articles.

Search strategy

Search syntax for each main electronic database (PubMed, Scopus, ISI Web of Science, EMBASE and Clinicaltrial.gov) will be generated according to their rules and Mesh terms.[23–25] An example of the PubMed/MEDLINE search strategy is presented in table 1. A filter for study type, review and clinical trial will be used to minimise the presence of unrelated articles in the recovery search. All the retrieved references will be deposited in a single Endnote file, and after duplicate removal they will undergo a title review for relevance.

Selection process

After retrieval of relevant articles and duplicate removal, two individual authors, PS and MN, will go through the title and abstracts of the relevant article to select the relevant qualified articles for the data mining process. In case of any disagreement between the two authors, it will be fixed via consensus and then will be checked by two other authors (SMMZ and AR). Irrelevant studies and studies with controversial results will be excluded at this stage. DA and MA will be asked to build a consensus in cases where discrepant opinions exist.

Data collection process

Relevant qualified articles will undergo a full-text review in order to extract data from them. Two individual authors, PS and FHA, will extract data according to the checklist summarised in Excel from each study individually regarding the immunological responses and survival rates. AM and VFR will do so for radiological response rates. In case of any disagreement between the two authors, it will be fixed via consensus and then will be checked by two other authors (SMMZ and AR). At last, DA and MA will build consensus for discrepant reports.

The reports of data mining will be presented in tables for each cell-based immunotherapy (eg, CAR T cells, DC cells, adoptive T cells, CIK cells and NK cells) summarising in detail the aforementioned parameters. The radiological responses reported according to the guidelines Response Assessment in Neuro-Oncology Criteria (RANO), immunotherapy response assessment for Neuro-oncology (iRANO), Response evaluation criteria in solid tumors (RESICT), WHO oncology response criteria, Macdonald and AVAglio[26–30] will be summarised as depicted in table 2.

Table 1 Representative example of the search syntaxes generated for the comprehensive search

Search syntax for PubMed	
#1	((Glioma[tiab]) OR (Gliomas[tiab]) OR “Glial Cell Tumor*”[tiab] OR (Tumor*[tiab] AND Glial Cell[tiab]) OR “Mixed Glioma” [tiab] OR (Glioma*[tiab] AND Mixed[tiab]) OR “Mixed Glioma*”[tiab] OR “Malignant Glioma*”[tiab] OR (Glioma*[tiab] AND Malignant[tiab]) OR (glioblastoma[tiab]) OR “anaplastic astrocytoma” [tiab] OR “diffuse astrocytoma”[tiab] OR “anaplastic oligodendroglioma”[tiab] OR (oligodendroglioma[tiab]))
#2	((Immunotherapy[tiab] AND Adoptive[tiab]) OR “Cytokine-Induced Killer Cells”[tiab] OR “Dendritic Cells”[tiab] OR (Killer Cells AND Natural[tiab]) OR “cytokine induced killer”[tiab] OR “tumor infiltrating lymphocytes”[tiab] OR “lymphokine activated killer” [tiab] OR (autolymphocyte[tiab]) OR “activated T cells”[tiab] OR “activated killer cells” [tiab] OR “gamma delta T cells”[tiab] OR “γδ T cells” [tiab] OR “NKT cells” [tiab] OR “natural killer”[tiab] OR “NK cells” [tiab] OR “Adoptive Immunotherapy” [tiab] OR “Adoptive Immunotherapies”[tiab] OR (Immunotherapies[tiab] AND Adoptive[tiab]) OR (“Cellular Immunotherapy”[tiab] AND Adoptive[tiab]))
#3	(1992/01/01:2022/11/02[dp])
	#1 AND #2 AND #3

Quality assessment

The Cochrane Collaboration’s tool will be used as the checklist of choice to assess the risk of bias among included studies, which comprises five major domains: selection bias (random sequence generation and allocation), performance bias, detection bias, attribution bias and reporting bias. Each domain will be scored as high, low or unclear as implemented in our previous work.[31–34]

Statistical analysis

For the assessment of heterogeneity among included studies, the I2 statistic defined as the fraction of variance

Table 2 Data extraction checklist for each study

Study features	Patients feature	Treatment strategy features	Immunological response parameters	Survival features	Radiological response parameters
First author's surname	Estimated/actual number of enrolled patients	Immunotherapy strategy (innate or acquired)	INFγ increase	Overall survival rate	Complete response%
Publication date	Tumour pathology and grade	Product type (eg, CAR T, DC)	Induction of delayed type hypersensitivity (DTH)	Progression-free survival rate	Partial response%
Study design, allocation and randomisation		Adjuvants	Blood flow cytometry tests	Progression/recurrent rate	Stable disease%
University/institute		doses	TIL* flow cytometry tests	Mean/median overall survival (months)	Progression%
Phase		boosters		Mean/median progression-free survival (months)	
Estimated/actual study completion date		Antigens/targeting moieties		HR for overall survival	
Trial submission date				HR for progression-free survival	
Country					
Completion status					
Clinical trial submission number					

TIL, Tumor-infiltrating lymphocyte.

that is due to heterogeneity will be used.[35] Heterogeneity will be categorised as negligible (I2=0%–25%), low (I2=25%–50%), moderate (I2=50%–75%) or high (I2>75%). Cochran's Q will also be encountered as a complementary measure for heterogeneity.[36] If we face high heterogeneity, Random Effect Model will be applied by Dersimonian and Laird method and when the heterogeneity is low, the fixed effect model will be applied for meta-analysis.[37] Egger's and Begg's tests will be used to investigate the presence of publication bias.[38 39] For dose estimation meta-analysis, as a continuous measure, the 'Hedges g' statistic, as a function for standardised mean difference (SMD) will be used at a significant threshold of <0.05.[40] For proportional data meta-analysis (for radiological and immune response assessment), Freeman-Tukey Transformation (arcsine square root transformation) will be used as the method of choice.[41] For survival meta-analysis of survival rates (overall or PFS) at specific time points, also Freeman-Tukey Transformation will be performed; however, for survival meta-analysis with hazard ratios from KM analysis, the generic inverse variance method will be used.[42] Furthermore, in order to visualise the data for better interpretation, the pooled effect size will be depicted by forest plots for each study and also funnel plots will be used for depicting the publication bias status.[43] The asymmetry of the funnel plot will show the presence of publication bias.[44]

The results of the bias risk assessment through Cochrane Collaboration's tool and meta-analysis will be summarised in tables depicting each variable, heterogeneity parameters for (I^2 and Q) for the variable and overall effect size with 95%CIs, and also the forest and funnel plot for each variable will be included.

Patient and public involvement

Patients and the public are not involved in the preparation of this protocol and will not be directly involved in the final systematic review.

DISCUSSION

In the discussion and conclusion parts, the results of the survival analyses performed will be discussed in detail and also the impact of using adjuvants on improving survival outcomes will be further discussed. In the later sections, previous adjuvants will be summarised and discussed. Regarding the immunological response rates, also a detailed discussion on the overall validity of each parameter for assessing the efficacy of immunotherapy will first be discussed and then the results will be compared for each therapy group.

ETHICS AND DISSEMINATION

This review will retrieve published data, so it will not require ethical approval. The findings of this systematic review and meta-analysis will be disseminated via an international peer-reviewed journal publication and several scientific conference presentations.

Author affiliations

[1]Department of Neurosurgery, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Tehran, Iran
[2]Firoozgar Clinical Resrarch Development Center, Iran University of Medical Sciences, Tehran, Tehran, Iran
[3]Faculty of Medicine, Iran University of Medical Sciences, Tehran, Tehran, Iran
[4]Department of Molecular Imaging, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran
[5]Department of Pathology, Shahid Beheshti Medical University, Tehran, Iran
[6]Department of Molecular Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran
[7]Oncopathology Research Center, Iran University of Medical Sciences, Tehran, Iran
[8]Department of Biophysics, Iran University of Meidcal Sciences, Tehran, Iran
[9]Cellular Molecular Pharmacology School, School of Medicine, University of California San Francisco, San Francisco, California, USA
[10]Department of Physics, Institute for Advanced Studies in Basic Sciences, (IASBS), University of Zanjan, Zanjan, Zanjan, Iran
[11]Advanced Cellular Therapeutics Facility, David and Etta Jonas Center for Cellular Therapy, Hematopoietic Cellular Therapy Program, The University of Chicago Medical Center, Chicago, Illinois, USA

Twitter Mahzad Akbarpour @mahzad1980

Contributors DA, MN, AM and MA developed the search strategy and participated in writing up the draft of the protocol and SMMZ reviewed the manuscript and edited the final manuscript. All the authors read and approved the final draft. Data screening and selecting phases of the systematic review and meta-analysis will be performed by SMMZ and PS. Quality assessment and meta-analysis will be executed by PS, MR, FH and AR. Data extraction and preparing the draft of the manuscript will be performed by SMMZ, VF and AM. Moreover, PS, MN and SMMZ will be responsible for reviewing the manuscript and editing the final manuscript. EN contributed to designing the schemas and also revising the protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This review will retrieve published data, so it will not require ethical approval. The findings of this systematic review and meta-analysis will be disseminated via an international peer-reviewed journal publication and several scientific conference presentations.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Seyed Mostafa Mostafavi Zadeh http://orcid.org/0000-0002-1068-1837

REFERENCES

1. Ostrom QT, Bauchet L, Davis FG, *et al*. "The epidemiology of glioma in adults: a "state of the science" review". *Neuro Oncol* 2014;16:896–913.
2. Nabors LB, Portnow J, Ahluwalia M, *et al*. Central nervous system cancers, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2020;18:1537–70.
3. Hinshaw DC, Shevde LA. The tumor Microenvironment Innately modulates cancer progression. *Cancer Res* 2019;79:4557–66.
4. Artene S-A, Turcu-Stiolica A, Ciurea ME, *et al*. Comparative effect of Immunotherapy and standard therapy in patients with high grade glioma: a meta-analysis of published clinical trials. *Sci Rep* 2018;8:11800.
5. Ogbomo H, Cinatl J Jr, Mody CH, *et al*. Immunotherapy in gliomas: limitations and potential of natural killer (NK) cell therapy. *Trends Mol Med* 2011;17:433–41.
6. Burger MC, Zhang C, Harter PN, *et al*. CAR-engineered NK cells for the treatment of glioblastoma: turning innate effectors into precision tools for cancer Immunotherapy. *Front Immunol* 2019;10:2683.
7. Sozzani S, Allavena P, Vecchi A, *et al*. Chemokines and Dendritic cell traffic. *J Clin Immunol* 2000;20:151–60.
8. Datsi A, Sorg RV. Dendritic cell vaccination of glioblastoma: road to success or dead end. *Front Immunol* 2021;12:770390.
9. Reardon DA, Mitchell DA. The development of dendritic cell vaccine-based immunotherapies for glioblastoma. *Semin Immunopathol* 2017;39:225–39.
10. Kruse CA, Cepeda L, Owens B, *et al*. Treatment of recurrent glioma with intracavitary Alloreactive cytotoxic T lymphocytes and Interleukin-2. *Cancer Immunol Immunother* 1997;45:77–87.
11. Merchant RE, Ellison MD, Young HF. Immunotherapy for malignant glioma using human recombinant Interleukin-2 and activated Autologous lymphocytes: a review of pre-clinical and clinical investigations. *J Neurooncol* 1990;8:173–88.
12. Ghazi A, Ashoori A, Hanley PJ, *et al*. Generation of polyclonal CMV-specific T cells for the adoptive Immunotherapy of glioblastoma. *J Immunother* 2012;35:159–68.
13. Rajabzadeh A*et al*. A VHH-based anti-Muc1 Chimeric antigen receptor for specific Retargeting of human primary T cells to Muc1-positive cancer cells. *Cell Journal (Yakhteh*) 2021;22:502.
14. Sharifzadeh Z, Rahbarizadeh F, Shokrgozar MA, *et al*. Genetically engineered T cells bearing Chimeric Nanoconstructed receptors harboring TAG-72-specific Camelid single domain antibodies as targeting agents. *Cancer Lett* 2013;334:237–44.
15. Jamnani FR, Rahbarizadeh F, Shokrgozar MA, *et al*. T cells expressing VHH-directed Oligoclonal Chimeric Her2 antigen receptors: towards tumor-directed Oligoclonal T cell therapy. *Biochim Biophys Acta* 2014;1840:378–86.
16. Petersen CT, Krenciute G. Next generation CAR T cells for the Immunotherapy of high-grade glioma. *Front Oncol* 2019;9:69.
17. Migliorini D, Dietrich P-Y, Stupp R, *et al*. CAR T-cell therapies in glioblastoma: a first look. *Clin Cancer Res* 2018;24:535–40.
18. Chandran M, Candolfi M, Shah D, *et al*. Single vs. combination Immunotherapeutic strategies for glioma. *Expert Opin Biol Ther* 2017;17:543–54.
19. Dietrich P-Y, Dutoit V, Tran Thang NN, *et al*. T-cell Immunotherapy for malignant glioma: toward a combined approach. *Curr Opin Oncol* 2010;22:604–10.
20. Tang B, Guo ZS, Bartlett DL, *et al*. Synergistic combination of Oncolytic Virotherapy and Immunotherapy for Gliomacombination treatment cures gliomas. *Clin Cancer Res* 2020;26:2216–30.
21. Jung G, Brandl M, Eisner W, *et al*. Local Immunotherapy of glioma patients with a combination of 2 Bispecific antibody fragments and resting Autologous lymphocytes: evidence for in situ T-Cell activation and therapeutic efficacy. *Int J Cancer* 2001;91:225–30.
22. Methley AM, Campbell S, Chew-Graham C, *et al*. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014;14:579.
23. DeLuca JB, Mullins MM, Lyles CM, *et al*. Developing a comprehensive search strategy for evidence based systematic reviews. *EBLIP* 2008;3:3–32.
24. Montori VM, Wilczynski NL, Morgan D, *et al*. Optimal search strategies for retrieving systematic reviews from MEDLINE: Analytical survey. *BMJ* 2005;330:68.
25. Lai M-C, Lombardo MV, Baron-Cohen S. Autism. *The Lancet* 2014;383:896–910.
26. Chinot OL, Macdonald DR, Abrey LE, *et al*. Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of Antiangiogenic therapy. *Curr Neurol Neurosci Rep* 2013;13:347.

27 Henson JW, Ulmer S, Harris GJ. Brain tumor imaging in clinical trials. *AJNR Am J Neuroradiol* 2008;29:419–24.
28 Macdonald DR, Cascino TL, Schold SC Jr, *et al*. Response criteria for phase II studies of Supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–80.
29 Chinot OL, de La Motte Rouge T, Moore N, *et al*. Avaglio: phase 3 trial of Bevacizumab plus Temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. *Adv Ther* 2011;28:334–40.
30 Okada H, Weller M, Huang R, *et al*. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol* 2015;16:e534–42.
31 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
32 Savović J, Weeks L, Sterne JAC, *et al*. Evaluation of the Cochrane collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev* 2014;3:37.
33 Jørgensen L, Paludan-Müller AS, Laursen DRT, *et al*. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. *Syst Rev* 2016;5:80.
34 Shamshiripour P, Nikoobakht M, Mansourinejad Z, *et al*. A comprehensive update to Dendritic cell therapy for glioma: A systematic review and meta-analysis. *Expert Rev Vaccines* 2022;21:513–31.
35 von Hippel PT. The heterogeneity Statistic I2 can be biased in small meta-analyses. *BMC Med Res Methodol* 2015;15:1–8.
36 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
37 Nikolakopoulou A, Mavridis D, Salanti G. How to interpret meta-analysis models: fixed effect and random effects meta-analyses. *Evid Based Ment Health* 2014;17:64.
38 Peters JL, Sutton AJ, Jones DR, *et al*. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676–80.
39 Lin L, Chu H, Murad MH, *et al*. Empirical comparison of publication bias tests in meta-analysis. *J Gen Intern Med* 2018;33:1260–7.
40 Kromrey JD*et al*. Robustness in meta-analysis: an empirical comparison of point and interval estimates of standardized mean differences and cliff's Delta. In: *Joint Statistical Meetings*. Minneapolis, MN, 2005.
41 Lin L, Xu C. Arcsine-Based transformations for Meta-Analysis of proportions: pros, cons, and alternatives. *Health Sci Rep* 2020;3:e178.
42 Yang W-F, Wong MCM, Thomson PJ, *et al*. The Prognostic role of PD-L1 expression for survival in head and neck squamous cell carcinoma: A systematic review and meta-analysis. *Oral Oncol* 2018;86:81–90.
43 Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. *BMJ* 2001;322:1479–80.
44 Sterne JAC, Harbord RM. Funnel plots in meta-analysis. *The Stata Journal* 2004;4:127–41.

Supplemental Table 1. Some Examples of Cell-based Immunotherapy Strategies (DC) for Glioma

Cells used	Year published	Adult/Childhood gliomas	First author	Affiliated as	ref
DC cells	2020	adult	Jeremy D. Rudnick	Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, United States	1
autologous dendritic cell vaccine	2018	adult	Linda M. Liau	University of California Los Angeles (UCLA) David Geffen School of Medicine & Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA	2
Dendritic cell-based immunotherapy targeting Wilms' tumor 1	2015	adult	Keiichi Sakai	Department of Neurosurgery, National Hospital Organization, Shinshu Ueda Medical Center, Ueda, Nagano, Japan	3
Intraventricular B7-H3 CAR T Cells	2023	Childhood (DIPG*)	Nicholas A. Vitanza	Ben Towne Center for Childhood Cancer Research, Seattle Children's Research Institute, Seattle, Washington.	4
IL13Rα2 CAR T cell	2016	Adult	Christine E. Brown	Department of Hematology and Hematopoietic Cell Transplantation, T Cell Therapeutics Research Laboratory, City of Hope Beckman Research Institute and Medical Center, Duarte, CA	5
Autologous CMV-specific T cells	2020	Adult	Corey Smith	QIMR Berghofer Centre for Immunotherapy and Vaccine Development and Tumor Immunology Laboratory, Department of Immunology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. 2 NEWRO Foundation, Brisbane, Queensland, Australia	6
Autologous HER2 CMV bispecific CAR T cells	2015	Adult	Nabil Ahmed	Department of Pediatrics, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA	7
EGFRvIII CAR T Cell	2021	Adult	Joseph S. Durgin	Glioblastoma Translational Center of Excellence, The Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States	8
HER2-Specific CAR T cells	2017	Adult	Nabil Ahmed	Center for Cell and Gene Therapy, Texas Children's Hospital, Houston Methodist Hospital, Baylor College of Medicine, Houston	9
EGFRvIII-directed CAR T cells	2017	Adult	DONALD M. O'ROURKE	Department of Neurosurgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.	10

* DIPG: Diffuse Intrinsic Pontine Glioma

References:

1. Rudnick, Jeremy D., et al. "A phase I trial of surgical resection with Gliadel Wafer placement followed by vaccination with dendritic cells pulsed with tumor lysate for patients with malignant glioma." Journal of Clinical Neuroscience 74 (2020): 187-193.
2. Liau, Linda M., et al. "First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma." Journal of translational medicine 16.1 (2018): 1-9.
3. Sakai, Keiichi, et al. "Dendritic cell–based immunotherapy targeting Wilms' tumor 1 in patients with recurrent malignant glioma." Journal of Neurosurgery 123.4 (2015): 989-997.
4. Vitanza, Nicholas A., et al. "Intraventricular B7-H3 CAR T cells for diffuse intrinsic pontine glioma: preliminary first-in-human bioactivity and safety." Cancer discovery 13.1 (2023): 114-131.
5. Brown, Christine E., et al. "Regression of glioblastoma after chimeric antigen receptor T-cell therapy." New England Journal of Medicine 375.26 (2016): 2561-2569.
6. Smith, Corey, et al. "Autologous CMV-specific T cells are a safe adjuvant immunotherapy for primary glioblastoma multiforme." The Journal of clinical investigation 130.11 (2020): 6041-6053.
7. Ahmed, Nabil, et al. "Autologous HER2 CMV bispecific CAR T cells are safe and demonstrate clinical benefit for glioblastoma in a Phase I trial." Journal for immunotherapy of cancer 3 (2015): 1-1.
8. Durgin, Joseph S., et al. "Case report: prolonged survival following EGFRvIII CAR T cell treatment for recurrent glioblastoma." Frontiers in Oncology 11 (2021): 669071.
9. Ahmed, Nabil, et al. "HER2-specific chimeric antigen receptor–modified virus-specific T cells for progressive glioblastoma: a phase 1 dose-escalation trial." JAMA oncology 3.8 (2017): 1094-1101.
10. O'Rourke, Donald M., et al. "A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma." Science translational medicine 9.399 (2017): eaaa0984.