Targeted therapies in patients with newly diagnosed glioblastoma – a systematic meta-analysis of randomized clinical trials

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3,4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3,4 and Suppl. File 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5, 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5, 6
Study characteristics	17	Cite each included study and present its characteristics.	Table 1/List of references
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. Fig. 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6, 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 6, 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6, 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6, 7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7, 8
	23b	Discuss any limitations of the evidence included in the review.	Page 8
	23c	Discuss any limitations of the review processes used.	Page 8
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 5

PRISMA 2020 Checklist

Search Documentation:

Information sources

Name of Database	Provider / Interface	Time period covered
MEDLINE	Wolters Kluwer OvidSP	1946–current
Cochrane Library:		
CDRS (Cochrane Database of Systematic Reviews)	Wiley Online Library	1995–current
CENTRAL (Cochrane Central Register of Controlled Trials)	Wiley Online Library	1948–current
ClinicalTrials.gov	NLM	2000–current
International Clinical Trials Registry Platform	WHO	1990–current
Google Scholar	Google	unknown–current

Searches on 2021-07-27

MEDLINE

Database	
Ovid MEDLINE(R) ALL 1946 to July 26, 2021 (medall)	
Platform/Host	
Ovid	
Temporal coverage of database	
ca. 1946–2021	
Filter by date	
No limit	
Published search filters	
• Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), Ovid format (http://handbook-5-1.cochrane.org/chapter_6/box_6.4.d_cochrane_hsss_2008_sensprec_ovid.htm) • Filter P3 for Phase III Clinical Trials. From: Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. Journal of Clinical Epidemiology. 2019;112:12–9. doi: 10.1016/j.jclinepi.2019.04.002. PubMed PMID: 30986533. These filters were combined with OR to achieve higher sensitivity.	
Other limits	
No limits	
Date of search	
2021-07-27	
Peer Review of search strategy	
No	
Number of records before deduplication	
4365	
File(s) with database accession numbers	available upon request
MEDLINE_AN_2021-07-27.txt	

Search history

ID	Search statement	Record count	Annotation
1	exp glioma/ or (glioma* or glioblastoma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or GBM).ti,ab,kw.	123163	high-grade glioma
2	randomized controlled trial.pt.	538221	
3	controlled clinical trial.pt.	94306	
4	randomized.ab.	527972	
5	placebo.ab.	219938	
6	clinical trials as topic.sh.	196758	
7	randomly.ab.	362291	
8	trial.ti.	244279	
9	2 or 3 or 4 or 5 or 6 or 7 or 8	1382409	
10	exp animals/ not humans.sh.	4865254	
11	9 not 10	1272199	Cochrane Highly Sensitive Search Strategy 2008 sensitive and precise MEDLINE Ovid
12	Clinical Trial, Phase III/ or ("phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.	79572	Filter P3 for Phase III Clinical Trials. From: Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. Journal of Clinical Epidemiology. 2019;112:129. doi: 10.1016/j.jclinepi.2019.04.002

				. PubMed PMID: 30986533.
13	1 and 11	3953	high-grade glioma AND Cochrane Highly Sensitive Search Strategy 2008 sensitive and precise
14	1 and 12	865	high-grade glioma AND P3 filter
15	13 or 14	4365	high-grade glioma AND methodological filters

Cochrane Library

Databases	
Cochrane Library: • CDRS (Cochrane Database of Systematic Reviews) • CENTRAL (Cochrane Central Register of Controlled Trials)	
Platform/Host	
Wiley Online Library	
Temporal coverage of database	
• CDRS (Cochrane Database of Systematic Reviews): 1993–current • Cochrane Protocols: ?-current • CENTRAL (Cochrane Central Register of Controlled Trials): 1948–current	
Filter by date	
No limit	
Published search filters	
No filters	
Other limits	
No limits	
Date of search	
2021-07-27	
Peer Review of search strategy	
No	
Number of records before deduplication	
Total: 3631	
File(s) with database accession numbers	available upon request
Cochrane_CDSR_AN_2021-07-27.txt Cochrane_CENTRAL_AN_2021-07-27.txt Cochrane_ClinicalAnswers_AN_2021-07-27.txt Cochrane_Protocols_AN_2021-07-27.txt	
Notes	
No MESH terms used as this would only return records found through MEDLINE, too.	

Search history

ID	Search	Hits
#1	(glioma* OR glioblastoma* OR astrocytoma* OR oligodendroglioma* OR oligoastrocytoma* OR GBM):ti,ab,kw	3631

ClinicalTrials.gov

Databases	
ClinicalTrials.gov	
Platform/Host	
https://clinicaltrials.gov/ct2/home	
Temporal coverage of database	
?–current	
Filter by date	
No limit	
Published search filters	
No filters	
Other limits	
No limits	
Date of search	
2021-07-27	
Peer Review of search strategy	
No	
Number of records before deduplication	
2637	
File(s) with database accession numbers	available upon request
ClinicalTrials_AN_2021-07-27.txt	

Search history

2637 Studies found for: glioma OR glioblastoma OR astrocytoma OR oligodendroglioma OR oligoastrocytoma OR GBM

WHO's International Clinical Trials Registry Platform

The platform's Search interface was not functioning on 2021-07-27 (and has been in this state for a while) so that the update search could not be carried out on this date.

Google Scholar

Databases	
Google Scholar	
Platform/Host	
Google Scholar, from a German ID address. Searched using the program "Harzing's Publish or Perish", Version 7.29.3156.7695	
Temporal coverage of database	
?-present	
Filter by date	
No limit	
Published search filters	
No filters	
Other limits	
No limits	
Date of search	
2021-07-27	
Peer Review of search strategy	
No	
Number of records before deduplication	
200 (only the first 200 exported using the default ranking by relevance)	
Notes	
There are no accession numbers in Google Scholar so none are documented.	

Search history

Search string and illustration of the structure of the search strategy created with 2Dsearch (https://app.2dsearch.com/).
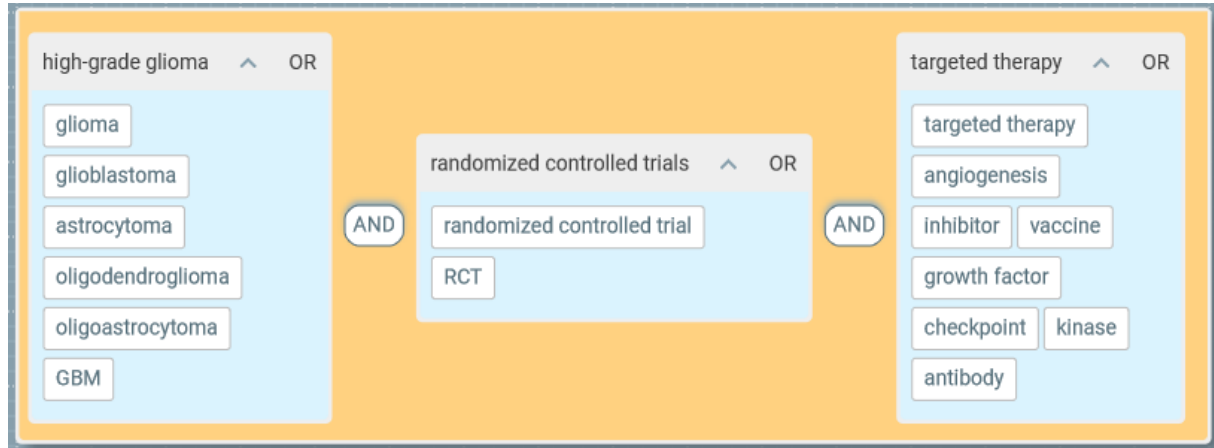
Google Scholar was searched using the program *Publish or Perish 7.29.3156.7695*

Search terms
Keywords:
(glioma|glioblastoma|astrocytoma|oligodendroglioma|oligoastrocytoma|GBM)("randomized controlled trial"|RCT)("targeted therapy"|angiogenesis|inhibitor|vaccine|"growth factor"|checkpoint|kinase|antibody)
Years: all

Update search of ICTRP on 2022-03-18

WHO's International Clinical Trials Registry Platform

Database(s)	
WHO's International Clinical Trials Registry Platform	
Platform/Host	
https://trialsearch.who.int/ Version 3.6	
Temporal coverage of database	
?–current	
Filter by date	
No limit	
Published search filters	
No filters	
Other limits	
No limits	
Date of search	
2022-03-18	
Peer Review of search strategy	
No	
Number of records before deduplication	
3412 records for 3018 trials	
File(s) with database accession numbers	available upon request
ICTRP_AN_2022-03-18.txt	

Search history

3412 records for 3018 trials found for: glioma OR glioblastoma OR astrocytoma OR oligodendroglioma OR oligoastrocytoma OR GBM

Synonyms used in search:
glioma; Astrocytoma; Carcinoma of brain; Cystic astrocytoma; Diencephalic glioma; Ependymoma; Ganglioglioma; Glioblastoma; Glioblastoma Multiforme Pathway; gliosarcoma; Malignant Glioma; Malignant neoplasm of brain; mixed gliomas; Mouse Neuroglia Neoplasm; oligodendroglioma; Pseudoglioma || glioblastoma; Adult Glioblastoma; Anaplastic astrocytoma; Childhood Glioblastoma; Choriocarcinoma of the Mouse Nervous System; Cystic astrocytoma; Diffuse Melanocytosis of the Mouse Nervous System; Dysplastic Lhermitte-Duclos Gangliocytoma of Mouse Cerebellum; Glioblastoma Multiforme; Mouse Glioblastoma || astrocytoma; Adult Astrocytic Tumor; Anaplastic astrocytoma; Astrocytoma, low grade; astrocytoma involving frontal lobe only; astrocytoma involving occipital lobe only; astrocytoma involving parietal lobe only; astrocytoma involving temporal lobe only; Astrocytoma of brain; Brain; Childhood Astrocytoma; Cystic astrocytoma; Diffuse Astrocytoma; Glioblastoma; Mouse Astrocytic Tumours || oligodendroglioma; Adult Oligodendroglioma; Anaplastic Oligodendroglioma; Childhood Oligodendroglioma; Glioma; Mouse Oligodendroglioma; well-differentiated oligodendroglioma, adult; Well Differentiated Oligodendroglioma || oligoastrocytoma; Anaplastic oligoastrocytoma of central nervous system || gbm; Anti-glomerular basement membrane tubulointerstitial nephritis; GBM antibody measurement; IMA950; Inactivated whole Hepatitis A virus GBM strain antigen; Inactivated whole Hepatitis A virus GBM strain antigen only vaccine product

PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Material and Methods - Study design and systematic literature search
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	Supplementary file 2
Study registries	3	List any study registries searched.	Material and Methods - Study design and systematic literature search
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	N.A.
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	Material and Methods - Study design and systematic literature search
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	N.A.
Other methods	7	Describe any additional information sources or search methods used.	N.A.
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Supplementary file 2
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Material and Methods - Study design and systematic literature search; Supplementary file 2
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	Material and Methods - Study design and systematic literature search
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	N.A.
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	Material and Methods - Study design and systematic literature search
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	Supplementary file 2
PEER REVIEW			
Peer review	14	Describe any search peer review process.	Material and Methods - Study design and systematic literature search
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Figure 1; Supplementary file 2
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Material and Methods - Study design and systematic literature search

N.A. = Not applicable/not done.

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews
Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.
Last updated February
27, 2020.
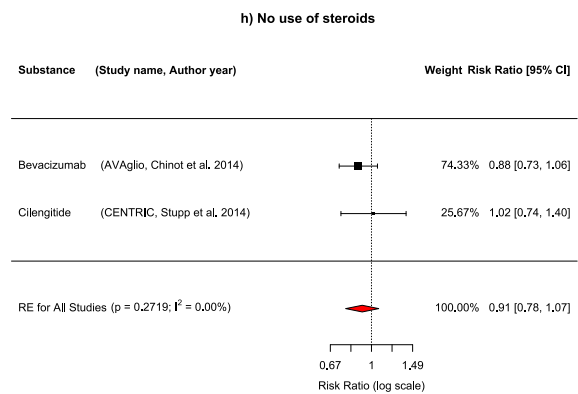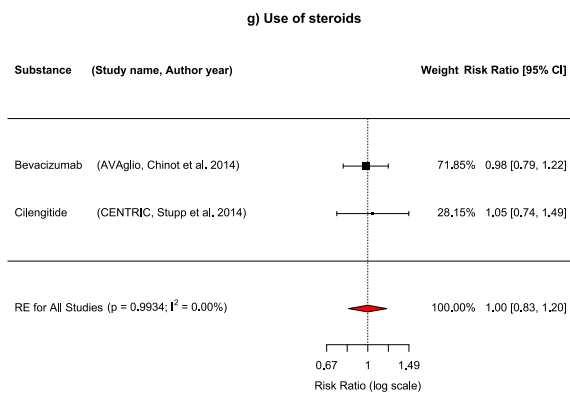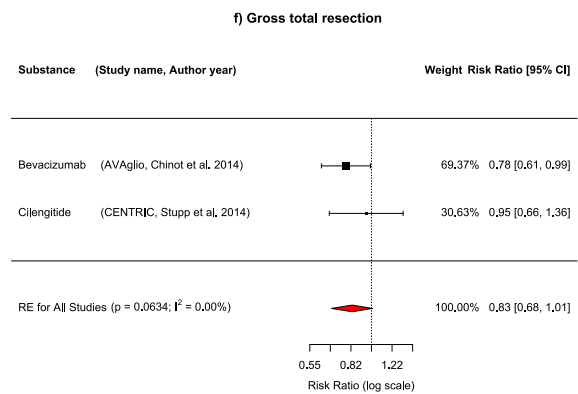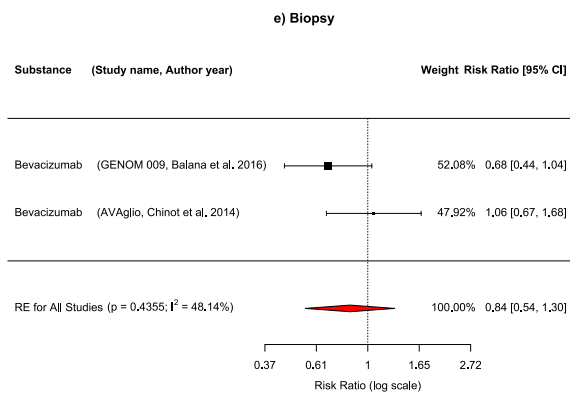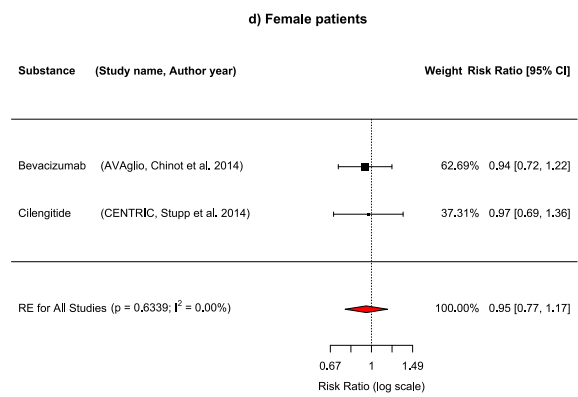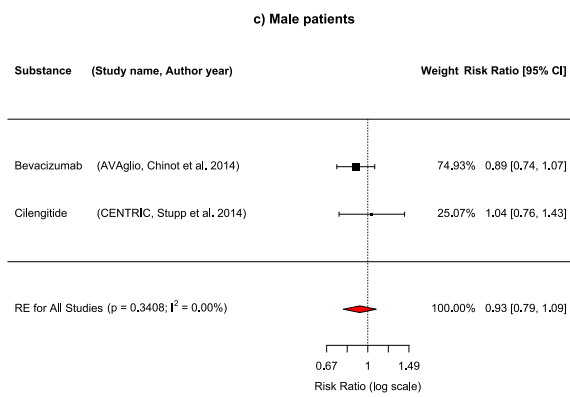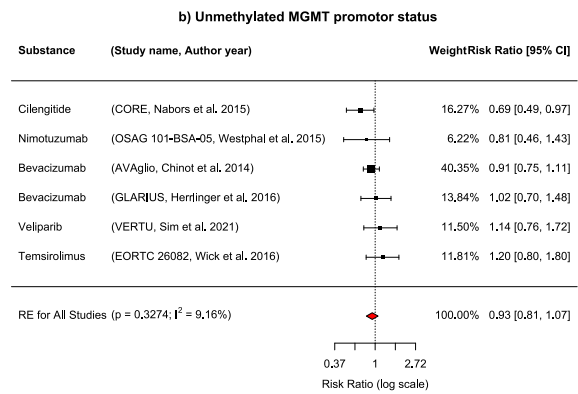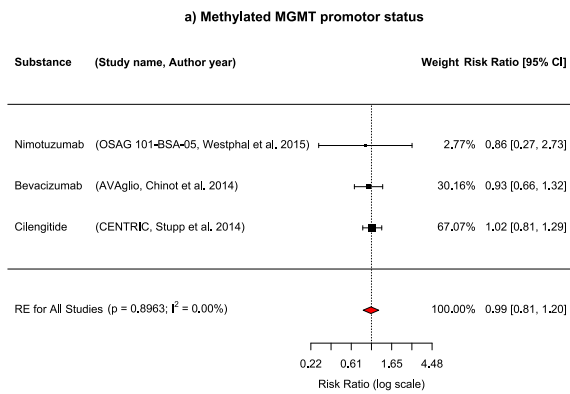
Supplementary Figure 1: Forest plot displaying the subsequent patient analyses of the pooled estimated risk ratio (red diamond) for overall survival. Abbreviations: MGMT = O6-methylguanin-DNA-methyltransferase; MMSE = Mini-mental State Examination; RPA = recursive partitioning analysis; RE = risk estimate.

i) Caucasian patients

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	73.85%	0.92 [0.78, 1.08]
Cilengitide	(CENTRIC, Stupp et al. 2014)	26.15%	0.97 [0.74, 1.27]
RE for All Studies (p = 0.3226; I² = 0.00%)		100.00%	0.93 [0.81, 1.07]

Risk Ratio (log scale)
0.74 1 1.35

j) Non-caucasian patients

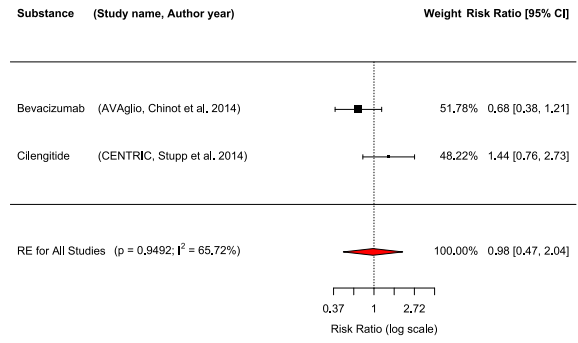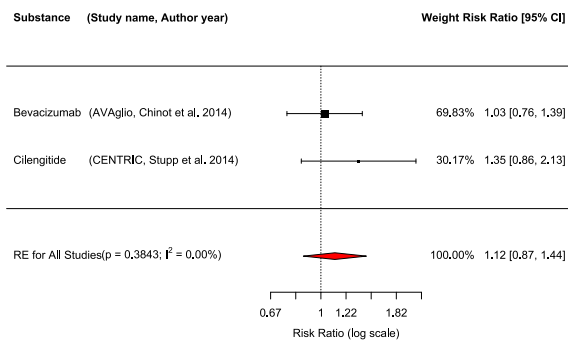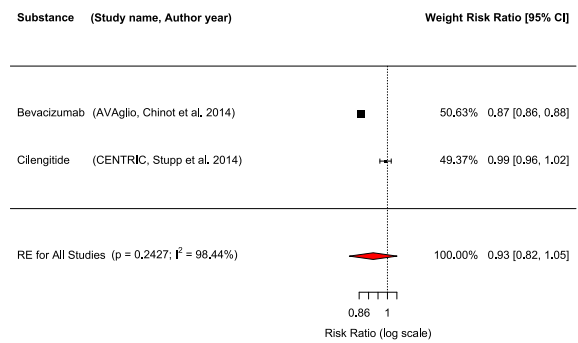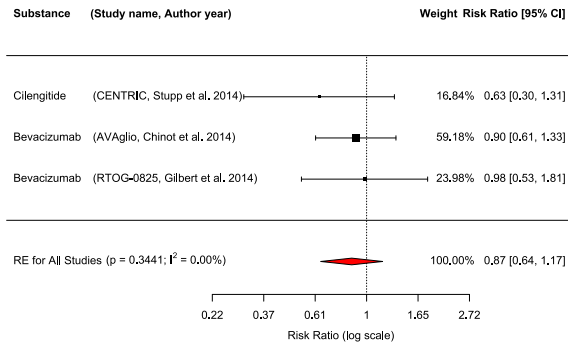| Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	51.78%	0.68 [0.38, 1.21]
Cilengitide	(CENTRIC, Stupp et al. 2014)	48.22%	1.44 [0.76, 2.73]
RE for All Studies (p = 0.9492; I² = 65.72%)		100.00%	0.98 [0.47, 2.04]

Risk Ratio (log scale)
0.37 1 2.72

k) MMSE < 27

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	69.83%	1.03 [0.76, 1.39]
Cilengitide	(CENTRIC, Stupp et al. 2014)	30.17%	1.35 [0.86, 2.13]
RE for All Studies(p = 0.3843; I² = 0.00%)		100.00%	1.12 [0.87, 1.44]

Risk Ratio (log scale)
0.67 1 1.22 1.82

l) MMSE ≥ 27

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	50.63%	0.87 [0.86, 0.88]
Cilengitide	(CENTRIC, Stupp et al. 2014)	49.37%	0.99 [0.96, 1.02]
RE for All Studies (p = 0.2427; I² = 98.44%)		100.00%	0.93 [0.82, 1.05]

Risk Ratio (log scale)
0.86 1

m) RPA class III

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Cilengitide	(CENTRIC, Stupp et al. 2014)	16.84%	0.63 [0.30, 1.31]
Bevacizumab	(AVAglio, Chinot et al. 2014)	59.18%	0.90 [0.61, 1.33]
Bevacizumab	(RTOG-0825, Gilbert et al. 2014)	23.98%	0.98 [0.53, 1.81]
RE for All Studies (p = 0.3441; I² = 0.00%)		100.00%	0.87 [0.64, 1.17]

Risk Ratio (log scale)
0.22 0.37 0.61 1 1.65 2.72

n) RPA class IV

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	53.18%	0.88 [0.72, 1.07]
Bevacizumab	(RTOG-0825, Gilbert et al. 2014)	46.82%	1.14 [0.90, 1.44]
RE for All Studies (p = 0.9591; I² = 63.95%)		100.00%	0.99 [0.77, 1.28]

Risk Ratio (log scale)
0.67 1 1.49

o) RPA class V

Substance	(Study name, Author year)	Weight	Risk Ratio [95% CI]
Bevacizumab	(AVAglio, Chinot et al. 2014)	68.33%	0.90 [0.67, 1.21]
Bevacizumab	(RTOG-0825, Gilbert et al. 2014)	31.67%	1.01 [0.65, 1.56]
RE for All Studies (p = 0.5813; I² = 0.00%)		100.00%	0.93 [0.73, 1.19]

Risk Ratio (log scale)
0.55 0.82 1.22 1.82
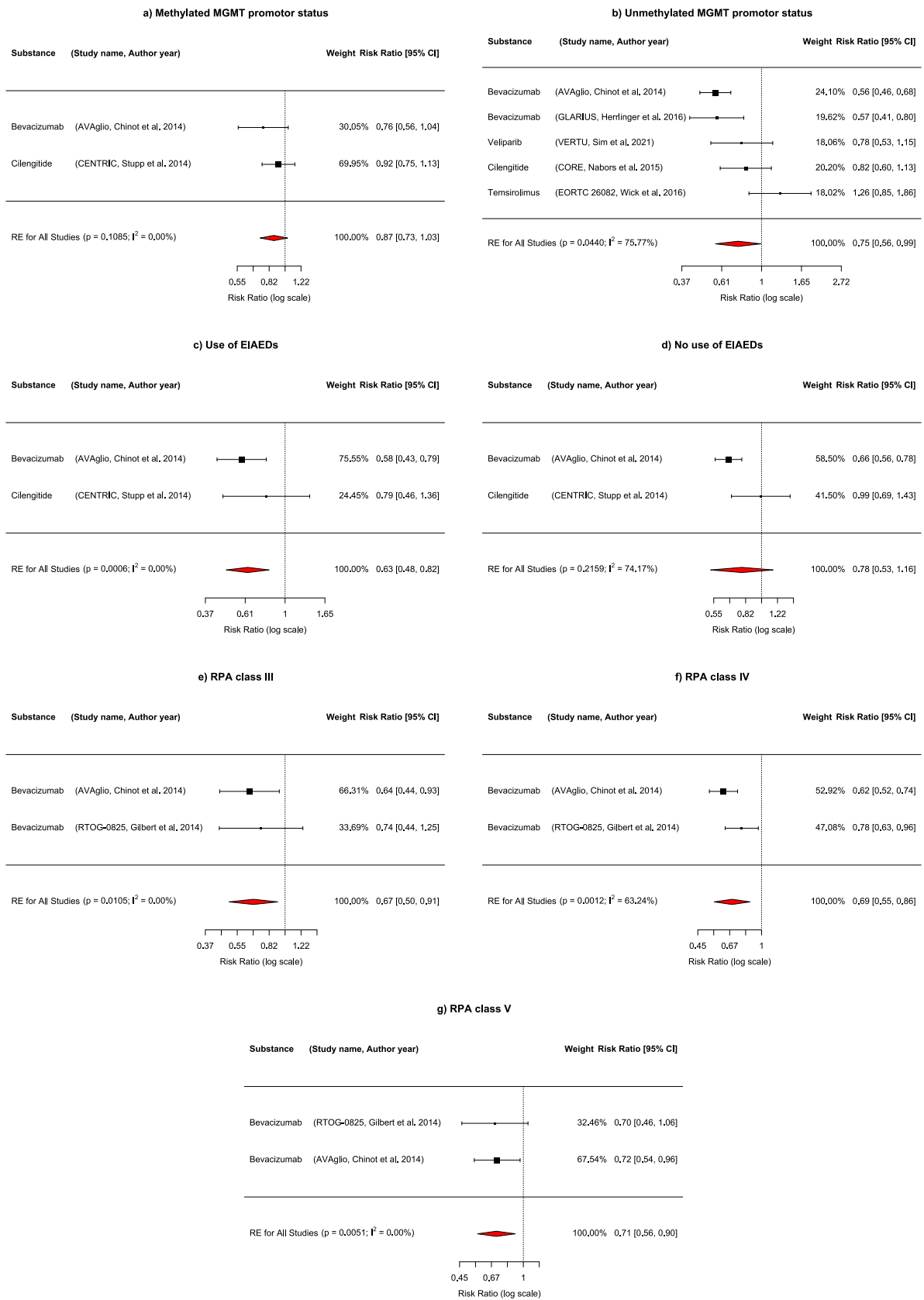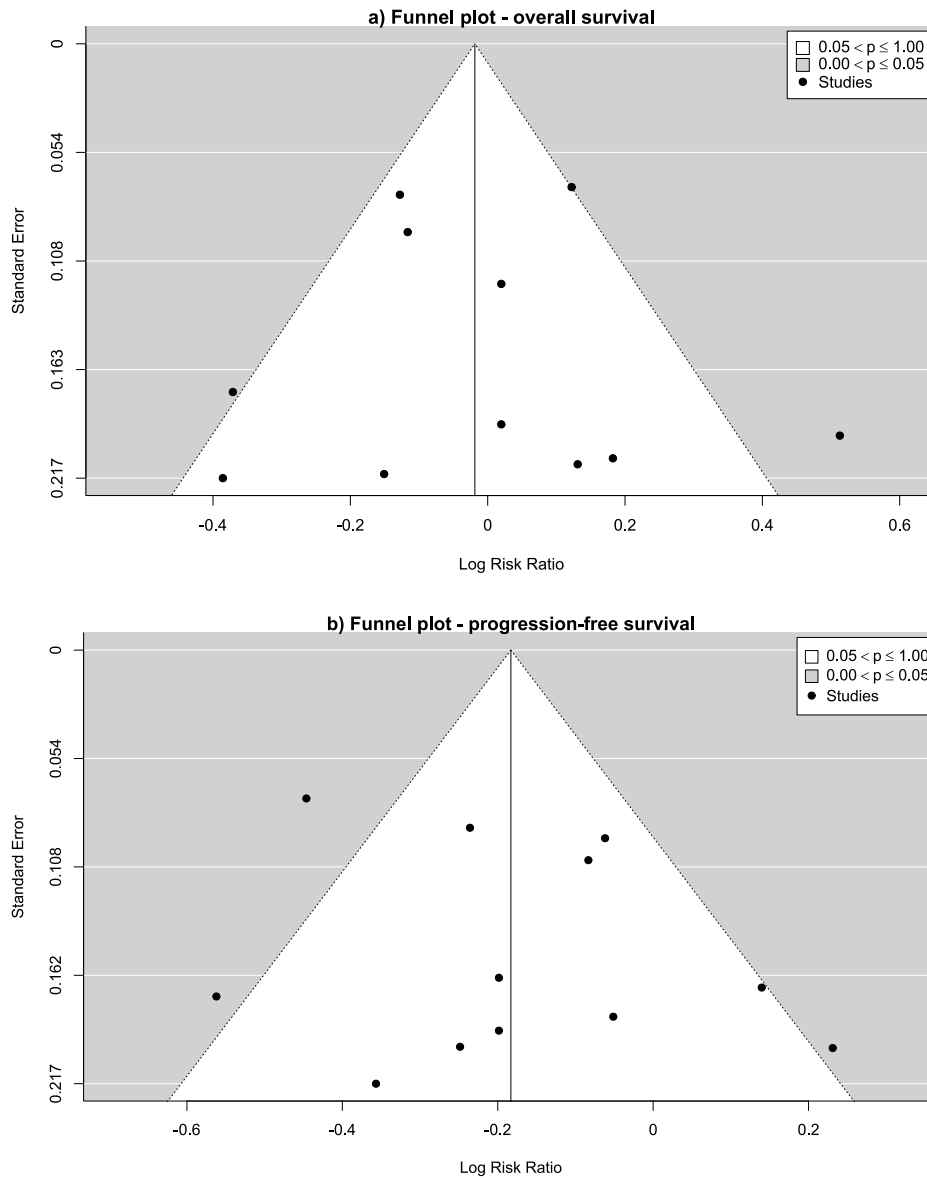
Supplementary Figure 1: (continued)

Supplementary Figure 2: Forest plot displaying the subsequent patient analyses of the pooled estimated risk ratio (red diamond) for progression-free survival. Abbreviations: MGMT = O6-methylguanin-DNA-methyltransferase; EIAEDs = enzym-inducing antiepileptic drugs; RPA = recursive partitioning analysis; RE = risk estimate.

Supplementary Figure 3: Funnel plots for risk of overall survival and disease progression depicting log risk ratio for a) OS = overall survival, b) PFS = progression-free survival displaying an almost symmetrical distribution, indicating no publication bias.