# INPLASY PROTOCOL

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**None declared.**

# Comparative Efficacy and Safety of Therapeutics for Elderly Glioblastoma: a Bayesian Network Analysis

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**Review question / Objective:** **At this time, a comprehensive systematic review and network meta-analysis (NMA) was conducted to: (1) fill the research gap by giving rankings on treatment efficacy; (2) provide statistical evidence of not head-to-head comparisons; (3) seek out the best and up-to-date therapeutic strategy reported in latest RCTs; (4) address potential adverse events (AEs) of available treatments.**
**Condition being studied:** **The incidence of glioblastoma (GBM) increases with age, until now, there has been less evidence on the optimal treatments for elderly GBM since only general GBM populations were included in clinical trials. Given the poor survival of elderly GBM, we collected randomized controlled trials about newly diagnosed GBM (ndGBM) and recurrent GBM, and conducted a Bayesian network meta-analysis on ndGBM regarding overall survival (OS) and progression-free survival (PFS). We revealed TTF + TMZ and TMZ + HFRT were likely to be best treatments for OS; BEV + HFRT and TMZ + HFRT were likely to be best options for PFS. Current study is the most comprehensive and powered network analysis on elderly GBM until now, it also provides more insights for elderly GBM management.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 March 2022 and was last updated on 19 March 2022 (registration number INPLASY202230094).

## INTRODUCTION

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reported in latest RCTs; (4) address potential adverse events (AEs) of available treatments.

**Rationale:** The incidence of glioblastoma (GBM) increases with age, until now, there has been less evidence on the optimal treatments for elderly GBM since only general GBM populations were included in clinical trials. Given the poor survival of elderly GBM, we collected randomized controlled trials about newly diagnosed GBM (ndGBM) and recurrent GBM, and conducted a Bayesian network meta-analysis on ndGBM regarding overall survival (OS) and progression-free survival (PFS). We revealed TTF + TMZ and TMZ + HFRT were likely to be best treatments for OS; BEV + HFRT and TMZ + HFRT were likely to be best options for PFS. Current study is the most comprehensive and powered network analysis on elderly GBM until now, it also provides more insights for elderly GBM management.

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## METHODS

**Search strategy:** We reviewed PubMed, EMBASE, Cochrane Library and Clinical Trials.gov for related literature from inception to Dec. 31, 2021. The following keywords were used: “Elderly”, “Aging”, “Age”, “Glioma, WHO Grade 4”, “Glioblastoma”, “Randomized controlled trials” and “RCTs”. No restrictions were applied on the language. Reference lists of the retried studies were also manually searched.

**Participant or population:** Elderly individuals (≥ 60 years) diagnosed by GBM (no restrictions on the WHO CNS Tumor Classification version). Both ndGBM and recurrent GBM were considered. Clinical trials including small part of grade 3 astrocytoma if necessary were also considered12,14,22. Elderly GBM data in subgroups would also be selected. No restrictions were set on additional individual-level characteristics (ie. sex, race, ethnicity, nations).

**Intervention:** Reasonable systematic interventions, including pharmaceutical, surgical, radiological, tumor treating field (TTF), vaccine and combined therapy, etc., were considered since this is a comprehensive network study.

**Comparator:** Reasonable systematic interventions, including pharmaceutical, surgical, radiological, tumor treating field (TTF), vaccine and combined therapy, etc., were considered since this is a comprehensive network study.

**Study designs to be included:** Published RCTs with useful data.

**Eligibility criteria:** Searched articles were initially screened by two authors (Bh-Zhao and Jm-Wu) for titles and abstracts. The full texts of potentially included studies were reviewed by the same two authors, and any disagreements were resolved with a discussion in a panel involving another author who is an expert in oncology and evidence-based medicine(H-Xing). Detailed eligibility criteria following PICOS were as follows:Populations: Elderly individuals (≥ 60 years) diagnosed by GBM (no restrictions on the WHO CNS Tumor Classification version). Both ndGBM and recurrent GBM were considered. Clinical trials including small part of grade 3 astrocytoma if necessary were also considered12,14,22. Elderly GBM data in

subgroups would also be selected. No restrictions were set on additional individual-level characteristics (ie. sex, race, ethnicity, nations).Intervention/ Comparison: Reasonable systematic interventions, including pharmaceutical, surgical, radiological, tumor treating field (TTF), vaccine and combined therapy, etc., were considered since this is a comprehensive network study.Outcomes: Analyzed outcomes included overall survival (OS), progression-free survival (PFS), and AEs. Other related outcomes such as response rate, 1-yr OS, 1-yr PFS etc. were recorded but not specially analyzed because limited available information.Study: Published RCTs with useful data. Only the most recent and informative study could be incorporated to avoid duplication. Some useful data was retrieved from subgroup analysis of included studies. We excluded trials comparing different administration schemes (ie. dose) with the same administration. Reviews/meta-analysis, observational studies, single-arm trials, case reports, conference abstracts, experimental studies and dose-expansion trials were excluded.

**Information sources:** We reviewed PubMed, EMBASE, Cochrane Library and Clinical Trials.gov for related literature from inception to Dec. 31, 2021. The following keywords were used: “Elderly”, “Aging”, “Age”, “Glioma, WHO Grade 4”, “Glioblastoma”, “Randomized controlled trials” and “RCTs”. No restrictions were applied on the language. Reference lists of the retried studies were also manually searched.

**Main outcome(s):** Analyzed outcomes included overall survival (OS), progression-free survival (PFS), and adverse events (AEs).

**Additional outcome(s):** Other related outcomes such as response rate, 1-yr OS, 1-yr PFS etc. were recorded but not specially analyzed because limited available information.

**Data management:** The useful information was extracted by two independent authors (Y-Xia and Hz-Li) following the prespecified protocol. The extracted information included the characteristics of the eligible trials (the first author, publication year, region, trial registration information, number of intervention arms, etc.), characteristics of the populations (median age, sample size, proportion of elderly GBM, proportion of female, etc.), and characteristics of the program (systematic intervention arms, various outcomes of endpoints, final statistical results for both total and elderly GBM in eligible studies, etc.). All risk estimates were evaluated and extracted in full-variable adjusted models. Blinded independent review committee data as well as intention-to-treat (ITT) principles were applied if available. We would contact the primary authors for some necessary missing data. The analyses would still have been undertaken without these data if no response was received. Currently, we identified total 11 types of interventions in ndGBM: supportive care (SPC), standard radiotherapy (STRT) (58-62 Gy/30-33 fractions), hyperfractionated radiotherapy (HFRT) (defined as total radiation dose less than STRT, typically 40 Gy/15 fractions, 34 Gy/10 fractions, 30 Gy/5 fractions), TMZ, bevacizumab + STRT (BEV + STRT), TMZ + HFRT, TTF + HFRT, CpG-oligodeoxynucleotides + SPC (CpG-ODN + SPC), rindopepimut + TMZ (Rindo + TMZ), BEV +HFRT, hydroxychloroquine + HFRT (HCQ +HFRT), And 9 types of interventions in recurrent GBM: cediranib + gefitinib (Ced + Gef), BEV + CCNU (lomustine), CCNU, regorafenib (Rego), personalized peptide vaccination (PPV), placebo, Rindo + BEV, BEV. Following the principles of NMA and statistical convenience, some changes on the trial intervention arms were made. In Chinot et al, we assigned the comparisons as BEV +STRT vs. STRT to discriminate concurrent and adjuvant TMZ; in Ursu et al, we assigned the comparisons as CpG-ODN + SPC vs. SPC although both groups would go through concurrent RT/TMZ after the treatment.

**Quality assessment / Risk of bias analysis:** To evaluate the quality of the included studies, we firstly applied the modified Cochrane Collaboration's risk of bias tool29. Seven items of: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were applied in the tool. Assessed quality were categorized as high, low or unclear. Two of the coauthors (Bh-Zhao and Yn-Wang) independently performed assessment on all of the included RCTs based on the tool. They would re-evaluate the primary studies and achieve a final consensus after discussion in case of any discrepancies. Afterwards, we applied the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to identify the level rating of main outcomes of OS and PFS as very low, low, moderate, or high quality. The rating system follows 5 items: risk of bias, imprecision, inconsistency, indirectness, publication bias, large effect size, dose-response gradient and all residual confounding reducing an effect size. If there were one "serious" item, the evidence level could have been regarded as "low"; and if there were one "very serious", the evidence level been "very low".

**Strategy of data synthesis:** Detailed OS and PFS time for all included GBM as well as elderly GBM in eligible trials were extracted, the hazard ratios (HRs) and confidence intervals (CIs) were extracted from the original studies directly or calculated through the algorithms suggested by Tierney et al. HRs of OS in Weller et al and Chinot et al were calculated by combining two groups into ITT populations. For no response to the requirement for extra data, we ran the program Engauge Digitizer 4.1 (http://digitizer.sourceforge.net) to obtain the exact data from the survival curves. All grade and ≥ 3 grade AEs were reviewed and deposited in standardized tables. Because there were no abundant clinical trials on recurrent GBM, the quantitative analyses (NMA) were specially conducted on ndGBM, qualitive analyses were prescribed for both ndGBM and recurrent GBM. A NMA with a Bayesian algorithm was conducted with random-effects model to estimate the HR and 95% credible interval (95% CrI) for direct and indirect evidence on OS and PFS for elderly GBM, which had the merits of using posterior probability for the rankings of all analyzed interventions and more stable and accurate estimation value. The Markov chain Monte Carlo (MCMC) method was used to estimate the posterior distribution of each parameter, the fit of the random-effects model was assessed by the deviance information criteria (DIC). A hierarchical Bayesian model synthesizes comparisons between the treatment pairs and simultaneously summarizes all outcomes of interest by assuming a common heterogeneity parameter (a derived I2 statistic > 50% or a P value for the Cochran Q chi-square test < 0.1 was regarded as significant heterogeneity); the inconsistency and stability of this model was evaluated by the node-splitting method based on all direct and indirect evidence if possible. The probability rankings were carried out, and a cumulative sorting graph was generated. The surface under the cumulative ranking curve (SUCRA) metric was adopted to identify the relative effectiveness of each treatment and the best treatments. To our knowledge, the SUCRA value showed the situation for all possible rankings and uncertainties in the treatment effects. If the SUCRA value was close to 1, it was the best without uncertainty; close to 0, it was the worst without uncertainty. Thus, rankings could be determined according to the distinct SUCRAs of each treatment. For NMA process, statistical significance was established when the 95% CrI did not cover 1. Besides, we carried out a head-to-head meta-analysis and forest mapping of two or more clinical trials of the same treatment regimen to confirm the NMA results. Similarly, a derived I2 > 50% or a P value for the Cochran Q test < 0.1 indicated significant heterogeneity for head-to-head comparisons. In subgroup analyses, we compared the NMA results to RCTs results on elderly GBM with O6-methylguanine-

DNA-methyltransferase (MGMT) promoter methylation. Funnel plots and Egger's test were developed to assess the publication bias. Calculations were performed in R software (version 3.5.3, http://www.r-project.org) with the publicly available gemtc, rjags and meta packages. All bilateral P < 0.05 was considered statistically significant.

**Subgroup analysis:** In subgroup analyses, we compared the NMA results to RCTs results on elderly GBM with O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation.

**Sensitivity analysis:** No sensitivity analysis was conducted in this study.

**Language:** None.

**Country(ies) involved:** China.

**Other relevant information:** None.

**Keywords:** Glioblastoma, elderly, Bayesian, network-meta-analysis.

**Dissemination plans:** The study is wished to be published on high-impact study and will be updated on time.

**Contributions of each author:**

Author 1 - Binghao Zhao - Wrote the paper, helped design the study, revised the statistical methodology, read and approved the final manuscript.
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