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Anti-epidermal growth factor receptor therapy for glioblastoma in adults (Protocol)

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[Intervention Protocol]

Anti-epidermal growth factor receptor therapy for glioblastoma in adults

Adrian Lee[1], Malmaruha Arasaratnam[1], David Lok Hang Chan[1], Mustafa Khasraw[2], Viive M Howell[1], Helen Wheeler[3], Joanne Platt[4]

[1]Department of Medical Oncology, Royal North Shore Hospital, Sydney, Australia. [2]NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia. [3]Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia. [4]Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, Royal United Hospital, Bath, UK

Contact address: Adrian Lee, Department of Medical Oncology, Royal North Shore Hospital, Kolling Institute, Sydney, New South Wales, 2065, Australia. adrian.lee@sydney.edu.au.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and harms of anti- therapies for glioblastoma.

BACKGROUND

Description of the condition

Glioblastomas are highly aggressive primary brain cancers which present with significant clinical challenges. Despite recent public concerns around potential causality between mobile phones and glioblastoma diagnoses, incidence rates did not increased between 1982 and 2013 (AIHW 2017; Nilsson 2017). Peak incidence occurs in the 50 to 70 years old age group and no specific causative agent has been identified.

Disease morbidity for glioblastomas is multifactorial. Neurological deficits may arise acutely and vary depending on tumour location. Some people develop postoperative deficits, and some have neurocognitive sequelae such as concentration and memory. Others require ongoing anticonvulsant medication or corticosteroids to control cerebral oedema (Lapointe 2015). Additional morbidities include immunosuppression from chemotherapy, radiation treatment or corticosteroids and predispose to opportunistic infection, thrombocytopenia (reduced platelet counts), and increased risk of thrombosis (blood clots) (Qian 2016; Thaler 2013; Thaler 2014). Often people with glioblastoma are premorbidly high functioning and active but subsequently become dependent on their family and friends, thus increasing psychosocial stresses that are often underestimated.

Glioblastoma treatment consists of maximal safe resection followed by concurrent chemoradiotherapy and adjuvant chemotherapy using temozolomide resulting in a median overall survival (OS) of 14.6 months (Stupp 2005). Since 2005, there have been multiple phase III clinical trials that have tried to add various chemotherapy combinations and monoclonal antibodies to this standard of care. However, they have all been unsuccessful in im-

proving survival outcomes in a clinically and statistically meaningful manner (Chinot 2014; Gilbert 2014; Khasraw 2016; Stupp 2014).

Success of future trials may hinge on better participant selection with particular attention to molecular changes. Verhaak 2010 have documented the complexity of molecular changes commonly appearing in glioblastomas and suggested four molecularly distinct clinically relevant subgroups can be identified: proneural, neural, mesenchymal and classical. Aldape 2015 further investigated the importance of these molecular changes and demonstrated the need to respect these unique genetic signatures in predicting treatment sensitivity and prognosticating survival.

Other cancers have witnessed great successes with the use of targeted therapeutic agents. Small molecule tyrosine kinase inhibitors (TKI) targeting epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations in non-small cell lung cancer (NSCLC); v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibition in metastatic melanoma; anti-EGFR antibodies in Kirsten RAt Sarcoma virus (KRAS) wild-type colorectal cancers have all led to great improvements in progression-free survival (PFS) and OS in genomically selected participants (Hauschild 2012; Karapetis 2008; Mok 2009; Shaw 2013). However, despite the discovery of many genetic alterations in glioblastoma, the successes with targeted therapy in other solid tumours have yet to be replicated in the treatment of glioblastoma. There are certainly additional factors that are unique to neuro-oncology that need to be considered, including drug delivery through the blood-brain barrier, intratumoural heterogeneity and variability of the genetic targets.

Description of the intervention

In normal cellular physiology, the binding of a growth factor (e.g. epidermal growth factor, EGF) to a receptor (e.g. EGFR) initiates a cascade of downstream intracellular events which regulate cell proliferation, survival and differentiation. Overactivity of this pathway leads to uncontrolled cell growth, replication and tumour development. This can be achieved by overexpression of the receptor, autocrine overproduction of the ligand and constitutive activation by mutations in the receptor complex (Castillo 2004). The most frequent genetic alterations in glioblastoma are overexpression or amplification of EGFR, reported to occur in 30% to 60% of cases (Brennan 2013; Huang 2009). These EGFR abnormalities can be detected by immunohistochemistry looking for protein overexpression, fluorescence in-situ hybridisation looking for gene amplification and polymerase chain reaction for EGFR variant III (EGFRvIII) mutation. EGFRvIII mutation is a shortened form of the gene due to loss of part of the gene (exons 2 to 7). Both EGFR overexpression and EGFRvIII can enhance glioblastoma cell growth, migration and invasiveness (Bastien 2015; Cloughesy 2014; Haas-Kogan 2005).

The classical genomic subtype as described by Verhaak 2010 is typically associated with EGFR amplification with a high proportion of EGFRvIII mutations. This group also has a lower median OS of 12.2 months compared to other glioblastomas in general (14.6 months) and is generally associated with an older population (over 70 years of age) (Stupp 2005, Verhaak 2010). In particular, the EGFRvIII mutant subgroup has a lower OS (less than one year) (Heimberger 2005; Shinojima 2003).

Currently, there are three main therapeutic methods to target EGFR overactivity: anti-EGFR monoclonal antibodies, EGFR TKIs and EGFR vaccines. Anti-EGFR monoclonal antibodies target the extracellular ligand binding domain of the receptor and blocks activation of the receptor and its subsequent downstream activation. EGFR TKIs target the intracellular component of the receptor associated with an activating mutation which subsequently inhibits auto-phosphorylation and subsequent downstream signalling. Anti-EGFR vaccines have been designed to target the specific novel amino acid sequence arising from EGFRvIII deletion mutation and generating an immunological response.

Anti-EGFR vaccines and EGFR TKIs are specific to particular mutations and alterations in EGFR while monoclonal antibodies are target the extracellular domain of EGFR, so are effective when EGFR is amplified regardless of mutational status. Monoclonal antibodies are typically intravenous injections given every one to two weeks. EGFR TKIs are typically oral tablets given daily and EGFR vaccines are given monthly after a loading dose and via a subcutaneous route.

In this report, the experimental treatment is tested against the standard of care which is combined chemoradiation following maximal safe resection and adjuvant chemotherapy or the best standard of care at the time of the clinical trial. This is summarised in Table 1.

How the intervention might work

The aberrant EGFR pathway is an attractive therapeutic target and inhibition in other tumour types such as NSCLC and colorectal cancer has led to significant clinical responses. In both NSCLC and colorectal cancers, the use of EGFR TKI and monoclonal antibodies have led to improvements in OS and PFS. In NSCLC, the use of gefitinib among EGFR-mutated tumours improved PFS compared to cytotoxic chemotherapy (hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.36 to 0.64; P less than 0.0001). This was further supported in the OPTIMAL study that used erlotinib as first-line chemotherapy in people with EGFR-mutated NSCLC where the PFS improvement was 13.1 months versus 4.6 months with chemotherapy (Mok 2009; Zhou 2011). In people with colorectal cancer, those with wild-type EGFR benefited from the use of monoclonal antibody where OS improved with cetuximab (9.5 months with cetuximab plus best supportive care versus 4.8 months with best supportive care alone) (Karapetis 2008).

Our hypothesis is that anti-EGFR therapies in EGFR-overexpressing glioblastomas may inhibit cell proliferation and result in cell death, leading to improved survival and achieve similar results as those seen in NSCLC and colorectal cancers.

Why it is important to do this review

The purpose of this review is to find, organise and summarise high level evidence in terms of benefits and harms of anti-EGFR therapies in people with glioblastoma to provide meaningful conclusions for clinical practice and further research. This review is driven by the encouraging results observed in phase II clinical trials involving anti-EGFR vaccines (ACT II) where the median OS reached was 21.6 to 26 months, a significant increase compared to standard of care which led to subsequent phase III randomised controlled trials (RCTs) (Sampson 2010; Schuster 2015). Targeting EGFR in glioblastoma is an active area of interest with ongoing trials in progress. Newer compounds such as ABT-414, an antibody-drug conjugate that can target EGFR or EGFRvIII in glioblastomas, allowing potent chemotherapy to be released inside targeted cancer cells (NCT02573324; NCT02343406). The review will form a platform to review new data in this area as they mature.

The current standard of care for people with glioblastoma is maximum resection followed by concurrent temozolomide radiotherapy then adjuvant temozolomide, irrespective of molecular signatures. This review will investigate if the addition of anti-EGFR therapy will improve outcomes in EGFR overexpressing glioblastomas.

OBJECTIVES

To evaluate the efficacy and harms of anti- therapies for glioblastoma.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing anti-epidermal growth factor receptor (EGFR) therapy versus a control treatment without anti-EGFR therapy in people with glioblastoma.

Types of participants

Adults (aged 18 years and over) with histologically confirmed glioblastoma diagnosis, either newly diagnosed or with recurrent disease.

Types of interventions

Interventions can be grouped into three as described by their site and mode of action against the EGFR pathway. These include anti-EGFR monoclonal antibodies, EGFR TKIs and anti-EGFR vaccines. We included studies investigated of any of these anti-EGFR agents against placebo or standard of care. We included studies that combined a secondary intervention in the treatment group (such as chemotherapy or radiotherapy) if this secondary treatment was the same in the control group. The control group could receive the standard of care/active intervention (such as chemotherapy - as long as anti-EGFR therapy was not used), placebo or best supportive care.

In summary, the three groups will be:

- anti-EGFR monoclonal antibodies with or without chemotherapy versus placebo or standard of care with or without chemotherapy;
- EGFR TKIs with or without chemotherapy versus placebo or standard of care with or without chemotherapy;
- anti-EGFR vaccine with or without standard of care versus placebo or standard of care with or without chemotherapy

In the event there is a direct head-to-head comparison between two or more different anti-EGFR therapy (with or without standard of care in either arms), we will assess this and if deemed eligible include it in future analyses.

Types of outcome measures

Studies including at least one of the following outcomes will be considered for evaluation.

Primary outcomes

- Overall survival (OS): defined as time from randomisation to death from any cause.
- Adverse events: classified according to National Cancer Institute Common Terminology Criteria (NCI-CTC) (NCI 2010), including percentage of treatment-related deaths.

Secondary outcomes

- Progression free survival (PFS): defined as time from randomisation to disease progression. Disease progression can be defined by two criteria - MacDonald (Macdonald 1990), and Response Assessment in Neuro-Oncology Criteria (RANO) (Wen 2010). MacDonald's criteria was the accepted standard assessment tool in older neuro-oncology trials until the advent of

RANO criteria. RANO is now recognised to be the standard response assessment tool in neuro-oncology trials.

- Quality of life (QoL): measured against objective scales such as European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30; Scott 2008), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Brain Neoplasm (EORTC QLQ-BN20) (Taphoorn 2010), or as defined by trial investigators.

Search methods for identification of studies

Electronic searches

Two review authors (AL, MA) will independently search the following databases.

- the Cochrane Central Register of Controlled Trials (CENTRAL; latest issue), in the Cochrane Library;
- MEDLINE via Ovid (1946 to date);
- Embase via Ovid (1980 to date).

We will apply no language restrictions to any of the searches. The draft MEDLINE search strategy is detailed in Appendix 1. For databases other than MEDLINE, we will adapt the search strategy accordingly.

Searching other resources

Two review authors (AL, MA) will independently search the following databases between 2016 to date of search; Cochrane Methodology Register, ACP Journal Club, Database of Abstracts of Reviews of Effects (Ovid Technologies), and abstracts and reports from major conferences, including American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), Society of Neuro-oncology and European Association of Neuro-oncology.

In addition, we will search through relevant journals including *Journal of Clinical Oncology*, *Annals of Oncology*, *Lancet*, *Lancet Oncology*, *New England Journal of Medicine*, *European Journal of Cancer*, *Neuro-oncology*, and *Journal of Neurology and Neurosurgery*.

Data collection and analysis

Two review authors (AL, MA) will independently collect data and prepare the manuscript for analysis using Review Manager 5 (Review Manager 2014).

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database (Endnote). Two review authors (AL, MA) will independently screen records identified from electronic and handsearches for RCTs and exclude those studies that obviously do not meet the inclusion criteria as listed in Criteria for considering studies for this review. We will retrieve all possibly relevant full-text reports and assess eligibility with reference to the inclusion criteria. We will list studies that do not meet the inclusion criteria in the 'Characteristics of excluded studies' table with the reasons for exclusion. We will resolve any uncertainties or disagreements by discussion or, if required we will consult a third review author (MK). We will identify and exclude duplicate reports and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram. We will list comprehensive details of included studies in the 'Characteristics of included studies' table. We will include abstracts and unpublished data only if there is some information on study design and characteristics of participants, interventions and outcomes. We will contact primary or corresponding study authors for further information and clarification to aid in this process.

Data extraction and management

Two review authors (AL, MA) will independently perform data extraction. We will follow Cochrane methodology as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and will use a pre-piloted standardised data extraction form on 2 studies (see Appendix 2) and enter the data into Review Manager 2014 for analysis. For each eligible form, we will record: title, authors, study design, participants, setting, interventions and quality components, duration of follow-up, efficacy outcomes, QoL scores and adverse effects. We will extract data for studies with more than one publication from the most recent publication. We will highlight short-term adverse events if considered significant. We will collect additional study-related information including contact address, country, published/unpublished, language, year of publication and sponsor of trial.

We will resolve any differences in data extraction by consensus with a third review author (MK, VMH or HRW), with reference to the original article.

For time to event (OS, PFS), we will extract HRs and 95% CIs, log rank Chi^2, log rank P values, numbers of events, numbers of participants per group and medians. Where HRs are not available, we will calculate them following the methods of Tierney 2007 for incorporating summary time-to-event data into meta-analysis.

For dichotomous data such as adverse events, we will extract the raw data and calculate odds ratios (OR) with 95% CIs.

For non-time to event and continuous outcomes (QoL measures), we will extract data to calculate the mean difference (MD) with

95% CIs. Where possible, we will perform quantitative analysis on collected and calculated data. If there are insufficient data, we will present a descriptive analysis.
When possible, we will extract data for intention-to-treat analysis for all outcomes. We will collect the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

Two review authors (AL, MA) will independently apply the 'Risk of bias' tool and resolve differences by discussion or by appeal to a third review author (MK, VMH or HRW). We will judge each item at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011 and provide a quote from the study report or a statement as justification for the judgement for each item in the 'Risk of bias' table, or both. For attrition bias, we will judge a trial to be low risk of bias if at least 80% of participants were assessed at endpoint for all outcomes. We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

Measures of treatment effect

We will present summary statistics for the primary endpoints (time to event data). For time to event analyses (survival and disease progression), we will extract HRs and 95% CIs, numbers of events, numbers of participants per group and median values. Where HRs are not available, we will calculate them following the methods of Tierney 2007 for incorporating summary time-to-event data into meta-analysis. For dichotomous data such as adverse events, we will extract the incidence and total number of people evaluated and calculate for ORs. For continuous outcomes (QoL measures), we will extract data to calculate MDs. Where possible, we will perform quantitative analysis on collected and calculated data. If there are insufficient data, we will present a descriptive analysis.
We will perform a meta-analysis on the outcomes listed above, if two or more trials of the appropriate clinical setting are available, appreciating that some statistical heterogeneity might occur from pooling of trials investigating different therapies. We will use standard meta-analytical techniques employing a random-effects model if heterogeneity in participant characteristics and treatments exists; heterogeneity will be defined as I^2 statistic more than 30% or P value less than 0.10.

Unit of analysis issues

We will base measurement of PFS on different response criteria (Macdonald 1990; Wen 2010). Nevertheless, the use of HRs for comparison will minimise the significance of this issue, as the control group will be subject to the same response criteria. However, the different response criteria will be considered when the pooled analysis of PFS data are interpreted.

Dealing with missing data

We will contact the first or corresponding author of the most recent publication in cases of missing data. We will not impute missing data for any of the outcomes.

Assessment of heterogeneity

We will assess heterogeneity between studies using the Cochrane Q-test, with a significance threshold of alpha = 0.1. and by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation.
In cases of substantial heterogeneity, the extra variation will be incorporated into the analysis by using a random-effects model. We will consider 30% or greater to represent a degree of heterogeneity worthy of further investigation. We will consider the following factors as possible sources of heterogeneity:

- differing clinical settings (adjuvant versus recurrent disease);
- different types of anti EGFR therapies (as classified above);
- differences in prognostic factors between studies;
- study quality.

We will consider these factors in the sensitivity and subgroup analyses, except in cases of differing prognostic factors.

Assessment of reporting biases

If we include 10 or more studies that investigate a particular outcome, we will examine funnel plots corresponding to meta-analysis of the outcome to assess the potential for small-study effects such as publication bias. We plan to assess funnel plot symmetry visually, and if asymmetry is suggested, we will perform exploratory analyses to investigate it.

Data synthesis

We will pool results in a meta-analysis where three or more trials are evaluable. Trials will be grouped into first-line, second-line or recurrent settings for analysis as this better correlates with real-world clinical purposes.
For time-to-event data, we will pool HRs using the generic inverse variance facility of Review Manager 2014.
In trials with multiple treatment groups, we will combine time-to-event outcomes by performing a separate meta-analysis of the two-arm HRs. Subsequently, the resulting HRs will be the summary statistic for the overall trial. We will follow the method as described in Chapter 16.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We will consider the following variables for subgroup analyses where the data are available:

- first-line therapy;
- second-line or recurrent disease.

If there are insufficient data for statistical analysis, we will perform and report a descriptive analysis.

Sensitivity analysis

We will conduct predefined sensitivity analyses to assess the robustness of the conclusions based on studies with a higher risk of bias versus lower risk of bias.

'Summary of findings' table for assessing the certainty of the evidence

We will present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT (Appendix 3). We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Classes of anti-EGFR therapies

Drug class	Description and examples
Anti-EGFR monoclonal antibodies	• Targets extracellular ligand-binding domain on EGFR. • Blockage prevents signal molecules (EGF or transforming growth factor A) from binding to receptor and propagating downstream signal through tyrosine kinase complex. • e.g. cetuximab, panitumumab.
Anti-EGFR (tyrosine kinase inhibitors)	• Reversible and irreversible binding at adenosine triphosphate site of receptor to prevent formation of phosphotyrosine residues and halting the downstream signalling cascade. • e.g. erlotinib, gefitinib, afatinib.

Table 1. Classes of anti-EGFR therapies (*Continued*)

Anti-EGFR vaccines	• Specific peptide sequence associated with EGFRvIII mutation. • e.g. rindopepimut.

EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; EGFRvIII: EGFR variant III.

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. Glioblastoma/
2. (glioblastoma* or GBM* or GB* or astrocyt*).mp.
3. 1 or 2
4. Receptor, Epidermal Growth Factor/
5. (EGFR* or EGF* or ERBB* or HER1* or Oncogene ERB* or ErbB-1* or epidermal growth factor receptor* or sErbB-1* or TGF-alpha* or transforming growth factor alpha receptor*).mp.
6. exp Antibodies, Monoclonal/
7. (monoclonal antibod* or MAB*).mp.
8. exp Protein Kinase Inhibitors/
9. (tyrosin* adj5 (kinase* or inhibitor*)).mp.
10. (PTK inhibit* or TK inhibitors* or TKI* or tyrphostins* or tyrosine phosphorylation inhibitor* or EC2* or hydroxyarl-protein* or tyrosine* or tyrosylprotein* or phosphotransferases* or transphosphorylases* or phosphokinases*).mp.
11. (nilotinib* or tasigna* or AMN107* or getfitnib* or ZD1839* or iressa* or erlotinib* or imatinib* or gleevec* or glivec* or STI-571*).mp.
12. Cancer Vaccines/
13. ((cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumour* or tumor* or malignan* or antigen* or dendritic* or vector*) adj5 (vaccin* or immuno*)).mp.
14. (rindopepimut* or CDX-110*).mp.
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. clinical trials as topic.sh.
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. (animals not (humans and animals)).sh.
26. 24 not 25
26. 16 and 26

Appendix 2. Standardised data extraction form

Title	
Lead Author, Senior Author	
Year published	
Publication	
Type of study	
Trial phase	
Intervention	
Control	
No. of participants	
1st line or recurrent disease	
Type of participants	
Primary outcome	
Secondary outcome	
Toxicity	

Appendix 3. 'Summary of findings' table

Antiepidermal growth factor receptor therapy for glioblastoma						
Patient or population: Adult (aged ≥ 18 years) with histologically confirmed glioblastoma diagnosis, either newly diagnosed or with recurrent disease were included **Intervention:** anti-EGFR therapy (including anti-EGFR monoclonal antibodies, EGFR tyrosine kinase inhibitors or vaccines) alone or in combination with standard of care **Comparison:** standard of care or placebo						
Outcomes	**Illustrative comparative risks**		**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of evidence (GRADE)**	**Comment**
	Assumed risk	**Corresponding risk**				

(*Continued*)

Overall survival						
Progression-free survival						
Adverse effects						
Quality of life						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **EGFR:** epidermal growth factor receptor.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

Appendix 4. Glossary

Term	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
BRAF	v-Raf murine sarcoma viral oncogene homolog B
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGFRvIII	EGFR variant III
FISH	Fluorescence in-situ hybridisation
KRAS	Kirsten RAt Sarcoma virus
OS	Overall survival
PCR	Polymerase chain reaction

(*Continued*)

PFS	Progression-free survival
QoL	Quality of life
RANO	Response Assessment in Neuro-Oncology Criteria
RCT	Randomised controlled trial
RR	Response rate
SAE	Severe adverse event
TKI	Tyrosine kinase inhibitor

WHAT'S NEW

Date	Event	Description
7 January 2019	Amended	CoI statement revised for MK.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the planning and editing of the report.

AL prepared the first draft of this report.

DECLARATIONS OF INTEREST

AL: has received honorarium and grants from Eisai, Mundipharma, Sanofi and Bayer for non-Glioma conditions.

MA: none known.

DC: has received honoraria from Novartis and Ipsen for educational activities outside the submitted work.

MK: has served on AbbVie GBM advisory boards and his institution received research grants from AbbVie and BMS to fund clinical trials in GBM

VH: none known.

HW: the analysis for this Cochrane review is based on peer reviewed data which was prepared by an independent steering trials committee. My involvement in the Australian Roche advisory board was to discuss completed trial results and how the drug may be introduced into the clinic in Australian centres. My participation on the Merck Serono centric steering committee was to review ongoing trial recruitment and SAEs. None of these activities influenced the analysis of the review data or contributed to any presented/published conclusions.

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