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

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[Intervention Review]

Anti-epidermal growth factor receptor therapy for glioblastoma in adults

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ABSTRACT

Background

Glioblastoma is an uncommon but highly aggressive type of brain tumour. Significant gains have been achieved in the molecular understanding and the pathogenesis of glioblastomas, however clinical improvements are difficult to obtain for many reasons. The current standard of care involves maximal safe surgical resection followed by chemoradiation and then adjuvant chemotherapy European Organisation for Research and Treatment of Cancer and the NCIC Clinical Trials Group (EORTC-NCIC) protocol with a median survival of 14.6 months. Successive phase III international randomised controlled studies have failed to significantly demonstrate survival advantage with newer drugs.

Epidermal growth factor receptor (EGFR) is observed to be aberrant in 30% to 60% of glioblastomas. The receptor aberrancy is driven by abnormal gene amplification, receptor mutation, or both, in particular the extracellular vIII domain. EGFR abnormalities are common in solid tumours, and the advent of anti-EGFR therapies in non-small cell lung cancer and colorectal adenocarcinomas have greatly improved clinical outcomes. Anti-EGFR therapies have been investigated amongst glioblastomas, however questions remain about its ongoing role in glioblastoma management. This review aimed to report on the available evidence to date and perform a systematic analysis on the risks and benefits of use of anti-EGFR therapies in glioblastomas.

Objectives

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

Search methods

We searched CENTRAL, MEDLINE, Embase, EBM Reviews databases, with supplementary handsearches to identify all available and relevant studies to 20 April 2020.

Selection criteria

All randomised controlled trials (RCTs) using anti-EGFR therapies in adults with glioblastoma were eligible for inclusion. Anti-EGFR therapies included tyrosine kinase inhibitors, monoclonal antibodies, or vaccines. The comparison included investigational product added to standard of care versus standard of care or placebo, or investigational product against standard of care or placebo.

Data collection and analysis

The authorship team screened the search results and recorded the extracted data for analysis. We used standard Cochrane methodology to performed quantitative meta-analysis if two or more studies had appropriate and available data. Otherwise, we conducted a qualitative

and descriptive analysis. We used the GRADE system to rate the certainty of the evidence. The analysis was performed along the two clinical settings: first-line (after surgery) and recurrent disease (after failure of first line treatment). Where information was available, we documented overall survival, progression-free survival, adverse events, and quality of life data from eligible studies.

Main results

The combined searches initially identified 912 records (after removal of duplicates), and further screening resulted in 19 records for full consideration. We identified nine eligible studies for inclusion in the review. There were three first-line studies and six recurrent studies. Five studies used tyrosine kinase inhibitors (TKIs); two studies used monoclonal antibodies; and two studies used targeted vaccines. More recent studies presented greater detail in the conduct of their studies and thus had a lower risk of bias.

We observed no evidence benefit in overall survival with the use of anti-EGFR therapy in the first-line or recurrent setting (hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.76 to 1.04; 3 RCTs, 1000 participants, moderate-certainty evidence; and HR 0.79, 95% CI 0.51 to 1.21, 4 RCTs, 489 participants, low-certainty evidence, respectively). All the interventions were generally well tolerated with low-certainty evidence for lymphopenia (odds ratio (OR) 0.97, 95% CI 0.19 to 4.81; 4 RCTs, 1146 participants), neutropenia (OR 1.29, 95% CI 0.82 to 2.03; 4 RCTs, 1146 participants), and thrombocytopenia (OR 3.69, 95% CI 0.51 to 26.51; 4 RCTs, 1146 participants). A notable toxicity relates to ABT-414, where significant ocular issues were detected.

The addition of anti-EGFR therapy showed no evidence of an increase in progression-free survival (PFS) in the first-line setting (HR 0.94, 95% CI 0.81 to 1.10; 2 RCTs, 894 participants, low-certainty evidence). In the recurrent setting, there was an increase in PFS with the use of anti-EGFR therapy (HR 0.75, 95% CI 0.58 to 0.96, 3 RCTs, 275 participants, low-certainty evidence). The available quality of life assessment data showed that anti-EGFR therapies were neither detrimental or beneficial when compared to standard care (not estimable).

Authors' conclusions

In summary, there is no evidence of a demonstrable overall survival benefit with the addition of anti-EGFR therapy in first-line and recurrent glioblastomas. Newer drugs that are specially designed for glioblastoma targets may raise the possibility of success in this population, but data are lacking at present. Future studies should be more selective in pursuing people displaying specific EGFR targets.

PLAIN LANGUAGE SUMMARY

Drugs that target abnormal growth protein in high-grade, aggressive brain tumours

Background

Glioblastomas are highly aggressive brain tumours. They often appear quickly with devastating effects depending on the part of the brain they are located. They often affect previously well and high functioning individuals without any ‘warning signs’. There are no known risk factors. The impact on people with glioblastomas, their family, friends, and society is highly problematic. Standard therapy involves resection of the tumour, then combined chemotherapy and radiation therapy followed by an additional six months of chemotherapy. This strategy aims only to control and contain the disease and delay its return because at present there is no cure.

Researchers have investigated and found multiple gene changes in glioblastoma tissue samples, leading to clinical trials testing new drug therapies. The protein epidermal growth factor receptor (EGFR), which normally controls cell growth, is abnormal in glioblastomas in about 30% to 60% of cases. This abnormality can lead to unrestrained cell growth, replication, and an increase in the cancer's aggressive potential. It is currently recognised that people with glioblastomas with an abnormal EGFR may have shorter survivals.

Some clinical trials with drugs targeting this protein have been conducted. This review aimed to collect all available evidence and investigate the risks and benefits for this type of therapy in glioblastomas, and in particular whether anti-EGFR drugs can improve survival whilst remaining a tolerable therapy without side effects.

Methods

We searched medical databases for randomised controlled trials (a type of study in which participants are assigned to one of two or more treatment groups using a random method) that used anti-EGFR therapies in people with glioblastoma up to April 2020.

Key results

Overall, no benefits were seen in improving overall survival with the use of anti-EGFR therapy in newly diagnosed people with glioblastoma or in the recurrent setting. The use of anti-EGFR therapies was not associated with increased side effects such as low white cells or platelet counts. There were some expected side effects including skin rashes and diarrhoea, but these were not severe and did not seem to impact participant quality of life. Anti-EGFR therapy did not delay disease worsening in newly diagnosed people with glioblastomas but there was an improvement seen amongst those with recurrent disease.

Conclusions

At present, there is insufficient evidence to support the use of anti-EGFR therapy in newly diagnosed or recurrent glioblastoma. Whilst the therapy is in general expected as with other anti-EGFR therapies, significant eye side effects can arise with ABT-414. Overall, anti-EGFR therapies did not appear to affect quality of life. The future use of anti-EGFR therapy in the management of glioblastoma requires more investigation. Future research should be promoted and tailored towards people with glioblastoma with known abnormal EGFR receptors.

SUMMARY OF FINDINGS

Summary of findings 1. Anti-EGFR therapy compared to placebo or standard of care for glioblastoma in adults

Anti-EGFR therapy compared to placebo or standard of care for glioblastoma in adults

Patient or population: glioblastoma in adults
Setting: Hospital (outpatients and inpatients)
Intervention: anti-EGFR therapy
Comparison: placebo or standard of care

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo or standard of care	Risk difference with anti-EGFR therapy
Overall survival - first-line studies	1000 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1 2]	HR 0.89 (0.76 to 1.04)	Study population	
				280 per 1000	26 fewer per 1000 (59 fewer to 9 more)
Overall survival - recurrent disease studies	489 (4 RCTs)	⊕⊕⊖⊖ LOW [3 4 5 6]	HR 0.79 (0.51 to 1.21)	Study population	
				250 per 1000	47 fewer per 1000 (114 fewer to 44 more)
Lymphopenia	1146 (4 RCTs)	⊕⊕⊖⊖ LOW [7 8]	OR 0.97 (0.19 to 4.81)	Study population	
				97 per 1000	3 fewer per 1000 (77 fewer to 243 more)
Neutropenia	1146 (4 RCTs)	⊕⊕⊖⊖ LOW [7 8]	OR 1.29 (0.82 to 2.03)	Study population	
				9 per 1000	3 more per 1000 (2 fewer to 9 more)
Thrombocytopenia	1146 (4 RCTs)	⊕⊕⊖⊖ LOW [7 8]	OR 3.69 (0.51 to 26.51)	Study population	
				2 per 1000	5 more per 1000 (1 fewer to 44 more)
Progression-free survival - first-line studies	894 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	HR 0.94 (0.81 to 1.10)	Study population	
				250 per 1000	22 more per 1000

					(32 fewer to 75 more)
Progression-free survival - recurrent disease studies	275 (3 RCTs)	⊕⊕⊖⊖ LOW [2]	HR 0.75 (0.58 to 0.96)	Study population	
				250 per 1000	56 fewer per 1000 (96 fewer to 9 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) 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; **HR:** hazard ratio; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
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.

[1] Lee 2015 and Westphal 2015 are both open-label trials, hence blinding would not have been preserved.
[2]The three included studies all used different anti-EGFR agents, thus affecting the directness and applicability of the evidence and requiring that it be downgraded.
[3]The randomisation and blinding procedures have not been clarified in Reardon 2015. van den Bent 2019 was an open-label trial.
[4]High degree of heterogeneity amongst the three included studies.
[5]Different mechanisms of action amongst the three included studies, raising concerns about the directness of the evidence.
[6]Wide confidence interval, raising concerns about the precision of the outcome.
[7]Three of the included studies were open-label trials, increasing the risk of bias.
[8]There is a degree of heterogeneity amongst these studies with regard to lines of therapy and drug mechanisms.

BACKGROUND

Description of the condition

Glioblastomas are highly aggressive brain tumours that present with significant clinical challenges. Despite recent public concerns around potential causality between mobile phones and glioblastoma diagnoses, incidence rates have not increased between 1982 and 2013 (AIHW 2017; Nilsson 2017). Peak incidence occurs in the 50 to 70 yearold 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, or both. Others require ongoing anticonvulsant medication or corticosteroids to control cerebral oedema (Lapointe 2015). Additional morbidities include immunosuppression from chemotherapy, radiation treatment, or corticosteroids and predisposition to opportunistic infection, thrombocytopenia (reduced platelet counts), and increased risk of thrombosis (blood clots) (Qian 2016; Thaler 2013; Thaler 2014). People with glioblastoma are often 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 added various chemotherapy combinations and monoclonal antibodies to this standard of care. However, they have all been unsuccessful in improving survival outcomes in a clinically and statistically meaningful manner (Chinot 2014; Gilbert 2014; Khasraw 2016; Stupp 2014).

The success of future trials may hinge on better participant selection with particular attention to molecular changes. Verhaak and colleagues documented the complexity of molecular changes commonly appearing in glioblastomas and suggested the identification of four molecularly distinct, clinically relevant subgroups: proneural, neural, mesenchymal, and classical (Verhaak 2010). Aldape and colleagues 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 (Aldape 2015).

There have been great successes with the use of targeted therapeutic agents in other cancers. 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; and 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).

There are currently three main therapeutic methods to target EGFR overactivity: anti-EGFR monoclonal antibodies, EGFR TKIs, and EGFR vaccines (Table 1). Anti-EGFR monoclonal antibodies target the extracellular ligand binding domain of the receptor and block 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, whilst monoclonal antibodies target the extracellular domain of EGFR, so are effective when EGFR is amplified regardless of mutational status. Monoclonal antibodies are typically administered as 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 review, 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 has led to improvements in OS and PFS. In NSCLC, the use of gefitinib amongst EGFR-mutated tumours improved PFS compared to cytotoxic chemotherapy (hazard ratio 0.48, 95% confidence interval 0.36 to 0.64; P < 0.001). This was further supported in the OPTIMAL study, which 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).

We hypothesise that anti-EGFR therapies in EGFR-overexpressing glioblastomas may inhibit cell proliferation and result in cell death, leading to improved survival and achieving similar results as those seen in NSCLC and colorectal cancer.

Why it is important to do this review

The purpose of this review was to find, organise, and summarise high-level evidence in terms of the benefits and harms of anti-EGFR therapies in people with glioblastoma to provide meaningful conclusions for clinical practice and further research. This review was 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 (Sampson 2010; Schuster 2015). Targeting EGFR in glioblastoma is an active area of interest with ongoing studies in progress. Newer compounds such as depatuxizumab mafodotin (ABT-414), an antibody–drug conjugate that can target EGFR or EGFRvIII in glioblastomas, which allows potent chemotherapy to be released inside targeted cancer cells (NCT02573324). This 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 investigated if the addition of anti-EGFR therapy improves outcomes in EGFR-overexpressing glioblastomas.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

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 categorised into three groups 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 of any 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 would 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 was a direct head-to-head comparison between two or more different anti-EGFR therapies (with or without standard of care in either arm), we would assess this and if deemed eligible will include it in future analyses.

Types of outcome measures

We considered for evaluation any studies including at least one of the following outcomes.

Primary outcomes

- Overall survival (OS): defined as time from randomisation to death from any cause.
- Severe adverse events: classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (NCI 2017), including percentage of treatment-related deaths.

Secondary outcomes

- 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 the trial investigators.
- Progression-free survival (PFS): defined as time from randomisation to disease progression. Disease progression may be defined by two criteria: MacDonald and Response Assessment in Neuro-Oncology Criteria (RANO) (Macdonald 1990; 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 as the standard response assessment tool in neuro-oncology trials.

All trials included in this review used RANO criteria for their measurements and assessments.

We presented the following outcomes in Summary of findings 1.

1. OS in first-line glioblastoma studies
2. OS in recurrent glioblastoma studies
3. Severe adverse events
   a. Lymphopenia
   b. Neutropenia
   c. Thrombocytopenia
4. PFS in first-line glioblastoma studies
5. PFS in recurrent glioblastoma studies
6. Quality of life

Search methods for identification of studies

Electronic searches

The following databases were searched on 20 April 2020:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 4), in the Cochrane Library (Appendix 1);
- MEDLINE via Ovid (1946 to April week 3, 2020) (Appendix 2);
- Embase via Ovid (1980 to 2020 week 16) (Appendix 3).

We applied no language restrictions to any of the searches.

Searching other resources

Two review authors (AL, MA) independently searched the following databases up to 20 February 2020 using the search strings provided by Cochrane Gynaecological, Neuro-oncology and Orphan Cancers. These searches were also conducted in Cochrane Methodology Register, ACP Journal Club, EBM reviews, 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 searched 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) independently collected data and prepared the manuscript for analysis using Review Manager 5 (Review Manager 2014).

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (Endnote and Covidence). Two review authors (AL, MA) independently screened the records identified from electronic and handsearches for RCTs and excluded those studies that obviously did not meet the inclusion criteria as described in Criteria for considering studies for this review. We retrieved the full-text reports of all possibly relevant studies and assessed whether they met the inclusion criteria. We listed studies that did not meet the inclusion criteria in the Characteristics of excluded studies table with the reasons for exclusion. Any uncertainties or disagreements were resolved by discussion or by consulting a third review author (MK) if required. We identified and excluded duplicate reports and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram. We provided comprehensive details of the included studies in the Characteristics of included studies table.

We included abstracts and unpublished data only if information was available on study design and characteristics of participants, interventions, and outcomes. We contacted primary or corresponding study authors for further information and clarification to aid in this process.

Data extraction and management

Two review authors (AL, MA) independently performed data extraction. We followed Cochrane methodology as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and used a pre-piloted standardised data extraction form on two studies (see Appendix 4) and entered the data into Review Manager 5 for analysis (Review Manager 2014). For each eligible form, we recorded the following information: title, authors, study design, participants, setting, interventions, 'Risk of bias' items, duration of follow-up, efficacy outcomes, QoL scores, and adverse effects. We extracted data for studies with more than one publication from the most recent publication. We highlighted short-term adverse events if these were considered significant. We collected additional study-related information including contact address, country, published/unpublished, language, year of publication, and sponsor of trial.

Any differences in data extraction were resolved by consensus with a third review author (MK, VH, or HW), with reference to the original article.

For time-to-event data (OS, PFS), we extracted hazard ratios (HRs) and 95% confidence intervals (CIs), log rank Chi^2, log rank P values, numbers of events, numbers of participants per group, and medians. Where HRs were not available, we calculated 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 extracted the raw data and calculate odds ratios (OR) with 95% CIs.

For continuous outcomes (QoL measures), we extracted the number of responders, mean and standard deviation (SD) in each arm to calculate the mean difference (MD) with 95% CIs. Where possible, we performed quantitative analysis on collected and calculated data. If there were insufficient data, we presented a descriptive analysis.

When possible, we extracted data for intention-to-treat analysis for all outcomes. We collected the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

Two review authors (AL, MA) independently applied the 'Risk of bias' tool, resolving any differences by discussion or by appeal to a third review author (MK, VH, or HW). We judged each item at high, low, or unclear risk of bias as set out in the criteria provided

by Higgins 2011 and provided a quote from the study report or a statement (or both) as justification for the judgement for each item in the 'Risk of bias' table. For attrition bias, we judged a trial to be low risk of bias if at least 80% of participants were assessed at endpoint for all outcomes. We summarised results in both a 'Risk of bias' graph and 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we took 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 an investigator, we noted this in the 'Risk of bias' table.

Measures of treatment effect

We presented summary statistics for the primary endpoints (time-to-event data). Where HRs were not available, we calculated 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 extracted the incidence and total number of people evaluated and calculated for ORs. For continuous outcomes (QoL measures), we extracted data to calculate mean deviations. Where possible, we performed quantitative analysis on collected and calculated data. If there were insufficient data, we presented a descriptive analysis.

Unit of analysis issues

We have based measurement of PFS on RANO criteria (see Secondary outcomes) (Wen 2010).

Dealing with missing data

We contacted the first or corresponding author of the most recent publication in the case of missing data. We have not imputed missing data for any of the outcomes.

Assessment of heterogeneity

We have assessed heterogeneity between studies using the Cochran Q test, with a significance threshold of alpha = 0.1 and by estimation of the percentage of heterogeneity between trials that could not be ascribed to sampling variation.

In cases of substantial heterogeneity, the extra variation would have been incorporated into the analysis by using a random-effects model. We also planned to visually inspect forest plots for heterogeneity.

We considered an I^2 value of 30% or greater to represent a degree of heterogeneity worthy of further investigation. We considered 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 considered these factors in the sensitivity and subgroup analyses, except in cases of differing prognostic factors.

Assessment of reporting biases

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

Data synthesis

We performed a meta-analysis on the outcomes listed above if two or more trials of the appropriate clinical setting were available, appreciating that some statistical heterogeneity might have occurred from pooling of trials investigating different therapies. We used standard meta-analytical techniques, employing a random-effects model if heterogeneity in participant characteristics and treatments existed. We would group trials into first-line or recurrent settings for analysis, as this better correlates with real-world clinical purposes.

For time-to-event data, we pooled log HRs and standard error (SE) logHRs using the generic inverse variance facility of Review Manager 5 (Review Manager 2014). For dichotomous outcomes, we pooled ORs using the Mantel-Haenszel method.

In trials with multiple treatment groups, we combined time-to-event outcomes by performing a separate meta-analysis of the two-arm HRs. Subsequently, the resulting HRs was the summary statistic for the overall trial. We followed the method described in Section 16.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We considered the following variables for subgroup analyses where data were available:

- first-line therapy;
- recurrent disease.

Sensitivity analysis

We conducted predefined sensitivity analyses to assess the robustness of the conclusions based on studies with high or unclear risk of bias versus low risk of bias.

'Summary of findings' table and GRADE assessment of the certainty of the evidence

We have presented 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 created a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT (Summary of findings 1) (GRADEpro GDT). We used the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We downgraded 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.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies

Results of the search

The literature search was supported by the Information Specialist of the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, who helped to formulate the search strategies and conducted the searches in CENTRAL, MEDLINE, and Embase up to April 2020. Two review authors (AL and MA) conducted additional searches up to 20 April 2020 in Cochrane Methodology Register, ACP Journal Club, Database of Abstracts of Reviews of Effects (Ovid Technologies), and abstracts and reports from major conferences.

The main database searches identified 2879 references which were put through the Cochrane RCT Classifier. The RCT classifier is a machine learning routine that helps to distinguish between reports of RCTs (and quasi-RCTs) and non-RCTs. Following this step and de-duplication, there were 908 references imported for screening using Covidence (Covidence). Additional handsearches yielded four references. Consequently, there were 912 references available for screening. Two review authors (AL and MA) independently conducted the screening procedures, identifying keywords including glioblastoma, adult, randomised, trial, EGFR (and EGFR-related drugs – monoclonal antibodies, tyrosine kinase inhibitors, vaccines) from the title. We identified 851 references that were irrelevant. Two review authors (AL and MA) independently reviewed 61 abstracts. We excluded 42 abstracts, of which 29 abstracts had the wrong trial design, 10 were duplicate entries, 1 study was ongoing and 1 study did not have the outcomes listed as specified in our protocol. We independently reviewed the full texts of 19 records, of which 9 were found to be eligible and included in the review. This process is detailed in a PRISMA flow diagram (Figure 1).

Figure 1. PRISMA flow diagram.

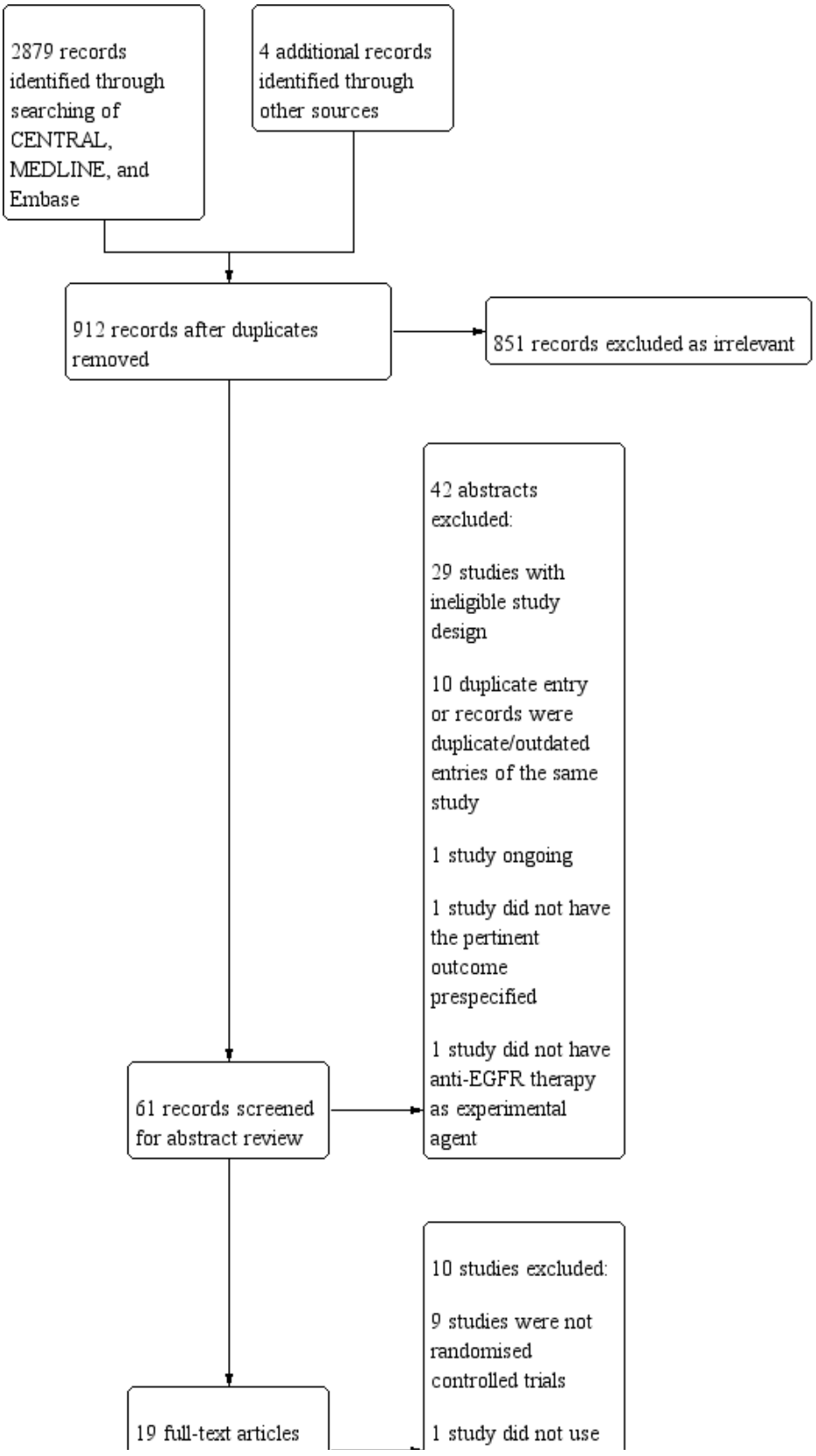
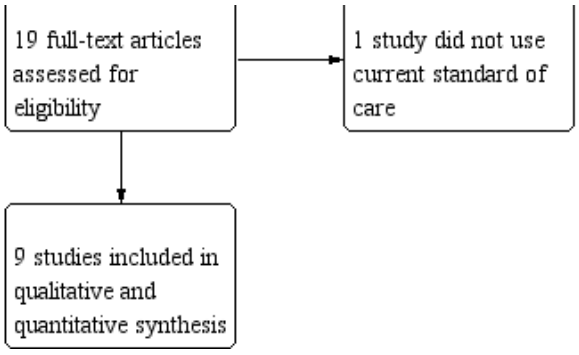


Figure 1. (Continued)



Included studies

The nine included studies can be categorised into first-line (treatment naïve), Lee 2015; Weller 2017; Westphal 2015, and recurrent (second-line or further setting) (Brown 2016; McNeill 2014; Reardon 2015 (ReACT); Reardon 2020; van den Bent 2009; van den Bent 2019). There were three first-line studies and six recurrent studies investigating the role of anti-EGFR therapies in glioblastoma. Three of the nine included studies had predefined selection for EGFR amplified or mutated glioblastomas (Reardon 2015; van den Bent 2019; Weller 2017).

The median/mean age of participants across the studies was 54 to 60 years. Three studies used OS as the primary endpoint (Lee 2015; van den Bent 2019; Weller 2017); two studies used PFS (Brown 2016; Westphal 2015); and the remaining four studies used PFS at six months (PFS6) as primary endpoint (McNeill 2014; Reardon 2015; Reardon 2020; van den Bent 2009). All of the included studies also reported secondary outcomes on OS, PFS, and toxicities. No adjustments to survival statistics were noted. However, we noted that two studies were terminated early: Brown 2016 was stopped due to cessation of the experimental drug, cediranib, by the pharmaceutical manufacturer, and Weller 2017 was closed after a second preplanned interim analysis due to futility. We also noted that Westphal 2015 presented two unplanned subgroup analyses by O6-methylguanine–DNA methyltransferase (MGMT) methylation and EGFR statuses.

We further evaluated the included studies for risk of bias according to Cochrane guidelines (Assessment of risk of bias in included studies).

First-line studies

Amongst the first-line treatment studies, one study investigated the use of nimotuzumab, a monoclonal antibody (Westphal 2015); one study investigated the use of vandetanib, a multi-TKI targeting EGFR, vascular epidermal growth factor receptor (VEGFR), and rearranged during transfection (RET) (Lee 2015); and the third study investigated the use of the EGFRvIII-targeting vaccine rindopepimut (Weller 2017). All three studies tested their respective investigational product against the standard European Organisation for Research and Treatment of Cancer and the NCIC Clinical Trials Group (EORTC-NCIC) protocol (Stupp 2005). The minimum Karnofsky Performance Status (KPS) was greater or equal to 60 (Karnofsky 1948). Weller 2017 specified maximal surgical resection (due to the potential risk of immunogenic flare from the vaccine), which may have inadvertently ruled out people with a poorer prognosis.

Recurrent disease studies

Amongst the recurrent treatment studies, four studies involved TKIs (Brown 2016; McNeill 2014; Reardon 2015; van den Bent 2009); one study used an antibody drug conjugate ABT-414 (van den Bent 2019); and the remaining study investigated the use of rindopepimut vaccine (Reardon 2020). As there is no recognised standard of care in recurrent glioblastomas, the control arm was generally either cytotoxic chemotherapy, physician's choice, or conservative management. In Brown 2016, cediranib, a TKI against VEGFR, was added to gefitinib (EGFR TKI) versus cediranib alone; van den Bent 2009 investigated the use of erlotinib (EGFR TKI) versus temozolomide or carmustine; and Reardon 2015 investigated the use of afatinib (EGFR TKI) versus temozolomide versus afatinib and temozolomide in a three-arm randomised study. These three studies had recruited participants at first recurrence only with a minimum KPS of 70. All eligible participants had received chemoradiation and adjuvant chemotherapy as per EORTC-NCIC protocol (Stupp 2005).

In McNeill 2014, the experimental arm was vandetanib and carboplatin versus carboplatin alone. No detail was provided regarding the number of prior treatments or any previous treatments. Reardon 2020 recruited participants at first or second recurrence who were bevacizumab naïve. Participants were randomised to bevacizumab and rindopepimut versus bevacizumab plus placebo. The placebo was specially designed to generate an immune skin reaction to maintain blinding. McNeill 2014 was only available in abstract form; we contacted the corresponding authors for further information.

van den Bent 2019 investigated the use of a new antibody drug conjugate ABT-414 (depatuxizumab mafodotin, or Depatux-M), an anti-EGFR monoclonal antibody drug conjugate. ABT-414 can target both EGFR and EGFRvIII mutations and is stable in the bloodstream until it meets its target and releases anti-microtubule agent monomethyl auristatin F (MMAF) (van den Bent 2019). This study, named INTELLANCE-2, had three arms, with arm A using ABT-414 only, arm B containing ABT-414 and temozolomide, and arm C temozolomide or lomustine (depending on the time to failure from last temozolomide use).

Excluded studies

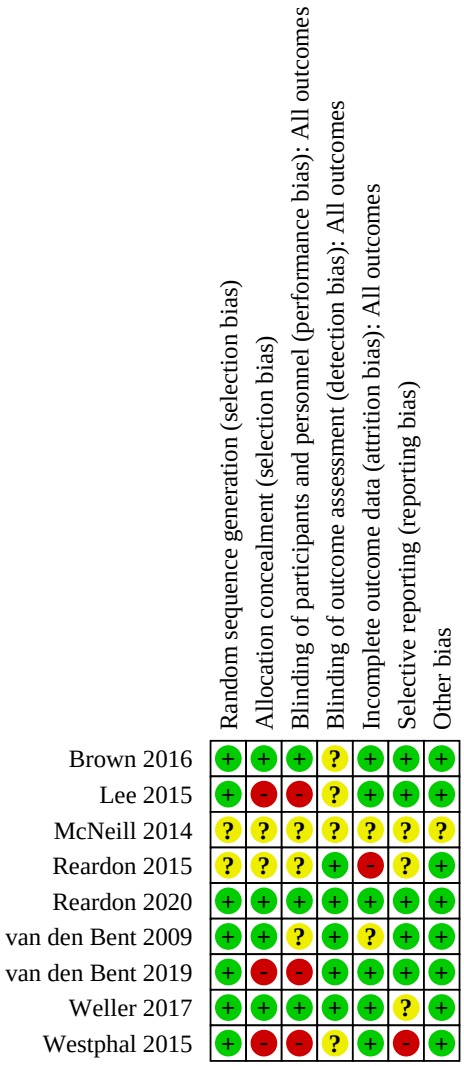
We excluded 10 studies after full-text review. We excluded nine studies that were not randomised trials (Daugherty 2014; Hong

2012; Neyns 2009; Schuster 2015; Sepulveda 2015; Solomon 2013; van den Bent 2016; Wen 2014; Wygoda 2002). In addition, we excluded Wygoda 2006 and Solomon 2013 due to the different standard of care used; specifically they did not use temozolomide, which is now part of standard of care.

Risk of bias in included studies

The summary of the 'Risk of bias' assessment in the included studies is shown in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation was well documented in seven of the included studies (Brown 2016; Lee 2015; Reardon 2020; van den Bent 2009; van den Bent 2019; Weller 2017; Westphal 2015), which we classified as at low risk of bias. It is unclear from the available sources how the random sequence generation was made in McNeill 2014 and Reardon 2015; we classified these two studies as at unclear risk of bias.

Four studies demonstrated adequate allocation concealment as part of their double-blind, randomised protocol, and were therefore classified as at low risk of bias (Brown 2016; Reardon 2020; van den Bent 2009; Weller 2017). In particular, Reardon 2020 and Weller 2017 added an immunostimulant in the placebo vaccines to generate the expected skin reaction similar to rindopepimut preparations. Lee 2015, van den Bent 2019, and Westphal 2015 were open-label studies and hence concealment could not be maintained, thus they were classified as at high risk of bias. It was unclear from the available sources how allocation concealment was preserved in McNeill 2014 and Reardon 2015, thus these two studies were classified as at unclear risk of bias.

Blinding

Three studies demonstrated evidence to support preserved blinding of participants and personnel and were assessed as at low risk of bias (Brown 2016; Reardon 2020; Weller 2017). Lee 2015, van den Bent 2019, and Westphal 2015 were open-label studies, thus blinding would not have been preserved, and as such these studies were graded as at high risk of bias. It is unclear if blinding of participants and personnel was preserved in McNeill 2014, Reardon 2015, and van den Bent 2009, thus these studies were graded as at unclear risk of bias.

Brown 2016, van den Bent 2009, and Weller 2017 mention blinding of outcome assessors in their reports. Reardon 2015, Reardon 2020, and van den Bent 2019 mentioned that they had an independent imaging review committee, therefore we considered that these studies were at low risk of bias. It is unclear whether assessor blinding took place in Lee 2015, McNeill 2014, and Westphal 2015, thus we classified these studies as at unclear risk of bias.

Incomplete outcome data

Most of the included studies had clear flow diagrams illustrating the distribution of all trial participants and were thus classified as at low risk of bias (Brown 2016; Lee 2015; Reardon 2020; van den Bent 2009; van den Bent 2019; Weller 2017; Westphal 2015). This information was missing from McNeill 2014, as the study was available in abstract form only. Reardon 2015 had 12 participants that were not randomised after enrolment, and as this was not explained we classified the study as at high risk of bias for this domain.

Selective reporting

Most of the included studies reported on all prespecified outcomes (Brown 2016; Lee 2015; Reardon 2015; Reardon 2020; van den Bent 2009; van den Bent 2019; Weller 2017). Westphal 2015 did not report on response rates as prespecified and was thus classified as at high risk of bias. This information was missing from McNeill 2014, as the study was available in abstract form only.

Other potential sources of bias

We detected no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Anti-EGFR therapy compared to placebo or standard of care for glioblastoma in adults

Primary outcomes

Overall survival

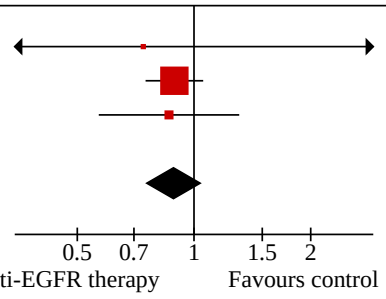
We performed meta-analysis separately for first-line and recurrent glioblastoma studies.

Meta-analysis of the three first-line studies demonstrated no reduction in the risk of death with anti-EGFR therapies (hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.76 to 1.04; 3 RCTs, 1000 participants, moderate-certainty evidence, Analysis 1.1, Figure 3, Summary of findings 1) (Lee 2015; Weller 2017; Westphal 2015).

Figure 3. Forest plot of comparison: 1 Overall survival, outcome: 1.1 First-line.

Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Lee 2015 (1)	-0.3011	1.1885	0.5%	0.74 [0.07 , 7.60]
Weller 2017 (2)	-0.1165	0.0873	85.2%	0.89 [0.75 , 1.06]
Westphal 2015 (3)	-0.1485	0.2128	14.3%	0.86 [0.57 , 1.31]
Total (95% CI)			**100.0%**	**0.89 [0.76 , 1.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

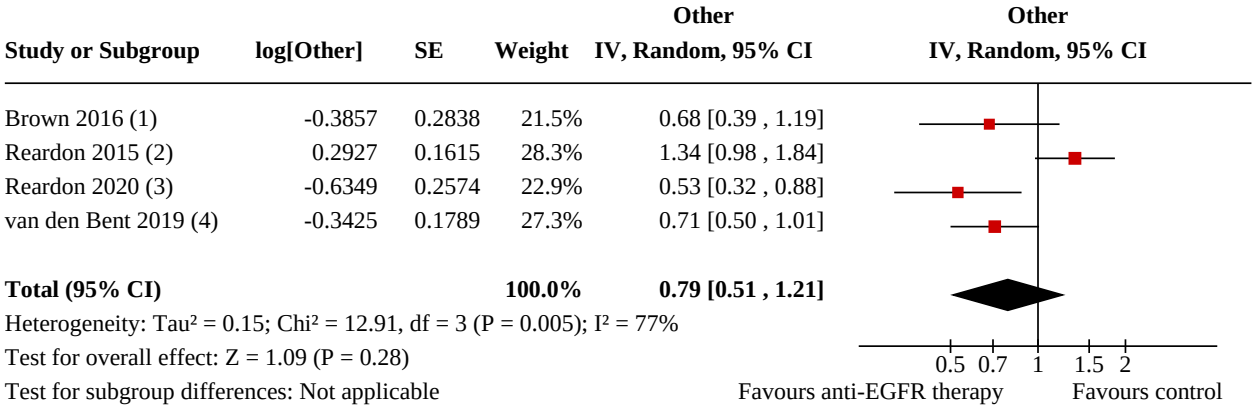


Footnotes
(1) Vandetanib vs placebo
(2) Rindopepimut vs placebo
(3) Nimotuzumab vs placebo

No heterogeneity was observed ($I^2 = 0\%$). Individually, these studies did not demonstrate a benefit with the respective experimental therapy. The median overall survival (OS) in months in the experimental arms was 16.6, 17.4, and 22.3 months for Lee 2015, Weller 2017, and Westphal 2015, respectively. These figures would be consistent with contemporary non-EGFR-related first-line glioblastoma therapy studies globally (Chinot 2014; Gilbert 2014; Nabors 2015; Stupp 2014; Stupp 2017). Both Weller 2017 and Westphal 2015 demonstrated the importance of maximal safe resection in improving outcome. In Weller 2017, the subgroup with maximal safe resection reported survival above 20 months, whereas the subgroup with significant residual disease had survival around 14 to 14.8 months. Similarly, in Westphal 2015, there was an approximate difference of three to four months between residual- and no-residual-disease OS.

Four recurrent glioblastoma studies provided HRs as part of their survival data reporting (Brown 2016; Reardon 2015; Reardon 2020; van den Bent 2019). Meta-analysis of these three studies did not show a statistically significant reduction in the risk of death with the use of anti-EGFR therapies (HR 0.79, 95% CI 0.51 to 1.21, 4 RCTs, 489 participants, low-certainty evidence, Analysis 1.2, Figure 4, Summary of findings 1). Significant heterogeneity was observed (I^2 = 77%), which was expected given the variation in the drugs used and the lack of a standardised therapy in the recurrent setting. The included studies in this recurrent setting demonstrated a wide range of survival results in the experimental arm, from 5.6 to 12.0 months.

Figure 4. Forest plot of comparison: 1 Overall survival, outcome: 1.2 Recurrent disease.



Footnotes

(1) Cediranib + Gefintib vs Cediranib
(2) Afatinib vs Afatinb and Temozolomide vs Temozolomide
(3) Rindopepimut + Bevacizumab vs Control + Bevacizumab
(4) ABT-414 + Temozolomide vs Temozolomide/Lomustine

The most recent recurrent glioblastoma study reported median OS of 9.6 months in the combination ABT-414 and temozolomide arm, 7.9 months in the ABT-414 arm and 8.2 months in the chemotherapy arm alone (HR 0.68, 95% CI 0.48 to 0.9, P = 0.024, 260 participants) (van den Bent 2019). Reardon 2020 demonstrated a survival advantage with the combination of bevacizumab and rindopepimut vaccine against bevacizumab alone (11.0 versus 9 months) (HR 0.53, 95% CI 0.32 to 0.88, P = 0.01, 72 participants). We noted that there was a protracted delay to the full publication of this report. The remaining studies did not demonstrate any survival benefit with the use of the experimental therapy. Brown 2016 evaluated combination cediranib and gefitinib, which showed an OS difference of 1.7 months (OS 7.2 versus 5.5 months) (HR 0.68, 90% CI 0.39 to 1.19). However, this trial was terminated early due to cessation of cediranib, thus any potential survival trends must be interpreted with caution. Reardon 2015 showed no OS advantage with afatinib alone or in combination with temozolomide against temozolomide alone in a three-arm randomised study, with OS data of 9.8 months (afatinib alone), 8.0 months (afatinib and temozolomide), and 10.6 months (temozolomide alone). McNeill 2014 reported OS data of 5.6 versus 5.2 months (vandetanib + carboplatin versus carboplatin), whilst van den Bent 2009 reported OS data of 7.7 versus 7.3 months (erlotinib versus temozolomide or carmustine).

We performed a pre-planned sensitivity analysis between high or unclear risk of bias versus low risk of bias (Analysis 1.3). Seven studies were found to be at low risk of bias (Brown 2016; Lee 2015; Reardon 2015; Reardon 2020; van den Bent 2019; Weller 2017; Westphal 2015) and the HR for these seven studies was 0.82 (95% CI 0.71-0.93). McNeill 2014 was the only study classified as high or unclear risk of bias and this study did not report HR for inclusion in the statistical calculations. While this sensitivity analysis demonstrated a survival benefit with the use anti-EGFR therapy, it should be interpreted with caution given the heterogeneous nature of the patient population, the different classes of anti-EGFR drugs used and the result was influenced heavily by one trial (Weller 2017) in particular.

The authorship team expressed concerns regarding comparative versus non-comparative studies and its influence on the outcome, and thus an additional sensitivity analysis based on comparative versus non-comparative studies was conducted (Analysis 1.4). Five of the six studies included in this primary outcome analysis were comparative RCTs, whilst Lee 2015 was a non-comparative RCT. The HR for the five comparative RCTs was 0.89 (95% CI 0.71 to 1.12). The HR for Lee 2015 was 0.74 (95% CI 0.07 to 7.60). This did not alter the assessment for this primary outcome (Analysis 1.5). A lack of information in McNeill 2014 (the other non-comparative study) prevented us from including this study in the statistical calculations. McNeill 2014 reported OS as 5.58 versus 5.22 months without further elaboration. This study was still in abstract form at the time of writing.

Toxicities

We identified no differences between groups in the meta-analysis of grade 3 or above toxicities amongst first-line studies. Certain adverse events seemed to occur more frequently in

the experimental arms, but these differences did not reach significance: lymphopenia (4 RCTs, 1146 participants, low-certainty evidence, Analysis 2.1); neutropenia (4 RCTs, 1146 participants, low-certainty evidence, Analysis 2.2); thrombocytopenia (4 RCTs, 1146 participants, low-certainty evidence, Analysis 2.3)(Summary of findings 1).

First-line studies

Westphal 2015 investigated the use of the monoclonal antibody nimotuzumab, and did not report significant skin toxicities as commonly seen in other anti-EGFR monoclonal antibodies. Westphal 2015 found an increase in grade 3 or 4 toxicities (22 versus 6 events) with combination nimotuzumab and temozolomide, with increased levels of nausea and thrombocytopenia. Westphal 2015 reported three significant pulmonary embolic events in the nimotuzumab arm, with no venous thromboembolic events seen in the control group.

Lee 2015 found increased incidences of moderate to severe haematological toxicities, documenting the following toxicities of grade 3 or 4 severity in the vandetanib arm: lymphopenia 43.5% (versus 27.6% in control), leukopenia 11.6% (versus 6.9% in control), neutropenia 11.6% (versus 10.3% in control). However, these are unlikely to be of significance due to the small number of events recorded.

Weller 2017 reported mild to moderate injection site reaction relating to rindopepimut. This was a very common finding, with up to 80% noted (versus 41% in placebo). Notable but uncommon grade 3 to 4 adverse events included thrombocytopenia, fatigue, brain oedema, headaches, and seizures (all less than 10% incidence). A grade 5 pulmonary embolus was assessed as potentially related to rindopepimut. Discontinuation rates were low and due mainly to hypersensitivity from the vaccine. Importantly, the study authors did not report significant increases in immune-related cerebral oedema or seizure.

Recurrent studies

In van den Bent 2019, significant side effects were reported in the experimental arms affecting the eyes and bone marrow. Grade 3 and 4 ocular toxicities were detected in 28.4% of participants who received ABT-414. Only 20% of participants administered ABT-414 did not suffer from any eye toxicities. Eye toxicities included: blurred vision, dry eye, keratitis, photophobia, and eye pain. This is a particular concern with ABT-414 given that these issues were also encountered in the previous study by Reardon 2017. Grade 3 and 4 thrombocytopenia were also seen in 5.23% of participants who received ABT-414.

Four recurrent studies investigated the use of oral TKIs. McNeill 2014 evaluated vandetanib, whilst the other three studies focused on specific EGFR TKI: Brown 2016 (gefitinib), Reardon 2015 (afatinib), and van den Bent 2009 (erlotinib). McNeill 2014 was similar to Lee 2015 in reporting increased incidences of moderate to severe haematological toxicities in the experimental arm. Reardon 2020 also reported mild to moderate injection site reaction relating to rindopepimut, and more detail is awaited as the data are still in abstract form. We have contacted the authors for further information.

In relation to the three specific reversible and irreversible EGFR TKI, Brown 2016 (gefitinib) found grade 3 or 4 adverse events in the combination of gefitinib and cediranib versus cediranib alone (89% versus 68%). The most frequent adverse events encountered in the combination included fatigue, hypertension, lymphopenia, anorexia, and ataxia. The study authors recorded one death from pulmonary embolus. Overall, treatment duration was longer with the combination, albeit with more dose reductions and side effects. Similarly in Reardon 2015, more adverse events were encountered with the use of afatinib both in combination with temozolomide (92.3%) or alone (85.4%) when compared to single-agent temozolomide (56.4%). The most severe and common adverse events with the use of afatinib included fatigue, skin rash, and diarrhoea. This also contributed to a significant discontinuation (28.2%) and dose reduction rates in the combination arm (17.9%). In van den Bent 2009, erlotinib was observed to be well tolerated, and grade 3 or 4 toxicities were mainly skin related, which are commonly observed in other erlotinib trials.

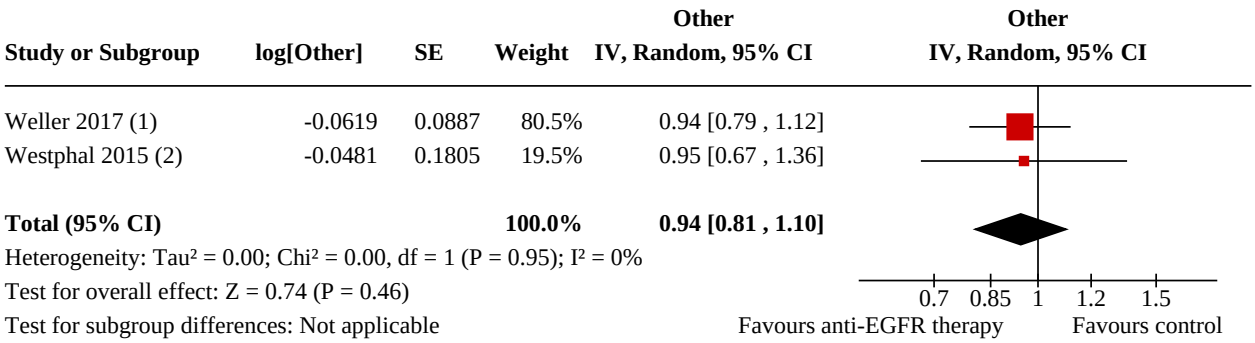
In summary, toxicities associated with experimental therapies showed a slight increase in severe adverse events and adverse events when compared to the control arms.

Secondary outcomes

Progression-free survival

We performed a meta-analysis on two of the first-line studies where progression-free survival (PFS) HRs were reported (Weller 2017; Westphal 2015). There was no reduction in the risk to disease progression with the use of anti-EGFR therapy (HR 0.94, 95% CI 0.81 to 1.10, 2 RCTs, 894 participants, low-certainty evidence) with no significant heterogeneity observed (I^2 = 0%) (Analysis 3.1, Figure 5, Summary of findings 1). These two studies found comparable PFS results ranging from 7.7 to 8.0 months. Individually, the studies did not demonstrate any PFS benefit with the addition of anti-EGFR therapy. Westphal 2015 found a PFS of 7.7 months in their experimental arms, and Weller 2017 documented PFS 8.0 months in the rindopepimut study. These figures are slightly lower than those reported in other first-line non-EGFR-related glioblastoma studies in contemporary literature such as AVAGLIO, Chinot 2014, and RTOG 0825, Gilbert 2014, where PFS was reported to be around 10.6 and 10.7 months, respectively. Lee 2015 did report a slight benefit towards vandetanib in prolonging PFS (7.7 versus 6.2 months, P = 0.6). No survival curves or HR was reported, thus this study could not be added to the meta-analysis.

Figure 5. Forest plot of comparison: 2 Progression-free survival, outcome: 2.1 First-line.



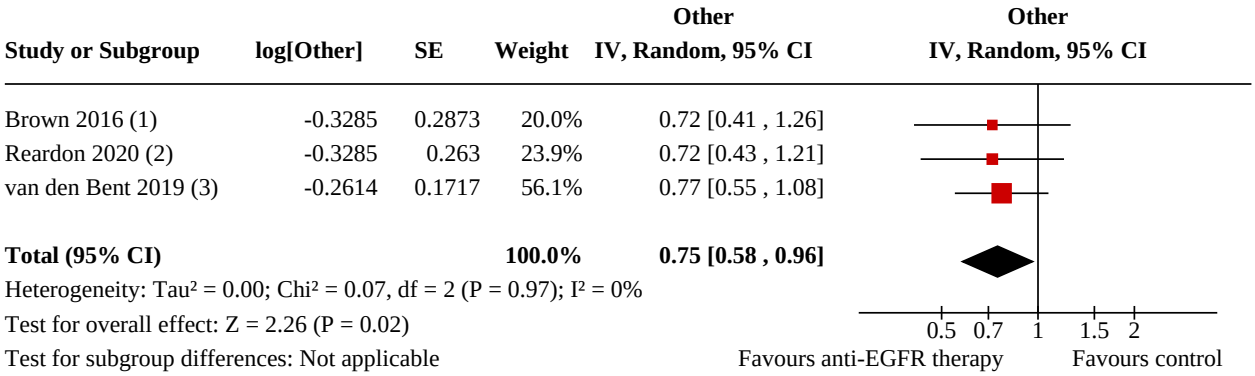
Footnotes

(1) Rindopepimut vs placebo

(2) Nimotuzumab vs placebo

We performed a meta-analysis on three of the recurrent studies (Brown 2016; Reardon 2020; van den Bent 2019), and there was a reduction in the risk to disease progression favouring anti-EGFR therapy (HR 0.75, 95% CI 0.58 to 0.96, 3 RCTs, 275 participants, low-certainty evidence) with no significant heterogeneity observed (I^2 = 0%) (Analysis 3.2, Figure 6, Summary of findings 1). In detail, Brown 2016 documented PFS of 3.6 months versus 2.8 months in the cediranib and gefitinib arm versus the cediranib-alone arm. With regard to recurrent glioblastoma studies, van den Bent 2019 showed a slight advantage with ABT-414 and temozolomide with a PFS of 2.7 months (compared to 1.9 months in the ABT-414 monotherapy and chemotherapy arms) (HR 0.77, 95% CI 0.55 to 1.07), and Reardon 2020 showed a PFS of 3.7 months in both groups (HR 0.72, 95% CI 0.43 to 1.21).

Figure 6. Forest plot of comparison: 3 Progression-free survival, outcome: 3.2 Recurrent disease.



Footnotes

(1) Cediranib + Gefintib vs Cediranib

(2) Rindopepimut + Bevacizumab vs Control + Bevacizumab

(3) ABT-414 +Temozolomide vs Temozolomide/Lomustine

Amongst the remaining recurrent studies, the average PFS duration was similar between the experimental arm and the standard/placebo arm: 1.92 months (range 0.99 to 3.6 months). McNeill 2014 demonstrated PFS 1.7 versus 0.9 months in the vandetanib and carboplatin versus carboplatin-alone groups, and van den Bent 2009 recorded a PFS of 1.8 months in the erlotinib group versus 2.4 months in the temozolomide or carmustine group. In Reardon 2015, there was an indication of harm in using afatinib in isolation, with a calculated HR 1.67 (0.99 months versus 1.87 months, P = 0.386), whilst the combination of afatinib and temozolomide versus temozolomide alone in the same study also showed a less favourable outcome with the addition of afatinib to temozolomide, with a calculated HR 1.31 (1.53 months versus 1.87 months, P = 0.119).

Quality of life

Four studies assessed quality of life (QoL) (Brown 2016; McNeill 2014; Weller 2017; Westphal 2015). Three studies used EORTC QLQ-C30-based assessment scales (Brown 2016; Weller 2017; Westphal

2015). Westphal 2015 conducted serial QoL assessments at study registration, first treatment, and then at weeks 10, 21, 33 and subsequently every 12 weeks. They found an improvement in multiple domains in favour of nimotuzumab with a maximal separation of 15 points at week 21. Weller 2017 (with the addition of MD Anderson Symptom Inventory - Brain Tumor (MDASI-BT) assessment score) found no significant differences in any of the domains between rindopepimut and placebo. Brown 2016 found that the addition of gefitinib did not have a negative impact on QoL, nor did it improve function or symptoms overall. McNeill 2014 mentioned that health-related quality of life assessments were performed at baseline and at week 4, and changes were not predictive of time to progression or survival. More detail is awaited from publication of the full manuscript.

DISCUSSION

Summary of main results

This review has not identified any benefit towards improved overall survival (OS) in the use of anti-EGFR therapy in first-line glioblastoma management (moderate-certainty evidence, low risk of bias) (Analysis 1.1). Each of the included studies did not demonstrate a survival benefit with the use of anti-EGFR therapy. It is disappointing that whilst anti-EGFR therapy has proven survival benefits in most other solid tumours containing EGFR amplification or mutations, this has not been reproduced in glioblastomas (another highly EGFR-expressing tumour) as yet. The INTELLANCE-1 study, which is selective for EGFR amplification, mutation, or both in its participant recruitment has been suspended due to safety signals concerning lack of efficacy in May 2019 (NCT02573324).

The meta-analysis in the recurrent setting also showed no OS benefit with the use of anti-EGFR therapy (low-certainty evidence, low risk of bias) (Analysis 1.2;), despite studies by Reardon 2020 and van den Bent 2019 both observing improvements in survival. Interestingly, this survival benefit has not been translated to the first-line setting for ABT-414 and rindopepimut (NCT02573324; Weller 2017). The other studies did not demonstrate any improvement in OS based on the available data. It is interesting to note that in the Reardon 2015 trial, temozolomide alone outperformed either afatinib alone or in combination with temozolomide. These results held true even in a post hoc analysis where the cohort was further defined by EGFR amplification or mutation status. This would suggest that tyrosine kinase inhibitors (TKI) intrinsically are ineffective against EGFR-drive glioblastomas.

Overall, anti-EGFR therapies were better tolerated than expected and did not negatively impact on quality of life. In our meta-analyses, no differences were observed between anti-EGFR therapy and the standard of care/placebo (low-certainty evidence, low risk of bias). The expected side effects of skin rashes and diarrhoea were generally not severe. Ocular toxicity with ABT-414 is a particular concern given the number of participants who experienced any-grade eye problems (van den Bent 2019). Special eye precautions have been promoted by the manufacturer to combat these problems, and frequent reviews with ophthalmologists are recommended. Deaths were recorded amongst the studies that were due to venous thromboembolic events (VTE) (second to disease progression). It is widely noted that glioblastoma has one of the highest rates of VTE amongst solid tumours (Magnus 2013; Perry 2012). It is uncertain whether EGFR-targeted therapies would contribute to this increased risk (like anti-angiogenic therapies), and certainly this is not recognised amongst people with non-small cell lung cancer and colorectal cancer, where these drugs are more commonly used. It is also not known whether EGFR-driven glioblastomas have an inherent increased risk of VTE. This may explain the poorer morbidity and mortality data often recorded in EGFR-driven glioblastomas.

As a group, anti-EGFR therapies did not appear to delay the time to disease progression amongst the first-line trials (low-certainty evidence, low risk of bias) (Lee 2015; Weller 2017; Westphal 2015), which demonstrated a progression-free survival (PFS) duration of 6 to 8 months; this was less than that observed in both RTOG 0825 and AVAGLIO (around 10 months) (Chinot 2014; Gilbert 2014). This may be due to the ability of bevacizumab to delay/mask changes on magnetic resonance imaging (MRI) scans (Thompson 2011; Wick 2016). Whilst different radiological assessment methods were used in these trials, the differences encountered are unlikely to be explained by the assessment methods used in regard to Response Evaluation Criteria in Solid Tumours (RECIST) versus MacDonald versus RANO criteria. Amongst the included studies, only Brown 2016, van den Bent 2019, and Weller 2017 used RANO (the new accepted standard in neuro-oncology) as the imaging assessment tool.

Surprisingly, meta-analysis of three recurrent studies found a reduced risk of disease progression with the use of anti-EGFR therapy (low-certainty evidence, low risk of bias). These three studies all used different classes of EGFR drugs, and the result was largely driven by one study (van den Bent 2019), thus its importance must be interpreted with caution. Furthermore, whilst the analysis indicated a lowered risk of disease progression, this did not translate to an improvement in overall survival.

Overall completeness and applicability of evidence

The included studies were mixed in terms of the trial participants and the interventions used. We accounted for this by separating our analysis in line with the clinical situation (first-line versus recurrent disease). Toxicities associated with experimental therapy were higher when compared to control arms, and notably ocular toxicities with ABT-414 were particularly problematic. Most of the reported trials were not selective for people with EGFR amplification or mutation (except rindopepimut and ABT-414 trials, where encouraging trends were observed). Further research is needed to determine if selected people with glioblastoma with known EGFR drivers respond to anti-EGFR therapy. Use of anti-EGFR therapy in EGFR-driven glioblastomas may require combinations with other cytotoxic or targeted therapy agents to enhance its utility. At present, there is no evidence to support anti-EGFR therapy in glioblastoma patients outside of clinical trial settings.

It is important to highlight the heterogeneity of the trials and the experimental drugs used. Whilst there was no significant heterogeneity observed in our meta-analyses of first-line studies, there was significant heterogeneity observed amongst the recurrent studies. This is to be expected given that some studies have preselected for EGFR-amplified or -mutated glioblastomas (Reardon 2020; van den Bent 2019; Weller 2017), and others did not (Brown 2016; Lee 2015; McNeill 2014; Reardon 2015; van den Bent 2009; Westphal 2015). Only three of the nine included studies selected for the presence of EGFR amplification/mutation

in their inclusion criteria (Reardon 2020; van den Bent 2019; Weller 2017). Reardon 2020 and Weller 2017 were investigating the use of rindopepimut vaccine. Interestingly, it was the recurrent study that showed a survival benefit (Reardon 2020), whereas the first-line trial did not (Weller 2017). This may be attributed to some of the prespecified entry criteria in Weller 2017 (maximal surgical resection, completion of chemoradiation without progression, and maximum dexamethasone dose of 2 mg), which excluded patients with a poorer prognosis, creating a better-than-expected control arm. This is reflected in the whole cohort achieving medial overall survival duration of around 20 months.

The types of drugs used in these studies were also vastly different and thus contributed to the high heterogeneity and inconsistency of the results. Rindopepimut and ABT-414 can be considered to be specially crafted towards use in glioblastomas, whilst most of the other anti-EGFR therapies described in this review have already been commonly used in other solid tumours. The EGFR TKIs have not been able to achieve the same levels of success like that has been observed amongst non-small cell lung cancer patients (Mok 2009). These TKIs target activating mutations in the intracellular catalytic domain of EGFR that are found in lung adenocarcinomas, whereas in glioblastomas the EGFR pathway is hyperactivated by overexpression or a mutated extracellular domain (vIII) of EGFR. ABT-414 is designed to target the extracellular component of the receptor, and thus may explain the positive trend observed in INTELLANCE-2 (van den Bent 2019).

Tumour heterogeneity in glioblastoma is well recognised and is increasingly seen as a contributor to the failures of targeted therapy (Eder 2014). Expression of targets or presence of mutation may vary within the tumour itself and between individuals. The development of resistance may have originated at the onset of tumour development, or indeed through evolution over time, especially when tumours are placed under stress from targeted therapy (Inda 2014). The molecular changes underlying these developments have been previously documented by Parker and colleagues (Parker 2016), and may be particularly relevant amongst EGFR-overexpressed glioblastomas, leading to the current difficulties encountered in achieving success with anti-EGFR therapy (Inda 2014; Sottoriva 2013). This may also help to explain the disconnect between improvements in PFS data (recurrent studies) and the lack of success in overall survival. It is likely that the experimental therapies were successful in removing the targeted population, but that ultimately led to the survival and propagation of a resistant population, thus having no impact on overall survival.

Quality of the evidence

The more recent studies were of high quality and clear and detailed in reporting their study procedures and outcomes, with a low of risk of bias (Brown 2016; Lee 2015; Reardon 2020; van den Bent 2019; Weller 2017; Westphal 2015). The remaining studies were also conducted rigorously as evidenced by the balanced nature of the randomisation. McNeill 2014 was more difficult to assess due to the lack of information and data obtained.

There is moderate degree of certainty of the overall survival trend observed amongst first-line trials, with 1000 participants reported from 3 contributing studies. As mentioned above, these three studies all used different classes of anti-EGFR agents, thus the applicability of these data remains uncertain and requires further validation. The other outcomes of OS (recurrent studies), toxicities, and PFS (first-line) were not estimable, with low- to very low-certainty evidence.

Potential biases in the review process

The search strategy was overseen by the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group to reduce the risk of introducing bias into the review process. We applied no limitations with regard to language or date of publication and made deliberate efforts to search for ongoing clinical trials. We obtained additional unpublished data through correspondence with study authors, and included this information in the review. Two review authors independently made decisions regarding study eligibility, 'Risk of bias' assessment, data collection, and grading of evidence, with any disagreements settled by a third review author.

The main bias relates to the small number of included studies, especially the older studies with smaller participant numbers and were of low or very low methodological quality, which meant that it was frequently not possible to conduct a meta-analysis and prevented the drawing of firm conclusions regarding the clinical effectiveness of the intervention. It also meant that it was not possible to assess for publication bias. No conflicts of interest were identified for any of the study authors.

Agreements and disagreements with other studies or reviews

Given their frequency and importance in pathogenesis, EGFR alterations in glioblastomas remain an attractive target for therapies. Unfortunately, the main takeaway from this review would be the lack of survival benefit identified in the first-line or recurrent setting with the use of anti-EGFR therapies amongst glioblastoma patients, with significant toxicities. Other reviews have found similar results, where none of the current anti-EGFR therapies have been truly demonstrated to be effective (An 2018; Westphal 2017), but project hope that new generations of anti-EGFR therapies may be able to overcome past failures.

Whilst the overall results did not demonstrate survival benefit with the use of anti-EGFR therapy, the OS data would indicate that improvements in glioblastoma care have been achieved over time, with the most recent first-line glioblastoma studies demonstrating OS of 16 to 18 months (Chinot 2014; Gilbert 2014; Weller 2017), compared to the initial report by Stupp and colleagues in 2005, where median survival was 14.7 months (Stupp 2005).

AUTHORS' CONCLUSIONS

Implications for practice

In summary, we have not found evidence of overall survival benefit with the use of epidermal growth factor receptor (EGFR)-targeted therapies in glioblastoma management. EGFR-targeted therapies were reasonably well tolerated (with special precautions required against ocular toxicities with ABT-414). There was no evidence that they delayed disease progression in first line setting while a benefit in delaying disease progression was observed in the recurrent setting. Rindopepimut appeared promising with strong recurrent data, but no evidence of a survival benefit in the first-line setting. Their first-line study did achieve an overall survival of 20 months in both arms, indicating that the field has progressed from the early days of Stupp protocol and the advantage of maximal surgical resection. At present, isolated cases may still benefit from anti-

EGFR therapies, but the selection should depend on the presence of EGFR amplification or mutations as evidenced by van den Bent 2019 and Reardon 2020.

Implications for research

Our review indicates that there are some encouraging signs from anti-EGFR therapy in glioblastoma. The small encouraging signs identified in this report should be seen as support for further research and future studies where patient selection is driven by molecular changes and specialised drugs are designed that focus on these specific molecular targets seen in glioblastomas.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brown 2016

Study characteristics	
Methods	Phase II multicentre, randomised, placebo-controlled

Brown 2016 *(Continued)*

Participants	Recurrent/progressive glioblastoma patients, 38 participants in total
Interventions	Cediranib and gefitinib combination versus cediranib and placebo
Outcomes	• OS: 7.2 vs 5.5 months (HR 0.68, 90% CI 0.39 to 1.19) • PFS: 3.6 vs 2.8 months (HR 0.72, 90% CI 0.41 to 1.26) • PFS6: 15.8% vs 15.8% • OS12: 15.8% vs 10.5% • Toxicity: fatigue, hypertension, lymphopenia, anorexia, ataxia
Notes	Cediranib discontinued by AstraZeneca – trial terminated early in August 2012.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation system was managed independent of the trial management team. Registration fax from the recruiting site trial staff would use an online randomisation system to produce container numbers for the assigned treatment.
Allocation concealment (selection bias)	Low risk	Contents of the bottles were concealed from site staff, participants, and trial management.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned, insufficient information (likely low risk)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing information
Selective reporting (reporting bias)	Low risk	All prespecified endpoints reported.
Other bias	Low risk	Early termination of study due to cessation of cediranib production, decision made by manufacturer.

Lee 2015

Study characteristics

Methods	Randomised 2:1, open-label, non-comparative, multicentre
Participants	106 randomised. First-line glioblastomas
Interventions	Vandetanib + Stupp protocol vs no vandetanib + Stupp protocol
Outcomes	• OS: 16.6 vs 15.9 months (P = 0.8, HR not available) • PFS: 7.7 vs 6.2 months (HR not available)

Lee 2015 *(Continued)*

	• PFS12: 0.25 vs 0.39 • Toxicities: mostly haematological – 4.3% clots
Notes	Used MacDonald criteria for radiological assessments

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were randomly assigned 2:1 at registration to receive RT and temozolomide…"
Allocation concealment (selection bias)	High risk	Not concealed. Open-label trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not concealed. Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uncertain
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 patients registered but did not proceed to randomisation.
Selective reporting (reporting bias)	Low risk	All prespecified endpoints reported.
Other bias	Low risk	

McNeill 2014

Study characteristics	
Methods	Phase II randomised non-comparative
Participants	66 recurrent glioblastoma patients (the trial also included 46 anaplastic astrocytoma patients)
Interventions	Vandetanib and carboplatin versus carboplatin
Outcomes	• OS: 5.58 vs 5.22 months (HR not available) • PFS6: 1.71% vs 0.89% (HR not available) Toxicity results reported on all trial participants (n = 112). SAE: vandetanib combination 37.5% vs carboplatin alone 17.85% Grade 3 thrombocytopenia (n = 14), lymphopenia (n = 12), neutropenia (n = 7), seizure (n = 5), hypertension (n = 4)
Notes	Still in abstract form only. Results have been published on ClinicalTrials.gov.
Risk of bias	

McNeill 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Uncertain
Allocation concealment (selection bias)	Unclear risk	Uncertain
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uncertain
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uncertain
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Uncertain
Selective reporting (reporting bias)	Unclear risk	Uncertain
Other bias	Unclear risk	Manuscript not published in full.

Reardon 2015

Study characteristics	
Methods	Phase I/randomised phase II, multicentre
Participants	Phase II - 119 recurrent glioblastoma patients
Interventions	Afatinib (A) vs afatinib and temozolomide (AT) vs temozolomide (T) (1:1:1)
Outcomes	• OS: A 9.8 months, AT 8.0 months, T 10.6 months (HR not available) • PFS6: A 3%, AT 10%, T 23% • PFS: A 0.99 months, AT 1.53 months, T 1.87 months (HR not available) • ORR: A 1%, AT 3%, T 4% • AEs: A 85.4%, AT 92.3%, T 56.4%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Uncertain
Allocation concealment (selection bias)	Unclear risk	Uncertain

Reardon 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Uncertain
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent review committee (ICON medical imaging) mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 patients were not randomised but no clear explanation.
Selective reporting (reporting bias)	Unclear risk	Uncertain
Other bias	Low risk	

Reardon 2020

Study characteristics	
Methods	Phase II randomised controlled trial
Participants	72 recurrent glioblastoma patients
Interventions	Rindopepimut (CDX-110) and bevacizumab versus bevacizumab + KLH control
Outcomes	• OS: 11 vs 9 months, HR 0.53 (95% CI 0.32 to 0.88, P = 0.01) • PFS: 3.7 vs 3.7 months, HR 0.72 (95% CI 0.43 to 1.21, P = 0.22) • PFS6: 28% vs 16% (P = 0.12) • ORR: 30% vs 18% (P = 0.38) • Toxicities: arthralgia 23% vs 5%, convulsion 23% vs 24%, back pain 17% vs 8%, diarrhoea 17% vs 5%, fatigue 23% vs 27%, nausea 26% vs 11%, vomiting 17% vs 5% • Signficant grade 3 AEs: convulsion 11% in experimental group vs 0 in control
Notes	Long delay to publication - 5 years from first results released in abstract form to full manuscript publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Prespecified randomisation list created by biostatistician.
Allocation concealment (selection bias)	Low risk	Participants and investigators remained blinded to treatment assignments.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes – double-blind, placebo controlled Unblinded pharmacists who were otherwise uninvolved in study conduct obtained randomised treatment assignments and managed study treatment.

Reardon 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent review committee (ICON medical imaging) mentioned. Expert review committee members were otherwise independent of study conduct and were blinded to treatment allocation and investigator assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None
Selective reporting (reporting bias)	Low risk	All prespecified endpoints reported.
Other bias	Low risk	

van den Bent 2009

Study characteristics	
Methods	Phase II randomised
Participants	110 recurrent glioblastoma patients
Interventions	Erlotinib versus carmustine (if no prior temozolomide) or temozolomide
Outcomes	• OS: 7.7 vs 7.3 months (HR not available) • PFS: 1.8 vs 2.4 months (HR not available) • Response: 20.4% vs 44.2% (PR and SD) • Toxicity: grade 3 or 4 rashes with erlotinib, grade 3 or 4 leukopenia/thrombocytopenia with control arm
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned centrally at EPRTC Data Centre either by internet or phone.
Allocation concealment (selection bias)	Low risk	Not mentioned but likely preserved
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central review of imaging
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All accounted for.

van den Bent 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified endpoints reported.
Other bias	Low risk	

van den Bent 2019

Study characteristics	
Methods	Phase II randomised, open-label
Participants	260 recurrent glioblastoma patients
Interventions	ABT-414 (A) versus ABT-414 and temozolomide (B) versus lomustine or temozolomide (C)
Outcomes	• OS: ABT-414 + temozolomide vs lomustine/temozolomide (HR 0.68, 95% CI 0.48 to 0.95, P = 0.024), 9.6 vs 8.2 months respectively • OS: ABT-414 vs lomustine/temozolomide vs lomustine/temozolomide (HR 1.04, 95% CI 0.73 to 1.48), 7.9 months vs 8.2 months • Toxicity: * Ocular toxicity: ☐ Grade 3: 30.7% (ABT-414 + temozolomide), 23.8% (ABT-414 alone) ☐ Grade 4: 1.1% to 1.2% for both ABT414 arms * Grade 3 to 4 haematological toxicities: thrombocytopenia: ABT-414 + temozolomide (10.2%), ABT-414 (1.2%), lomustine (25%), temozolomide only (14.3%)
Notes	Multiple abstracts with updates - no published manuscript Comparison is between Arm A and Arm C, and Arm B and Arm C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assumed to be low risk as not mentioned in manuscript; evidence from study protocol
Allocation concealment (selection bias)	High risk	Open-label trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central imaging review was conducted by an independent neuroradiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram demonstrated that all participants were accounted for.
Selective reporting (reporting bias)	Low risk	None

van den Bent 2019 *(Continued)*

Other bias	Low risk

Weller 2017

Study characteristics	
Methods	Phase III randomised, double-blind
Participants	First-line glioblastoma patient: randomisation (1:1) - 195 rindopepimut and temozolomide, 210 standard of care (temozolomide)
Interventions	Rindopepimut + temozolomide vs temozolomide

Outcomes	• OS: HR 0.89, P = 0.22 (17.4 vs 17.4 months ITT analysis)
	• PFS: HR 1.01 (8.0 vs 7.4 months)
	• QoL: no difference
	• Toxicity:
	  * Injection site reactions, transient grade 1 to 2 erythema, pruritus, rash
	  * Thrombocytopenia, fatigue, brain oedema, seizure, headache

Notes	Terminated early at second preplanned interim analysis – futility boundary crossed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment to treatment groups with a prespecified randomisation sequence with a block size of 4.
Allocation concealment (selection bias)	Low risk	Double-blinded study – unblinded pharmacists obtained randomly assigned treatment assignments and managed study treatment via interactive response technology
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study Placebo vaccine - preloaded with immunostimulant
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Local assessors (blinded), central assessors (also blinded for PFS and ORR assessments)
Incomplete outcome data (attrition bias) All outcomes	Low risk	None
Selective reporting (reporting bias)	Unclear risk	None
Other bias	Low risk	

Westphal 2015

Study characteristics	
Methods	Phase III randomised, open-label
Participants	142 first-line glioblastoma patients
Interventions	Nimotuzumab versus placebo
Outcomes	• OS: 22.3 vs 19.6 months (HR not available) • PFS: 7.7 vs 5.8 months (P = 0.79) • PFS12: 22% vs 18% • QoL: maximal difference of 15 points until week 21 • Toxicity: skin toxicities were rare and mild; overall, headaches, fatigue, nausea, vomiting
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation took place by fax after histological diagnosis of glioblastoma by local neuro-pathological review.
Allocation concealment (selection bias)	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	High risk	Response rates not reported. Unplanned subgroup analyses by MGMT methylation and EGFR status presented.
Other bias	Low risk	

OS: overall survival
PFS: progression-free survival
PFS6: progression-free survival at 6 months
PFS12: progression-free survival at 12 months
AE: adverse events
SAE: Serious adverse events
ORR: overall response rate
KLH: keyhole limpet hemocyanin
PR: partial response
SD: stable disease
ITT: intention to treat

QoL: quality of life
MGMT: O6-methylguanine–DNA methyltransferase
EGFR: epidermal growth factor receptor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Daugherty 2014	Not a randomised study
Hong 2012	Mixed grade III/IV, not randomised
Neyns 2009	Not a randomised study
Schuster 2015	Not a randomised study. Initially planned as a randomised phase II/III study, but due to voluntary attrition of first 16 participants in standard-of-care arm, the study was converted to open-label, single-arm phase II trial.
Sepulveda 2015	Not a randomised study
Solomon 2013	Not current standard of care
van den Bent 2016	Phase I study, 3 arms but not randomised
Wen 2014	Not a randomised study
Wygoda 2002	Not a randomised study
Wygoda 2006	Intervention not eligible

Characteristics of ongoing studies *[ordered by study ID]*

NCT02573324

Study name	A study of ABT-414 in subjects with newly diagnosed glioblastoma (GBM) with epidermal growth factor receptor (EGFR) amplification (INTELLANCE-1)
Methods	Phase II/III randomised, placebo controlled
Participants	640 first-line EGFR-amplified glioblastoma patients
Interventions	ABT-414 vs placebo
Outcomes	Overall survival, progression-free survival
Starting date	7 December 2015
Contact information	AbbVie Inc Study Director
Notes	

DATA AND ANALYSES

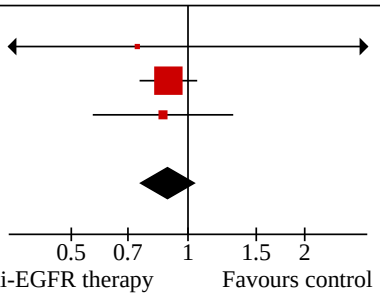
Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 First-line	3		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.76, 1.04]
1.2 Recurrent disease	4		Hazard Ratio (IV, Random, 95% CI)	0.79 [0.51, 1.21]
1.3 Sensitivity analysis low risk of bias	7		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.71, 0.93]
1.4 Sensitivity analysis for comparative and non-comparative studies	6		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.72, 1.10]
1.4.1 Comparative studies	5		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.71, 1.12]
1.4.2 Non-comparative studies	1		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.07, 7.60]
1.5 Sensitivity analysis (6 studies)	6		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.72, 1.10]

Analysis 1.1. Comparison 1: Overall survival, Outcome 1: First-line

Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Lee 2015 (1)	-0.3011	1.1885	0.5%	0.74 [0.07 , 7.60]
Weller 2017 (2)	-0.1165	0.0873	85.2%	0.89 [0.75 , 1.06]
Westphal 2015 (3)	-0.1485	0.2128	14.3%	0.86 [0.57 , 1.31]
Total (95% CI)			**100.0%**	**0.89 [0.76 , 1.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

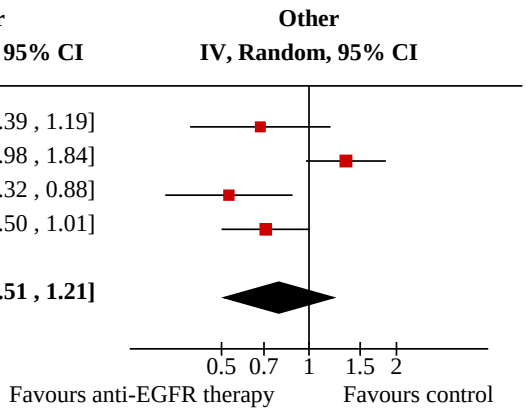


Footnotes
(1) Vandetanib vs placebo
(2) Rindopepimut vs placebo
(3) Nimotuzumab vs placebo

Analysis 1.2. Comparison 1: Overall survival, Outcome 2: Recurrent disease

Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Brown 2016 (1)	-0.3857	0.2838	21.5%	0.68 [0.39 , 1.19]
Reardon 2015 (2)	0.2927	0.1615	28.3%	1.34 [0.98 , 1.84]
Reardon 2020 (3)	-0.6349	0.2574	22.9%	0.53 [0.32 , 0.88]
van den Bent 2019 (4)	-0.3425	0.1789	27.3%	0.71 [0.50 , 1.01]
Total (95% CI)			**100.0%**	**0.79 [0.51 , 1.21]**

Heterogeneity: Tau² = 0.15; Chi² = 12.91, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable

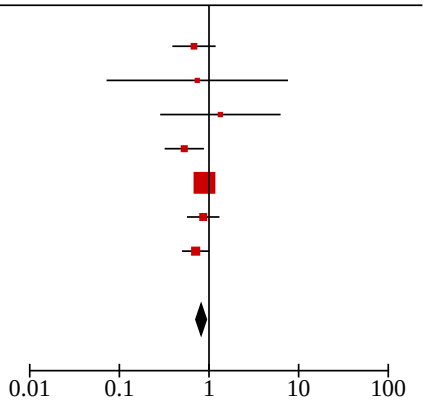


Footnotes
(1) Cediranib + Gefintib vs Cediranib
(2) Afatinib vs Afatinb and Temozolomide vs Temozolomide
(3) Rindopepimut + Bevacizumab vs Control + Bevacizumab
(4) ABT-414 + Temozolomide vs Temozolomide/Lomustine

Analysis 1.3. Comparison 1: Overall survival, Outcome 3: Sensitivity analysis low risk of bias

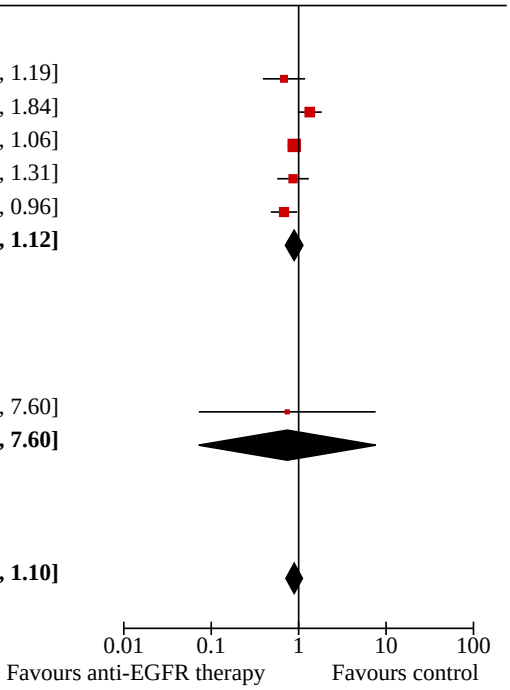
Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Brown 2016	-0.3857	0.2838	5.8%	0.68 [0.39 , 1.19]
Lee 2015	-0.3011	1.1888	0.3%	0.74 [0.07 , 7.61]
Reardon 2015	0.2927	0.789	0.7%	1.34 [0.29 , 6.29]
Reardon 2020	-0.6349	0.2574	7.0%	0.53 [0.32 , 0.88]
Weller 2017	-0.1165	0.0873	61.2%	0.89 [0.75 , 1.06]
Westphal 2015	-0.1485	0.2128	10.3%	0.86 [0.57 , 1.31]
van den Bent 2019	-0.3425	0.1789	14.6%	0.71 [0.50 , 1.01]
Total (95% CI)			**100.0%**	**0.82 [0.71 , 0.93]**

Heterogeneity: Tau² = 0.00; Chi² = 5.29, df = 6 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.96 (P = 0.003)
Test for subgroup differences: Not applicable



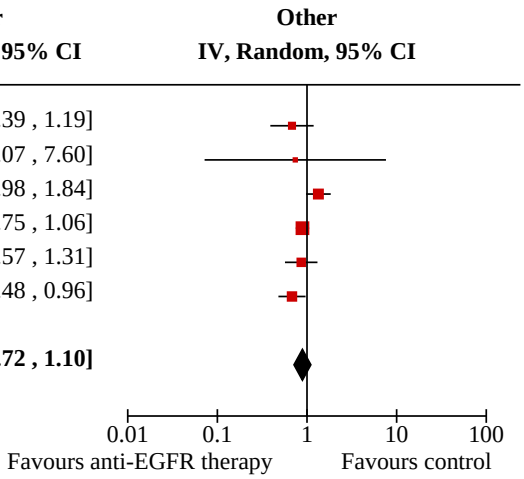
Analysis 1.4. Comparison 1: Overall survival, Outcome 4: Sensitivity analysis for comparative and non-comparative studies

Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
1.4.1 Comparative studies				
Brown 2016	-0.3857	0.2837	10.9%	0.68 [0.39 , 1.19]
Reardon 2020	0.2927	0.1615	21.3%	1.34 [0.98 , 1.84]
Weller 2017	-0.1165	0.0873	31.6%	0.89 [0.75 , 1.06]
Westphal 2015	-0.1485	0.2128	15.9%	0.86 [0.57 , 1.31]
van den Bent 2019	-0.3857	0.1777	19.4%	0.68 [0.48 , 0.96]
Subtotal (95% CI)			**99.2%**	**0.89 [0.71 , 1.12]**
Heterogeneity: Tau² = 0.04; Chi² = 9.60, df = 4 (P = 0.05); I² = 58%				
Test for overall effect: Z = 1.01 (P = 0.31)				
1.4.2 Non-comparative studies				
Lee 2015	-0.3011	1.1885	0.8%	0.74 [0.07 , 7.60]
Subtotal (95% CI)			**0.8%**	**0.74 [0.07 , 7.60]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.25 (P = 0.80)				
Total (95% CI)			**100.0%**	**0.89 [0.72 , 1.10]**
Heterogeneity: Tau² = 0.03; Chi² = 9.62, df = 5 (P = 0.09); I² = 48%				
Test for overall effect: Z = 1.07 (P = 0.29)				
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%				



Analysis 1.5. Comparison 1: Overall survival, Outcome 5: Sensitivity analysis (6 studies)

Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Brown 2016	-0.3857	0.2837	10.9%	0.68 [0.39 , 1.19]
Lee 2015	-0.3011	1.1885	0.8%	0.74 [0.07 , 7.60]
Reardon 2020	0.2927	0.1615	21.3%	1.34 [0.98 , 1.84]
Weller 2017	-0.1165	0.0873	31.6%	0.89 [0.75 , 1.06]
Westphal 2015	-0.1485	0.2128	15.9%	0.86 [0.57 , 1.31]
van den Bent 2019	-0.3857	0.1777	19.4%	0.68 [0.48 , 0.96]
Total (95% CI)			**100.0%**	**0.89 [0.72 , 1.10]**
Heterogeneity: Tau² = 0.03; Chi² = 9.62, df = 5 (P = 0.09); I² = 48%				
Test for overall effect: Z = 1.07 (P = 0.29)				
Test for subgroup differences: Not applicable				



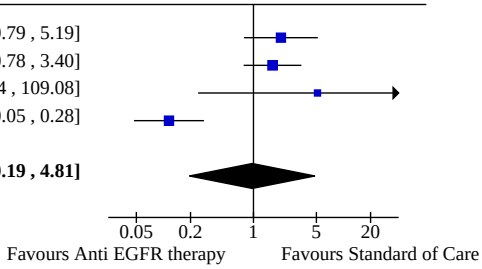
Comparison 2. Toxicities of first-line anti-EGFR therapies - grade 3 and above

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Lymphopenia	4	1146	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.19, 4.81]
2.2 Neutropenia	4	1146	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.82, 2.03]
2.3 Thrombocytopenia	4	1146	Odds Ratio (M-H, Random, 95% CI)	3.69 [0.51, 26.51]
2.4 Rash	4	1146	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.14, 12.87]
2.5 Diarrhoea	5	1218	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.07, 6.35]
2.6 Fatigue	5	1218	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.18, 4.52]

Analysis 2.1. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 1: Lymphopenia

	Experimental		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Lee 2015	30	69	8	29	28.0%	2.02 [0.79 , 5.19]	
Weller 2017	19	369	12	372	29.1%	1.63 [0.78 , 3.40]	
Westphal 2015	2	71	0	71	14.6%	5.14 [0.24 , 109.08]	
van den Bent 2019	7	88	33	77	28.3%	0.12 [0.05 , 0.28]	
Total (95% CI)		**597**		**549**	**100.0%**	**0.97 [0.19 , 4.81]**	
Total events:	58		53				

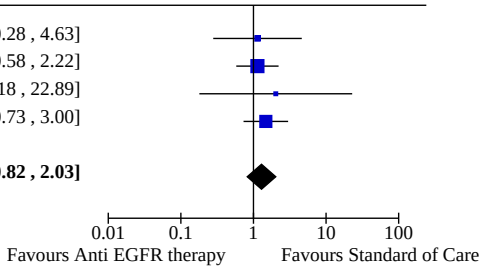
Heterogeneity: Tau² = 2.16; Chi² = 26.89, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 2: Neutropenia

	Experimental		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Lee 2015	8	69	3	29	10.3%	1.14 [0.28 , 4.63]	
Weller 2017	19	369	17	372	45.3%	1.13 [0.58 , 2.22]	
Westphal 2015	2	71	1	71	3.5%	2.03 [0.18 , 22.89]	
van den Bent 2019	26	88	17	77	40.8%	1.48 [0.73 , 3.00]	
Total (95% CI)		**597**		**549**	**100.0%**	**1.29 [0.82 , 2.03]**	
Total events:	55		38				

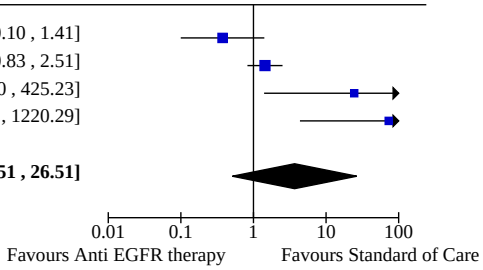
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 3: Thrombocytopenia

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lee 2015	5	69	5	29	28.7%	0.38 [0.10 , 1.41]
Weller 2017	32	369	23	372	32.1%	1.44 [0.83 , 2.51]
Westphal 2015	10	71	0	71	19.5%	24.41 [1.40 , 425.23]
van den Bent 2019	28	88	0	77	19.7%	73.02 [4.37 , 1220.29]
Total (95% CI)		**597**		**549**	**100.0%**	**3.69 [0.51 , 26.51]**
Total events:	75		28			

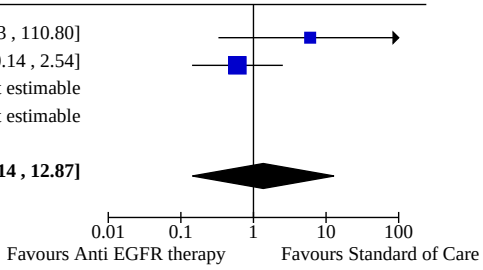
Heterogeneity: Tau² = 3.08; Chi² = 19.34, df = 3 (P = 0.0002); I² = 84%
Test for overall effect: Z = 1.30 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 4: Rash

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lee 2015	6	69	0	29	35.5%	6.04 [0.33 , 110.80]
Weller 2017	3	369	5	372	64.5%	0.60 [0.14 , 2.54]
Westphal 2015	0	71	0	71		Not estimable
van den Bent 2019	0	88	0	77		Not estimable
Total (95% CI)		**597**		**549**	**100.0%**	**1.36 [0.14 , 12.87]**
Total events:	9		5			

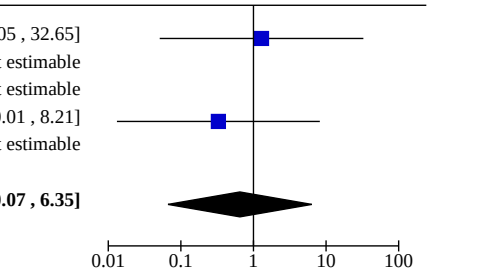
Heterogeneity: Tau² = 1.49; Chi² = 2.09, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 5: Diarrhoea

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lee 2015	1	69	0	29	49.8%	1.29 [0.05 , 32.65]
Reardon 2020	0	35	0	37		Not estimable
Weller 2017	0	369	0	372		Not estimable
Westphal 2015	0	71	1	71	50.2%	0.33 [0.01 , 8.21]
van den Bent 2019	0	88	0	77		Not estimable
Total (95% CI)		**632**		**586**	**100.0%**	**0.65 [0.07 , 6.35]**
Total events:	1		1			

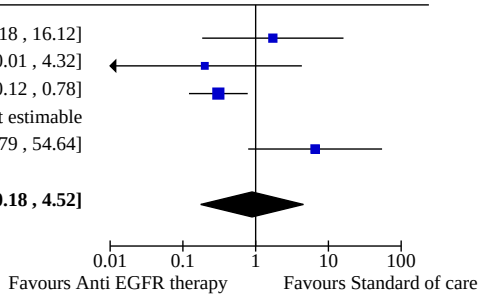
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Toxicities of first-line anti-EGFR therapies - grade 3 and above, Outcome 6: Fatigue

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lee 2015	4	69	1	29	23.1%	1.72 [0.18 , 16.12]
Reardon 2020	0	35	2	37	16.6%	0.20 [0.01 , 4.32]
Weller 2017	6	369	19	372	36.2%	0.31 [0.12 , 0.78]
Westphal 2015	0	71	0	71		Not estimable
van den Bent 2019	7	88	1	77	24.2%	6.57 [0.79 , 54.64]
Total (95% CI)		**632**		**586**	**100.0%**	**0.89 [0.18 , 4.52]**
Total events:	17		23			

Heterogeneity: Tau² = 1.67; Chi² = 8.34, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



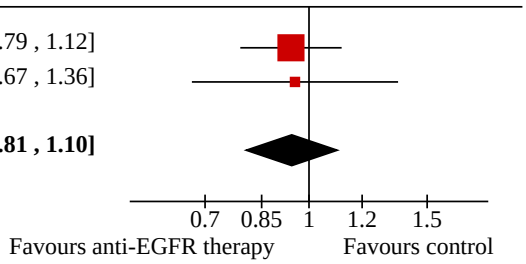
Comparison 3. Progression-free survival

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 First-line	2		Hazard Ratio (IV, Random, 95% CI)	0.94 [0.81, 1.10]
3.2 Recurrent disease	3		Hazard Ratio (IV, Random, 95% CI)	0.75 [0.58, 0.96]
3.3 Sensitivity analysis low risk of bias PFS	5		Hazard Ratio (IV, Random, 95% CI)	0.88 [0.77, 1.01]

Analysis 3.1. Comparison 3: Progression-free survival, Outcome 1: First-line

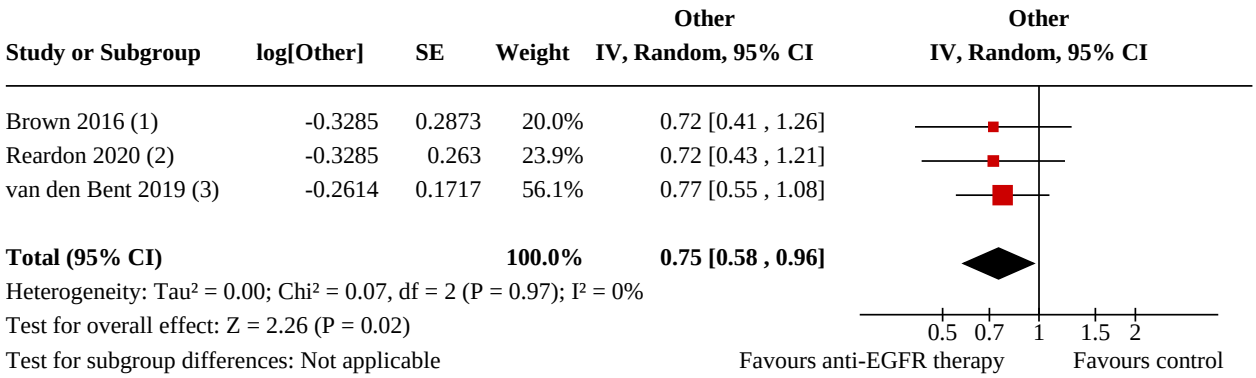
Study or Subgroup	log[Other]	SE	Weight	Other IV, Random, 95% CI
Weller 2017 (1)	-0.0619	0.0887	80.5%	0.94 [0.79 , 1.12]
Westphal 2015 (2)	-0.0481	0.1805	19.5%	0.95 [0.67 , 1.36]
Total (95% CI)			**100.0%**	**0.94 [0.81 , 1.10]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Footnotes
(1) Rindopepimut vs placebo
(2) Nimotuzumab vs placebo

Analysis 3.2. Comparison 3: Progression-free survival, Outcome 2: Recurrent disease



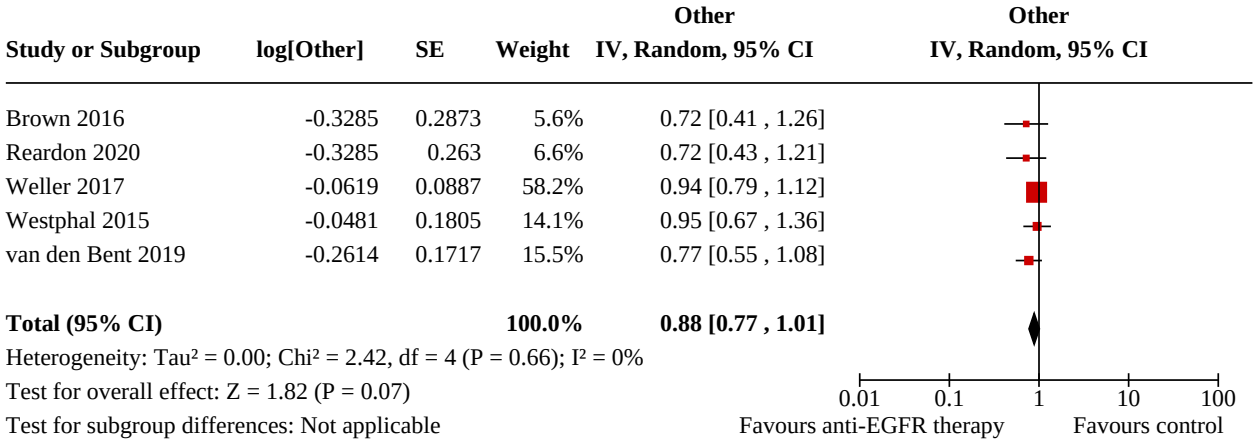
Footnotes

(1) Cediranib + Gefintib vs Cediranib

(2) Rindopepimut + Bevacizumab vs Control + Bevacizumab

(3) ABT-414 +Temozolomide vs Temozolomide/Lomustine

Analysis 3.3. Comparison 3: Progression-free survival, Outcome 3: Sensitivity analysis low risk of bias PFS



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. CENTRAL search strategy

#1 MeSH descriptor: [Glioblastoma] this term only
#2 glioblastoma* or GBM* or GB* or astrocyt*
#3 #1 or #2
#4 MeSH descriptor: [Receptor, Epidermal Growth Factor] this term only
#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*
#6 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#7 monoclonal antibod* or MAB*
#8 MeSH descriptor: [Protein Kinase Inhibitors] explode all trees
#9 tyrosin* near/5 (kinase* or inhibitor*)
#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*
#11 nilotinib* or tasigna* or AMN107* or getfitnib* or ZD1839* or iressa* or erlotinib* or imatinib* or gleevec* or glivec* or STI-571*
#12 MeSH descriptor: [Cancer Vaccines] this term only
#13 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumour* or tumor* or malignan* or antigen* or dendritic* or vector*) near/5 vaccin*
#14 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumour* or tumor* or malignan* or antigen* or dendritic* or vector*) near/5 immuno*
#15 rindopepimut* or CDX-110*
#16 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#16 #3 and #16

Appendix 2. 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. randomised controlled trial.pt.
18. controlled clinical trial.pt.
19. randomised.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 3. Embase 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

Key:
mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
sh = subject heading
ti = title

Appendix 4. Standardised data extraction form

Title
Lead Author, Senior Author
Year published
Publication
Type of study

(Continued)

Trial phase
Intervention
Control
No. of participants
First-line or recurrent disease
Type of participants
Primary outcome
Secondary outcome
Toxicity

HISTORY

Protocol first published: Issue 1, 2019
Review first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

All authors contributed to the planning and editing of the review.
AL prepared the first draft of this review; screening and searches of studies; correspondence and communication; planning of the review.
MA assisted in the preparation of drafts of the review; screening and searches for studies.
DC provided statistical support; addressed reviewers comments; and expertise on Cochrance reporting, editorial management.
MK provided editorial reviews for the review, expertise on Cochrance reporting, and statistical advice.
VH provided editorial review and supervised the planning of the review.
HW provided editorial review and supervised the planning of the review.

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 glioblastoma.
VH: none known.
HW: the analysis for this Cochrane Review is based on peer-reviewed data 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 severe adverse events. None of these activities influenced the analysis of the review data or contributed to any presented/published conclusions.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

With the advent of antibody drug conjugates, this report will include this an additional class of agents within the monoclonal antibodies group. Antibody drug conjugates are compounds based on monoclonal antibodies with a linker joining up with a cytotoxic drug (or payload). The mechanism of action is similar in principle to other monoclonal antibodies. The antibody component of antibody drug conjugates will track down their target protein; this will subsequently trigger an internalisation process in the recipient cell, absorbing and releasing the cytotoxic drug/payload inside and thus leading to cell kill. This was a new drug development that was utilised in clinical trials (phase II/III) after the initial protocol for this review was published.

Another separation from the protocol relates to the addition of a sensitivity analysis regarding comparative and non comparative studies. There was disagreement within the authorship team about comparative and non-comparative studies and the decision was to add a sensitivity analysis to confirm whether the inclusion or exclusion of Lee 2015 would alter the findings.