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## Treatment options for progression or recurrence of glioblastoma: a network meta-analysis (Review)

McBain C, Lawrie TA, Rogozińska E, Kernohan A, Robinson T, Jefferies S

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[Intervention Review]

# Treatment options for progression or recurrence of glioblastoma: a network meta-analysis

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## ABSTRACT

### Background

Glioblastoma (GBM) is a highly malignant brain tumour that almost inevitably progresses or recurs after first line standard of care. There is no consensus regarding the best treatment/s to offer people upon disease progression or recurrence. For the purposes of this review, progression and recurrence are considered as one entity.

### Objectives

To evaluate the effectiveness of further treatment/s for first and subsequent progression or recurrence of glioblastoma (GBM) among people who have received the standard of care (Stupp protocol) for primary treatment of the disease; and to prepare a brief economic commentary on the available evidence.

### Search methods

We searched MEDLINE and Embase electronic databases from 2005 to December 2019 and the Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library; Issue 12, 2019). Economic searches included the National Health Service Economic Evaluation Database (NHS EED) up to 2015 (database closure) and MEDLINE and Embase from 2015 to December 2019.

### Selection criteria

Randomised controlled trials (RCTs) and comparative non-randomised studies (NRSs) evaluating effectiveness of treatments for progressive/recurrent GBM. Eligible studies included people with progressive or recurrent GBM who had received first line radiotherapy with concomitant and adjuvant temozolomide (TMZ).

### Data collection and analysis

Two review authors independently selected studies and extracted data to a pre-designed data extraction form. We conducted network meta-analyses (NMA) and ranked treatments according to effectiveness for each outcome using the random-effects model and Stata software (version 15). We rated the certainty of evidence using the GRADE approach.

### Main results

We included 42 studies: these comprised 34 randomised controlled trials (RCTs) and 8 non-randomised studies (NRSs) involving 5236 participants. We judged most RCTs to be at a low risk of bias and NRSs at high risk of bias. Interventions included chemotherapy, re-

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operation, re-irradiation and novel therapies either used alone or in combination. For first recurrence, we included 11 interventions in the network meta-analysis (NMA) for overall survival (OS), and eight in the NMA for progression-free survival (PFS). Lomustine (LOM; also known as CCNU) was the most common comparator and was used as the reference treatment. No studies in the NMA evaluated surgery, re-irradiation, PCV (procarbazine, lomustine, vincristine), TMZ re-challenge or best supportive care. We could not perform NMA for second or later recurrence due to insufficient data. Quality-of-life data were sparse.

### First recurrence (NMA findings)

Median OS across included studies in the NMA ranged from 5.5 to 12.6 months and median progression-free survival (PFS) ranged from 1.5 months to 4.2 months. We found no high-certainty evidence that any treatments tested were better than lomustine. These treatments included the following.

*Bevacizumab plus lomustine:* Evidence suggested probably little or no difference in OS between bevacizumab (BEV) combined with lomustine (LOM) and LOM monotherapy (hazard ratio (HR) 0.91, 0.75 to 1.10; moderate-certainty evidence), although BEV + LOM may improve PFS (HR 0.57, 95% confidence interval (CI) 0.44 to 0.74; low-certainty evidence).

*Bevacizumab monotherapy:* Low-certainty evidence suggested there may be little or no difference in OS (HR 1.22, 95% CI 0.84 to 1.76) and PFS (HR 0.90, 95% CI 0.58 to 1.38; low-certainty evidence) between BEV and LOM monotherapies; more evidence on BEV is needed.

*Regorafenib (REG):* REG may improve OS compared with LOM (HR 0.50, 95% CI 0.33 to 0.76; low-certainty evidence). Evidence on PFS was very low certainty and more evidence on REG is needed.

*Temozolomide (TMZ) plus Depatux-M (ABT414):* For OS, low-certainty evidence suggested that TMZ plus ABT414 may be more effective than LOM (HR 0.66, 95% CI 0.47 to 0.92) and may be more effective than BEV (HR 0.54, 95% CI 0.33 to 0.89; low-certainty evidence). This may be due to the TMZ component only and more evidence is needed.

*Fotemustine (FOM):* FOM and LOM may have similar effects on OS (HR 0.89, 95% CI 0.51 to 1.57, low-certainty evidence).

*Bevacizumab and irinotecan (IRI):* Evidence on BEV + irinotecan (IRI) versus LOM for both OS and PFS is very uncertain and there is probably little or no difference between BEV + IRI versus BEV monotherapy (OS: HR 0.95, 95% CI 0.70 to 1.30; moderate-certainty evidence).

When treatments were ranked for OS, FOM ranked first, BEV + LOM second, LOM third, BEV + IRI fourth, and BEV fifth. Ranking does not take into account the certainty of the evidence, which also suggests there may be little or no difference between FOM and LOM.

### Other treatments

Three studies evaluated re-operation versus no re-operation, with or without re-irradiation and chemotherapy, and these suggested possible survival advantages with re-operation within the context of being able to select suitable candidates for re-operation. A cannabinoid treatment in the early stages of evaluation, in combination with TMZ, merits further evaluation.

### Second or later recurrence

Limited evidence from three heterogeneous studies suggested that radiotherapy with or without BEV may have a beneficial effect on survival but more evidence is needed. Evidence was insufficient to draw conclusions about the best radiotherapy dosage. Other evidence suggested that there may be little difference in survival with tumour-treating fields compared with physician's best choice of treatment. We found no reliable evidence on best supportive care.

### Severe adverse events (SAEs)

The BEV+LOM combination was associated with significantly greater risk of SAEs than LOM monotherapy (RR 2.51, 95% CI 1.72 to 3.66, high-certainty evidence), and ranked joint worst with cediranib + LOM (RR 2.51, 95% CI 1.29 to 4.90; high-certainty evidence). LOM ranked best and REG ranked second best. Adding novel treatments to BEV was generally associated with a higher risk of severe adverse events compared with BEV alone.

### Authors' conclusions

For treatment of first recurrence of GBM, among people previously treated with surgery and standard chemoradiotherapy, the combination treatments evaluated did not improve overall survival compared with LOM monotherapy and were often associated with a higher risk of severe adverse events. Limited evidence suggested that re-operation with or without re-irradiation and chemotherapy may be suitable for selected candidates. Evidence on second recurrence is sparse. Re-irradiation with or without bevacizumab may be of value in selected individuals, but more evidence is needed.

## PLAIN LANGUAGE SUMMARY

### Treatment options for people with recurrent and progressive glioblastoma

## Why this is important

Glioblastoma multiforme (GBM) is a very aggressive type of brain tumour. Even after treatment involving surgery, radiotherapy and chemotherapy the tumour may continue growing (progress) and almost always comes back (recurs). In this review, we consider progression and recurrence as one entity. A number of different treatments have been tested, but there has been no agreement about the best treatment/s to offer when someone's tumour progresses or recurs.

## Objectives

To evaluate which are the most effective treatments for people with progressive or recurrent GBM who have already received surgery, radiotherapy and chemotherapy. We looked at effectiveness in terms of length of overall survival (OS), survival without disease progression (progression free survival, PFS), serious side effects, and whether treatments affected quality of life. We looked at treatments given when the disease first progressed or recurred (first recurrence) and when it came back again after that (second or subsequent recurrences).

## Methods

We searched for relevant research studies comparing the effectiveness of different treatments for recurrent GBM. We used network meta-analysis (NMA) to compare different treatments. NMA is a statistical method that allows different treatments to be looked at together to decide which is best. This method allows different treatments to be ranked according to their effectiveness, even if treatments have not been directly compared with each other in research studies.

## Main results

We included 42 studies (34 randomised controlled trials (RCTs) and 8 non-randomised studies) involving 5236 people. Interventions included chemotherapy, re-operation, re-irradiation and newly developed treatments either used alone or in combination. NMA could not be performed for second or later recurrence due to insufficient data.

### *Survival outcomes for people with a first recurrence*

We found no good evidence that any of the treatments tested were better than lomustine (also known as CCNU). Adding bevacizumab to lomustine (BEV + LOM) did not improve overall survival compared with lomustine alone. Other chemotherapy and novel agents either did not work, or the evidence on them was uncertain. Unfortunately, we did not find any studies on several commonly used treatments, such as PCV (procarbazine, CCNU, vincristine) and TMZ re-challenge, to include.

Limited evidence suggested that a second operation with or without other treatments may have survival advantages for some individuals with a first recurrence. A small study of a cannabinoid treatment suggests this merits further investigation.

### *Survival outcomes for people with a second or later recurrence*

For second or later recurrence, insufficient evidence meant that we were not able to carry out statistical analysis. Findings suggested that radiotherapy with or without BEV may have some survival advantages but this evidence is uncertain. We found no reliable evidence on best supportive care.

### *Serious adverse events (SAEs) from treatment*

Most treatments caused some serious side effects (SAEs). The BEV + LOM combination was associated with a significantly greater risk of SAEs than lomustine alone. In general, adding treatments to bevacizumab was associated with more SAEs compared with BEV alone.

## Authors' conclusions

For treatment of first recurrence of GBM, lomustine appears the most effective chemotherapy treatment and other combination therapies tested had a higher risk of serious side effects. A second operation or radiotherapy, or both, may be of value in selected individuals. For second recurrence, radiotherapy with or without bevacizumab may have a role but more evidence is needed. Several commonly used treatments were not evaluated, such as PCV (lomustine plus procarbazine and vincristine) and temozolomide re-challenge. More research is needed.

## SUMMARY OF FINDINGS

### Summary of findings 1. Summary of overall survival findings

**Estimates of effects, certainty assessment and rankings of different treatment options compared with lomustine on overall survival in people with first recurrence of glioblastoma**

**Patient or population:** people with first recurrence of glioblastoma

**Interventions:** bevacizumab (BEV), BEV + lomustine (LOM), regorafenib (REG), fotemustine (FOM), ABT414 + temozolomide (TMZ); BEV + irinotecan (IRI), BEV + onartuzumab (ONA), cediranib (CED), CED + LOM

**Comparison:** lomustine

**Outcome:** overall survival

All intervention options	Relative effect and 95% CI (network estimate) **	Certainty of the evidence (GRADE)	Ranking*
<b>(9 RCTs; 1734 participants in total)*</b>			
LOM (5 RCTs; 403 participants)	Reference comparator	Reference comparator	5.9
REG (1 RCT; 59 participants)	<b>HR 0.50 (0.33 to 0.76)</b>	⊕⊕⊕⊕ <b>low<sup>1</sup></b>	1.3
Depatux-M (ABT414) + TMZ (1 RCT; 88 participants)	<b>HR 0.66 (0.47 to 0.92)</b>	⊕⊕⊕⊕ <b>moderate<sup>2</sup></b>	2.1
BEV + LOM (3 RCTs, 401 participants)	<b>HR 0.91 (0.75 to 1.10)</b>	⊕⊕⊕⊕ <b>moderate<sup>4</sup></b>	4.4
FOM (1 RCT; 32 participants)	<b>HR 0.89 (0.51 to 1.57)</b>	⊕⊕⊕⊕ <b>low<sup>3</sup></b>	4.6
ABT414(Depatux-M) (1 RCT; 86 participants)	<b>HR 0.96 (0.69 to 1.34)</b>	⊕⊕⊕⊕ <b>low<sup>4,6</sup></b>	5.4
CED + LOM (1 RCT, 129 participants)	<b>HR 1.15 (0.76 to 1.74)</b>	⊕⊕⊕⊕ <b>moderate<sup>4</sup></b>	7.2
BEV + IRI (1 RCT; 82 participants)	<b>HR 1.16 (0.71 to 1.88)</b>	⊕⊕⊕⊕ <b>very low<sup>4,5</sup></b>	7.4
BEV (4 RCTs; 259 participants)	<b>HR 1.22 (0.84 to 1.76)</b>	⊕⊕⊕⊕ <b>low<sup>4,6</sup></b>	8.1
CED (1 RCT 131 participants)	<b>HR 1.43 (0.97 to 2.12)</b>	⊕⊕⊕⊕ <b>moderate<sup>4</sup></b>	9.5
BEV + ONA	<b>HR 1.76 (0.94 to 3.30)</b>	⊕⊕⊕⊕	10.3

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(1 RCT, 64 participants)

very low<sup>4</sup>

Estimates are reported as HR: Hazard Ratio. CI: confidence interval.

\*This refers to the number of studies in the network evaluating the given intervention and the number of participants involved in these studies.

GRADE Working Group grades of evidence

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

\*We excluded REG and ABT414 on sensitivity analysis, which ranked FOM first, BEV + LOM second, LOM third, BEV+irinotecan (IRI) fourth, and BEV fifth.

- <sup>1</sup> Downgraded –2 as sparse data from single small open-label study
- <sup>2</sup> Downgraded for intransitivity (~ 30% of control arm received TMZ not LOM)
- <sup>3</sup> Downgraded for imprecision and sparse data from single small study
- <sup>4</sup> Imprecision
- <sup>5</sup> No direct evidence and HR for direct effect was estimated from trial report
- <sup>6</sup> Risk of bias

## Summary of findings 2. Summary of progression-free survival findings

### Estimates of effects, certainty assessment and rankings of different treatment options compared with lomustine on overall survival in people with first recurrence of glioblastoma

**Patient or population:** people with first recurrence of glioblastoma

**Interventions:** bevacizumab (BEV), BEV + lomustine (LOM), regorafenib (REG), BEV + irinotecan (IRI), BEV + onartuzumab (ONA), cediranib (CED), CED+LOM

**Comparison:** lomustine

**Outcome:** Progression-free survival

All intervention options	Relative effect and 95% CI (network estimate) **	Certainty of the evidence (GRADE)	Ranking*
<b>(7 RCTs; 1383 participants in total)*</b>			
LOM (4 RCTs; 317 participants)	Reference comparator	Reference comparator	6.2
BEV+LOM (3 RCTs, 401 participants)	<b>HR 0.57 (0.44 to 0.74)</b>	⊕⊕⊕⊕ <b>low<sup>1,4</sup></b>	1.6
REG (1 RCT; 59 participants)	<b>HR 0.65 (0.42 to 1.01)</b>	⊕⊕⊕⊕ <b>very low<sup>1,2</sup></b>	2.7
CED + LOM (1 RCT, 129 participants)	<b>HR 0.76 (0.50 to 1.18)</b>	⊕⊕⊕⊕ <b>moderate<sup>2</sup></b>	3.8
BEV+IRI	<b>HR 0.80 (0.44 to 1.45)</b>	⊕⊕⊕⊕	4.2

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(1 RCT; 82 participants)		<b>very low<sup>1,3</sup></b>	
BEV (4 RCTs; 200 participants)	<b>HR 0.90 (0.58 to 1.38)</b>	⊕⊕⊕⊕ <b>low<sup>2,4</sup></b>	5.2
BEV + ONA (1 RCT, 64 participants)	<b>HR 0.98 (0.51 to 1.87)</b>	⊕⊕⊕⊕ <b>very low<sup>1,4</sup></b>	5.8
CED (1 RCT 131 participants)	<b>HR 1.05 (0.68 to 1.62)</b>	⊕⊕⊕⊕ <b>moderate<sup>2</sup></b>	6.4
Estimates are reported as HR: Hazard Ratio. CI: confidence interval.			

\*This refers to the number of studies in the network evaluating the given intervention and the number of participants involved in these studies.

GRADE Working Group grades of evidence

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

\*We excluded REG on sensitivity analysis, which ranked FOM first, BEV + LOM second, LOM third, BEV+irinotecan (IRI) fourth, and BEV fifth.

<sup>1</sup> Sparse data from single small open-label study

<sup>2</sup> Imprecision

<sup>3</sup> HRs for direct effect estimated from trial report

<sup>4</sup> Risk of bias

### Summary of findings 3. Summary of findings for severe adverse events - 1

**Estimates of effects, certainty assessment and rankings of different treatment options compared with lomustine for severe adverse events in people with any recurrence of glioblastoma**

**Patient or population:** people with any recurrence of glioblastoma

**Interventions:** bevacizumab (BEV) + lomustine (LOM), regorafenib (REG), cediranib (CED), CED + LOM, CED + gefitinib (GET)

**Comparison:** lomustine

**Outcome:** severe adverse events

Outcomes (5 RCTs, 1024 participants)	Illustrative comparative risks* (95% CI)**	Relative effect (95% CI)	Quality of the evidence (GRADE)	Ranking
	Corresponding risk			
LOM (5 RCTs; 330 participants)	39 per 100*	Reference comparator	N/A	1.7
CED (2 RCTs; 147 participants)	39 per 100 (21 to 72)	RR 1.00 (0.54 to 1.85)	⊕⊕⊕⊕ <b>moderate<sup>1</sup></b>	1.7



REG (1 RCT; 59 participants)	74 per 100 (36 to 100)	RR 1.90 (0.92 to 3.95)	⊕⊕⊕⊕ <b>low<sup>1,2</sup></b>	3.8
CED + GET (1 RCT; 19 participants)	96 per 100 (18 to 100)	RR 2.46 (0.46 to 13.26)	⊕⊕⊕⊕ <b>very low<sup>1,3</sup></b>	4.3
BEV+ LOM (2 RCTs, 346 participants)	98 per 100 (67 to 100)	RR 2.51 (1.72 to 3.66)	⊕⊕⊕⊕ <b>high</b>	4.7
CED + LOM (1 RCT, 123 participants)	98 per 100 (50 to 100)	RR 2.51 (1.29 to 4.90)	⊕⊕⊕⊕ <b>high</b>	4.7

\*The basis for this **risk** is the mean risk of SAEs with lomustine across the 5 studies that evaluated lomustine. The **corresponding risk** (and its 95% confidence interval) is based on this risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

\*\* Where the CI exceeded 100 values were truncated (at 100)

**CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>1</sup> Downgraded -1 for imprecision

<sup>2</sup> Sparse data from single small open label trial

<sup>3</sup> Downgraded -2 for imprecision

#### Summary of findings 4. Summary of findings for severe adverse events - 2

**Patient or population:** people with any recurrence of glioblastoma

**Interventions:** bevacizumab (BEV)

**Comparison:** bevacizumab 9BEV, BEV+carboplatin (CAB), BEV+dasatinib (DAS), BEV+irinotecan (IRI), BEV+onartuzumab (ONA), BEV+TRC105, BEV+VB111, Fotemustine (FOM), BEV+HSPPC96 vaccine

**Outcome:** severe adverse events

Outcomes (5 RCTs, 1024 participants)	Illustrative comparative risks* (95% CI)**	Relative effect (95% CI)	Quality of the evidence (GRADE)	Ranking
	Corresponding risk			
BEV (8 RCTs; 498 participants)	36 per 100*	Reference comparator	N/A	3.1
FOM (1 RCT, 32 participants)	16 per 100 (4 to 62)	RR 0.44 (0.11 to 1.72)	??? (missing)	1.6

BEV+HSPPC96 (1 RCT; 53 participants)	36 per 100 (12 to 100)	RR 1.01 (0.33 to 3.10)	⊕⊕⊕⊕ <b>low<sup>1</sup></b>	3.4
BEV+ONA (1 RCT; 64 participants)	42 per 100 (21 to 86)	RR 1.17 (0.57 to 2.39)	⊕⊕⊕⊕ <b>low<sup>1</sup></b>	4.0
BEV+CAB (1 RCT; 58 participants)	46 per 100 (22 to 96)	RR 1.27 (0.61 to 2.66)	⊕⊕⊕⊕ <b>low<sup>1</sup></b>	4.4
BEV+DAS (2 RCTs, 83 participants)	19 per 100 (25 to 100)	RR 0.52 (0.69 to 3.34)	⊕⊕⊕⊕ <b>high</b>	5.1
BEV+HRI (1 RCT, 79 participants)	80 per 100 (43 to 100)	RR 2.22 (1.19 to 4.18)	⊕⊕⊕⊕ <b>high</b>	6.5
BEV+VB111 (1 RCT, 128 participants)	> 100 (92 to 100)	RR 3.77 (2.25 to 6.33)	⊕⊕⊕⊕ <b>high</b>	8.0
BEV+TRC 105 (1 RCT, 49 participants)	> 100 (92 to 100)	RR 6.86 (2.55 to 18.41)	⊕⊕⊕⊕ <b>high</b>	8.8

\*The basis for this **risk** is the mean risk of SAEs with lomustine across the 5 studies that evaluated lomustine. The **corresponding risk** (and its 95% CI) is based on this risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

\*\* Where the corresponding risk value and, or CI exceeded 100 values were truncated (at 100)

**CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

## BACKGROUND

### Description of the condition

Gliomas are brain tumours that develop from supporting tissue of the brain known as glial cells. The most common and most malignant type of glioma is glioblastoma (GBM). The standard of care (Stupp protocol) for treating GBM in the first instance is surgery (maximal safe resection, which could be biopsy, debulking or resection depending on the tumour's anatomical location) to remove as much of the tumour as possible, followed by radiotherapy (60 Gy in 30 fractions) and chemotherapy (concurrent and adjuvant temozolomide) (NCCN 2018). This initial treatment takes approximately nine months to complete. Chemoradiotherapy has been associated with a median progression-free survival of 6.5 months and a median overall survival of 14.6 months among reasonably fit people less than 70 years old (Stupp 2005). Approximately 25% of people receiving chemoradiotherapy are likely to be alive two years after diagnosis compared with approximately 10% who receive radiotherapy alone (Stupp 2005). With little improvement in five-year survival rates over the last 40 years, approximately 12% of people are alive five years after diagnosis (CRUK 2020).

Younger people respond better to first-line treatment than older people, and those with O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation respond better to temozolomide than those with MGMT-unmethylated status (Malmstrom 2012; Wick 2012). Amongst fitter elderly patients treated with chemoradiotherapy (using a shorter, 3-week RT regime), MGMT-methylated status confers a survival advantage, with a median survival of 13.5 months reported for this subgroup in a recent trial (Perry 2017). When GBM is diagnosed among patients who have had lower-grade gliomas initially treated with radiotherapy only, they are generally treated with temozolomide after surgical confirmation of recurrence as GBM. Not all people receive radiotherapy or chemotherapy (or both) after surgery, however, and best supportive care (palliative care) may be the preferred option, particularly for elderly people and those with poor performance status (NCCN 2018).

After the initial treatment phase, guidelines issued by the National Institute for Health and Care Excellence (NICE) suggest that routine follow-up by magnetic resonance imaging (MRI) be performed at three- to six-month intervals for the first two years, six- to 12-monthly until five years, and then annually thereafter (NICE 2018). Some tumours that are GBM to start with, after an initial response to treatment or stability in growth, can recur and grow. In some cases of GBM, there is no period of response or stability and they continue to grow. Lower-grade tumours (e.g. WHO Grade II or Grade III) can progress to GBM after many years of stability. In all cases, the continued growth is considered 'tumour progression'. Continued GBM growth or recurrence may be detected by these regular surveillance scans or identified upon the development of new symptoms (Thompson 2019). Making a diagnosis of GBM progression or recurrence can, however, be complicated in the first few months after initial treatment by the fact that its appearance on MRI may be indistinguishable from pseudoprogression (NCCN 2018).

As treatment of GBM is not curative, most people who respond to radiotherapy and temozolomide chemotherapy, in combination or sequentially, will experience a recurrence of the disease at

some point thereafter, which is usually in the form of local tumour progression (Thon 2013). Following recurrence after chemoradiotherapy, a proportion of people will go on to receive further treatment; however, elderly and frail people are likely to receive best supportive care only.

### Description of the intervention

Treatment options for recurrent GBM include the following.

#### Chemotherapy

This is the most common approach to treating recurrent disease (Thon 2013). The most commonly used chemotherapy regimes are either lomustine (CCNU) given as a single agent or given in combination with procarbazine and vincristine in the regime known as PCV or re-challenge with temozolomide (NICE 2018; Niyazi 2011). In a chemotherapy-naïve population (i.e. populations that have not received the Stupp protocol) with a first recurrence, single-agent temozolomide and PCV has been shown to have a similar effect on survival, with a median post-recurrence survival of approximately seven months (Brada 2010; Parasramka 2017).

#### Re-operation

A second surgical resection at recurrence may be possible in up to a quarter of people with recurrent disease depending on the infiltrative nature of the recurrence (Mandl 2008; Niyazi 2011). This also gives the opportunity for molecular analysis, which is helpful in guiding further treatment.

#### Re-irradiation

Re-irradiation in the context of recurrent GBM is usually given as hypofractionated radiotherapy, where the required dose is divided into a number of fractions for larger tumour volumes, with or without chemotherapy (concurrently or adjuvantly, or both), but may also be given as a single high-fraction dose for small tumour volumes (stereotactic radiosurgery (SRS); Chapman 2019; Niyazi 2011).

#### Novel agents

There are several novel treatments for GBM recurrence that have been evaluated or are undergoing evaluation in clinical trials but none have been introduced into routine clinical practice. These include anti-angiogenic therapy, local drug delivery, targeted molecular therapy, vaccines, and electric field therapy (tumour-treating fields). The most intensively investigated of these alternatives is the anti-angiogenic agent, bevacizumab. While this agent is currently licensed for use in the USA for treatment of recurrent GBM (Thon 2013), a 2018 review of anti-angiogenic agents for GBM concluded that there was insufficient evidence to support the use of bevacizumab in recurrent disease (Ameratunga 2018).

#### Best supportive care

Best supportive (palliative) care only is considered a valid alternative to active treatment of recurrent GBM (Easaw 2011; NICE 2018). The Multinational Association for Supportive Care in Cancer defines supportive care as "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience, from diagnosis through anti-cancer treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention,

survivorship and end of life care are integral to supportive care” (MASCC 2019). People with GBM experience deteriorating neurological function as well as cancer effects; therefore supportive (palliative) care to improve quality of life and mitigate these effects has an important role to play in the management of this disease from an early stage (EANO 2017).

### How the intervention might work

The mechanism of action of the alkylating chemotherapy agents (e.g. temozolomide, nitrosoureas, procarbazine, carboplatin) is to interfere with DNA synthesis by causing cross-linkage between the strands and DNA breakage, thereby preventing tumour cell division (Drugs.com). Repeated surgical resection aims to reduce the tumour bulk and may only be effective if followed by chemotherapy or radiotherapy (Mandl 2008). Local re-irradiation aims to deliver targeted radiotherapy to the tumour whilst sparing the surrounding normal tissue (Kim 2019; Niyazi 2011). Bevacizumab, the most common targeted therapy, is a monoclonal antibody that binds to and inhibits vascular endothelial growth factor, interfering with tumour blood supply and inhibiting vessel proliferation (Niyazi 2011). Supportive care in the context of GBM commonly includes the treatment of seizures, steroids (e.g. dexamethasone) to control brain oedema, neurocognitive dysfunction, nausea, and venous thromboembolism (Batchelor 2006).

### Why it is important to do this review

There is a general acceptance that the two most effective treatment modalities in GBM are radiotherapy and temozolomide. However, there is no consensus on how to use these and other modalities after initial, first line GBM treatment. The 2015 James Lind Alliance research prioritisation-setting process highlighted the need for more research guidance on GBM treatment after second recurrence (JLA 2015). In particular, a better understanding of the balance between desirable and undesirable effects associated with active treatment of recurrent GBM is necessary.

There are also significant resource implications associated with the management of GBM. A review by Messali 2014 found that the reported costs of managing GBM ranged from USD 4755 to USD 195,773 across five cost-of-illness studies (US dollar (USD) 2013). A greater understanding of the optimum management strategies for GBM will aid in the allocation of future healthcare resources in the most efficient way to maximise patient health. The aim of this review is therefore to identify and evaluate the best evidence on first and subsequent treatment options for when GBM recurs. This should inform conversations between people affected and health professionals, and the effective use of healthcare resources.

### OBJECTIVES

To evaluate the effectiveness of further treatment/s for first and subsequent progression or recurrence of glioblastoma (GBM) among people who have received the standard of care (Stupp protocol) for primary treatment of the disease; and to prepare a brief economic commentary on the available evidence.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs), quasi-randomised trials, non-randomised studies, and controlled before-and-after studies that included relevant concurrent comparison groups. We did not expect to find cluster-randomised trials. In view of the non-stable nature of the conditions under review we did not include studies using cross-over designs, nor did we include case-control studies, or studies without a control group. As many novel interventions evaluated in this field are abandoned after early phase I/II studies due to futility, studies had to include a minimum of 20 participants. We excluded dose-finding studies.

#### Types of participants

People aged 16 years of age and older diagnosed with recurrent or progressive disease following primary treatment (surgery and chemoradiotherapy) for glioblastoma (GBM). This included participants whose GBM continued to grow despite standard therapy and those whose disease was initially controlled by standard therapy but which subsequently recurred. Clinical trials included participants with either/both progressive or recurrent disease; definitions were determined by study investigators. For the purposes of this review, these are therefore considered as one entity. Where studies included mixed primary treatments, they were included if at least 80% of participants had received chemoradiotherapy using the standard 6-week ‘Stupp protocol’. Participants with first and subsequent recurrences were included. Where studies included participants with grades 3 and 4 gliomas, we included them if data were reported separately for the GBM subgroup or if at least 80% of the sample had grade 4 gliomas.

#### Types of interventions

Any active treatment (chemotherapy, radiotherapy, surgery or another experimental treatment) or treatment combination compared with another active treatment, best supportive (palliative) care or no active treatment.

#### Types of outcome measures

##### Primary outcomes

- Overall survival: survival from study entry until death from all causes, or as reported by investigators
- Health-related quality of life (QoL): as measured using a standardised questionnaire, e.g. the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or QLQ-BN20 (specific for brain cancer), or the Functional Assessment of Cancer Therapy scale (FACT-G (general) or FACT-Br (specific for brain cancer))

##### Secondary outcomes

- Progression-free survival (survival from study entry to disease relapse, or as defined by investigators)
- Severe adverse events (grade 3 or higher according to a standardised measurement tool, such as the Common Terminology Criteria for Adverse Events (CTCAE))

## Search methods for identification of studies

### Electronic searches

For evidence on the effectiveness of interventions, we prepared the search strategies and conducted the searches of the following databases from January 2005 (the threshold for the start of the current standard of care, namely maximal surgical resection followed by chemoradiotherapy) onwards ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)).

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12), in the Cochrane Library
- MEDLINE via Ovid (2005 to December week 1 2019)
- Embase via Ovid (2005 to 2019 week 50)

For economic evidence, we searched the NHS EED database from January 2005 up to the end of December 2014 (when the last records were added to that database); and MEDLINE and Embase from 1 January 2015 to 16 December 2019, as NHS EED already included comprehensive searches of these databases prior to 2015. We also considered relevant grey literature — such as health technology assessments, reports and working papers — for inclusion.

We did not apply language restrictions to any of the searches.

### Searching other resources

Study authors searched the following for ongoing trials.

- [ClinicalTrials.gov](#)
- International Clinical Trials Registry Platform (ICTRP) ([apps.who.int/trialsearch](https://apps.who.int/trialsearch))

We handsearched the reference lists of included studies to identify newly published articles and additional studies of relevance. We searched neuro-oncology conference abstracts from 2014 onwards.

## Data collection and analysis

### Selection of studies

The Information Specialist at the Gynaecological, Neuro-oncology and Orphan Cancer Group (GNOC) downloaded all titles and abstracts retrieved by electronic searching to EndNote® and removed duplicates and those studies that clearly did not meet the inclusion criteria. A minimum of two reviewers (TL, ER, IL) independently screened the search results, rejecting all clearly irrelevant records and categorising the remaining articles into included studies, excluded studies, ongoing studies and studies awaiting classification. We recorded reasons for exclusion and identified any articles that related to the same study and grouped them. We obtained the full text of potentially eligible articles. We resolved any disagreements about eligibility by discussion with the other review authors.

### Data extraction and management

Two reviewers (TL, ER, IL) independently extracted data, including the following items, from eligible studies using a piloted data extraction form.

- Author contact details
- Country

- Setting
- Dates of participant accrual
- Trial registration number/identification
- Funding source
- Declarations of interest
- Participant inclusion and exclusion criteria
- Study design and methodology
- Study population and baseline characteristics
  - \* Number of participants enrolled/analysed
  - \* Age
  - \* Gender
  - \* Performance status
  - \* MGMT-methylation status
  - \* Type of primary surgery (biopsy or resection)
  - \* Details of initial treatment
  - \* Details of treatment of first recurrence
  - \* Time from initial diagnosis
- Intervention details
  - \* Description of intervention
  - \* Description of comparator
- Primary outcome/s of the study
- Risk of study bias (see below)
- Review outcomes
  - \* For time-to-event data (survival and disease progression), we extracted the log of the hazard ratio (log(HR)) and its standard error from trial reports. Where they were not explicitly reported, we estimated them from Kaplan-Meier plots where possible.
  - \* For dichotomous outcomes, we recorded the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed.
  - \* For continuous outcomes, we recorded the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time point in each group. We also recorded change-from-baseline score data where reported and noted the type of scale used.

We extracted both unadjusted and adjusted statistics where reported. Where possible, we extracted data to allow an intention-to-treat analysis, in which we analysed participants in the groups to which they were assigned. We resolved any differences between reviewers by discussion or by appeal to the other review authors.

### Assessment of risk of bias in included studies

For randomised trials, we assessed risk of bias using Cochrane's tool and the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019](#)). This included assessment of:

- random sequence generation;
- allocation concealment;
- blinding of participants and healthcare providers;
- blinding of outcome assessors;
- incomplete outcome data (we considered more than 20% missing data to be high risk);
- selective reporting of outcomes;

- other possible sources of bias, e.g. lack of a power calculation, baseline differences in group characteristics.

For non-randomised studies we used the ROBINS-I tool for assessing risk of bias (Sterne 2016). This included assessment of:

- bias due to confounding (e.g. baseline differences in prognostic factors, or post-baseline prognostic factor differences, or switching interventions);
- bias due to participant selection (both intervention and comparison groups should comprise the same representative group);
- bias in classification of interventions (e.g. differential misclassification of intervention status that is related to the outcome or the risk of the outcome);
- bias due to deviations from intended interventions;
- bias due to missing data (e.g. differential loss to follow-up that is affected by prognostic factors);
- bias due to outcome measures (e.g. outcome assessors were aware of intervention status, different methods were used to assess the outcome, or measurement errors were related to intervention status or effects);
- bias in selection of the reported result.

Two review authors (TL, TD, ER) assessed risk of bias independently and resolved differences by discussion. We summarised judgements in 'Risk of bias' tables along with the characteristics of the included studies. We include both a risk of bias graph and a risk of bias summary. We considered the 'Risk of bias' assessment in our interpretation of the evidence.

### Measures of treatment effect

We used the following measures to evaluate treatment effect.

- For time-to-event data (e.g. death or disease progression) we used the hazard ratio (HR) with 95% confidence intervals (CIs).
- For dichotomous outcomes, we calculated the effect size as a risk ratio (RR) with its 95% CIs.
- For continuous outcomes measured using the same scale, we reported the mean difference (MD) between treatment groups with 95% CIs. For continuous outcomes (e.g. QoL scores) in which different measurement scales had been used, or if studies report change-from-baseline instead of final values, we combined these data using the (unstandardised) mean difference method in Review Manager 5 (RevMan 5) (Review Manager 2014).

### Network structure

Where possible, we aimed to compare and rank the following types of interventions.

- Different chemotherapy agents and regimens (temozolomide, PCV, lomustine/CCNU, etc.)
- Targeted antiangiogenic agents (e.g. bevacizumab) and other anti-growth-factor agents
- Other immunotherapy, e.g. tumour-derived vaccines, viral therapy
- Re-operation
- Re-irradiation
- Tumour-treating fields

- Supportive care

### Unit of analysis issues

Two review authors (TL and ER) reviewed any unit-of-analysis issues according to Higgins 2019 for each included study and we resolved any differences through discussion. We considered issues such as where there are multiple observations for the same outcome, e.g. repeated measurements with different scales, or outcomes measured at different time points to those stipulated in the review protocol.

### Multi-arm trials

For multi-arm trials, we treated the multiple comparisons as independent in pairwise meta-analyses. In the network meta-analysis, we accounted for the correlation between the effect sizes derived from the same study.

### Dealing with missing data

We did not impute missing data. Where missing data were substantial, we took this into consideration in our grading of the evidence.

### Assessment of heterogeneity

#### Assessment of clinical and methodological heterogeneity

We assessed clinical heterogeneity between studies by comparing the studies' characteristics of included participants, and interventions in each meta-analysis of each comparison; by visual inspection of forest plots; by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003); and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated it and reported the possible reasons for it.

#### Assessment of consistency across treatment comparisons

We examined the assumption of consistency by assessing the distribution of potential effect modifiers across the pair-wise comparisons. The assumption held if the following were true.

- The common treatment used to compare different interventions indirectly is similar when it appears in different trials.
- All pairwise comparisons do not differ with respect to the distribution of effect modifiers.

The potential treatment modifiers are as follows.

- Re-operation
- MGMT-methylation status
- First or subsequent recurrence
- Time from primary diagnosis

### Assessment of statistical heterogeneity and inconsistency

#### Assumptions when estimating the heterogeneity

We estimated heterogeneity indicators for each pairwise comparison. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons.

### Measures and tests for heterogeneity

We assessed the presence of statistical heterogeneity within the pairwise comparisons using the  $I^2$  statistic, which is the percentage of variability that cannot be attributed to random error. We based the assessment of statistical heterogeneity in the network on the magnitude of the heterogeneity variance parameter ( $\tau^2$ ) estimated from the network meta-analysis models.

### Assessment of statistical inconsistency

We evaluated the statistical agreement between the various sources of evidence in a network of interventions (consistency) by global and local to complement the evaluation of consistency (Efthimiou 2016).

### Assessment of reporting biases

We assessed each paper for the extent and transparency of reporting and for suggestion of reporting bias. We did not find sufficient studies of similar interventions to assess publication bias using funnel plots.

### Data synthesis

#### For effectiveness studies

##### Methods for direct treatment comparisons

We carried out meta-analyses in Stata software (version 15), pooling data from studies measuring the same outcomes in similar populations (first recurrence and any recurrence, including mixed populations). Assuming that we found at least two included studies that were sufficiently similar for the findings to be clinically meaningful, we used the random-effects models with inverse variance weighting for all meta-analyses. If any studies contributing to a meta-analysis had multiple intervention groups, we divided the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and treated the split comparison group as independent comparisons. If meta-analysis was not possible due to the timing of assessment or the type of outcome measure used, we described these data narratively.

##### Methods for indirect and mixed comparisons

We conducted network meta-analyses providing that populations of included studies were sufficiently similar to satisfy the assumption of joint randomisation and that the interventions connected, creating a network. This led to two separate networks, one for studies evaluating populations experiencing first recurrence and one for those experiencing any, first and second and subsequent recurrences. The latter populations would be expected to have a worse prognosis than the first recurrence group. We used the random-effects model in Stata software (version 15) fitting a multivariate network meta-analysis (White 2015). In 'Summary of findings' tables, we report the value of mean rank for included treatments (Chaimani 2015).

For data where meta-analysis was not possible, we attempted narrative synthesis but did not grade the evidence. In general, we interpreted the quality of the evidence based on the Cochrane Effective Practice and Organisation of Care (EPOC) Group's guidance (EPOC 2015).

### 'Summary of findings' table and results reporting

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), we prepared a 'Summary of findings' table to present the results of the following outcomes, namely:

- overall survival;
- progression free survival; and
- severe adverse events.

There were insufficient data to present QoL findings. We used the GRADE system to rank the quality of the evidence (Schünemann 2019). Two review authors (TL and ER) independently graded the evidence and resolved any differences by discussion or, if necessary, by involving a third review author. We interpreted the results of the graded evidence based on Cochrane Effective Practice and Organisation of Care guidance (EPOC 2015).

### Brief economic commentary

We included a brief economic commentary that summarises the availability and principal findings of the economic evaluations relevant to this review. This includes evaluations alongside trials and model-based evaluations. The work was performed in line with current guidelines, including a supplementary search to identify economic studies (Shemilt 2019).

### Subgroup analysis and investigation of heterogeneity

We analysed data according to studies of populations experiencing a first recurrence and studies with other populations experiencing any (mixed group) or second or subsequent recurrences. We did not conduct subgroup analyses and investigate heterogeneity according to second or subsequent recurrence, MGMT promoter methylation status, and time from primary diagnosis, as data were insufficient for this purpose. We did not find studies specifically of transformed GBM and therefore did not conduct separate analysis of these data.

### Sensitivity analysis

In the network meta-analyses, we explored how the following factors affect the ranking of interventions.

- Study quality, by excluding studies at high risk of bias to investigate how study quality affected the evidence on effects and the certainty of findings.
- If the effects from a multi-arm trial created a single loop in the network (no other loops available), we explored how exclusion of one of the arms affected the NMA findings.

## RESULTS

### Description of studies

#### Results of the search

The original search conducted by the CGNOC Information Specialist on 16 December 2019 identified the following records.

#### Searches for studies of effectiveness

- CENTRAL Issue 12 2019 – 524 references
- MEDLINE: 2005 to December week 1 2019 – 1632 references
- Embase: 2005 to 2019 week 50 – 956 references

- Preliminary de-duplication combined total n = 2738 references

**Economic searches**

- NHS EED – 9 refs
- MEDLINE: 2015 to December week 1 2019 – 23 references
- Embase: 2015 to 2019 week 50 – 58 references
- Preliminary de-duplication combined total n = 88 references

For studies of effectiveness, we shortlisted 182 records and obtained the full text of these papers where applicable (several

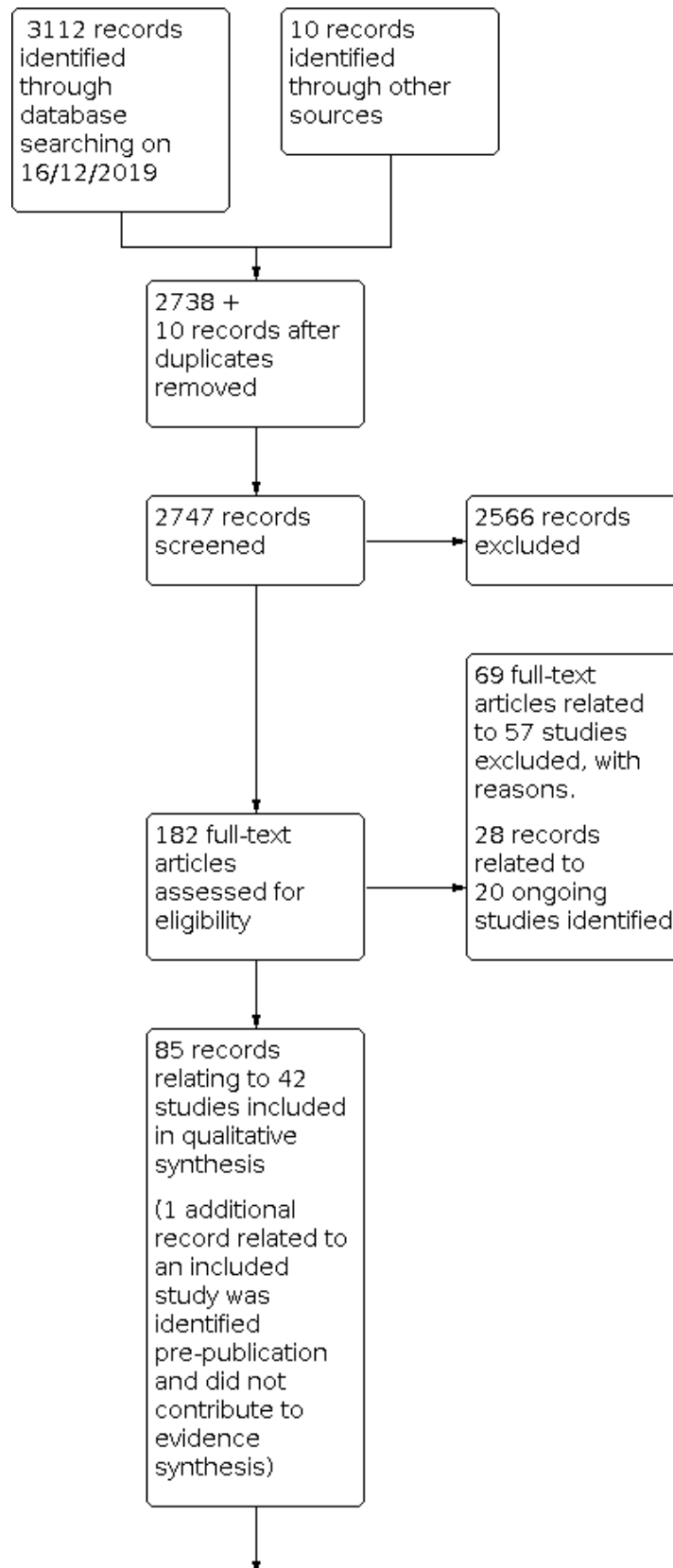
were conference abstracts). Where clinical trial registrations were identified, we visited ClinicalTrials.gov for further trial details. These records were classified as follows.

- Included: 42 studies with 85 related records (including 35 conference abstracts and 6 clinical trial registrations)
- Excluded: 57 studies with 69 related records
- Ongoing: 20 studies with 28 related records

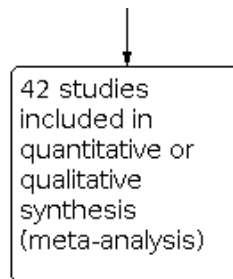
See [Figure 1](#).



**Figure 1. Flow diagram of searches for studies of effectiveness conducted on 16/12/2019**



**Figure 1. (Continued)**



We identified one new (May 2020) trial report related to an already included study after the review was completed ([van den Bent 2018](#)).

**Included studies**

We included 34 RCTs and 8 non-RCTs. Most RCTs were conducted in multiple centres across several countries with accrual occurring between 2004 and 2018. All participants had recurrent GBM and the vast majority had received chemoradiotherapy as first line treatment. The treatment of first recurrence was most commonly evaluated (20 studies; [Azoulay 2017](#); [Batchelor 2013](#); [Brandes 2016a](#); [Brandes 2016b](#); [Brandes 2018](#); [Brown 2016](#); [Cloughesy 2017](#); [Dresemann 2010](#); [Kunwar 2010](#); [Lombardi 2019](#); [Narita 2019](#); [Omuro 2018](#); [Puduvalli 2018](#); [Reardon 2015b](#); [Scorsetti 2015](#); [Suchorska 2016](#); [Taal 2014](#); [Twelves 2017](#); [van den Bent 2018](#); [Wick 2017](#)). Treatment of first and second recurrences were evaluated in six studies ([Friedman 2009](#); [Reardon 2018a](#); [Reardon 2018b](#); [Reardon 2020](#); [Wick 2010](#); [Wick 2014](#)); first, second and third recurrence in one study ([Weathers 2016](#)); any recurrence in seven studies ([Duerinck 2018](#); [Field 2015](#); [Galanis 2017](#); [Gilbert 2017](#); [Modh 2018](#); [Reardon 2011](#); [Stupp 2012](#)); and in the remainder the number of recurrences was not clear. Data were rarely reported separately for first and subsequent recurrences where populations were mixed.

Nine of the RCTs were phase 3 studies ([Batchelor 2013](#); [Cloughesy 2017](#); [Cloughesy 2018](#); [Dresemann 2010](#); [Kunwar 2010](#); [Narita 2019](#); [Stupp 2012](#); [Wick 2010](#); [Wick 2017](#)); the rest were phase 2. Most RCTs recruited patients from Europe and America in multicentre study designs; two RCTs were conducted in Japan ([Narita 2019](#); [Omuro 2018](#)).

Sample sizes ranged from 20 to 437 participants, with the total number of participants enrolled to the RCTs numbering 4607 (2573 with first recurrence and 2034 with mixed populations). Participants studied in non-randomised studies numbered 629, bringing the total number taking part in included studies to 5236 people.

**Interventions evaluated in the RCTs**

Most interventions were evaluated in single studies leading to 33 different comparisons evaluated in the RCTs alone. (Underlined studies reported hazard ratios (HRs) for survival outcomes; studies that did not report HRs usually reported survival outcomes as median survival). Included RCTs were:

1. cediranib (CED) + lomustine (LOM) vs lomustine (LOM)([Batchelor 2013](#));
2. HSPPC-96 vaccine + bevacizumab (BEV) vs BEV; ([Bloch 2017](#));
3. galunisertib (GAL) + LOM vs LOM([Brandes 2016a](#));

4. BEV vs fotemustine (FOT) ([Brandes 2016b](#));
5. BEV + LOM vs LOM([Brandes 2018](#); [Wick 2017](#));
6. CED + gefitinib (GET) vs CED ([Brown 2016](#));
7. onartuzumab (ONA) + BEV vs BEV([Cloughesy 2017](#));
8. VB-111 + BEV vs BEV ([Cloughesy 2018](#));
9. Imatinib + hydroxyurea (HU) vs HU ([Dresemann 2010](#));
10. axitinib (AXI) + LOM vs AXI ([Duerinck 2018](#));
11. BEV + carboplatin (CAB) vs BEV ([Field 2015](#));
12. BEV + irinotecan (IRI) vs BEV ([Friedman 2009](#));
13. BEV vs BEV + TRC105 ([Galanis 2017](#));
14. desatinib + BEV vs BEV ([Galanis 2019](#));
15. BEV + IRI vs BEV + TMZ ([Gilbert 2017](#));
16. convection enhanced cintredekin besudotox vs gliadel wafers ([Kunwar 2010](#));
17. regorafenib (REG) vs LOM ([Lombardi 2019](#));
18. fractionated stereotactic radiosurgery with BEV vs BEV with chemotherapy ([Modh 2018](#));
19. personalized peptide vaccination (PPV) vs placebo + best supportive care ([Narita 2019](#));
20. nivolumab (NIV) vs nivolumab (NIV) + ipilimumab (IPI) ([Omuro 2018](#));
21. BEV vs BEV + vorinostat ([Puduvalli 2018](#));
22. metronomic etoposide + BEV vs temozolomide + BEV ([Reardon 2011](#));
23. afatinib (AFA) vs TMZ vs AFA + TMZ ([Reardon 2015b](#));
24. rindopemimut vaccine + BEV vs placebo + BEV ([Reardon 2020](#));
25. pembrolizumab vs PEM + BEV ([Reardon 2018b](#));
26. tumour-treating fields (TTF) vs chemotherapy (various)([Stupp 2012](#));
27. BEV + LOM vs BEV or LOM ([Taal 2014](#));
28. hypofractionated radiotherapy + BEV vs BEV ([Tsien 2019](#));
29. cannabidiol:delta-9-tetrahydrocannabinol (CBD:THC) vs placebo ([Twelves 2017](#));
30. Depatux-m (ABT414) vs depatux-m + TMZ vs TMZ or LOM ([van den Bent 2018](#));
31. BEV vs low dose BEV + LOM ([Weathers 2016](#));
32. enzastaurin (ENZ) vs LOM ([Wick 2010](#));
33. asunercept (APG110) + radiotherapy vs radiotherapy ([Wick 2014](#)).

Underlined studies reported hazard ratios (HRs) for survival outcomes; studies that did not report HRs, usually reported survival outcomes as median survival. [Bloch 2017](#), [Galanis 2017](#), [Modh 2018](#), [Puduvalli 2018](#), [Reardon 2018b](#), and [Tsien 2019](#) were published

as conference abstracts that contained little data. The studies of novel agents imatinib (Dresemann 2010), cediranib (Batchelor 2013), PPV (Narita 2019); nivolumab ± ipilimumab (Omuro 2018), pembrolizumab (Reardon 2018b), enzastaurin (Wick 2010), and afatinib (Reardon 2015b) did not show clinically meaningful survival benefits. Similarly, no survival benefits were noted when onartuzumab (Cloughesy 2017), HSPPC-96 vaccine (Bloch 2017), carboplatin (Field 2015), irinotecan (Friedman 2009), TRC105 (Galanis 2017), desatinib (Galanis 2019), vorinostat (Puduvalli 2018), or metronomic etoposide or TMZ (Reardon 2011) were added to BEV.

Interventions evaluated in the seven non-RCTs were the following.

1. Re-operation vs no re-operation (Azoulay 2017; retrospective)
2. Re-operation vs no re-operation (Suchorska 2016; prospective)
3. BEV vs best supportive care (Cuncannon 2019; prospective);
4. Gamma Knife surgery (GKS) vs TMZ vs GKS + TMZ, vs re-operation vs other (Kim 2015; retrospective);
5. Re-operation ± radiotherapy + chemotherapy vs chemotherapy (fotemustine + re-challenge TMZ) (Scorsetti 2015; retrospective)
6. Trebananib (TNB) vs TNB + BEV (Reardon 2018a)

7. BEV+CCNU (LOM) vs BEV (Heiland 2016; retrospective study)
8. Intranasal perillyl alcohol (IPA) + ketogenic diet vs IPA + standard diet (Santos 2018)

For details of individual studies please see [Characteristics of included studies](#).

#### Excluded studies

Excluded studies numbered 57 and reasons for exclusion and reasons for exclusion of individual studies can be found in the [Characteristics of excluded studies](#) section. WE also identified 20 ongoing studies, and details of these can be found in the [Characteristics of ongoing studies](#) section.

#### Risk of bias in included studies

We summarise risk of bias in included studies in [Figure 2](#) and [Figure 3](#). In general, we judged RCTs to be at low or unclear risk of bias, and judged non-RCTs to be at high risk of bias. We generally judged studies reported as conference abstracts only as being at unclear risk of bias as they contained insufficient information to make judgements (Bloch 2017; Galanis 2017; Modh 2018; Puduvalli 2018; Reardon 2018b; Tsien 2019; Twelves 2017).

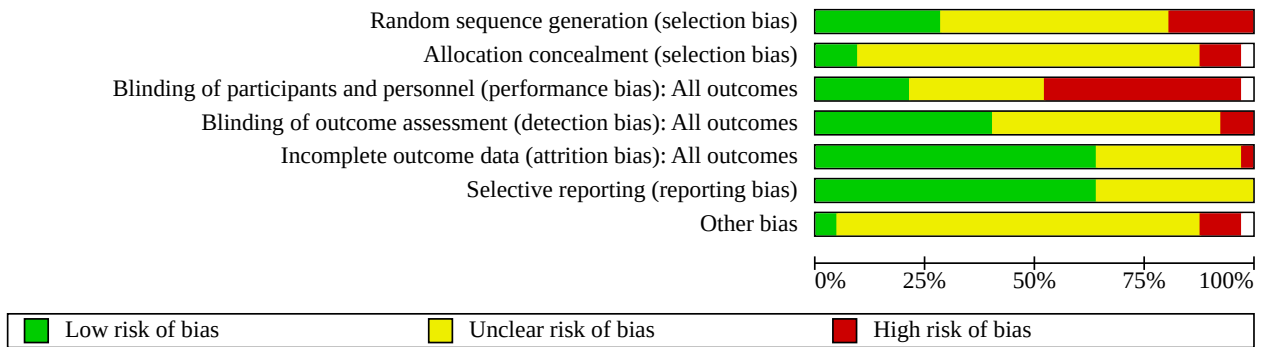
**Figure 2. Risk of bias of included studies**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Azoulay 2017	+	+	+	?	+	?	+
Batchelor 2013	?	?	+	+	+	+	?
Bloch 2017	?	?	+	?	?	?	?
Brandes 2016a	+	?	+	?	+	+	?
Brandes 2016b	?	?	+	?	+	+	?
Brandes 2018	?	?	+	+	?	+	?
Brown 2016	+	+	+	?	?	+	?
Cloughesy 2017	+	+	+	?	+	+	?
Cloughesy 2018	+	+	+	+	+	+	?
Cuncannon 2019	+	+	?	?	+	+	+
Dresemann 2010	?	?	+	+	+	+	?
Duerinck 2018	?	?	?	+	?	?	?
Field 2015	?	?	+	+	+	+	?
Friedman 2009	?	?	+	+	?	?	?
Galanis 2017	?	?	+	?	?	?	?
Galanis 2019	?	?	+	+	+	+	?
Gilbert 2017	?	?	?	?	+	+	?
Heiland 2016	+	+	?	?	?	?	?
Kim 2015	+	?	?	?	?	+	+
Kunwar 2010	?	?	?	+	+	+	+
Lombardi 2019	+	?	+	+	+	+	?
Modh 2018	?	?	?	?	?	?	?
Narita 2019	+	?	+	+	+	+	?

**Figure 2. (Continued)**

Modh 2018	?	?	?	?	?	?	?
Narita 2019	+	?	+	+	+	+	?
Omuro 2018	?	?	?	?	+	+	?
Puduvalli 2018	?	?	?	?	?	?	?
Reardon 2011	?	?	-	?	+	?	-
Reardon 2015b	?	?	?	+	+	+	?
Reardon 2018a	-	?	-	-	+	+	?
Reardon 2018b	?	?	?	?	?	?	?
Reardon 2020	+	?	+	+	+	+	?
Santos 2018	-	?	-	?	-	?	+
Scorsetti 2015	-	-	-	?	?	?	?
Stupp 2012	+	?	-	?	?	+	?
Suchorska 2016	-			+	+	+	
Taal 2014	+	?	-	-	+	+	?
Tsien 2019	?	?	?	?	?	?	?
Twelves 2017	?	?	+	?	?	?	?
van den Bent 2018	+	+	-	+	+	+	?
Weathers 2016	?	?	?	+	+	?	?
Wick 2010	?	?	-	+	+	+	?
Wick 2014	+	?	-	?	+	+	?
Wick 2017	+	?	-	+	+	+	?

**Figure 3.**



**Allocation**

Most randomised studies were at an unclear risk of selection bias as the randomisation and treatment allocation process was seldom clearly reported. All non-randomised studies were at a high risk of selection bias, as patients in [Azoulay 2017](#), [Heiland 2016](#), [Kim 2015](#), [Santos 2018](#), [Scorsetti 2015](#) and [Suchorska 2016](#) were most likely selected for different study treatments based on clinical factors. [Cuncannon 2019](#) selected patients according to willingness to pay for treatment with bevacizumab, which may have been influenced by patient prognosis. [Reardon 2018a](#) was a non-randomised study with little information on how patients were allocated to the different treatment arms.

**Blinding**

Most studies were open label studies. Less than 25% had blinding of participants and personnel and less than 40% applied assessor blinding to assessments. In grading the findings, however, we assumed a low risk of bias for this criterion with respect to overall survival, which is an objective outcome.

**Incomplete outcome data**

Most studies were judged to be at low (~ 60%) or unclear risk (~ 35%) of attrition bias. We judged one non-randomised study to be at high risk of attrition bias because less than half the participants completed the study ([Santos 2018](#)).

**Selective reporting**

The majority of studies (~ 70%) reported overall survival, progression free survival and toxicity outcomes and we judged them to be at low risk of bias for this criterion; the remainder we judged as having an unclear risk of bias.

**Other potential sources of bias**

RCTs were usually sponsored by the intervention's manufacturer and affiliated pharmaceutical companies and most had authors with declared interests. The risk of bias implications of these potential sources of bias was judged as unclear in all instances.

**Effects of interventions**

See: **Summary of findings 1** Summary of overall survival findings; **Summary of findings 2** Summary of progression-free survival findings; **Summary of findings 3** Summary of findings for severe adverse events - 1; **Summary of findings 4** Summary of findings for severe adverse events - 2

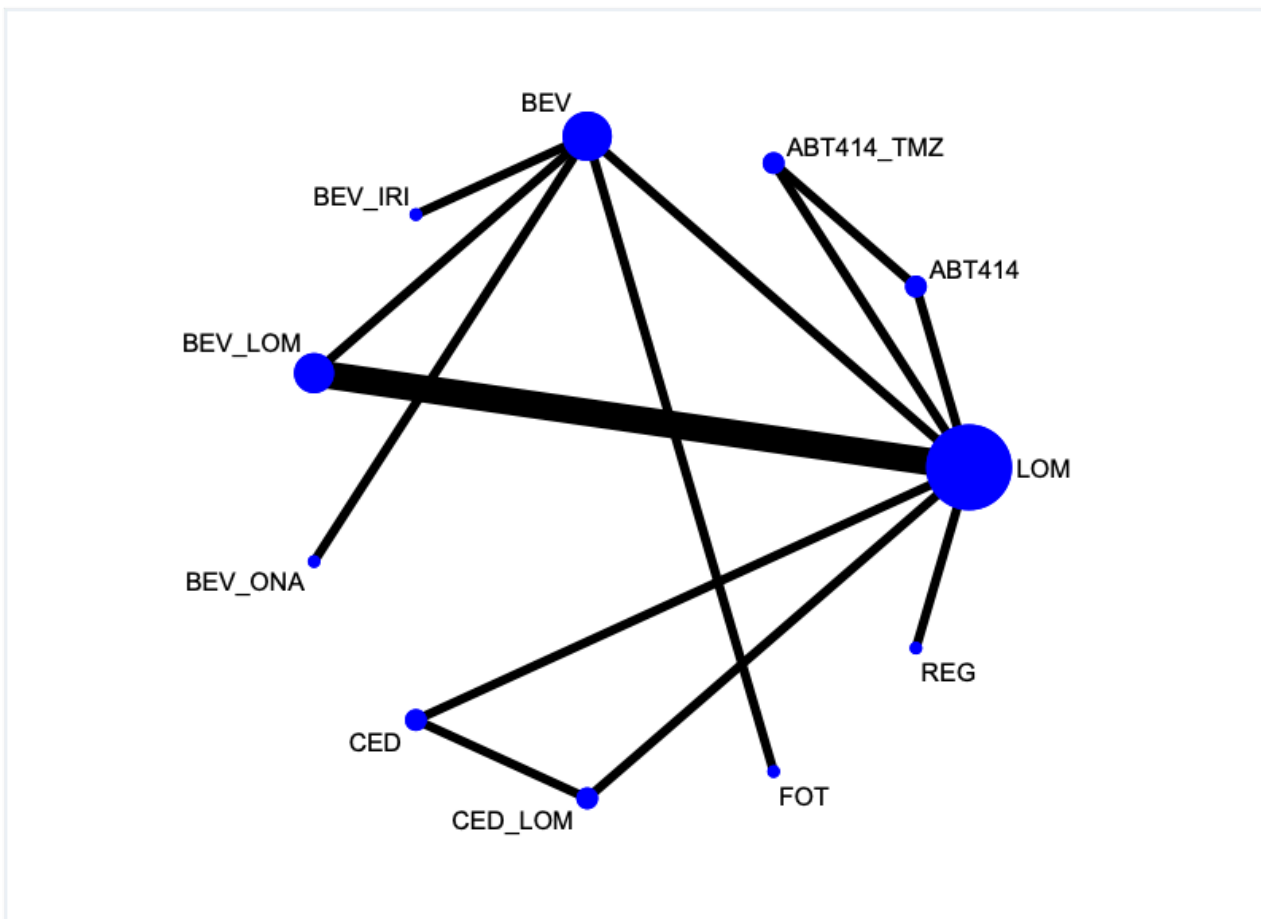
We found median survival data for most included studies and these are presented in [Table 1](#), grouped according to the level of recurrence. NMAs for survival outcomes were performed for studies evaluating treatments for first recurrence only. Where studies evaluated further recurrence or mixed recurrence, we did not perform NMA as networks connecting these mainly single phase 2 studies of novel interventions among mixed populations that were mostly shown not to warrant further investigation would produce very low certainty results. Several of the studies in the latter network did not report hazard ratios and were not powered to test efficacy, and most reported no clinically meaningful survival effects or were terminated early for futility.

**Overall survival (first recurrence)**

**The NMA findings**

Nine RCTs involving the following 11 treatments contributed to this network ([Figure 4](#)). Median overall survival estimates across this group of studies ranged from 5.5 months (LOM arm of [Brandes 2018](#)) to 12.6 months (BEV arm of [Cloughesy 2017](#)) ([Table 1](#)).

**Figure 4. Network for Overall Survival (first recurrence)**



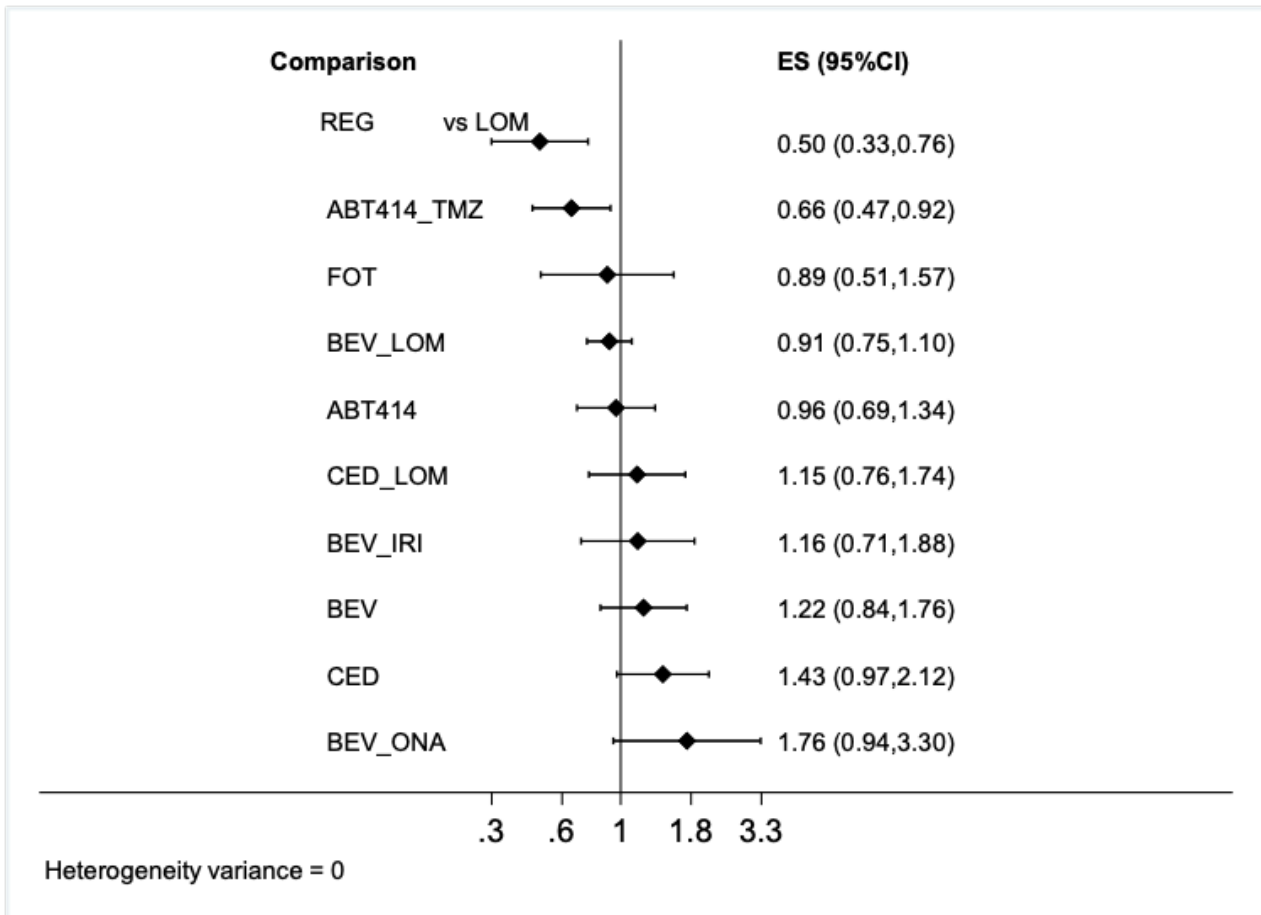
- Five trials (403 participants) involving lomustine (LOM) ([Brandes 2018](#); [Lombardi 2019](#); [Taal 2014](#); [van den Bent 2018](#); [Wick 2017](#))
- Four trials (259 participants) involving bevacizumab (BEV) ([Brandes 2016b](#); [Cloughesy 2017](#); [Friedman 2009](#); [Taal 2014](#))
- Three trials (401 participants) involving BEV + LOM ([Brandes 2018](#); [Taal 2014](#); [Wick 2017](#))
- One trial (64 participants) involving BEV + ONA ([Cloughesy 2017](#))
- One trial (88 participants) involving ABT414 (Depatux-M) +TMZ ([van den Bent 2018](#))

- One trial (86 participants) involving ABT414 ([van den Bent 2018](#))
- One trial (82 participants) involving BEV + irinotecan (IRI) ([Friedman 2009](#))
- One trial (32 participants) involving fotemustine (FOM) ([Brandes 2016b](#))
- One trial (59 participants) involving regorafenib (REG) ([Lombardi 2019](#))
- One trial (131 participants) involving cediranib (CED) ([Batchelor 2013](#))

- One trial (129 participants) involving CED+LOM ([Batchelor 2013](#))

Results for this network can be found in the forest plot ([Figure 5](#)) and also in the league table showing HRs and 95% CI estimates for all intervention comparisons ([Table 2](#)). The global test for inconsistency was not statistically significant ( $P = 0.15$ ). We found no high-certainty evidence that any of the treatments evaluated were superior to lomustine monotherapy. Graded pooled network estimates for overall survival of treatments compared with lomustine monotherapy suggest the following.

**Figure 5. Forest plot of effects on overall survival of different treatments compared with lomustine**



- There is probably little or no difference between BEV + LOM and LOM only (HR 0.91, 95% CI 0.75 to 1.10; moderate-certainty evidence).
- There may be little or no difference between FOM and LOM (HR 0.89, 95% CI 0.51 to 1.57; low-certainty evidence)
- There is probably little or no difference between BEV and LOM (HR 1.22, 95% CI 0.84 to 1.76; low-certainty evidence)
- REG may be more effective than LOM (HR 0.50, 95% CI 0.33 to 0.76; low-certainty evidence)
- ABT414 + TMZ may be more effective than LOM (HR 0.66, 95% CI 0.47 to 0.92; low-certainty evidence)
- CED is probably less effective than LOM (HR 1.43, 95% CI 0.97 to 2.12; moderate-certainty evidence)

- There is probably little or no difference between CED + LOM and LOM (HR 1.15, 95% CI 0.76 to 1.74; moderate-certainty evidence)
- Evidence on BEV + ONA versus LOM (HR 1.76, 95% CI 0.94 to 3.30) and BEV + IRI versus LOM (HR 1.16, 95% CI 0.71 to 1.88) was very low certainty.

When treatments other than LOM were compared with BEV monotherapy, there was no clear difference in effect between any of the treatments and BEV for this outcome, except for ABT414 + TMZ, which the evidence suggested may be more effective than BEV (HR 0.54, 95% CI 0.33 to 0.89; low-certainty evidence). The evidence also suggested that there is probably little or no difference between BEV + IRI compared with BEV monotherapy (HR 0.95, 95% CI 0.70 to 1.30; moderate-certainty evidence).

On sensitivity analysis, when we excluded [Lombardi 2019](#) (a small study of REG) and [van den Bent 2018](#) (a study of ABT414; 73% of control participants received LOM, the others received TMZ), FOT ranked first, BEV + LOM ranked second, and LOM ranked third, BEV + IRI ranked fourth, and BEV ranked fifth. Ranking does not take into account the certainty of the evidence, which indicated that there was little or no difference between BEV + LOM and LOM, probably little or no difference between FOT and LOM, and probably little or no difference between BEV + IRI and BEV. ABT414, CED and ONA were not associated with clinical benefits. See [Summary of findings 1](#).

Other studies conducted among patients with first recurrence that could not be included in the NMA due to insufficient data did not

report encouraging results and were considered not to warrant further investigation in the context of recurrent GBM. We found no studies assessing TMZ re-challenge (without ABT414) in this context.

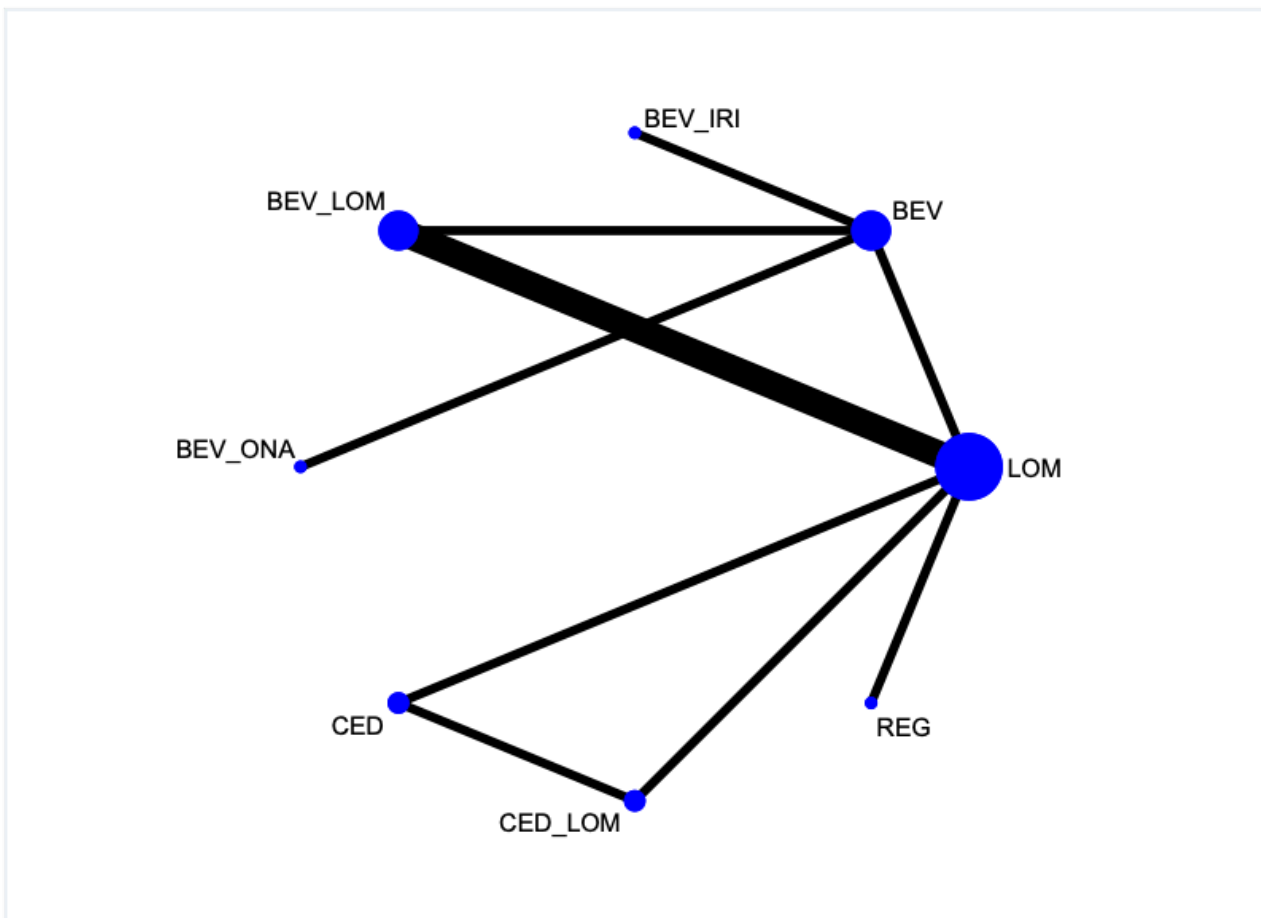
**Progression-free survival (first recurrence)**

Median PFS across all RCTs reporting this outcome ranged from 1.5 months (LOM arm of [Wick 2014](#)) to 4.2 months (BEV + LOM arm of [Wick 2017](#)).

**The NMA findings**

Seven RCTs involving the following eight treatments contributed data to this NMA ([Figure 6](#)).

**Figure 6. Network for progression free survival (first recurrence)**



- Four trials (317 participants) involving lomustine (LOM) ([Brandes 2018](#); [Lombardi 2019](#); [Taal 2014](#); [Wick 2017](#))
- Three trials (401 participants) involving bevacizumab (BEV) + LOM ([Brandes 2018](#); [Taal 2014](#); [Wick 2017](#))
- Three trials (200 participants) involving BEV ([Cloughesy 2017](#); [Friedman 2009](#); [Taal 2014](#))
- One trial (64 participants) involving BEV + onartuzumab (ONA) ([Cloughesy 2017](#))
- One trial (82 participants) involving BEV + irinotecan ([Friedman 2009](#))

- One trial (59 participants) involving regorafenib (REG) ([Lombardi 2019](#))
- One trial (131 participants) involving cediranib (CED) ([Batchelor 2013](#))
- One trial (129 participants) involving CED + LOM ([Batchelor 2013](#))

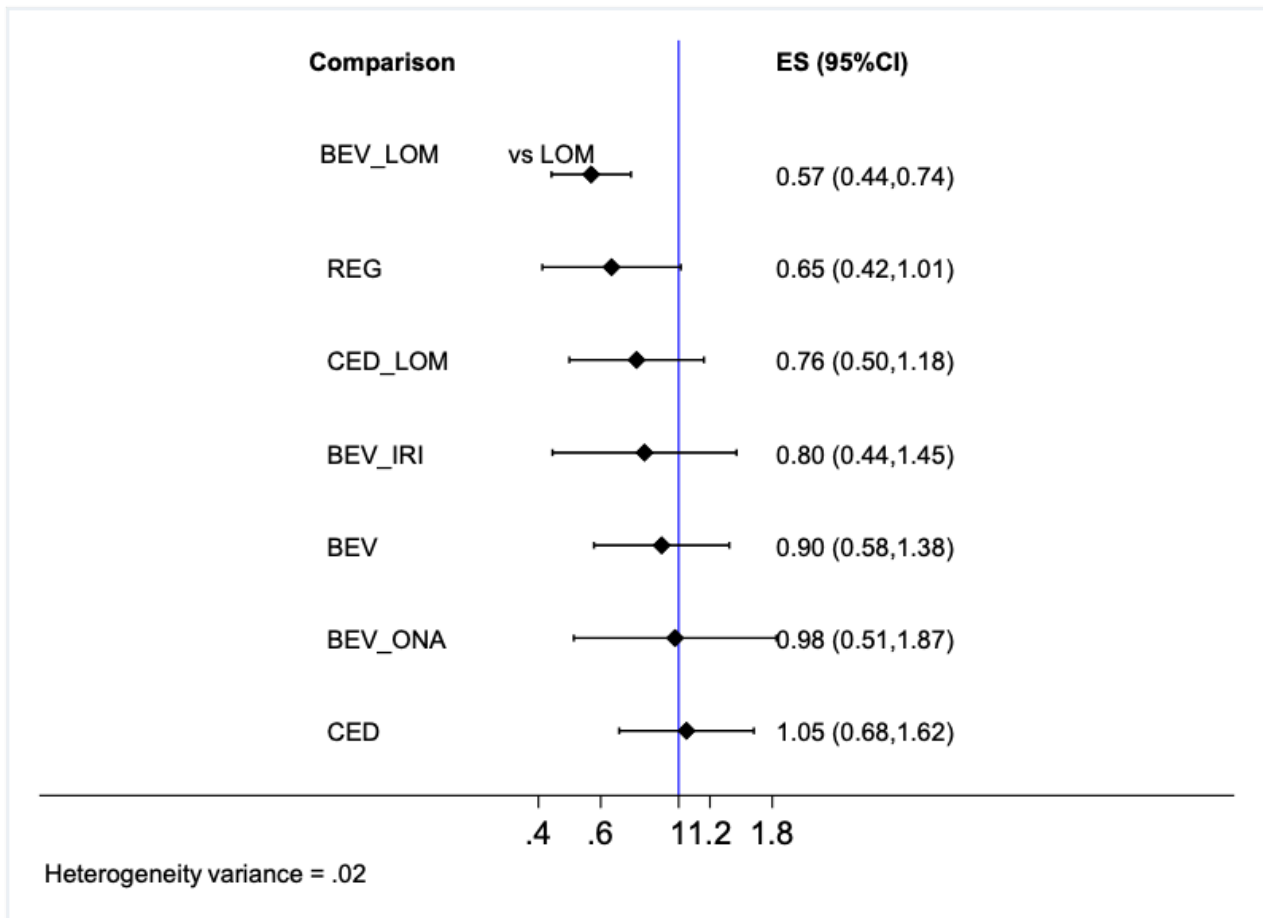
Effect estimates for this network can be found in the forest plot ([Figure 7](#)) and also in the league table showing HRs and 95% CI estimates for all intervention comparisons ([Table 3](#)). The global test for inconsistency was not statistically significant (P = 0.80). Again, we found no high-certainty evidence that any of the



treatments evaluated were superior to lomustine monotherapy. Graded pooled network estimates for progression-free survival

of treatment compared with lomustine monotherapy suggest the following.

**Figure 7. Forest plot of PFS for different treatments compared with lomustine (first recurrence)**



- BEV + LOM may be more effective than LOM only (HR 0.57, 95% CI 0.44 to 0.74; low-certainty evidence);
- There may be little or no difference between BEV and LOM (HR 0.90, 95% CI 0.58 to 1.38; low-certainty evidence);
- There is probably little or no difference between CED + LOM and LOM (HR 0.76, 95% CI 0.50 to 1.18; moderate-certainty evidence);
- There is probably little or no difference between CED and LOM (HR 1.05; 95% CI 0.68 to 1.62; moderate-certainty evidence);
- Evidence on BEV + ONA versus LOM (HR 0.98, 95% CI 0.51 to 1.87) and BEV + IRI versus LOM (HR 0.80, 95% CI 0.44 to 1.45) and REG versus LOM (HR 0.65, 95% CI 0.42 to 1.01) was very low certainty.

When treatments other than LOM were compared with BEV monotherapy there were no clear differences, with the exception of BEV + LOM, the evidence for which suggested that BEV + LOM may be more effective than BEV monotherapy (0.64, 95% CI 0.41 to 0.99; high-certainty evidence). For BEV + IRI versus BEV, the evidence suggested that there may be little or no difference (0.90, 95% CI 0.60 to 1.34; low-certainty evidence).

In terms of ranking, BEV + LOM ranked first, REG ranked second, BEV + IRI ranked third, BEV ranked fourth, LOM ranked fifth and BEV +

ONA ranked last. See [Summary of findings 2](#). Ranking does not take into account the certainty of the evidence above.

**Other study findings evaluating interventions at first recurrence**

The studies of novel agents imatinib (Dresemann 2010), axitinib (Duerinck 2018), personalised peptide vaccination (PPV; Narita 2019), nivolumab with or without ipilimumab (Omuro 2018), pembrolizumab (Reardon 2018b), enzastaurin (Wick 2010), and afatinib (Reardon 2015b) could not be included in the NMA, either due to insufficient data (no HRs reported) or due to no common nodes; however they did not show clinically meaningful survival benefits. Similarly, we could not include studies of HSPPC-96 vaccine (Bloch 2017), VB111 (Cloughesy 2018), carboplatin (Field 2015), TRC105 (Galanis 2017), desatinib (Galanis 2019), vorinostat (Puduvalli 2018), or metronomic etoposide or TMZ (Reardon 2011) added to BEV in the NMA due to insufficient data or no common nodes; however, we noted no survival benefits with these combinations and published findings suggest that they do not warrant further investigation in the context of recurrent GBM.

One randomised study evaluated the novel intervention cintredekin besudotox compared with gliadel wafers in patients with a first recurrence and no survival differences (median OS ~ 9

months) (Kunwar 2010); however, the risk of pulmonary embolism was increased with cintredekin besudotox ( $P = 0.014$ ).

A small pilot study evaluated a cannabidiol:delta-9-tetrahydrocannabinol (CBD:THC) oro-mucosal spray among 12 people with recurrent GBM randomised to the intervention and 9 randomised to placebo (Twelves 2017). All participants also received dose-intense TMZ. The median survival in the CBD:THC group was better than the placebo group (~ 18.3 months vs ~ 12.3 months, respectively). One-year survival was 83% and 56% in the CBD:THC and placebo groups, respectively.

#### Re-operation and re-irradiation

Three non-randomised studies evaluated re-operation among people with first recurrence (Table 1) (Azoulay 2017; Scorsetti 2015; Suchorska 2016). These non-randomised studies are at a high risk of selection bias and this evidence was not graded. Azoulay 2017 retrospectively compared re-operation (with or without salvage chemoradiotherapy) with salvage chemoradiotherapy or best supportive care at first recurrence (median time from diagnosis 7.43 months). Sixty-nine people had repeat surgery and 111 did not: the decision on treatment was made by a multi-disciplinary team and was based on prognostic factors such as tumour extent and location. The median survival after repeat surgery was 9.8 months compared to 5.0 months for those receiving other treatment ( $P < 0.0001$ ) (study authors acknowledge a "lack of consistent selection criteria for each treatment modality" as a study limitation).

Scorsetti 2015 retrospectively evaluated overall survival and progression-free survival in a retrospective study including 21 people receiving re-resection and/or re-irradiation plus chemotherapy (combined treatment) and 22 receiving chemotherapy alone. People selected for the different treatment groups had different clinical characteristics at the time of relapse. The median interval from initial diagnosis with glioblastoma was 13 months (6 to 78 months). Median overall and progression-free survival in the combined treatment group were reported to be 17 and 15 months versus 6 and 5 months in the group receiving chemotherapy alone.

Suchorska 2016 prospectively evaluated re-operation versus no re-operation in an exploratory sub-study of the DIRECTOR trial, which compared different dose-intense TMZ regimens among 105 people with recurrent GBM. Seventy-one participants in the cohort underwent re-operation. There was no significant difference in PFS (2.0 months vs 1.9 months, respectively) or post-recurrence survival (11.4 months versus 9.8 months, respectively) between those who had surgery and those who did not. However, complete resection was associated with better survival than incomplete resection (9.8 months versus 6.5 months, respectively).

In a retrospective study involving 144 patients at first progression of GBM, Kim 2015 and colleagues evaluated five different treatment options: Gamma Knife (stereotactic) radiosurgery (GKS) ( $n = 29$ ); temozolomide: either 50 mg/m<sup>2</sup> daily (metronomic dose) or 150 to 200 mg/m<sup>2</sup> for 5 days per 4 weeks ( $n = 31$ ); Gamma Knife radiosurgery + temozolomide: 67.9% received metronomic TMZ chemotherapy ( $n = 28$ ); re-operation ( $n = 38$ ); or 'other treatment': ( $n = 18$ ). We have set out results for each arm in the Characteristics of included studies table. The authors concluded that GKS with TMZ was associated with improved overall survival. However, as with the other retrospective studies, it was not clear how patients were

selected for the different treatment options (in this study average tumour volume differed across treatment arms).

#### Evidence on survival outcomes for treatment of second and/or subsequent recurrence

As described above, we could not perform NMAs of second and subsequent recurrence due to insufficient data. Twenty studies evaluated different interventions in mixed populations with first, second and/or subsequent recurrences. Ten of these studies were phase 2 studies that did not show meaningful clinical benefits. Wick 2014 was a phase 2 study of the novel intervention APG101, which the investigators considered to have potential for further development, but only 29% of these participants had second or subsequent recurrence, the majority had first recurrence. Similarly, a phase 2 study of BEV + dose dense TMZ versus BEV + irinotecan reported that both treatment arms passed pre-specified efficacy thresholds (Gilbert 2017); the proportion of second and subsequent recurrences in this study was unclear.

A few studies have evaluated mainly second or later recurrences. These included Cuncannon 2019, Galanis 2017 (terminated early for futility), Heiland 2016, Modh 2018 and Stupp 2012. Tsien 2019 is also discussed below, although the proportion of second and later recurrences in this study is unclear. Four studies evaluated re-irradiation but with diversity of line of treatment, fractionation and accompanying systemic therapy. Three studies evaluated BEV with or without radiotherapy.

- Cuncannon 2019 prospectively evaluated BEV compared with supportive care for chemo-refractory disease following treatment of relapsed GBM among 48 patients. BEV was offered to the 48 patients at a maximum cost of EUR 12,000; 15 refused for financial reasons and 28 accepted. Most patients were experiencing a second or third relapse and the median survival of patients accepting BEV was 6 months versus 1 month with supportive care only ( $P < 0.01$ ). Patients in the BEV arm ( $n = 16$ ) were more likely to receive radiotherapy (35 to 40 Gy in 15 fractions over 3 weeks) than those in the supportive care only arm ( $n = 0$ ), which authors suggested may have been facilitated by BEV. These findings are at high risk of bias.
- Modh 2018 compared BEV + fractionated stereotactic radiotherapy (8 Gy × 4 fractions over 2 weeks) with BEV + chemotherapy in an RCT involving 34 heavily pre-treated participants (median recurrence was 3). The BEV + radiotherapy arm experienced longer progression-free survival (5.3 months vs 1.8 months) and better local control. Overall survival was 7.1 months vs 4.8 months, respectively. This was reported in a conference abstract only and details were sparse.
- Tsien 2019, also reported as a conference abstract, was a phase 2 RCT of 170 participants comparing hypofractionated radiotherapy (35 Gy in 10 fractions) plus BEV versus BEV only. The proportion of participants with second or subsequent recurrence among this study sample is not clear as findings are available in a conference abstract only; however, the duration of overall survival (~ 10 months) suggests that the majority of participants had a first recurrence. Investigators reported no significant difference in overall survival; however, significantly more participants were progression-free at 6 months in the BEV + radiotherapy arm than the BEV arm (54% vs 29%). Authors conclude that the "role of BEV + RT should be limited to small volume recurrences, especially in previously non-irradiated

treatment areas at least 6 months following completion of previous RT." Evidence from these studies is difficult to interpret but suggest that BEV + radiotherapy may have a role in delaying disease progression in second and subsequent recurrence of GBM.

Twenty-nine per cent of participants in [Wick 2014](#) were experiencing second or third recurrences. This phase 2 RCT evaluated radiotherapy (36 Gy, 2 Gy fractions × 5 per week) plus APG101 (a CD95 inhibitor) compared with radiotherapy alone. Median PFS was 2.5 months (95% CI 2.30 to 3.80) months for radiotherapy and 4.5 (95% CI 3.70 to 5.40) months for radiotherapy + APG101 with a hazard ratio (HR) of 0.49 (95% CI 0.27 to 0.88;  $P = 0.0162$ ) adjusted for tumour size in favour of radiotherapy plus APG101, with no clear difference in overall survival. Authors reported that the novel agent APG101 warrants further clinical development.

[Heiland 2016](#) retrospectively evaluated "last-line" therapy in 43 patients at third recurrence. In this study, BEV monotherapy ( $n = 17$ ) was compared with combined BEV + LOM therapy ( $n = 18$ ). It was not clear how patients were selected for the two treatment options. Median overall survival after BEV monotherapy was 4.07 months (95% CI 3.02 to 12.98) while in the combined therapy group median overall survival was 6.59 months (95% CI 5.51 to 16.30). Median progression-free survival was 2.3 months (95% CI 1.87 to 4.39 months) compared with 6.11 months (95% CI 3.41 to 12.98 months) in the combined BEV + LOM group. We considered this study to be at a high risk of bias.

[Stupp 2012](#) was a phase 3 RCT in which more than 80% of 237 participants had failed two or more prior lines of chemotherapy (second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Participants were randomised to receive tumour-treating fields (TTF) or physicians best choice of treatment — most received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%). Interpretation of findings is difficult because the survival effects of TTF were similar to the control but it is unclear how effective the control arm treatments are, if at all.

### Quality of life

Seven studies reported findings on health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) ([Brandes 2016a](#); [Brown 2016](#); [Field 2015](#); [Galanis 2017](#); [Stupp 2012](#); [Suchorska 2016](#); [Taal 2014](#)). All but one of these studies ([Taal 2014](#)) also used the EORTC questionnaire relating to brain cancer (BN-20). In addition, [Galanis 2017](#) used the shorter EORTC QLQ-C15-PAL along with the BN-20 questionnaire.

A multi-centre trial in the Netherlands ([Taal 2014](#)) recruited patients at first recurrence and included three arms: bevacizumab alone ( $n = 46$ ), lomustine alone ( $n=45$ ), or combined treatment ( $n = 47$ ). At baseline, QoL scores were similar in the three groups and, compared with the general population, these patients had impaired scores. Following treatment there were no clear differences between arms for any of the five sub-scales assessed.

[Brandes 2016a](#) also examined bevacizumab for patients with recurrent disease. In this study participants were randomised in a 2:1 ratio to receive bevacizumab ( $n = 59$ ) or fotemustine ( $n = 32$ ). QoL was assessed at approximately eight weeks after study drug administration or at disease progression. Follow-up questionnaires were only completed by 15 (13.56%) in the bevacizumab group and eight (25%) in the fotemustine group. Authors reported an improvement in physical functioning from baseline; although there was no significant difference between groups and there appeared to be variability within groups (SDs were large). For other QLQ C-30 dimensions the authors reported deteriorations in scores for fatigue, nausea, insomnia and appetite loss for patients in the fotemustine group and in emotional functioning in the bevacizumab group. However, scores for these items were not reported for both groups, and it was not clear whether or not there were any significant differences between the two arms for any of these dimensions of QoL.

In another study ([Stupp 2012](#)), patients with recurrent glioblastoma were randomised to TTF ( $n = 120$ ) versus chemotherapy ("best available" according to physician choice) ( $n = 117$ ). At three months, post-treatment QoL scores were available for 27% ( $n = 63$ ) of patients randomised. Results were set out in graphs and authors report "no meaningful differences" between arms for global health and social functioning. For other QoL dimensions, symptoms appeared to be related to treatment-associated toxicity in the chemotherapy arm (loss of appetite, diarrhoea, constipation, nausea and vomiting). Authors also reported increased pain and fatigue in the chemotherapy arm. It was not clear whether apparent differences between groups for these symptoms were statistically significant.

A multi-centre RCT comparing cediranib plus gefitinib with cediranib plus placebo including patients at first progression was terminated early after recruitment of 38 patients (19 in each arm) ([Brown 2016](#)). Twenty-six patients completed questionnaires at six weeks and there were no clear differences between arms for global health status or for any of the sub-scales. The authors concluded that there was no evidence that the addition of gefitinib resulted in poorer QoL; but the study was most likely underpowered to detect possible differences between groups.

A trial including 122 patients with recurrent GMB compared bevacizumab alone with bevacizumab plus carboplatin ([Field 2015](#)). Authors reported change from baseline and there was no significant differences in overall scores detected between groups.

The study by [Galanis 2017](#) compared bevacizumab plus TRC105 with bevacizumab alone. Of 101 patients recruited 65 were included in the main QoL analysis. In terms of overall scores on the EORTC QLQ-C15-PAL questionnaire, there was no clear difference between groups ( $P = 0.19$ ). For the BN20 items, there were no significant differences between groups for any of the dimensions. At four weeks patients were asked whether they thought it had been worthwhile participating in the study and similar proportions in both arms said yes (BEV plus TRC105, 69.4% (25/36), BEV alone 71.9% (23/32).

[Suchorska 2016](#), a non-randomised study, evaluated QoL among 71 people who underwent re-operation and 34 who did not at the 8-week follow-up visit as part of the DIRECTOR trial. Surgery was associated with better cognitive functioning ( $P=0.46$ ). Constipation occurred more commonly in this group ( $P = 0.039$ ). Complete

resection was associated with better global health status compared with incomplete resection ( $P = 0.008$ ).

Finally, [Lombardi 2019](#) randomised patients with relapsed GMB and compared regorafenib with lomustine. One hundred and fourteen patients completed baseline QoL questionnaires but only 37 were available for follow-up (24 in the regorafenib group and 13 in the lomustine group). There were no significant differences on any dimensions of either the general or brain tumour questionnaires, other than for appetite loss which was worse in those patients treated with regorafenib: 9 out of 24 receiving regorafenib and none of 13 receiving lomustine had what was described as clinically meaningful worsening appetite ( $P = 0.0146$ ).

**Severe adverse events**

Two disconnected networks were constructed from the available data, one around lomustine and the other around bevacizumab.

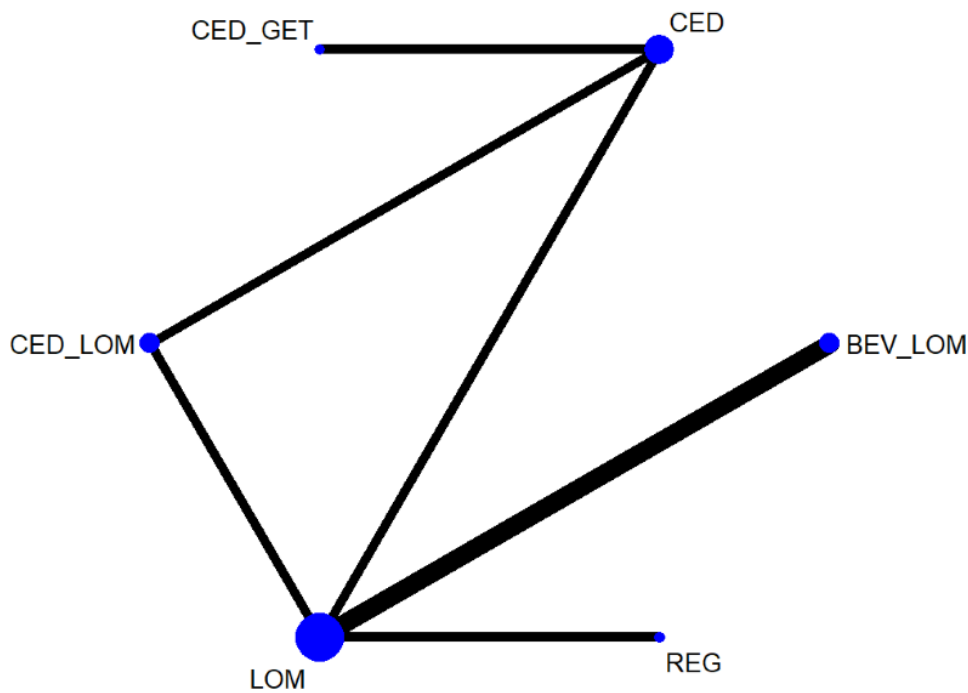
**Network 1: treatments versus lomustine**

Five RCTs contributed to the lomustine-based network involving six different treatments, including:

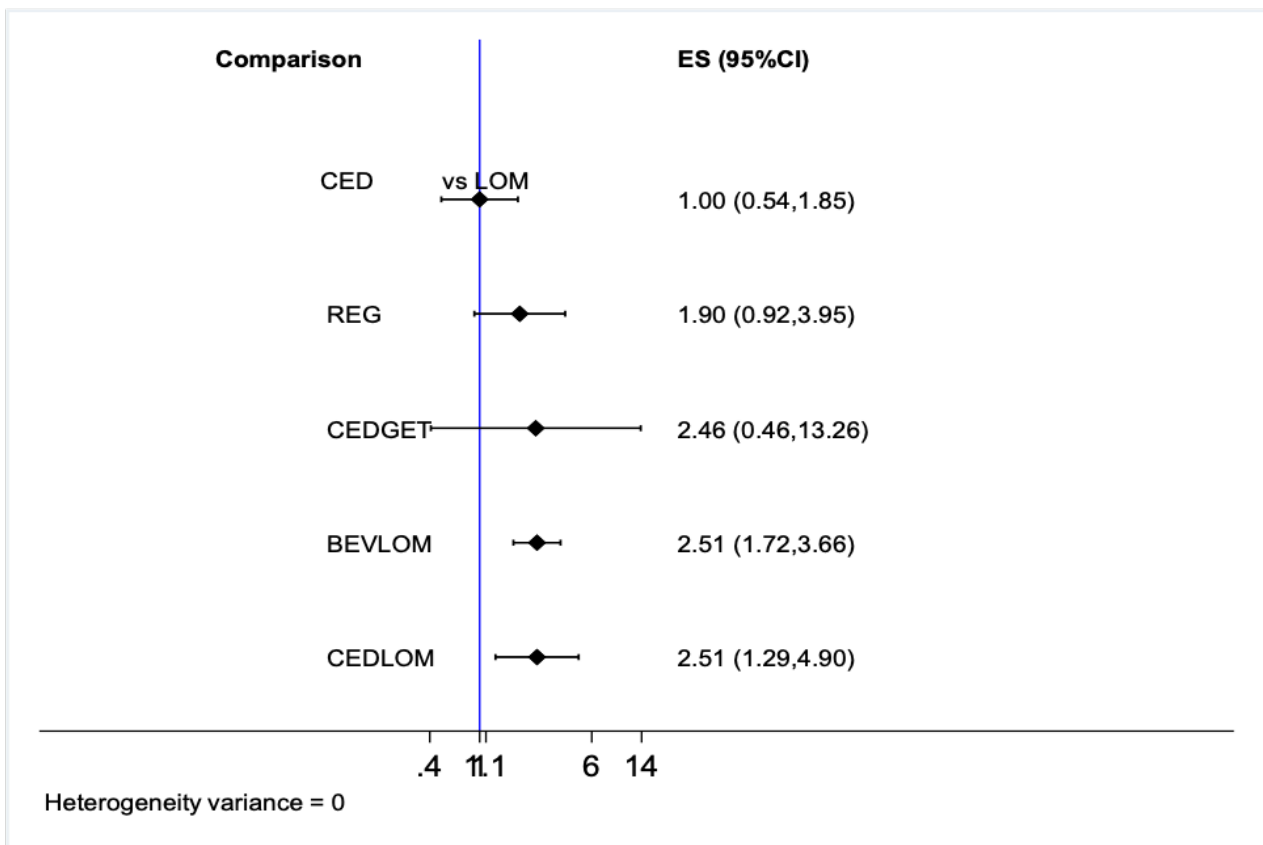
- four trials (330 participants) involving lomustine (LOM) ([Batchelor 2013](#); [Brandes 2018](#); [Lombardi 2019](#); [Wick 2017](#));
- two trials (346 participants) involving BEV + LOM ([Brandes 2018](#); [Wick 2017](#));
- two trials (147 participants) involving cediranib (CED) ([Batchelor 2013](#); [Brown 2016](#));
- one trial (123 participants) involving CED + LOM ([Batchelor 2013](#));
- one trial (19 participants) involving CED + gefitinib (GET) ([Brown 2016](#)); and
- one trial (59 participants) involving regorafenib (REG) ([Lombardi 2019](#)).

The network diagram is presented in [Figure 8](#), the league table showing HRs and 95% CI estimates for all intervention comparisons in [Table 4](#) and the forest plot in [Figure 9](#). We interpreted the evidence as follows.

**Figure 8. Severe adverse events - network 1**



**Figure 9. Severe adverse events forest plot for network 1 (treatments vs lomustine)**



- BEV + LOM is associated with significantly more severe adverse events than LOM (RR 2.51, 95% CI 1.72 to 3.66; high-certainty evidence)
- There may be little difference in the risk of severe adverse events between REG and LOM, but the point estimate favours LOM (RR 1.90, 95% CI 0.92 to 3.95; low-certainty evidence)
- There may be little difference in risk of severe adverse events between CED and LOM (RR 1.00, 95% CI 0.54 to 1.85; low-certainty evidence)
- CED + LOM is associated with significantly more severe adverse events than LOM (RR 2.51, 95% CI 1.29 to 4.90; high-certainty evidence)
- The evidence on CED + GET versus LOM is very low certainty.

In terms of ranking, lomustine and cediranib single therapies ranked best with the fewest severe adverse events. REG ranked second although the point estimate of REG suggesting more severe adverse events than lomustine was almost statistically significant. Bevacizumab plus lomustine ranked joint worst with CED + LOM (Figure 9). Ranking does not take into account the certainty of the evidence. See [Summary of findings 3](#).

**Network 2: treatments versus bevacizumab**

Eight RCTs contributed data to this network involving nine different treatments, including:

- eight trials (498 participants) involving BEV ([Bloch 2017](#); [Brandes 2016b](#); [Cloughesy 2017](#); [Cloughesy 2018](#); [Field 2015](#); [Friedman 2009](#); [Galanis 2017](#); [Galanis 2019](#));
- one trial (58 participants) involving BEV + carboplatin (CAB) ([Field 2015](#));
- one trial (83 participants) involving BEV + desatinib (DAS) ([Galanis 2019](#));
- one trial (79 participants) involving BEV + irinotecan (IRI) ([Friedman 2009](#));
- one trial (64 participants) involving BEV + onartuzumab (ONA) ([Cloughesy 2017](#));
- one trial (49 participants) involving BEV + TRC105 ([Galanis 2017](#));
- one trial (128 participants) involving BEV + VB111 ([Cloughesy 2018](#));
- one trial (32 participants) involving fotemustine (FOM) ([Brandes 2016b](#));
- one trial (53 participants) involving BEV + HSPPC96 vaccine ([Bloch 2017](#)).

The network diagram is presented in [Figure 10](#), the league table showing HRs and 95% CI estimates for all intervention comparisons in [Table 5](#) and the forest plot in [Figure 11](#). The network comprised mainly novel treatments added to bevacizumab compared with bevacizumab. As expected, pooled network estimates suggested that, compared with bevacizumab, adding treatments to bevacizumab was associated with a higher frequency of severe adverse events. Fotemustine was also compared with

bevacizumab and there was no clear difference [Summary of findings 4](#).

**Figure 10. Severe adverse events - network 2**

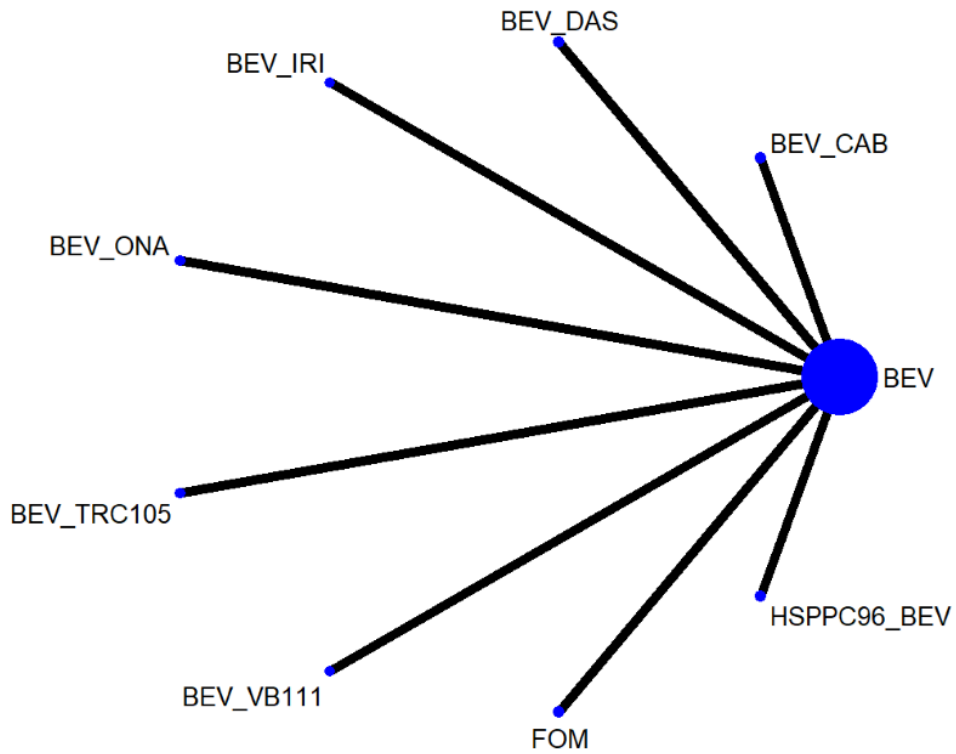
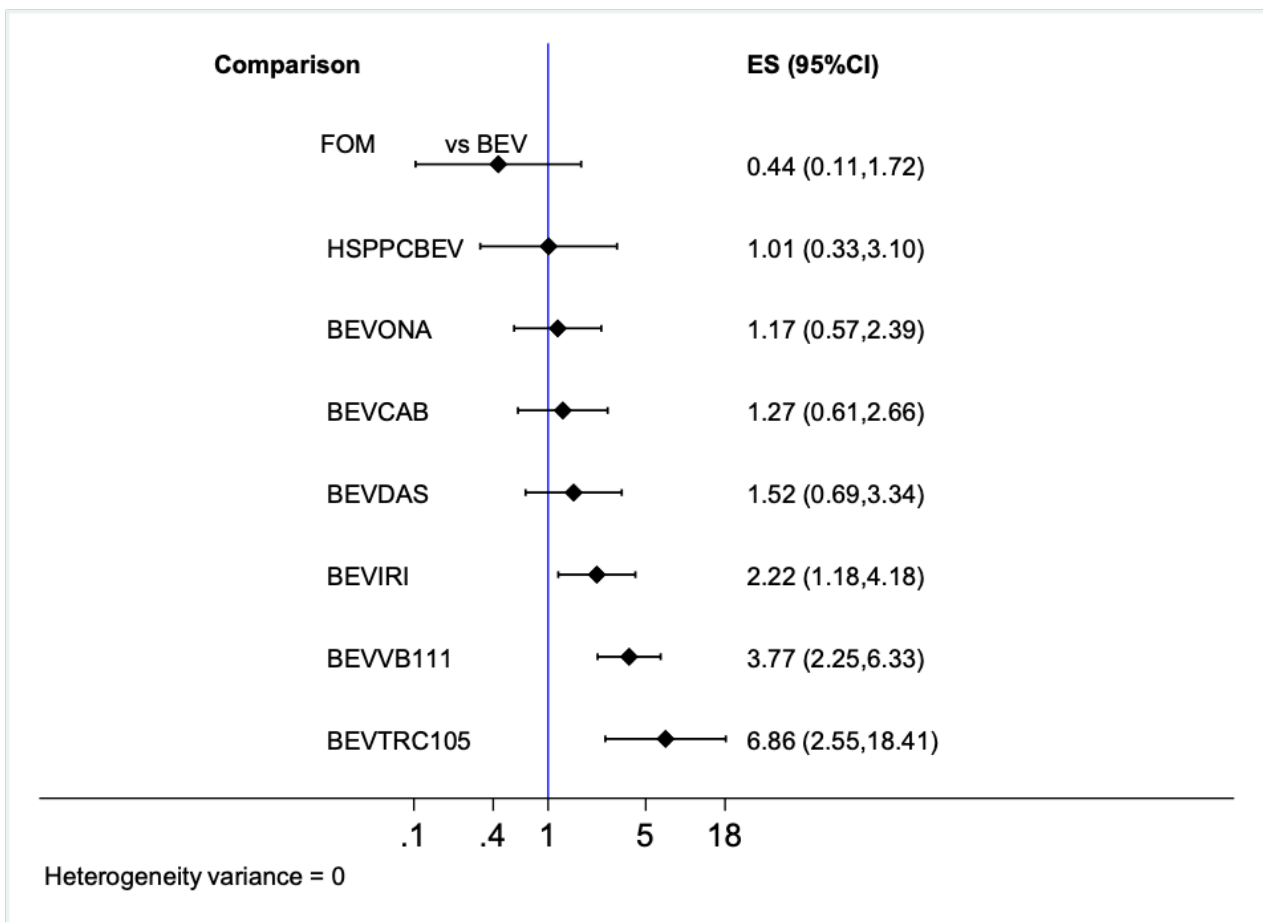


Figure 11. Severe adverse events forest plot for network 2 (treatments vs BEV)



In terms of ranking, fotemustine ranked best with fewest severe adverse events, BEV ranked second, BEV + HSPPV96 vaccine ranked third, BEV + ONA ranked fourth, BEV + CAB ranked fifth, BEV + DAS ranked sixth, BEV + IRI ranked seventh, BEV + VB111 ranked eighth and BEV + TRC105 ranked worst.

**Brief economic commentary**

For this brief economic commentary, we summarise the results of identified studies based upon what the study authors have said. These studies have not been critically appraised, and the studies may have used methods that are not consistent with accepted practice. For this reason and because the studies are conducted at different times and in different places, we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of the different strategies to manage recurrent glioma.

The results of the economic search yielded four economic evaluations that compare the costs and benefits of the management of recurrent glioma. Three of the studies were reported to be cost-effectiveness analyses (Conen 2017; Ruiz-Sanchez 2016; Voigt 2016). The other study was reported to be a cost-effectiveness analysis and cost-benefit analysis (Roussakow 2017). The studies were all conducted in different countries. One study was conducted in Switzerland (Conen 2017); one in Spain (Ruiz-Sanchez 2016); one in the USA (Voigt 2016); and one in Germany (Roussakow 2017). Two of the studies assessed the

use of bevacizumab (Conen 2017; Ruiz-Sanchez 2016); one study assessed modulated electrohyperthermia concurrent to dose-dense temozolomide (Roussakow 2017); and one assessed the value of laser interstitial thermal therapy (LITT) where maximal safe resection may not be feasible (Voigt 2016).

Conen 2017 is a study (reported in a conference abstract) that retrospectively used data from a GBM database over a five-year period to assess the cost-effectiveness of the use of bevacizumab in recurrent GBM. The study used a sample of 82 newly diagnosed GBM patients, of which 75 had a first line treatment, 36 had a second line treatment and 14 had a third line therapy. Forty per cent of patients were treated with bevacizumab at first or second recurrence. The authors conclude that bevacizumab treatment increased the overall treatment costs by 1.7 times. The population-adjusted incremental cost-effectiveness ratio (ICER) was CHF (Swiss francs) 75,669 per life-year gained (the price year was not stated). The authors conclude that patients who received bevacizumab treatment for GMB recurrences had longer overall survival and longer quality-adjusted survival at costs below the accepted threshold of CHF 100,000 per life year gained. The authors state that whether this estimated increase in lifespan is a direct result of bevacizumab treatment or a consequence of a selection bias needs to be addressed prospectively.

Ruiz-Sanchez 2016 carried out a cost-effectiveness analysis on the bevacizumab-irinotecan regimen in GBM recurrences in a

retrospective cohort study design with a control group. The intervention group included patients diagnosed with primary GBM between January 2001 and December 2011 in the Principality of Asturias (Spain) and treated in the Central University Hospital of Asturias (HUCA; Oviedo, Spain). The control cohort included all patients treated with TMZ between January 2001 and December 2006. There were 151 patients in the non-bevacizumab control cohort and 52 in the bevacizumab-irinotecan cohort. Costs, valued in 2014 EUR, were derived from the study data (including cost of the antineoplastic drug treatment, cost of the antineoplastics, administration and monitoring of administration and premedication). In the cohort with the regimen that included bevacizumab-irinotecan, the final cost for the 36 patients treated stood at EUR 629,278. The cost in the control cohort was EUR 16,771. In this way, increasing survival by 4.4 months for 36 patients came to EUR 612,506, meaning an additional cost of EUR 46,402 per person for each year of life gained. The authors conclude that bevacizumab-irinotecan is an effective therapy but it is not cost-effective. As such, they do not recommend adoptions by their specific local public health system.

The analysis by [Voigt 2016](#) carried out a model-based analysis that did not primarily focus on recurrent glioma, but did include a sensitivity analysis focusing on the effects of recurrence, and the subsequent impact of that on patient and cost outcomes. A decision tree was developed to evaluate the cost-effectiveness of using brain laser interstitial thermal therapy (LITT) versus current treatments. The model was purported to adopt the societal perspective; the included costs and benefits are primarily healthcare based, however, and do not include any wider costs. The decision tree evaluated the initial procedure and the resultant outcome (i.e. gross total resection, subtotal resection) using probabilities as identified in the literature. Costs are presented in 2015 US dollars (USD). Patients were followed through the treatment decision tree until they died. The incremental cost per life year gained was USD 48,552 when compared to biopsy. This authors conclude this is higher than is acceptable using an “International Threshold” of USD 32,575/LYG (which is based on Spanish systematic review of [Barrios 2012](#)) but acceptable from US threshold of USD 50,000/LYG. A one-way sensitivity analysis was carried out to assess how GBM recurrence affects this incremental cost-effectiveness. The authors report that the higher the occurrence of local GBM recurrence (vs. diffuse recurrence), the more likely brain LITT was to be cost-effective. This was based on willingness to pay (WTP) of USD 2714 per month based on the “International Threshold”.

[Roussakow 2017](#) assessed the efficacy and cost-effectiveness of modulated electrohyperthermia (mEHT) concurrent to dose-dense temozolomide (ddTMZ) 21/28 days regimen to five pooled ddTMZ 21/28 days cohorts (114 patients) enrolled between 2008 and 2013. A retrospective clinical and economic evaluation was based on the comparison and effect-to-treatment analysis (ETA) of a retrospective, single-arm study performed in two German centres between 2000 and 2005. The results of the regression analysis show the ddTMZ+mEHT cohort did not significantly improve mean survival time (mST) against the pooled ddTMZ 21/28 days cohorts. Using the effect-to-treatment analysis (ETA) suggests that mEHT significantly enhances the efficacy of the ddTMZ 21/28 days regimen, with significantly less toxicity and an estimated maximal attainable median survival time of 10.10 months. The author reported carrying out a cost-effectiveness analysis with results presented as a cost-utility ratio. They also reported carrying out

a cost-benefit analysis. Costs were expressed in 2017 US dollars and Euros. Two cost models were used for the cost-effectiveness analysis: conditionally termed ‘German’ and ‘US’. The first, so-called German option, is specific for a high-income country with rigid governmental regulation of the medical market, which leads to relatively low prices for pharmaceuticals with low variance. The second, so-called US option, is specific for a high-income country with lower governmental regulation, which leads to relatively high prices for pharmaceuticals with higher variance. The cost-utility ratio presented found that the ddTMZ+mEHT regimen, both in the German (EUR 19,871 per QALY (95% CI 17,719 to 22,024) and the US (USD 32,704/QALY (95% CI 27,215 to 38,193) models were less than that of the comparator. The sources of the utility values and how these QALY values are derived are not reported. The purported cost-effectiveness analysis and cost-benefit analysis only consider costs, not natural units or a monetary valuation of benefits and, thus, are in fact cost analysis, meaning that these elements of the study are only partial economic evaluations.

In summary, the economic evidence identified in this review found conflicting evidence on the use of bevacizumab in recurrent GBM. Of the two studies which evaluated its use, [Conen 2017](#) reported it to be a cost-effective intervention, whereas [Ruiz-Sanchez 2016](#) did not. [Voigt 2016](#) estimated the cost effectiveness of the use of brain LITT versus current treatments and concluded that it improves survival at a cost which appears to be of good value to society according to US thresholds for good value. [Roussakow 2017](#) reported evidence on the cost-effectiveness of modulated electrohyperthermia (mEHT) concurrent to dose-dense temozolomide (ddTMZ) and concluded that ddTMZ+mEHT is cost-effective, budget-saving and profitable, although methods used are not consistent with definitions of the different types of economic evaluation. Economic studies of most treatments evaluated in this review are lacking.

## DISCUSSION

### Summary of main results

We included 34 RCTs and 8 non-RCTs involving 5236 patients with progressive/recurrent GBM; 20 studies involved patients with first recurrences and the remainder involved patients with subsequent recurrence or the study sample comprised patients with mixed recurrences (e.g. first, second and/or third recurrences). Several studies lacked suitable data and we could not connect them in the network meta-analyses (NMA), hence we did not grade evidence from these single studies and non-randomised studies. We judged most RCTs to be at a low risk of bias and NRSs at high risk of bias. Most interventions were evaluated in single studies and included trials of systemic chemotherapy agents, re-operation, re-irradiation, anti-angiogenic agents, antibody therapies, tumour-treating fields, and vaccines alone or in combination. For first recurrence, 11 interventions (involving 9 RCTs and 1931 participants) were connected in the network for overall survival (OS), and eight (involving 7 RCTs and 1500 participants) in the network for progression-free survival (PFS). No studies in the NMA evaluated surgery, re-irradiation, PCV (procarbazine, lomustine, vincristine), TMZ re-challenge or best supportive care. We could not perform NMA for second or later recurrence due to insufficient data. Quality of life data were sparse. Only one NRS evaluated best supportive care.



## First recurrence (NMA findings)

Median overall survival (OS) across included studies in the NMA ranged from 5.5 to 12.6 months and median PFS across included studies ranged from 1.5 months to 4.2 months. We found no high-certainty evidence that any treatments tested were better than lomustine, including the following.

### **Bevacizumab plus lomustine**

Evidence suggested that there is probably little or no difference in OS between bevacizumab (BEV) combined with lomustine (LOM) and LOM monotherapy (HR 0.91, 0.75 to 1.10; moderate-certainty evidence).

Low-certainty evidence suggested that BEV + LOM may improve PFS compared with LOM monotherapy (HR 0.57, 95% CI 0.44 to 0.74) and more evidence is needed.

### **Bevacizumab monotherapy**

Low-certainty evidence suggested there may be little or no difference in OS between BEV and LOM monotherapies (HR 1.22, 95% CI 0.84 to 1.76) and that there may be little or no difference in PFS between BEV and LOM monotherapies (HR 0.90, 95% CI 0.58 to 1.38; low-certainty evidence); more evidence is needed.

### **Regorafenib (REG)**

Evidence suggested that REG may improve OS compared with LOM but more evidence is needed (HR 0.50, 95% CI 0.33 to 0.76; low-certainty evidence). Evidence on PFS was very low certainty.

### **Temozolomide (TMZ) plus Depatux-M (ABT414)**

With regard to OS, low-certainty evidence suggested that TMZ plus ABT414 may be more effective than LOM (HR 0.66, 95% CI 0.47 to 0.92) and may be more effective than BEV (HR 0.54, 95% CI 0.33 to 0.89; low-certainty evidence) but more evidence is needed.

### **Fotemustine (FOM)**

Evidence suggests that FOM and LOM may have similar effects on OS (HR 0.89, 95% CI 0.51 to 1.57, low-certainty evidence).

### **Bevacizumab and irinotecan (IRI)**

Evidence on BEV + irinotecan (IRI) versus LOM for both OS and PFS is very uncertain.

Evidence on BEV + IRI versus BEV monotherapy suggested that there is probably little or no difference between these options for OS (HR 0.95, 95% CI 0.70 to 1.30; moderate-certainty evidence) and PFS (HR 0.95, 95% CI 0.70 to 1.30; moderate-certainty evidence).

Treatments were ranked according to effectiveness on OS as follows: FOM ranked first, BEV + LOM ranked second, LOM ranked third, BEV + IRI ranked fourth and BEV ranked fifth. It is important to note that ranking does not take into account the certainty of the evidence, which indicated that there was little or no difference between BEV + LOM and LOM, probably little or no difference between FOM and LOM, and probably little or no difference between BEV + IRI and BEV.

## Other interventions for first recurrence

### **Re-operation with or without re-irradiation and chemotherapy**

Three non-randomised studies evaluated re-operation versus no re-operation with or without re-irradiation and chemotherapy and these suggested possible survival advantages with re-operation within the context of being able to select suitable candidates for re-operation (Azoulay 2017; Scorsetti 2015; Suchorska 2016).

### **Novel agents**

Findings of a small pilot study that evaluated a cannabidiol:delta-9-tetrahydrocannabinol (CBD:THC) oro-mucosal spray compared with placebo suggested that survival may be improved with CBD:THC among people receiving dose-intense TMZ (Twelves 2017).

## Second or later recurrence

Data on second and subsequent recurrence was sparse.

### **Bevacizumab monotherapy**

One non-randomised study compared BEV with best supportive care for people with chemorefractory disease (second and third recurrence) and showed a survival advantage with BEV; the study was at a high risk of bias, however, as participants selected their treatments and many in the BEV arm also received radiotherapy.

### **Radiotherapy plus bevacizumab**

Limited evidence from three heterogeneous studies (different control groups and populations with different levels of GBM recurrences) reported findings of improved PFS or OS with this intervention for all or for selected candidates. More evidence on radiotherapy with and without BEV is needed.

### **Tumour-treating fields**

Evidence from one RCT suggested that there may be little difference in effects on PFS or OS of tumour-treating fields (TTF) compared with physician's choice of treatment in this context.

## Severe adverse events (SAEs)

Two distinct networks were constructed around LOM (5 RCTs, 6 interventions, 1024 participants) and BEV (8 RCTs, 9 interventions, 1044 participants). In the LOM network, LOM ranked best and REG second best. BEV + LOM were associated with significantly greater risk of SAEs than LOM monotherapy (RR 2.51, 95% CI 1.72 to 3.66, high-certainty evidence), and ranked joint worst with CED + LOM.

The BEV network comprised mainly novel treatments added to BEV compared with BEV. In general, adding treatments to bevacizumab was associated with a higher frequency of SAEs compared with BEV monotherapy. FOM ranked best, BEV ranked third and BEV + IRI ranked seventh. Other ranked treatments were clinically ineffective. The SAE network connections did not facilitate ranking lomustine and bevacizumab against each other.

## Quality of life (QoL)

Quality of life data reported in seven studies of different interventions were sparse and unreliable, mainly due to high drop-out rates.

## Overall completeness and applicability of evidence

The 2015 JLA priority question was "In second recurrence glioblastoma, what is the effect of further treatment on survival and quality of life, compared with best supportive care?" (JLA 2015). We found little good-quality evidence that addressed this question as the one study that compared bevacizumab with best supportive care was at a high risk of bias (Cuncannon 2019). Evidence on other interventions, such as radiotherapy, systemic anti-cancer agents and best supportive care, was lacking. We found only one small study of cannabinoids, which have shown promising anti-cancer functions in GBM (Dumitru 2018), and the single study evaluating a ketogenic diet was at high risk of bias (Santos 2018); these types of interventions are of interest and high-quality RCTs on their effects in recurrent GBM are needed (Martin-McGill 2018).

Other evidence was very incomplete and the best treatment options compared with each other, even for first recurrence, remain uncertain. We found no RCTs comparing the commonly used regimen of PCV (procarbazine, lomustine and vincristine) and lomustine, or TMZ re-challenge. One trial that employed TMZ re-challenge used it in combination with a novel agent (Depatux-M/ABT414) and, although patients in this arm experienced improved survival relative to the control group who received LOM (73% of control participants) or TMZ (27% of control participants), it was not possible to determine whether these effects were due to the TMZ or ABT414 component of the treatment, or both (van den Bent 2018).

With respect to people with second or later recurrence, among included studies the following interventions have shown potential (see Table 1) and, although it was not possible to conduct a NMA for second recurrence, they appear to warrant further investigation, bearing in mind that combination treatments are frequently associated with a higher risk of severe adverse events: radiotherapy; radiotherapy + bevacizumab; radiotherapy + APG101; bevacizumab + temozolomide; and bevacizumab + irinotecan.

## Quality of the evidence

Quality of the evidence on lomustine with or without bevacizumab and bevacizumab monotherapy was generally of a moderate to high quality; these interventions had the most data and trials were at low risk of bias. Quality of evidence on other interventions was often from single studies and, therefore, tended to be of a lower quality due to the sparse data and open-label design of many of the phase 2 trials. Most included studies evaluated novel agents that were compared with or added to lomustine or bevacizumab and many novel agents tested in this patient population have not been investigated further in phase 3 trials because the early phase studies failed. A recent exception is regorafenib, which showed potential survival benefits compared with lomustine in a phase 2 trial. This evidence was of a generally low quality due to sparse data from a single, open-label study. A phase 3 trial of this intervention among patients with first recurrence of GBM is ongoing (NCT03970447 2019b). Another intervention for which the evidence was generally graded low-certainty is ABT414 (Depatux-M) + TMZ, and more evidence on these novel interventions is needed.

We did not grade the evidence on second recurrence because either the novel interventions did not show a clinical benefit, e.g. TRC105 + BEV (Galanis 2017), or narrative findings were based mainly on conference abstracts at unclear risk of bias and/or non-randomised

studies that were at high risk of bias, for example radiotherapy and bevacizumab (Cuncannon 2019; Modh 2018; Tsien 2019).

## Potential biases in the review process

We aimed to provide a balanced independent evaluation on this topic across a large number and wide range of interventions assessed since 2005, when the Stupp regimen became the standard of care for treatment of newly diagnosed GBM. We are mindful that the review process itself may introduce bias. We took steps to minimise the potential for such bias by ensuring that at least two members of the review team, working independently, screened titles identified by the search strategy, assessed full texts of reports for potentially eligible studies, extracted data and assessed risk of bias. Where we had any doubt, or where there was discrepancy between reviewers, we consulted the wider review team.

We acknowledge that a potential bias may have been introduced by including the TMZ/LOM arm of van den Bent 2018 in the LOM treatment node of our NMAs. This three-arm trial evaluated ABT414 (Depatux-M) versus ABT414 + TMZ versus TMZ or LOM. At the time of the analysis it was unclear what proportion of the participants in the TMZ/LOM arm had received LOM as limited findings were reported in conference abstracts. To investigate the effects of including this trial, we performed a sensitivity analysis by excluding this trial from analyses. This did not change the treatment rankings of LOM or the other treatments, and we concluded that it was unlikely that bias was introduced by including this trial in the NMA. Full details of this trial have since been published showing that 21 out of 77 participants received TMZ and the rest, 56 out of 77 or 73%, received LOM (van den Bent 2020).

## Agreements and disagreements with other studies or reviews

A study of patients from eight consecutive phase 2 clinical trials conducted in the USA between 1986 and 1995 showed that the median progression-free survival time for recurrent GBM was 9 weeks (95% CI 8 to 10 weeks) and the median OS time was 25 weeks (95% CI 21 to 28 weeks) (Wong 1999). With reference to Table 1, the review findings suggest that median survival for people with recurrent GBM in clinical trials in the post-Stupp era may not have improved substantially. For people with a first recurrence, median PFS ranged from 1.5 to 4.2 months (6.5 to 18.3 weeks) across included study arms; and median OS ranged from 5.5 months to 12.6 months (23.9 months to 54.8 months).

## Bevacizumab

With regard to bevacizumab, our findings are in agreement with other reviews, which have concluded that bevacizumab has little or no effect on overall survival in patients with recurrent GBM (Ameratunga 2018; Lombardi 2017). We found that bevacizumab improved progression-free survival but not overall survival compared with lomustine monotherapy. Progression-free survival is a less reliable outcome in this context compared with overall survival because pseudo-response can occur in which contrast-enhancing disease may seem improved or stable with bevacizumab when it is not. When bevacizumab was combined with lomustine, we also found an increased risk of severe adverse events; thus our findings suggest that the net clinical effect of bevacizumab added to lomustine may not necessarily be one of overall benefit and such combinations need to be carefully considered. We found no evidence of benefit with the bevacizumab-

irinotecan combination in recurrent GBM and agree with the [Abdel-Rahman 2015](#) review, that this regimen should be limited to a clinical trial setting until better evidence is available. Evidence on the effectiveness of BEV combined with re-irradiation is uncertain and needs further study.

### TMZ re-challenge

We included two RCTs that evaluated TMZ in recurrent GBM: one in combination with ABT414 ([van den Bent 2018](#)); and the other in combination with bevacizumab ([Gilbert 2017](#)). These data were insufficient to draw conclusions on the effectiveness of TMZ re-challenge, which may be more effective for MGMT methylated tumours compared with other options.

An excluded study, [Sun 2013](#), was an RCT conducted in patients with recurrent GBM or anaplastic astrocytoma comparing TMZ with semustine (Me-CCNU). Results were not reported separately for the GBM subgroup. Six-month PFS for the mixed population was 78.9% in the TMZ group compared with 55.9% in the Me-CCNU group ( $P < 0.05$ ) and study authors concluded that TMZ was better than Me-CCNU with mostly mild adverse events.

[Weller 2015](#) was a TMZ re-challenge study that compared two maintenance TMZ cycles in an RCT of 105 patients with recurrent GBM. It was not suitable for inclusion in this review because it was a dose-finding study (both arms received TMZ; one week on, one week off, versus three weeks on, one week off). Median time to treatment failure was longer among patients with MGMT-methylated tumours compared to those with MGMT-unmethylated tumours (3.2 months vs 1.8 months) but not significantly different between the treatment arms (median of ~ 2 months). Investigators concluded that TMZ re-challenge should no longer be used in patients with recurrence of MGMT-unmethylated tumours but that it may be appropriate for those with MGMT-unmethylated tumours at first recurrence.

### Re-operation and/or re-irradiation

We found little evidence on the effectiveness of re-operation and re-irradiation. Similarly, other reviews have highlighted the need for high-quality RCTs of re-irradiation for recurrent GBM to be conducted ([Kim 2019](#); [Kazmi 2019](#)). Evaluating limited evidence from 50 non-comparative studies, [Kazmi 2019](#) found that re-irradiation may improve survival with relatively low toxicity. However, the best salvage radiotherapy regimen in this context remains to be defined. [Kim 2019](#) highlights that narrow margins should be observed to limit irradiation of normal brain tissue. In addition, it has been suggested that prognostic scoring that makes use of MGMT methylation, age, tumour volume at recurrence and other predictive biomarkers could be used to facilitate selection of patients to different treatment options ([Chapman 2019](#); [Kim 2019](#)).

### Immunotherapies

Findings from this review show that none of the treatments that have been developed to harness the immune system to target cancer have had demonstrable clinical success in recurrent GBM. Arguably, bevacizumab is the only agent to date that may have an effect equivalent to established systemic chemotherapeutic agents, such as lomustine. It has been suggested that surgical debulking and localised delivery may enhance the effect of immunotherapies in recurrent GBM and more research in this area is anticipated ([Brown 2018](#)).

## AUTHORS' CONCLUSIONS

### Implications for practice

Based on the available evidence for people with a first recurrence of GBM previously treated with surgery and chemoradiotherapy (Stupp protocol), lomustine (LOM) monotherapy appears to be the best chemotherapy option. Findings suggested that adding bevacizumab to lomustine therapy probably does not improve overall survival and is associated with a significantly greater risk of severe adverse events. We found no evidence on TMZ re-challenge or PCV, two commonly used salvage regimens, in this context. Re-operation with or without re-irradiation and chemotherapy may be suitable for selected candidates.

In the course of conducting the review, we had hoped to answer the JLA question on best treatments for second recurrence; however, although several studies included people with a second recurrence, data were usually not separately analysed and reported for this subgroup. We found little reliable evidence on re-irradiation with or without bevacizumab and on best supportive care. The role of tumour-treating fields is also uncertain.

While there is an acceptance of the need to develop and test new agents, combination treatments for recurrent GBM are likely to be associated with a higher risk of severe adverse events than monotherapy and people should be informed of this when deciding whether or not to participate in such clinical trials.

The cost-effectiveness of different treatment options for recurrent GBM remains unclear as economic studies in this field are lacking.

### Implications for research

Findings of this review have highlighted the following research questions in this field. Trial participant randomisation and reporting of findings should be stratified by first and second recurrence. Prognostic scoring to select participants to different trials may be worthwhile.

- For patients with first or second recurrence, what are the effects of PCV versus lomustine, or lomustine or PCV versus TMZ re-challenge?
- For patients with first or second recurrence, what are the effects of radiotherapy or bevacizumab + radiotherapy compared with lomustine?
- Does delaying BEV to chemorefractory disease extend survival and improve quality of life beyond best supportive care alone?
- For patients with resectable tumours, what are the effects of re-operation?
- What are patients' and health care professionals' experiences and views on treatment of recurrent GBM at first and subsequent recurrences?

We identified several ongoing trials. These include a trial of bevacizumab + dose-dense TMZ versus bevacizumab alone ([JCOG1308C 2019](#)); surgery followed by second-line therapy versus second-line therapy alone ([NCT02394626 2015](#)); and a phase 3 trial of regorafenib versus lomustine ([NCT03970447 2019b](#)). Another ongoing trial is evaluating the effects of early palliative care (STEP care) among patients with various cancers including glioblastoma ([ACTRN12617000534381 2017](#)).

Early studies of some oncolytic virus treatments and vaccines have shown promise (e.g. see [Ji 2016](#); [Lang 2018](#); [Reardon 2020](#)) and further clinical trials of these therapies are anticipated. Alternative interventions, such as cannabinoid treatments and dietary measures, also need further study. Studies should evaluate economic outcomes.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Azoulay 2017

##### Study characteristics

Methods	<p>Retrospective study</p> <p>Country: Canada</p> <p>Accrual dates: patients receiving initial treatment between Jan 2005 and Dec 2012, this study was carried out at first progression (dates not clear)</p> <p>Trial registration: not trial</p> <p>Funding: not clear</p> <p>DOI: not clear</p>
Participants	<p>No. analysed: 183 (3 lost to follow-up)</p> <p>Inclusion/exclusion criteria: patients receiving initial treatment for GBM between January 2005 and December 2012 that had received standard treatment (maximal safe resection, concurrent chemoradiation with RT dose of 60 Gy (in 20 or 30 fractions) followed by adjuvant temozolomide chemotherapy (TMZ)</p> <p>Age: adults, median age 58</p> <p>Gender: 71 F (39.4%) 109 M (60.6%)</p> <p>Performance status:</p> <p>MGMT status: 70 unmethylated (50.4%) 69 methylated (49.6%),</p> <p>Initial treatment details: (at least 80% must have had chemoradiotherapy) All had standard treatment which included chemoradiation.</p> <p>Sort of recurrence: first progression</p> <p>Time from initial diagnosis: time to tumour progression from diagnosis was median 7.43 months.</p>
Interventions	<p>Arm 1: re-operation with or without salvage chemoradiotherapy (69)</p> <p>Arm 2: salvage chemoradiotherapy or best supportive care depending on MDT decision (111)</p> <p>The decision re treatment group was based on an MDT meeting decision taking into account prognostic factors such as tumour location and extent and patient characteristics. Patients who were re-operated on were "matched" to patients who were not operated on in further analysis.</p>
Outcomes	Survival from time of first progression.
Notes	
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement    Support for judgement</b>

**Azoulay 2017** (Continued)

Random sequence generation (selection bias)	High risk	Not RCT. This study is at high risk of selection bias. It included a cohort of patients with the decision whether or not to re-operate based on MDT meeting taking into account prognostic factors, tumour extent and location.
Allocation concealment (selection bias)	High risk	High risk of selection bias. Treatment modalities decided by MDT decision.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of patients or staff.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment but survival outcomes may be less susceptible to bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most patients were followed up.
Selective reporting (reporting bias)	Unclear risk	Not apparent. Although as the decision re treatment allocation was based on prognostic factors and outcome was progression/survival results are likely to be confounded.
Other bias	High risk	Authors state limitation: lack of consistent selection criteria for each treatment modality.

**Batchelor 2013**
**Study characteristics**

Methods	<p>A phase 3, 3-arm, multicentre RCT with partial blinding; ratio 2:2:1</p> <p>Country: Canada, Germany, France, the Netherlands, UK, USA</p> <p>Accrual dates: Oct 2008 to Sept 2009</p> <p>Trial reg: NCT00777153, REGAL</p> <p>Funding: AstraZeneca</p> <p>DOI: several authors declared stock interests and pharmaceutical funding</p>
Participants	<p>No. randomised: 325</p> <p>No. analysed: 323</p> <p>Inclusion criteria: People with recurrent GBM after TMZ + RT (first recurrence); Karnofsky PS &gt; 70%; MMSE &gt; 15; life expectancy of &gt; 12 weeks</p> <p>Exclusions: prior anti-VEGF therapy or cranial radiation within 3 months of study entry</p> <p>Age: median age = 54 years</p> <p>Gender: NR</p> <p>KPS PS: 70 to 80 = 50% group 1, 48% group 2 and 36.2% group 3; 80 to 100 = 50% group 1, 51.2% group 2; 62.5% group 3</p>

**Batchelor 2013** (Continued)

Resection for recurrent disease: group 1 = 38.2%, group 2 = 38%, group 3 = 36.9%

MGMT: NR

Initial treatment: TMZ + RT

Interventions	Arm 1: cediranib monotherapy (30 mg daily po) Arm 2: cediranib (20 mg daily po) + lomustine (110 mg po every 6 weeks) Arm 3: lomustine (110 mg po every 6 weeks) + placebo (once daily)
Outcomes	PFS, OS, SAEs, TTD
Notes	Group 3 had better PS than the other groups.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients randomly assigned, stratified by age and resection status". Not specifically stated.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical to the cediranib.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"independent, centralized, treatment-arm blinded radiographic review"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients excluded from analysis
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Bloch 2017**
**Study characteristics**

Methods	Design: open-label, 3-arm RCT; findings published in ClinicalTrials.gov Country: USA Accrual dates: NR Trial ID: NCT01814813 Funding: NIH support; U10CA180882, U10CA180821, U10CA180868, U24CA196171.
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**Bloch 2017** (Continued)

Declaration of interests: NR

Participants	Randomised: 90  Inclusion/exclusion: Patients with 1st/2nd recurrence of resectable GBM; must have received prior RT + TMZ; no prior treatment with anti-angiogenic agent targeting the VEGF pathway; no RT within 90 days; no gliadel wafers; Karnofsky functional status rating $\geq 70$  Gender: 27.8% F: 72.2% M  Performance status: KPS $\geq 70$  MGMT status: NR  Re-operation: all patients underwent re-operation  Time from diagnosis: NR
Interventions	Patients were randomized (1:1:1) to receive:  Arm 1: HSPPC-96 vaccine followed by bevacizumab at subsequent progression  Arm 2: concurrent HSPPC-96 vaccine and bevacizumab  Arm 3: bevacizumab alone
Outcomes	OS, PFS, toxicity (CTCAE v5)
Notes	Authors concluded that "The study failed to demonstrate a survival benefit for patients treated with HSPPC-96 alone or in combination with bevacizumab compared to bevacizumab alone" on pre-planned interim analysis.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement
Other bias	Unclear risk	All Principal Investigators are employed by the organization sponsoring the study

**Brandes 2016a**
**Study characteristics**

Methods	<p>Design: 3-arm, randomized Bayesian augmented control Phase II</p> <p>Country: multicounty (34 centres in 10 countries)</p> <p>Accrual dates: May 2012 and July 2014</p> <p>Trial reg: NCT01582269</p> <p>Funding: Eli Lilly and Company (Indianapolis Indiana).</p> <p>Declaration of interests: Dr. Brandes has received traveling grants for ASCO, SNO, and ESMO meetings from Eli Lilly and Company, Roche, and Pfizer. Dr. Wick has received research grants from Apogenix, Boehringer Ingelheim, Eli Lilly and Company, Immutics, MSD, and Roche as well as honoraria for lectures or advisory board participation from MSD and Roche. He is or has been the coordinating investigator for sponsored clinical trials evaluating APG101 (Apogenix), bevacizumab (Roche), galunisertib (Eli Lilly and Company), temozolomide (MSD), and temsirolimus (Pfizer). Dr. Steinbach has received a grant from Merck as well as honoraria for lectures, travel, or advisory board participation from Roche, Medac, and Mundipharma. Dr. Carpentier has served as a consultant for Roche. Drs. Capper, Cher, Chinot, Kesari, Rodon, Sepu ´ lveda-Sanchez, Specenier, and Wheeler have no financial disclosures. Drs. Gueorguieva, Desai, and Guba and Ms. Cleverly, Ms. Smith, and Mr. Miles are employees of Eli Lilly and Company (Indianapolis, Indiana) and may hold company stock. Dr. Lahn. is a former employee of Eli Lilly and Company and holds company stock.</p>
Participants	<p>No. randomised: 158 (180 patients entered)</p> <p>No. analysed: 158</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> <li>1. Patients must have had evidence of tumour progression as determined by Response Assessment in Neuro Oncology (RANO) criteria following at least 12 weeks after the end of standard chemoradiotherapy</li> <li>2. Patients must have completed 1 prior regimen (all patients were considered at first relapse)</li> <li>3. Patients were required to have adequate haematologic, hepatic, and renal function</li> <li>4. Patients had discontinued all previous therapies including chemotherapy (excluding palliative care for cancer) at least 4 weeks prior to study enrollment</li> </ol> <p>Exclusion criteria</p> <ol style="list-style-type: none"> <li>1. Medically uncontrolled cardiovascular illness, medically significant electrocardiogram abnormalities, and serious pre-existing medical conditions</li> <li>2. If person was enrolled in a clinical trial investigating galunisertib and/or vascular endothelial growth factor receptor (VEGFR) inhibitors</li> <li>3. If person had prior treatment for glioblastoma with nitrosourea (lomustine) and/or bevacizumab</li> </ol> <p>Median age: 58 years</p> <p>Gender: Male 64.6% &amp; Female 35.4%</p> <p>Performance status: 63.3% had ECOG PS ≤ 1</p> <p>MGMT: NR</p> <p>Resection/biopsy:</p> <p>Initial treatment details: standard chemoradiotherapy</p> <p>Details of treatment of first occurrence (2nd line?): not given</p>

**Brandes 2016a** (Continued)

Time from initial diagnosis: not given

Interventions	Arm 1: galunisertib monotherapy Arm 2: galunisertib plus lomustine Arm 3: lomustine monotherapy Oral galunisertib was given in a dose 300 mg/day (150 mg tablets twice a day, morning and evening) for 14 days followed by 14 days off in a 28-day cycle The first dose of lomustine was given as 100 mg/m <sup>2</sup> after 7 days of galunisertib treatment and thereafter (at the discretion of the investigator) was given orally once every 6 weeks at 100 to 130 mg/m <sup>2</sup>
Outcomes	OS, AEs, HRQOL and neurocognitive outcomes, response
Notes	Authors concluded that "Galunisertib + lomustine failed to demonstrate improved OS relative to placebo + lomustine. Efficacy outcomes were similar in all 3 arms."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized with a 2:1:1 allocation ratio; randomization used a <u>dynamic allocation method</u> to minimize imbalance according to the following factors:..."
Allocation concealment (selection bias)	Unclear risk	Not described in the study report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A "double-blinded study".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the study report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Slight imbalance between arms in % of men, and type of diagnosis at study entry. Funding and author interests noted.

**Brandes 2016b**
**Study characteristics**

Methods	Design: Phase 2 open-label, non-comparative, multicentre RCT Country: Italy Accrual dates: November 2011 and September 2012
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**Brandes 2016b** (Continued)

Trial reg: EudraCT: 2011-001363-46; NCT01474239 (AVAREG)

Funding: F. Hoffmann-La Roche Ltd.

Declaration of interests: A.A. Brandes: travel grants from Merck Serono Ltd and Pfizer Ltd; E. Franceschi: travel grant from F. Hoffmann-La Roche Ltd; E. Proietti: employee of Roche S.p.A. Italy as Medical Manager. All other authors have no conflicts of interest to declare.

Participants	<p>No. randomised: 91</p> <p>No. analysed: 91</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• Histologically confirmed glioblastoma (WHO classification) and (ii) first recurrence of glioblastoma following standard front-line RT/TMZ</li> <li>• Progression of documented disease as defined by RANO criteria at least 12 wks after completion of RT/TMZ, unless the recurrence was outside the radiation field or was histologically documented</li> <li>• Measurable disease by RANO criteria</li> <li>• Use of stable/decreasing corticosteroids within 7 days prior to randomization</li> <li>• Adequate haematologic, hepatic, and renal function</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• Prior antiangiogenic therapy for glioblastoma or MRI evidence of recent brain haemorrhage</li> <li>• History of clinically significant cardiovascular disease</li> <li>• History of pulmonary embolism/cerebral haemorrhage</li> <li>• Uncontrolled hypertension</li> <li>• Unhealed surgical wound</li> </ul> <p>Median age: 59 and 56 for BEV and FOT groups, resp.</p> <p>Gender: 62 Male (68%): 29 Female (32%)</p> <p>Performance status: ECOG 0 to 2, WHO performance status (PS) 0 to 2</p> <p>MGMT: data available from 73 participants of which 45 had MGMT+ (62% overall; 58% and 68% of patients treated with bevacizumab and fotemustine, respectively)</p> <p>Re-operation: 21 patients underwent surgical resection before study inclusion, 13 (22%) in the bevacizumab arm and 8 (25%) in the fotemustine arm.</p> <p>Initial treatment details: RT + TMZ</p> <p>Time from initial diagnosis: median from diagnosis to MRI at screening in days (range): BEV 331 (163 to 2271), FOT 462 (162 to 1383)</p>
Interventions	<p>Arm 1 (59 pts): bevacizumab (10 mg/kg i.v.) every 2 weeks.</p> <p>Arm 2 (32 pts): fotemustine 75 mg/m<sup>2</sup> i.v. was administered on days 1, 8, and 15 (induction phase); after a 35-day break, patients received fotemustine 100 mg/m<sup>2</sup> i.v. every 3 weeks (maintenance phase).</p>
Outcomes	OS, PFS, QOL and AEs
Notes	Since fotemustine was only a balancing arm, no formal efficacy comparison was made between the treatment arms.
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement    Support for judgement</b>

**Brandes 2016b** (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described in the report.
Allocation concealment (selection bias)	Unclear risk	Not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, but could be assumed “low” for primary outcome (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Brandes 2018**
**Study characteristics**

Methods	<p>Design: Phase 2 randomized, double-blind, placebo-controlled, multicentre (51 sites); ratio 1:1</p> <p>Country: Australia, Austria, Canada, Italy, Spain, Switzerland</p> <p>Accrual dates: August 2013 to December 2014</p> <p>Trial reg: NCT01860638 (TAMIGA)</p> <p>Funding: Not clear. F. Hoffmann-La Roche Ltd.</p> <p>Declaration of interests: Miguel Gil-Gil: F. Hoffmann-La Roche Ltd. (H, SAB); Frank Saran: F. Hoffmann-La Roche Ltd., Bristol-Myers Squibb (C/A); Antoine F. Carpentier: F. Hoffmann-La Roche Ltd. (C/A, H); Anna Nowak: F. Hoffmann-La Roche Ltd. (SAB); Warren Mason: F. Hoffmann-La Roche Ltd. (C/A); Gaetano Finocchiaro: Bristol-Meyers Squibb (C/A); George Fountzilas: Pfizer, Sanofi, Roche (SAB), AstraZeneca (H); Dana Michaela Cernea: F. Hoffmann-La Roche Ltd. (H); Oliver Chinot: F. Hoffmann-La Roche Ltd., Ipsen, AbbVie (C/A), Bristol-Myers Squibb, Celldex Therapeutics, Immatics, Servier Laboratories (H); Martina Makrutzki: F. Hoffmann-La Roche Ltd. (E); Chiedo Mpofo: F. Hoffmann-La Roche Ltd. (E, OI); Hans-Joerg Urban: F. Hoffmann-La Roche Ltd. (E); Josef Pichler: F. Hoffmann-La Roche Ltd. (H). The other authors declared no conflicts of interest</p>
Participants	<p>No. randomised: 123</p> <p>No. analysed: 123</p> <p>Inclusion/exclusion criteria following progressive disease after treatment with chemoradiotherapy and surgical resection: documented progression according to RANO criteria; eligibility for second-line treatment with lomustine and bevacizumab; ECOG PS 0-2; bevacizumab well tolerated and not interrupted for longer than 60 days during first-line treatment; tissue submission among participants for whom operation/re-operation is indicated before second-line treatment starts; operation/re-operation performed 28 days or more after last bevacizumab administration and second-line treatment initiated at</p>



**Brandes 2018** (Continued)

least 28 days after surgical wound healed; randomization within 28 days after progression among participants for whom operation/re-operation was not necessary

Exclusion: any other prior chemotherapy or RT for progression; prior or current anti-angiogenic treatment; treatment with any other investigational drug within 28 days or 2 investigational agent half-lives (whichever is longer) prior to study treatment; inadequate haematological, renal, or liver function; inadequately controlled hypertension; prior history of gastrointestinal perforation or abscess; clinically significant cardiovascular disease; history or evidence of central nervous system disease unrelated to cancer unless adequately treated with standard medical therapy; history or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding; serious non-healing wound, active ulcer, or untreated bone fracture; known hypersensitivity to any component of bevacizumab/placebo or any of the study drugs; active infection requiring IV antibiotics at start of study treatment; other malignancy within 5 years prior to study enrolment, except for carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ treated with curative intent; pregnant or lactating women; participation in any other study

Median age: 56 years (range 30 to 74)

Gender: Male n = 89 (72%) Female n = 34 (28%)

Performance status: ECOG 0 = 41%, ECOG 1 = 41% and ECOG 2 = 19%

MGMT: unmethylated: Arm 1 = 25, Arm 2 = 26. Methylated: Arm 1 = 12, Arm 2 = 11. Not all randomized patients had a valid MGMT status result.

Resection/biopsy: 8 underwent re-operation (7%), the remainder did not.

Initial treatment details: first-line treatment included RT plus TMZ and BEV, followed by maintenance treatment with 6 cycles of TMZ plus BEV, then BEV monotherapy until first disease progression (PD1).

Interventions	<p>Arm 1 (61 pts): CCNU + BEV</p> <p>Arm 2 (62 pts): CCNU + placebo</p> <p>The CCNU dose was 90 mg/m<sup>2</sup> (maximum of 160 mg) every 6 weeks, increasing to 110 mg/m<sup>2</sup> (maximum of 200 mg) in the absence of haematologic toxicity grade &gt; 1 during the first cycle.</p> <p>The BEV dose was 10 mg/kg every 2 weeks (intravenous). At PD2, patients continued to receive BEV or placebo (according to randomization at PD1) in addition to chemotherapy of investigator's choice.</p>
Outcomes	OS, SAE, HRQOL
Notes	<p>Participants in this study received BEV in addition to the Stupp protocol for primary treatment of GBM.</p> <p>This study was terminated prematurely because of a high drop-out rate and was underpowered to address the primary objective. "No survival benefit was observed with the use of BEV through multiple lines in patients with glioblastoma who had progressed after first-line treatment (radiotherapy + temozolomide + BEV). No new safety concerns arose from the use of BEV through multiple lines of therapy." No P values are reported and only 95% confidence intervals (CIs) are shown.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence generation was not clearly described in study report.
Allocation concealment (selection bias)	Unclear risk	This was not clearly described in study report.

**Brandes 2018** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Investigators and patients were blinded to this treatment".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators and patients were blinded to this treatment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The study was terminated prematurely because of a high drop-out rate during first-line treatment, implying underpowered (i.e. 60%) inferential testing; only 98 of the targeted 130 OS events for the primary endpoint were reached in the 123 randomized patients."
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Brown 2016**
**Study characteristics**

Methods	<p>Design: multi-centre, 2-armed, double-blinded phase II RCT; ratio 1:1</p> <p>Country: UK</p> <p>Accrual dates: May 2011 and August 2012</p> <p>Trial reg: NCT01310855</p> <p>Funding: AstraZeneca, Cancer Research UK E/10/044, the National Institute of Health Research/Wellcome University College Hospital (NIHR/UCH) Clinical Research Facility, the University College Hospital/University College London (UCH/UCL) Biomedical Research Centre and UCL Experimental Cancer Medicine Centre, and the National Brain Appeal.</p> <p>Declaration of interests: none of the authors declared any competing interests with respect to AstraZeneca.</p>
Participants	<p>No. randomised: 38</p> <p>No. analysed: 38</p> <p>Inclusion/exclusion criteria: life expectancy of 12 weeks; KPS &gt; 70. MMSE ≥ 15; presence of measurable tumour 7 days prior to enrolment; stable dose of steroids (8 mg/day) for at least 5 days prior to baseline MRI; adequate bone marrow reserve (absolute neutrophil count &gt; 1.5 × 10<sup>9</sup>/L); serum bilirubin &lt; 1.5 × ULRR; ALT and AST &lt; 5 × ULRR. Excluded if enzyme-inducing anti-epileptic drugs used within 2 weeks prior to enrolment, pregnancy or breast-feeding, and infection with HIV or hepatitis B or C.</p> <p>Median age: 57 (range 30 to 71)</p> <p>Gender: Female 11 (29%), Male 27 (71%)</p> <p>Performance status: KPS &gt; 80 = 68.4%; KPS 70 to 80 = 31.6%</p> <p>MGMT: NR</p> <p>Resection for recurrence: 6 patients (4 CED vs 2 GEF)</p> <p>Details of initial treatment: surgery + RT + TMZ</p>

**Brown 2016** (Continued)

Follow-up: at the time of the analysis, all patients had died, with a maximum follow-up time of 16.7 months.

Interventions	Arm 1 (19 pts): 30 mg CED plus 500 mg Gefitinib (both orally) Arm 2 (19 pts): 30 mg CED plus placebo (both orally)
Outcomes	PFS, OS, HRQOL, SAEs HRQOL was assessed using the EORTC QLQ-C30 and the EORTC brain tumour module BN-20. Patients were invited to complete forms at baseline, at 6-weekly intervals, and at discontinuation of treatment.
Notes	Authors concluded that there was a trend towards increased survival with CED + GEF compared with CED. Median OS was 7.2 months with CED + GEF and 5.5 months with CED + placebo. "Further studies of the combination...are warranted."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Online randomization system to produce/contain the numbers..." "Randomization was performed in the ratio 1:1 using an algorithm stratified by dichotomous factors of age..."
Allocation concealment (selection bias)	Low risk	"Upon receipt of registration...trial staff would use an online randomization system to produce container numbers for the assigned treatment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The contents of the bottles were concealed from site staff, patients and trial management"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"One patient on the cediranib plus gefitinib arm did not complete their medication diary so is excluded from the results."
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Cloughesy 2017**
**Study characteristics**

Methods	Design: randomized, double-blind, placebo-controlled, multicentre Phase II study Country: 42 centres across 8 countries (USA, Italy, Spain, France, UK, Canada, Germany, Switzerland). Accrual dates: June 2012 to January 2016 Trial reg: NCT01632228 (GO27819) Funding: F. Hoffmann-La Roche.
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**Cloughesy 2017** (Continued)

Declaration of interests: Timothy Cloughesy Consulting or Advisory Role: Genentech, Celgene, Tocagen, VBLTherapeutics, NewGen Therapeutics, Novartis, Upsher-Smith, Proximagen, Lpath, StemCycle, Amgen, INSYS Therapeutics Expert Testimony: Roche Gaetano Finocchiaro Travel, Accommodations, Expenses: Roche for 19th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology (2014). Cristobal Belda-Iniesta Employment: HM Hospitales, Merck Serono Honoraria: Roche, AbbVie, Merck Serono Consulting or Advisory Role: Roche, AbbVi. among others.

Participants	<p>No. randomised: 129</p> <p>No. analysed: 129</p> <p>Inclusion/exclusion criteria: prior treatment with chemoradiotherapy, no more than 1 prior line of chemotherapy, no prior treatment with bevacizumab, no sensitivity to bevacizumab or onartuzumab; Karnofsky performance status greater than or equal to (<math>\geq</math>) 70%</p> <p>Median age: 57 years in ONA + BEV group and 55 years in BEV group</p> <p>Gender: 83 Male (64%), 46 Female (36%)</p> <p>Performance status: all KPS <math>\geq</math> 70%.</p> <p>MGMT: 110 patients (ONA + BEV, n = 56; Pla + BEV, n = 54) were analyzed for MGMT methylation status. 47 patients had methylated MGMT, 57 had unmethylated MGMT, and 6 patients had unconfirmed MGMT status.</p> <p>Resection/biopsy: complete resection (70), partial resection (49) and biopsy(7)</p> <p>Initial treatment details: chemoradiotherapy (RT plus TMZ)</p> <p>Time from initial diagnosis: NR</p>
Interventions	<p>Arm 1 (64 patients): onartuzumab intravenous (IV) infusion followed by bevacizumab IV infusion every 3 weeks.</p> <p>Arm 2 (65 patients): placebo matched with onartuzumab followed by bevacizumab IV infusion every 3 weeks.</p>
Outcomes	OS, PFS, SAEs
Notes	<p>"Median PFS and OS were longer with ONA + BEV (n = 32) compared with Pla + BEV (n = 25) in patients with unmethylated MGMT; the median PFS was 4.2 v 2.8 months, respectively (HR, 0.46; 95% CI, 0.25 to 0.84; P= .0108) and the median OS was 10.9 v 7.5 months, respectively (HR, 0.53; 95% CI, 0.26 to 1.10; P= .0836)." Authors concluded that there was "no evidence of further clinical benefit with the addition of ONA to BEV compared with BEV plus placebo in unselected patients with glioblastoma in this study. However, further investigation into biomarker subgroups is warranted."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned 1:1 by interactive voice/Web response system..."
Allocation concealment (selection bias)	Low risk	"randomly assigned 1:1 by interactive voice/Web response system..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blinded"

**Cloughesy 2017** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported in the paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Cloughesy 2018**
**Study characteristics**

Methods	<p>Design: Phase 3 multi-site, international, randomized, open-label, controlled trial</p> <p>Country: Canada, Israel, USA</p> <p>Accrual dates: August 2015 and January 2017</p> <p>Trial reg: NCT02511405 (GLOBE)</p> <p>Funding: VBL Therapeutics</p> <p>Declaration of interests: YC, TRM, SFS, and NL-S are employees of VBL Therapeutics. LSF is a statistical consultant to VBL Therapeutics and his institute (Gertner Institute for Epidemiology and Health Policy Research) received payment for the statistical advice and analysis provided, among others.</p>
Participants	<p>No. randomised: 256</p> <p>No. analysed: 256</p> <p>Inclusion/exclusion criteria: adults aged &gt; 18 years with first or second progression of histologically confirmed recurrent GBM, who had received previous treatment with standard of care radiotherapy and temozolomide. Additional key inclusion criteria included KPS of at least 70%, life expectancy of at least 3 months, an interval of at least 12 weeks since the cessation of radiotherapy, and measurable disease by RANO criteria at time of progression. Patients treated with steroids had to be on a stable or decreasing dose. Exclusion criteria included prior anti-angiogenic therapy, history of recent grade 2 or higher CNS haemorrhage, gastrointestinal bleeding or pulmonary haemorrhage/haemoptysis, inherited bleeding diathesis or significant coagulopathy at risk of bleeding, surgical treatment or significant trauma within 4 weeks, active vascular disease, proliferative and/or vascular retinopathy, inadequately controlled hypertension, history of gastrointestinal perforation or abscess.</p> <p>Age: mean age of patients was 55 years, all patients were 18+.</p> <p>Gender: 171 Male (67%), 85 Female (33%)</p> <p>Performance status: PS of at least 70%; 21% had a KPS lower than 80</p> <p>MGMT: 18% methylated, 40% unmethylated, 42% unknown/missing</p> <p>Resection/biopsy: NA</p> <p>Initial treatment details: RT + TMZ</p> <p>Details of treatment of first recurrence:</p>

**Cloughesy 2018** (Continued)

Time from initial diagnosis: median time since initial diagnosis was 11.5 months.

Recurrence: approximately 74% had a first recurrence and 26% had a second recurrence

Interventions	Arm 1 (128 pts): VB-111 + bevacizumab Arm 2 (128 pts): bevacizumab
Outcomes	OS, PFS and SAEs
Notes	Authors concluded that "concomitant VB111+bEV failed to improve outcomes in rGBM. Change of treatment regimen with lack of VB111 monotherapy priming may explain the differences from the favourable phase 2 results."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"treatment assignment was determined by central randomisation"
Allocation concealment (selection bias)	Low risk	"treatment assignment was determined by central randomisation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	An open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessed both locally and by a central blinded independent radiology review"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All 256 patients...were included in the efficacy analysis"
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Cuncannon 2019**
**Study characteristics**

Methods	Design: prospective, 2-arm Country: Australia Accrual dates: March 2013 to December 2016 Trial reg: not found Funding: no funding was received. BEV required patient funding under a pharmaceutical access scheme involving a patient co-payment to a maximum of approximately EUR 12,000.
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**Cuncannon 2019** (Continued)

Declaration of interests: no competing interests

Participants	<p>No. analysed: 48</p> <p>Inclusion/exclusion criteria: consecutive patients managed at a regional cancer centre, with adjuvant chemo-radiation therapy as per the EORTC-NCIC Protocol for newly diagnosed GBM from March 2013 to December 2016 were entered into a prospective database, approved by an Institutional Ethics Review Board. Elderly patients managed with hypofractionated RT were not included in the analysis. No patients were enrolled onto an intercurrent clinical trial during this study period. (Not very clear on other criteria).</p> <p>Age: 18 to 70. 43/55 were &lt; 50 years</p> <p>Gender: 24 females (44%), 31 Male (56%)</p> <p>Performance status: median Karnofsky Performance Status score was 80 (range, 50 to 100).</p> <p>MGMT: MGMT methylation status was only available on 51% of patients, and of these 43% had methylated tumours.</p> <p>Resection/biopsy: 9 biopsys, 46 resections in total</p> <p>Re-operation: NR</p> <p>Initial treatment details: patients managed with adjuvant long course chemo-radiation therapy for GBM were entered into a prospective database. At chemorefractory symptomatic progression, patients were offered BEV or best supportive care. Re-irradiation (ReRT) was used with BEV in selected patients.</p> <p>Elderly patients managed with hypo-fractionated RT were not included in the analysis.</p> <p>Details of treatment of first occurrence:</p> <p>Time from initial diagnosis:</p>	
Interventions	<p>Arm 1: BEV was administered at 10 mg/kg intravenously every 2 weeks (N=28)</p> <p>Arm 2: Supportive care (N=15)</p>	
Outcomes	<p>PFS, OS.</p> <p>Only 1 patient had a GBM with IDH mutation; remaining progression-free at 15 months and thus not included in the relapse analysis. 28 patients (51%) had a near-total resection and 43 (78%) had ECOG 0/1 status at start of RT.</p> <p>MGMT methylation status was only available on 51% of patients, and of these 43% had methylated tumours. 45 patients have died with a median follow-up of 17.5 months in 10 remaining survivors at data censure. 1 patient death was unrelated to disease progression and was removed from analysis regarding BEV decision. Median OS from date of initial diagnosis was 17.0 months (95% CI 14.8 to 19.2).</p>	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High risk	This prospective non-randomised study has an inherent risk of patient selection bias because patients chose whether to receive BEV or not and the cost of BEV was usually the reason that patients chose not to participate (patients had to bear up to EUR 12,000 of the cost). Patients choosing not to bear the cost may have had a worse prognosis than those choosing to bear the cost.

**Cuncannon 2019** (Continued)

Allocation concealment (selection bias)	High risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not applicable.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not applicable.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Low risk	No suspicion of selective reporting.
Other bias	High risk	16 patients in the BEV group also received RT compared with none in the control group. This may represent a high risk of bias due to deviation from intended intervention.

**Dresemann 2010**
**Study characteristics**

Methods	<p>Design: A randomized, multi-centre, open-label, phase 3 study; ratio 1:1.</p> <p>Country: Multi-centre (Germany, Australia, Denmark, Norway)</p> <p>Accrual dates: October 2004 and July 2006</p> <p>Trial reg: NR</p> <p>Funding: NR</p> <p>Declaration of interests: NR</p>
Participants	<p>No. randomised: 240</p> <p>No. analysed: 240</p> <p>Inclusion/exclusion criteria: adult patients with a histologically confirmed GBM, measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance score <math>\leq 2</math> who had previously undergone surgery and received radiotherapy and prior chemotherapy were eligible for randomization. Patients on steroids were required to have been on a stable dose for <math>\geq 5</math> days. Patients at excessive risk of intracranial haemorrhagic events (evidence of intracranial haemorrhage in initial magnetic resonance imaging (MRI) scan or in MRI at less than 4 weeks after surgery) or with evidence of intratumoural haemorrhage at baseline scan, were not eligible.</p> <p>Age: median age was 51, range 19 to 73</p> <p>Gender: 152 Male (63%), 88 Female (37%)</p> <p>Performance status: median KPS score was 80 (range, 50 to 100).</p> <p>MGMT: NR</p>



**Dresemann 2010** (Continued)

Initial treatment details: surgery + RT + TMZ

Re-operation: NR

Time from initial diagnosis: mean 18 months, SD 23, range 0 to 230

Interventions	<p>Arm 1: HU alone (n = 120)</p> <p>Arm 2: HU plus imatinib (n = 120)</p> <p>Imatinib is an inhibitor of platelet derived growth factor receptor (PDGFR) and c-KIT receptors.</p> <p>Upon progression, patients with good performance status who were receiving HU alone were permitted to switch to the combination arm. Only the first progression on treatment was evaluated for the primary end point.</p>
Outcomes	OS, PFS and adverse events.
Notes	Authors concluded that "No clinically meaningful differences were found between the two treatment arms, and the primary study end point was not met."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified in the report.
Allocation concealment (selection bias)	Unclear risk	Not specified in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Blinded CIR data were used for the primary analyses on an intent to treat basis" and "all MRI scans and neurologic and steroid information were evaluated at the local (investigator) study sites in addition to a review by a blinded central independent reviewer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Expected outcomes were reported.
Selective reporting (reporting bias)	Low risk	None noted.
Other bias	Unclear risk	Investigator interests and funding not declared.

**Duerinck 2018**

**Study characteristics**

Methods	<p>Design: multicentre, randomised, non-comparative 2-arm phase II clinical trial</p> <p>Country: Belgium</p>
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**Duerinck 2018** (Continued)

Accrual dates: August 2011 and July 2015

Trial reg: EudraCT: 2011-000900-16 / NCT01562197 part of study before amendment

Funding: Pfizer Belgium provided the study with medication and a research grant.

Declaration of interests: NR.

Participants	<p>No. randomised: 101</p> <p>No. analysed: 79</p> <p>Inclusion/exclusion criteria: aged <math>\geq 18</math> years or older and have tumour recurrence or progression following prior treatment with surgery, radiation therapy and temozolomide. A measurable tumour lesion on gadolinium-enhanced T1-MRI of the brain was required. An interval of at least 3 months was needed after ending prior radiotherapy as well as an interval of at least 4 weeks after the last administration of a cytotoxic treatment or any other type of anti-glioblastoma treatment. No previous treatment with axitinib or other VEGF-targeted drugs (including bevacizumab).</p> <p>Age: <math>\geq 18</math> yrs; median age 56 (range 27 to 79)</p> <p>Gender: 51 males and 28 females</p> <p>Performance status: WHO PS 24% grade 0, 34% grade 1, 27% grade 2, 15% grade 3 or 4</p> <p>MGMT: methylated 19 unmethylated 43, unknown or missing 17</p> <p>Resection/biopsy: resection 80%, biopsy 20%</p> <p>Initial treatment details: surgery + RT + TMZ</p> <p>Time from initial diagnosis: NR</p>
Interventions	<p>Arm 1 (22 pts): Control arm – physicians' best alternative therapy</p> <p>Arm 2 (50 pts): Axitinib monotherapy (AXI)</p> <p>Arm 3 (31 pts): axitinib + lomustine (AXI + LOM)</p>
Outcomes	PFS, OS and safety outcomes
Notes	<p>PFS and OS were significantly longer in patients with MGMT-promoter hypermethylation (log-rank <math>P = 0.014</math> and <math>0.018</math>, respectively) and in patients who were not on steroid treatment at baseline (log-rank <math>P = 0.009</math> and <math>0.006</math>, respectively). Authors concluded that "This trial provides clinical evidence that axitinib as a monotherapy has anti-tumour activity in patients with recurrent GBM and that treatment can be administered with an acceptable safety profile. There is no indication that upfront combination of axitinib with lomustine improves the tumour response rate or survival and the risk for haematological toxicity is increased."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on how random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No details on whether the allocation concealment was implemented.
Blinding of participants and personnel (performance bias)	Unclear risk	This was not reported.

**Duerinck 2018** (Continued)

## All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Dropout rate was minimal.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcomes were reported.
Selective reporting (reporting bias)	Unclear risk	HRs not reported.
Other bias	Unclear risk	19/50 patients were allowed to cross over to AXI + LOM on progression.  The non-comparative findings are difficult to interpret in the absence of a concurrent non-AXI control group.

**Field 2015**
**Study characteristics**

Methods	<p>Design: multicenter, sequential, stratified, non-blinded, randomized phase 2 study</p> <p>Country: Australia</p> <p>Accrual dates: November 2010 and March 2012</p> <p>Trial reg: ACTRN12610000915055.</p> <p>Funding: Roche Products Australia Pty Ltd</p> <p>Declaration of interests: KF has received conference travel grants and honoraria from Roche for speaking invitations. EH has been a member of a Roche Advisory Board 2009 – 2013. AN has been a member of a Roche Advisory board 2013 and received honoraria from Roche for speaking invitations. MR has been a member of a Roche Advisory Board. JS has received research funding from Roche. HW has received research funding from Roche and has been a member of a Roche Advisory board. EB, GF, PP, KS, CB, AL, and LC declare no conflict of interest. There is no stated conflict of interest for RF.</p>
Participants	<p>No. randomised: 122</p> <p>No. analysed: 122</p> <p>Inclusion/exclusion criteria: a histological diagnosis of GBM (WHO grade IV glioma) following resection or biopsy; patients had received treatment with both radiotherapy and temozolomide (concurrently and/or sequentially). Patients with first or subsequent recurrences were eligible to participate, provided that prior therapy had only included radiotherapy and temozolomide. Exclusion criteria included prior chemotherapy other than temozolomide, prior bevacizumab or other investigational agent for the treatment of glioma, surgery within 4 weeks before treatment commencement, evidence of recent haemorrhage on MRI with the exception of asymptomatic punctate haemorrhage or resolving post-surgical change, inability to undergo MRI, inadequately controlled hypertension, clinically significant cardiovascular disease, history of coagulation disorder, prior or concurrent malignancy (except non melanomatous skin cancer or malignancy treated and disease-free for 5 years), pregnancy or lactation, or other concurrent physical, psychological, or sociological condition that could jeopardize patient safety or compliance.</p> <p>Age: 25 to 82</p> <p>Gender: 55 females (45%), 67 Males (55%)</p>

**Field 2015** (Continued)

 Performance status: ECOG performance status  $\leq 2$ 

MGMT: NR

Resection/biopsy: 15 biopsies, 70 resections

Details of treatment of first occurrence: all received radiotherapy and temozolomide.

Time from initial diagnosis: months from initial glioblastoma surgery to randomisation was median 11 months

Interventions	Arm 1: 10 mg bevacizumab monotherapy (N = 62) Arm 2: 10 mg bevacizumab + 5 AUC carboplatin (N = 60)
Outcomes	QOL, adverse events, PFS and OS.
Notes	Authors concluded that "Adding carboplatin resulted in more toxicity without additional clinical benefit."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary endpoint, as well as the secondary and exploratory radiological endpoints, were assessed by blinded central radiology review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and intention-to-treat analysis used.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Friedman 2009**
**Study characteristics**

Methods	Design: phase II, multicenter, open-label, non-comparative trial. Country: USA Accrual dates: June 2006 to February 2007
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**Friedman 2009** (Continued)

Trial reg: [NCT00345163](#).

Funding: Genentech

Declaration of interests: Numerous interests declared. Employment or leadership position: Jane Huang, Genentech © Maoxia Zheng, Genentech, Consultant or Advisory Role: Henry S. Friedman, Genentech; Michael D. Prados, Genentech; Patrick Y. Wen, Genentech, Schering-Plough; Tom Mikkelsen, Schering-Plough; David Schiff, Genentech; Lauren E. Abrey, Genentech; W.K. Alfred Yung, Schering-Plough, Novartis; James Vredenburgh, Genentech; Martin K. Nicholas, Genentech. Honoraria: Henry S. Friedman, Genentech; Tom Mikkelsen, Genentech, Schering-Plough; Lauren E. Abrey, Genentech; W.K. Alfred Yung, Schering-Plough, Novartis; Timothy Cloughesy, Genentech Research Funding: Henry S. Friedman, Genentech; Michael D. Prados, Genentech; Patrick Y. Wen, Genentech; Tom Mikkelsen, Genentech; Lauren E. Abrey, Genentech, Pfizer; W.K. Alfred Yung, Genentech; Nina Paleologos, Genentech; Martin K. Nicholas, Genentech; James Vredenburgh, Genentech; Timothy Cloughesy, Genentech Expert Testimony: Michael D. Prados; Timothy Cloughesy

Participants

No. randomised: 167

No. analysed: 167

Inclusion/exclusion criteria

- Confirmed GBM in 1st or 2nd relapse and had disease progression confirmed by MRI  $\leq$  14 days before the 1st study treatment
- Patients had been treated with standard RT + TMZ
- Life expectancy > 12 weeks
- Adequate haematologic (i.e. platelet count  $\geq$  100,000/ $\mu$ L, absolute neutrophil count  $\geq$  1500/ $\mu$ L), hepatic, and renal function.
- Patients taking corticosteroids were required to be on a stable or decreasing dose for 5 or fewer days before baseline MRI.
- Therapeutic systemic anticoagulation with low molecular weight heparin or warfarin was allowed.

Excluded if:

- previous treatment with prolifeoprospan 20 with carmustine wafer, CPT-11, or anti-VEGF agents;
- MRI evidence of recent intracranial haemorrhage;
- history of bleeding diathesis or coagulopathy;
- clinically significant cardiovascular disease;
- arterial thromboembolism less than 6 months before the first study treatment;
- uncontrolled hypertension.

Age: range 23 to 79 yrs

Gender: male & female

Performance status: KPS  $\geq$  70%

MGMT: not reported

Resection/biopsy: not specified in inclusion criteria; partial resection 49.4% BEV 53.7% BEV + CPT-11; complete resection 42.4% BEV 37.8% BEV + CPT-11; only biopsy 8.2% BEV 8.5% BEV + CPT-11

Initial treatment details: RT + TMZ

Details of treatment of first occurrence (2nd line?):

Time from initial diagnosis: "The median time from initial diagnosis to study random assignment was 8.6 months for the BV group and 9.8 months for the BV + CPT-11 group." (pg 4735)

Interventions

Arm 1: bevacizumab (N = 84)

**Friedman 2009** (Continued)

Arm 2: bevacizumab + carboplatin (N = 79)

Outcomes	Adverse events, PFS and OS and objective response
Notes	"The randomized design of the trial was intended only to prevent bias in treatment assignment, and there was no formal plan to compare outcomes in the two treatment groups." (pg. 4739)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the report.
Allocation concealment (selection bias)	Unclear risk	Not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Progression and objective response were assessed by a blinded, independent radiology facility according to WHO Response Evaluation Criteria, and corticosteroid dose was taken into account."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and most patients accounted for in analyses.
Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported, except no HRs
Other bias	Unclear risk	"The randomized design of the trial was intended only to prevent bias in treatment assignment, and there was no formal plan to compare outcomes in the two treatment groups."  Numerous investigator interests declared.

**Galanis 2017**
**Study characteristics**

Methods	Design: randomised phase 2 study; open-label; ratio 1:1
Participants	No. randomised: 101  No. analysed: 101  Inclusion criteria: histological confirmation of glioblastoma multiforme; evidence of tumour progression following most recent anti-tumour therapy; measurable disease; ECOG 0-2; life expectancy $\geq$ 12 weeks  Age: Mean 55.8 (10.8)  Gender: 72 males and 29 females  MGMT status: NR

**Galanis 2017** (Continued)

Performance status: ECOG 0-2

Initial treatment: NR

Time from diagnosis: NR

Interventions	Arm 1: bevacizumab and TRC105 Arm 2: BEV
Outcomes	PFS, SAEs, OS, QOL
Notes	Results data were obtained on the ClinicalTrials.gov website.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient details to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to make a judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients were analysed for the primary outcome. High risk for QoL outcome, as only 65 patients were evaluated.
Selective reporting (reporting bias)	Unclear risk	This study has not been published in a peer-reviewed journal.
Other bias	Unclear risk	There is an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

**Galanis 2019**
**Study characteristics**

Methods	Design: RCT, Phase 2, double blinded, 2 arms; ratio 2:1 Country: USA Accrual dates: October 2009 to November 2014 Trial reg: NCT00892177 Funding: supported by the National Cancer Institute of the National Institutes of Health under awards UG1CA189823 (Alliance for Clinical Trials in Oncology National Cancer Institute Community Oncolo-
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**Galanis 2019** (Continued)

gy Research Program Grant) U10CA180821, U10CA180882, and U10CA180833. Some funding also from Bristol-Myers Squibb and Genentech.

Declaration of interests: numerous interests declared. Evanthia Galanis - funding from MedImmune Inc, Denovo Biopharma, Tracon, Genentech, and Bristol-Myers Squibb; has acted as a paid member of the advisory board for (compensation to Mayo Clinic) Vyriad, Celgene Corporation, and KIYATEC; has acted as a paid general consultant (compensation to Mayo Clinic) for F. Hoffman La Roche Ltd; and has acted as a paid general consultant for Tactical Therapeutics Inc and Oncorus for work performed outside of the current study.

Participants	<p>No. randomised: 128</p> <p>No. analysed: 121</p> <p>Inclusion/exclusion criteria</p> <ul style="list-style-type: none"> <li>• Evidence of tumour progression and measurable and evaluable disease by MRI or CT</li> <li>• Acceptable haematologic, liver, and renal function</li> <li>• Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2</li> <li>• <math>\geq 12</math> weeks from the completion of prior radiotherapy; <math>\geq 4</math> weeks from prior chemotherapy (6 weeks for nitrosourea-based regimens)</li> <li>• having received up to 2 prior chemotherapy regimens with <math>\leq 1</math> regimen for recurrent disease; and no prior treatment with angiogenesis inhibitors or dasatinib</li> </ul> <p>The main exclusion criteria were inadequately controlled hypertension; comorbid systemic illnesses or other severe concurrent disease; other active malignancy <math>\leq 3</math> years prior to registration, with the exception of non-melanotic skin cancer or carcinoma in situ of the cervix; history of myocardial infarction or unstable angina <math>\leq 6</math> months prior to registration</p> <p>Age: 115 patients were <math>&lt; 70</math> (95%), 6 patients were <math>&gt; 70</math> (5%). Median age was 57, range was 18 to 79.</p> <p>Gender: 44 Female (36%), 77 Male (67%)</p> <p>Performance status: ECOG <math>\leq 2</math></p> <p>MGMT: NR</p> <p>Resection/biopsy: NR</p> <p>Initial treatment details: not clear but likely RT + TMZ.</p> <p>Details of treatment of first recurrence: varied.</p> <p>Time from initial diagnosis: 7.3 months and 7.7 months, respectively</p>
Interventions	<p>Arm A (N = 83): bevacizumab plus dasatinib, (100 mg twice daily dasatinib orally, 10 mg/kg of iv bevacizumab (<math>&gt; 90</math> minutes) on day 1 of each 14-day cycle)</p> <p>Arm B (N = 38): bevacizumab plus placebo, (placebo from day 1 to day 14 of each 14-day cycle and 10 mg/kg of IV bevacizumab (<math>&gt; 90</math> minutes) on day 1 of each 14-day cycle)</p>
Outcomes	QOL, PFS, Objective response, OS, TTD, SAEs
Notes	Authors concluded that "...the combination of bevacizumab with dasatinib did not appear to significantly improve the outcomes of patients with recurrent GBM compared with bevacizumab alone."
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement    Support for judgement</b>



**Galanis 2019** (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described in the report.
Allocation concealment (selection bias)	Unclear risk	Not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiographic responses were verified by central review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated for the primary end-points.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Gilbert 2017**
**Study characteristics**

Methods	<p>Design: randomised, multicentre, phase 2 trial</p> <p>Country: USA</p> <p>Accrual dates: 1 March 2007,</p> <p>Trial reg: RTOG 062</p> <p>Funding: this project was supported by grants U10CA21661, U10CA180868, U10CA180822, U10CA37422, and U24CA180803 from the National Cancer Institute (NCI).</p> <p>Declaration of interests: Dr. Gilbert reports personal fees and non-financial support from Merck, personal fees from Genentech Roche, personal fees from Abbvie, personal fees from Wellcome Trust, and personal fees from Foundation Medicine, outside the submitted work. Dr. Sorensen reports employment by Siemens Healthcare, outside the submitted work. Dr. Mikkelsen has a consulting or advisory role with Roche Genentech and has received honoraria, travel and research funding from Roche Genentech, outside the submitted work. Dr. Penas-Prado has received research funding from Bayer, Genentech, Glaxo, and Novartis, outside the submitted work. Dr. Mehta has a leadership role with Pharmacyclics, stock or ownership interest in Pharmacyclics, consulting or advisory roles with Cavion, Elekta, Novartis and Novocure, and has received research funding from Novocure and Novellos, outside the submitted work</p>
Participants	<p>No. randomised: 123</p> <p>No. analysed: 117</p> <p>Inclusion/exclusion criteria</p> <p><b>Inclusion</b></p> <ul style="list-style-type: none"> <li>• Recurrent or progressive GBM or gliosarcoma</li> </ul>

**Gilbert 2017** (Continued)

- Failed RT + TMZ
- KPS  $\geq$  70
- No limits placed on the number of prior treatment regimens
- Patients with prior treatment with interstitial brachytherapy, stereotactic radiosurgery or Gliadel® wafers (polifeprosan 20 with carmustine implant) were required to have histologic evidence of recurrent tumour
- Measurable tumour was not required if the patient underwent a repeat tumour resection prior to enrolment
- RT completed at least 42 days prior enrolment
- Age  $\geq$  18
- Karnofsky Performance status  $\geq$  70
- Systolic blood pressure  $\leq$  160 mg Hg or diastolic pressure  $\leq$  90 mg Hg
- Adequate haematologic function (white blood cell count (WBC)  $\geq$  3,000/ $\mu$ L, absolute neutrophil count (ANC)  $\geq$  1,500/ $\mu$ L, platelet count  $\geq$  100,000 cells/ $\mu$ L, and haemoglobin  $\geq$  10 gm/ $\mu$ L) renal and hepatic function
- On a stable or decreasing dose of corticosteroids for the 5 days prior to study enrolment

**Exclusion**

- Ongoing treatment with a hepatic-enzyme-inducing anticonvulsant
- Acute intratumoural haemorrhage on MR imaging
- Active comorbid condition including recent (< 6 months) myocardial infarction
- Unstable angina
- Uncontrolled hypertension or history of recent (< 6 months) stroke or transient ischemic attack
- Major surgical procedure or history of abdominal abscess or fistula or gastrointestinal perforation within 28 days of study enrollment

Age: median 58 yrs (range 24 to 82) BEV + TMZ, 55 yrs (range 23 to 78) BEV CPT

Gender: male 58% vs female 42%

Performance status: KPS 70 to 80 52%, KPS 90 to 100 48%

MGMT: not reported

Resection/biopsy: not reported

Initial treatment details: RT + TMZ

Details of treatment of first recurrence: not reported

Time from initial diagnosis: not reported

Interventions	Arm 1 (N = 60): BEV (10 mg/kg q 2 wk) + IRI (125 mg/m <sup>2</sup> q 2 wk)
	Arm 2 (N = 60): BEV (10 mg/kg q 2 wk) + TMZ (75 to 100 mg/m <sup>2</sup> 21/28)
Outcomes	PFS, SAEs, OS, objective response
Notes	
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement</b> <b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk                      No details reported.

**Gilbert 2017** (Continued)

Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given on blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and all patients accounted for.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Heiland 2016**
**Study characteristics**

Methods	<p>Design: retrospective, 2-arm study.</p> <p>Country: Germany</p> <p>Accrual dates: 2010 and 2014</p> <p>Trial reg: NR</p> <p>Funding: NR</p> <p>Declaration of interests: author AW has received honorarium from Roche Pharma AG and was a member of the scientific advisory board at Roche Pharma AG.</p>
Participants	<p>No. randomised: 43</p> <p>No. analysed: 35</p> <p>Inclusion criteria: age older than 18 years; histopathological confirmation of a glioblastoma multiforme (WHO criteria); recurrent GBM after adjuvant radiochemotherapy with TMZ and following TMZ high-dose therapy; repetitive surgery, CCNU monotherapy and/or re-radiotherapy.</p> <p>Age: mean age in BEV arm 39.5, mean age in BEV/CCNU arm was 50 years.</p> <p>Gender: 16 Female (43%), 21 Male (57%)</p> <p>Performance status: NR</p> <p>MGMT: methylated 6 vs 4 in arm 1 and arm 2, respectively; unmethylated 10 vs 13 in arm 1 and arm 2 respectively.</p> <p>Resection/biopsy: NR</p> <p>Initial treatment details: all patients with first diagnosis of GBM were treated with a total or near total resection of the brain tumour followed by standard chemoradiation (60 Gy, concomitant TMZ 75 mg/kg BW) followed by adjuvant TMZ (5/23 regimen, 150 to 200 mg/kg)</p>

**Treatment options for progression or recurrence of glioblastoma: a network meta-analysis (Review)**

**Heiland 2016** (Continued)

Time from initial diagnosis: NR

Interventions	<p>Arm 1: BEV monotherapy group were treated with 10 mg/kg BW every 2 weeks. (N = 17)</p> <p>Arm 2: BEV/CCNU group was treated with CCNU in the dose of 90 mg/m<sup>2</sup> every 6 weeks and BEV in the dose of 5 mg/kg BW every 2 weeks.(N = 18)</p>
Outcomes	PFS, OS, Adverse events.
Notes	This study evaluated "last line" or third-line therapy. Authors concluded that "Last-line therapy with BEV/CCNU results in a longer PFS and OS compared to BEV monotherapy and is well-tolerated."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised study (retrospective).
Allocation concealment (selection bias)	High risk	This study is at risk of selection bias as patients would most likely have been selected for treatments based on clinical factors. Patients had various pre-treatments and it is not clear why they were selected to receive the treatments studied.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not applicable.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but the OS outcome can be assumed to be at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 (18.6%) out of 43 were excluded due to missing data.
Selective reporting (reporting bias)	Unclear risk	None suspected.
Other bias	Unclear risk	Baseline characteristics reported were similar between the 2 groups, except that the average age of patients in the BEV arm was younger than the BEV + LOM arm, and there were slightly more IDH-1 wild types (13/17 vs 10/18).

**Kim 2015**
**Study characteristics**

Methods	<p>Design: retrospective, 5-arm study</p> <p>Country: Korea</p> <p>Accrual dates: January 2002 and December 2011</p> <p>Trial reg: NA</p> <p>Funding: not stated.</p>
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**Kim 2015** (Continued)

Declaration of interests: the authors declare that they have no financial or other conflicts of interest in relation to this research and its publication

Participants	<p>No. randomised: NA</p> <p>No. analysed: 144</p> <p>Inclusion/exclusion criteria: maximum debulking surgery (excluding biopsy only) followed by combined chemoradiotherapy. Patients who did not complete combined chemoradiotherapy due to unexpected surgical or medical complications were excluded from this study, whereas those with disease progression after CCRT but before completion of adjuvant TMZ treatment were included in the analysis.</p> <p>Age: 23 to 87</p> <p>Gender: 63 Women (44%) 81 Male (64%)</p> <p>Performance status: ECOG during first recurrence between 0 and 3</p> <p>MGMT: NA</p> <p>Initial treatment details: as above.</p> <p>Time from initial diagnosis: the median time to first progression from initial diagnosis was 8.8 months.</p>	
Interventions	<p>Arm 1: Gamma Knife radiosurgery (GKS) (N = 29)</p> <p>Arm 2: Temozolomide: either 50 mg/m<sup>2</sup> daily (metronomic dose) or 150 to 200 mg/m<sup>2</sup> for 5 days per 4 weeks (N = 31)</p> <p>Arm 3: Gamma Knife radiosurgery + temozolomide: 67.9% received metronomic TMZ chemotherapy (N = 28)</p> <p>Arm 4: Re-operation (N = 38)</p> <p>Arm 5: 'Other treatment': (N = 18)</p>	
Outcomes	OS and PFS	
Notes	<p>Authors report that "The median overall survival (OS) of the five different treatment groups; GKS, TMZ, GKS+TMZ, reoperation, and "other treatment", was 9.2, 5.6, 15.5, 13.2, and 8.0 months, respectively. Median progression-free survival (PFS) was 3.6, 2.3, 6.0, 4.3, and 2.6 months, respectively. Pairwise comparison of OS of the GKS + TMZ group with the other groups showed that the OS of the GKS + TMZ group was significantly better than all others except the reoperation group. Statistically significant prolongation of PFS was observed in the GKS + TMZ group compared with the TMZ group and the "other treatment" group. GKS followed by TMZ salvage treatment was a good prognostic factor for both PFS and OS in multivariate analysis. Retrospectively, GKS + TMZ as a salvage treatment tended to provide a superior survival benefit at the time of recurrence."</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High risk	This is a non-randomised study at high risk of selection bias.
Allocation concealment (selection bias)	Unclear risk	This non-randomised study is at risk of selection bias because it is not clear why patients received 1 treatment or another.
Blinding of participants and personnel (performance bias)	Unclear risk	Not applicable.

**Kim 2015** (Continued)

## All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	222 pts were eligible but 78 were excluded due to inadequate follow up data or because they received no further salvage therapy due to progressive disease.
Selective reporting (reporting bias)	Low risk	Not suspected.
Other bias	High risk	Baseline characteristics were reported as having "no significant differences in age, sex, performance status at first progression, the extent of surgery, adjuvant TMZ cycles and the time to first progression in the five groups". However, tumour volume was smaller in those receiving GKS, GKS + TMZ and other treatments, and larger amongst those receiving TMZ only and re-operation. These factors are likely to influence the effectiveness of the treatments.

**Kunwar 2010**
**Study characteristics**

Methods	<p>Randomised phase III multicentre trial; ratio 2:1</p> <p>Country: 52 medical centres, mainly in USA but also Germany, Israel, the Netherlands, Canada and the UK</p> <p>Accrual dates: March 2004 to December 2005</p> <p>Trial reg: NCT00076986</p> <p>Funding: Commercial funding. NeoPharm Inc</p> <p>Declaration of interests: 1 author reports an agreement between the Food and Drug Administration and NeoPharm Inc with a patent on the therapeutic agent evaluated, along with NIH and Val-Chum. A second author serves as a consultant and receives a fee from NeoPharm Inc, Eisai, and Schering-Plough and lecture fees from Schering-Plough and Genentech.</p>
Participants	<p>No. randomised: 296 in a 2:1 ratio</p> <p>No. analysed: 276. (269 included in safety evaluation: i.e. received any study drugs)</p> <p>Inclusion/exclusion criteria: adult patients with first recurrence of GBM. Patients were excluded if they were unable to undergo surgical procedures necessary for the placement of the GW. Patients that had previously received either of the 2 study drugs, had had prior brachytherapy, radiosurgery or other investigational intracerebral agents were also excluded.</p> <p>Age: 48% &lt; 55, 52% ≥ 55. Similar proportions in each treatment group. Mean age CB 54.8 (sd 11.23); GW 54.7 (SD 11.06)</p> <p>Gender: 90 (33%) female 62 (34%) CB; 28 (30%) GW. 186 (67%) male 121 (66%) CB; 65 (70%) GW.</p> <p>Performance status: KPS similar proportions in both treatment arms: 70, 13%; 80, 21%; 90, 45%; 100, 20%. Mean CB: 86.9 (SD 9.46); GW 87.7 (SD 9.22)</p> <p>MGMT status: not stated</p> <p>Initial treatment details: surgery plus chemoradiotherapy (&gt; 80% of cases)</p>

**Kunwar 2010** (Continued)

Sort of recurrence: first recurrence

Time from initial diagnosis: (time from initial diagnosis to study resection) median weeks SB 32.14; GW 30.43.

Interventions	<p>Arm 1: (192 patients) Convection enhanced delivery (CED) of intraparenchymal cintredekin besudotox (CB) (also known as IL13-PE38QQR). Catheter placement (2 to 4 catheters) 2 to 7 days post-operatively after tumour resection in areas at greatest risk of infiltrating disease. A CT scan was used to confirm appropriate catheter placement and infusion started 24 hours later at a concentration of 0.5 microg/mL and a total rate of 0.750 mL/h for 96 hours. (Neurosurgeons had received training in catheter placement).</p> <p>Arm 2: (104 patients) Intraparenchymal gliadel wafers (GW). Wafers were placed immediately following resection and MRI performed within 48 hours.</p>	
Outcomes	<p>Clinical and radiographic assessment every 8 weeks.</p> <p>Primary outcome: overall survival (from randomisation)</p> <p>Secondary outcomes: safety and toxicity. Health related quality of life.</p> <p>Toxicity was assessed using the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0.</p>	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Randomisation before gross total resection of their tumour. Methods not described in report.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study treatments were not masked. Staff (and probably patients) would be aware of treatment allocation. OS probably unaffected by lack of blinding but other outcomes such as QoL may have been affected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was reported that the investigators and sponsor were blind to allocation and results until after efficacy analysis was performed by an independent data monitoring committee. A blinded committee assessed compliance with surgical procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was some loss to follow-up but it appeared balanced across groups (296 randomised, 276 underwent treatments, 269 available for safety analysis)
Selective reporting (reporting bias)	Low risk	Not apparent, ITT and by protocol analysis (patients that had received 90% of study drug). Power calculation based on median survival. Interim analysis after 160 deaths, and efficacy analysis after 250 deaths.
Other bias	Low risk	Patient characteristics were similar in the 2 arms.

**Lombardi 2019**
**Study characteristics**

Methods	<p>Design: randomised, multicentre, open-label phase 2 trial done in 10 centres in Italy</p> <p>Country: Italy</p> <p>Accrual dates: 27 November 2015, and 23 February 2017</p> <p>Trial reg: NCT02926222.</p> <p>Funding: Veneto Institute of Oncology and Bayer Italy.</p> <p>Declaration of interests: Veneto Institute of Oncology received a grant from Bayer to partially support the study. GL received personal fees from Bayer, outside the submitted work. GL, GLDS, and SI are co-inventors in a pending patent application: development of a biomarker predictive of response to regorafenib in glioblastoma patients (number: 102018000003449). BD reports personal fees and non-financial support from Bayer and Bristol-Myers Squibb; personal fees from IPSEN, Eisai, Lilly, MSD and Merck; and non-financial support from Sanofi, outside the submitted work. VZ reports personal fees and an advisory role from Bristol-Myers Squibb; an advisory role and travel and accommodation expenses from Celgene; non-financial support, an advisory role, and travel and accommodation expenses from Merck; personal fees and non-financial support from Bayer and Roche; and personal fees from Pfizer, Janssen, Novartis, Astellas, and Servier, outside the submitted work.</p>
Participants	<p>No. randomised: 119</p> <p>No. analysed: 119</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• Histologically confirmed glioblastoma with first progression after surgery followed by RT + TMZ</li> <li>• Disease progression on MRI as defined by Response Assessment in Neuro-Oncology (RANO) criteria 26 at least 12 weeks after completion of radiotherapy</li> <li>• At least 1 target lesion with a diameter of at least 10 mm; on a stable or decreasing dose of steroids for 1 week before the base-line MRI scan</li> <li>• Adequate bone marrow and liver function</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• Previous chemotherapy for recurrent disease</li> <li>• Previous treatment with regorafenib or any other VEGFR-targeting kinase inhibitor</li> <li>• Treatment with temozolomide within the previous 4 weeks</li> <li>• Recurrent disease located outside of the brain</li> <li>• Uncontrolled hypertension (systolic blood pressure &gt; 140 mm Hg or diastolic blood pressure &gt; 90 mm Hg); myocardial infarction less than 6 months before the start of study treatment; arterial thrombotic or embolic events within 6 months before the start of study treatment; active or chronic hepatitis B or C virus infection requiring treatment with antiviral therapy; and use of strong cytochrome P3A4 (CYP3A4) inhibitors or inducers.</li> </ul> <p>Age: 18+</p> <p>Gender: 35 women (29%), 84 men (71%)</p> <p>Performance status: Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or lower (or Karnofsky performance score <math>\geq</math>70).</p> <p>MGMT: arm 1 49% vs arm 2 46% methylated</p> <p>Initial treatment details: RT + TMZ</p> <p>Time from initial diagnosis: median time between diagnosis and first recurrence were 10.7 months vs 9.8 months, respectively.</p>



**Lombardi 2019** (Continued)

Interventions	<p>Arm 1: regorafenib 160 mg (given as 4× 40 mg tablets) orally once daily for the first 3 weeks of each 4-week cycle N = 59</p> <p>Arm 2: lomustine 110 mg/m<sup>2</sup> (in 40 mg capsules, up to a maximum dose of 200 mg) orally on day 1 of every 6-week cycle until disease progression N = 60</p>
Outcomes	OS, HRQOL, PFS, SAEs, objective response
Notes	<p>Authors concluded "REGOMA showed an encouraging overall survival benefit of regorafenib in recurrent glioblastoma. This drug might be a new potential treatment for these patients and should be investigated in an adequately powered phase 3 study."</p> <p>Also reported in a conference abstract that "HRQOL did not change during REG treatment. Pts treated with REG and LOM reported no significant difference in HRQoL."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned (1:1) to receive regorafenib or lomustine by a web-based system, stratified in block sizes of four by centre and surgery at recurrence (yes vs no)"
Allocation concealment (selection bias)	Unclear risk	Not clear from the study report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Neither investigators nor patients were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Neither investigators nor patients were masked to treatment allocation." "Response was evaluated by the local investigator based on RANO criteria."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in main paper.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Modh 2018**
**Study characteristics**

Methods	Design: randomized trial Country: USA Accrual dates: February 2012 to December 2016 Trial reg: NR Funding: NR
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**Modh 2018** (Continued)

	Declaration of interests: NR
Participants	<p>No. randomised: 34</p> <p>No. analysed: 34</p> <p>Inclusion/exclusion criteria: high-grade glioma patients with tumour progression after 2 previous treatment regimens were enrolled.</p> <p>Age: 18+</p> <p>Gender: NR</p> <p>Performance status: NR</p> <p>MGMT: NR</p> <p>Resection/biopsy: NR</p> <p>Initial treatment details: NR</p> <p>Details of treatment of first recurrence: NR. The median number of prior recurrences was 3.</p> <p>Time from initial diagnosis: NR</p>
Interventions	<p>Arm 1 (n = ?): fractionated radiosurgery with bevacizumab (FSRS was delivered as 32 Gy (8 Gy × 4 treatments within 2 weeks) to the gross target volume (gadolinium enhancing lesion and DWI abnormality), and 24 Gy (6 Gy × 4) to the clinical target volume (FLAIR abnormality).</p> <p>Arm 2 (n = ?): bevacizumab with irinotecan, temozolomide, or carboplatin (discretion of the treating provider)</p>
Outcomes	PFS, OS
Notes	Trial data were reported as a conference abstract only.

**Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement

**Modh 2018** (Continued)

Other bias	Unclear risk	7/34 (20.6%) patients had AA and 27/34 (79.4%) had GBM, therefore borderline for review participant criteria.
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**Narita 2019**
**Study characteristics**

Methods	Design: randomised, double-blind, phase 3 trial  Country: Japan  Accrual dates: January 2012 to March 2016.  Trial reg: NR  Funding: Japan Agency for Medical Research and Development.  Declaration of interests: Kyogo Itoh received a grant from Taiho Pharmaceutical Co. Kyogo Itoh and Shigeki Shichijo gained income by selling stock of BrightPath Biotherapeutics Co., Ltd. Tetsuo Sasada received a grant from BrightPath Biotherapeutics.Co. Akira Yamada.is a part-time executive of Bright-Path Biotherapeutics Co. The other authors have no competing interests to declare.
Participants	No. randomised: 90  No. analysed: 88  Inclusion/exclusion criteria: <ul style="list-style-type: none"> <li>• HLA-A24–positive patients with supratentorial rGBM that had been diagnosed histologically and proven refractory after standard temozolomide and radiotherapy</li> <li>• age of 18 to 74 years</li> <li>• positive IgG responses to at least 2 of 12 warehouse peptides (ITK-1) in prevaccination plasma; Eastern Cooperative Oncology Group performance status (PS) of 0, 1, or 2; neurological PS3.</li> </ul> Age: 20 to 74  Gender: 32 females (36%), 56 males (64%)  Performance status: ECOG ≤ 2  MGMT: NR  Resection/biopsy: NR  Initial treatment details: standard RT + TMZ  Details of treatment of first occurrence: standard temozolomide and radiotherapy study  Time from initial diagnosis: median of 12 and 13 months for vaccine and placebo groups, respectively.
Interventions	Arm 1: personalized peptide vaccination (ITK-1) (N = 58)  Arm 2: Placebo injection (N = 30)
Outcomes	OS
Notes	Authors concluded that "This phase III trial met neither the primary nor secondary endpoints."

**Risk of bias**

**Narita 2019** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"2:1 allocation was performed by computer-generated block randomization"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail for judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind". OS was the primary outcome which one can assume is free from bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition - "two dropped out before receiving their first treatment".
Selective reporting (reporting bias)	Low risk	None suspected.
Other bias	Unclear risk	Funding and author interests noted.

**Omuro 2018**
**Study characteristics**

Methods	Design: RCT, multicentre  Country: USA  Accrual dates: February 2014 and September 2014  Trial reg: NCT02017717  Funding: Bristol-Myers Squibb.  Declaration of interests: none stated.
Participants	No. randomised: 20  No. analysed: 20  Inclusion criteria <ul style="list-style-type: none"> <li>• <math>\geq 18</math> and had a histologically confirmed diagnosis GBM or gliosarcoma</li> <li>• at least 1 measurable lesion with at least 2 perpendicular enhancing diameters measuring <math>\geq 10</math> mm.</li> </ul> Exclusion <ul style="list-style-type: none"> <li>• If they had more than 1 recurrence of GBM; diagnosis of secondary GBM; evidence of extracranial metastatic or leptomeningeal disease; active, known, or suspected autoimmune disease; or prior treatment with an anti-PD-1 or anti-CTLA-4 therapy.</li> </ul> Age: NIV median 58.5 (range 42 to 73), NIVO1 + IPI3 median 57 (range 37 to 68), NIVO3 + IPI1 median 60 (range 27 to 73)

**Omuro 2018** (Continued)

Gender: male = 25, female = 15

Performance status: KPS of  $\geq 70\%$

MGMT: 20 % methylated, 50% unmethylated

Resection/biopsy/re-operation: NR

Initial treatment details: standard first-line treatment with at least radiotherapy and temozolomide

Time from initial diagnosis: Mths (range) 9.7 (3.7 to 48.9) median 8.4 (5.1 to 23), respectively

Interventions	Arm 1: nivolumab (NIV) (n = 10) Arm 2: NIV+ipilimumab (IPI) (n = 10)
Outcomes	Safety, tolerability, objective response, PFS OS was analysed as an exploratory ad hoc objective.
Notes	Authors concluded that "Nivolumab monotherapy was better tolerated than nivolumab + ipilimumab; the tolerability of the combination was influenced by ipilimumab dose. These safety and exploratory findings merit further investigation of immunotherapies in glioblastoma."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Low risk	None suspected.
Other bias	Unclear risk	Small sample size. "OS was analysed as an ad hoc exploratory objective"

**Puduvalli 2018**
**Study characteristics**

Methods	Design: adaptive randomised phase 2 trial; data from conference abstract only
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**Puduvalli 2018** (Continued)

Country: USA

Accrual dates: NR

Trial ID: NR

Funding: NR

Participants	No. randomised: 90 No. analysed: 74 Included if: adults ( $\geq 18$ yrs) with histologically confirmed GBMs recurrent after prior radiation and temozolomide therapy, adequate organ function, KPS $\geq 60$ , and no prior bevacizumab/HDAC inhibitors Age: NR Gender: NR Performance status: KPS $\geq 60$ MGMT status: Initial treatment: RT +TMZ Time from diagnosis: NR
Interventions	Arm 1: BEV + vorinostat Arm 2: BEV
Outcomes	PFS, OS, QOL, toxicity
Notes	Sparse data as conference abstract only.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient details to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to make a judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details to make a judgement. 90 randomised but only 74 analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient details to make a judgement. Not reported in full yet. QoL data not reported in the conference abstract.

**Puduvalli 2018** (Continued)

Other bias	Unclear risk	Insufficient details to make a judgement.
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**Reardon 2011**
**Study characteristics**

Methods	<p>Design: 2-arm, open-label, phase II randomised study</p> <p>Country: USA</p> <p>Accrual dates: August 2008 and January 2010</p> <p>Trial reg: NR</p> <p>Funding: 5 R37 CA11898; NIH Grant MO1 RR 30, GCRCProgram, NCRR; and NCI SPORE 1 P20 CA096890; and a grant from Genentech Pharmaceuticals.</p> <p>Declaration of interests: not stated</p>
Participants	<p>No. randomised: 23</p> <p>No. analysed: 23</p> <p>Inclusion/exclusion criteria: patients with recurrent GBM including progression on prior bevacizumab-based therapy. Eligible patients were also: on a stable corticosteroid dose for at least 1 week; at least 4 weeks between surgical resection or chemotherapy, and at least 12 weeks between radiotherapy. There were no limits based on either the number of prior episodes of progression or therapeutic regimens received.</p> <p>Patients were excluded for: grade <math>\geq 3</math> toxicity on prior bevacizumab; progressive disease or grade <math>\geq 3</math> toxicity on any prior protracted temozolomide schedule; progressive disease or grade <math>\geq 3</math> toxicity on prior metronomic etoposide; uncontrolled hypertension; therapeutic anticoagulation use; acute haemorrhage on baseline MRI; urine protein: creatinine ratio <math>&gt; 1</math>; pregnancy or nursing; active infection requiring intravenous antibiotics; and prior stereotactic radiosurgery, radiation implants, or radiolabeled monoclonal antibody therapy unless there was unequivocal disease progression.</p> <p>Age: 18+</p> <p>Gender: 25 Male 100%</p> <p>Performance status: had a KPS <math>\geq 60\%</math></p> <p>MGMT: NR</p> <p>Resection/biopsy: NA</p> <p>Initial treatment details: RT + TMZ + BEV</p> <p>Time from initial diagnosis: range time from initial diagnosis 39.1 to 217.9 weeks.</p>
Interventions	<p>Arm 1: metronomic temozolomide (50 mg/m<sup>2</sup>/day orally) plus bevacizumab (10 mg/kg intravenously every 14 days) N = 10</p> <p>Arm 2: metronomic etoposide (50 mg/m<sup>2</sup> of etoposide daily for 21 consecutive days of each 28 day cycle) plus bevacizumab (10 mg/kg intravenously every 14 days) N = 13</p>
Outcomes	PFS, OS, SAEs

**Reardon 2011** (Continued)

Notes Heavily pretreated patients with recurrent GBM. Authors concluded that "Metronomic etoposide or temozolomide is ineffective when administered with bevacizumab among recurrent GBM patients who have progressed on prior bevacizumab therapy".

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the report.
Allocation concealment (selection bias)	Unclear risk	Not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	An open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study closed after interim analysis and findings were reported for 23 patients.
Selective reporting (reporting bias)	Unclear risk	OS data are not reported.
Other bias	High risk	This study was terminated after interim analysis due to lack of efficacy in both intervention groups.

**Reardon 2015b**

**Study characteristics**

Methods	<p>Multicentre phase I/II trial. Phase II was 3-arm in ratio 1:1:1</p> <p>Country: Canada and USA</p> <p>Accrual dates: July 2008 to May 2011</p> <p>Funding: Boehringer Ingelheim</p> <p>Declaration of interests: David A. Reardon is a paid member of the advisory boards for Genentech/Roche, Novartis, Merck/Schering, and EMD/Serono. Agnieszka Cseh, Yali Fu, Julie Cong, Sven Wind are employees of Boehringer Ingelheim. David D. Eisenstat has received honoraria from Merck (formerly Schering Oncology Canada) and 1-time consultancy fees from Boehringer Ingelheim. Others have nothing to declare.</p>
Participants	<p>Randomised 119</p> <p>Analysed 119</p> <p>Inclusion criteria</p>



**Reardon 2015b** (Continued)

- Histologically confirmed WHO grade 4 malignant glioma at first recurrence after temozolomide chemoradiotherapy
- Bidimensionally measurable disease (tumour  $\geq 10$  mm in 1 diameter)
- KPS  $\geq 70\%$ .

Exclusion criteria were

- 12 weeks from radiotherapy
- 2 weeks from surgery, chemotherapy, or investigational drugs
- progressive disease (PD) or toxicity with prior protracted temozolomide dosing
- previous EGFR-targeted therapy or bevacizumab
- $\geq 2$  disease recurrences
- or known interstitial lung disease

Age: mean 56.3 years  $\pm$  10.3

Gender: 61.3% male

Performance status: KPS  $\geq 70$

Resection: NR

Initial treatment: standard chemoradiotherapy

Time from diagnosis: NR

Interventions	Arm 1: afatinib 40 mg/day (n = 41) Arm 2: Afatinib 40 mg/day plus TMZ 75 mg/n <sup>2</sup> (n = 39) Arm 3: TMZ 75 mg/day
Outcomes	PFS, SAEs, OS
Notes	Authors concluded that "Afatinib has a manageable safety profile but limited single-agent activity in unselected recurrent GBM patients."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"response assessment was evaluated before odd cycles by both the investigator and an independent review committee (ICON Medical Imaging)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for.

**Reardon 2015b** (Continued)

Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Reardon 2018a**
**Study characteristics**

Methods	<p>Design: Phase 2, multicenter, open-label, 2-cohort study</p> <p>Country: USA</p> <p>Accrual dates: November 2012 and January 2015</p> <p>Trial reg: NCT01609790</p> <p>Funding: Amgen, Inc. funded this study and provided trebananib to study participants.</p> <p>Declaration of interests: David A. Reardon reports grants from Amgen; grants from Acerta Pharmaceuticals, Agenus, Celldex, EMD Serono, Incyte, Inovio, Midatech, and Tragara outside the submitted work; and personal fees from AbbVie, Amgen, Bristol-Myers Squibb, Cavion, Celldex, EMD Serono, Genentech/Roche, Inovio, Merck, Momenta Pharmaceuticals, Novartis, Novocure, Oncurus, Oxigene, Regeneron, and Stemline outside the submitted work. Further declarations were made by the other authors.</p>
Participants	<p>No. analysed: 48</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>Eligible patients were at least age 18 years, were in first or second relapse of histologically confirmed glioblastoma after standard therapy (maximum feasible resection or biopsy, radiation, and temozolomide), adequate haematologic, renal, and hepatic function.</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>Prior receipt of VEGF/VEGF receptor (VEGFR) or ANG-targeting agents</li> </ul> <p>Age: 18+</p> <p>Gender: 48 Male (100%)</p> <p>Performance status: KPS of at least 70</p> <p>MGMT: 5 (10.4%) methylated; 20 (41.7%) unmethylated, rest unknown</p> <p>Resection/biopsy: 10 gross total resections, 2 subtotal resections before study (25%); 71% had no additional surgery.</p> <p>Initial treatment details: standard RT + TMZ</p> <p>Details of treatment of first occurrence:</p> <p>Time from initial diagnosis: NR</p>
Interventions	<p>Arm 1: trebananib (N=11)</p> <p>Arm 2: trebananib + bevacizumab 10 mg/kg biweekly (N = 37)</p>
Outcomes	OS, PFS, SAEs, objective response

**Reardon 2018a** (Continued)

Notes Authors reported that "Trebananib had no single-agent activity, and all treated patients exhibited progressive disease within 2 months."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised cohort study
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for.
Selective reporting (reporting bias)	Low risk	None suspected.
Other bias	Unclear risk	Funding and author interests noted.

**Reardon 2018b**
**Study characteristics**

Methods	Design: RCT, ratio: ? Conference abstract. Trial ID: NCT02337491 Funding: NR Declaration of interest: NR
Participants	No. randomised: 80 Inclusion criteria: BEV-naive patients with first or second recurrence of GBM requiring $\leq 4$ mg dexamethasone/day.
Interventions	Arm 1: pembrolizumab (P) (n = 50) Arm 2: pembrolizumab + BEV (n = 30)
Outcomes	PFS "assessed independently per cohort relative to historical benchmarks"
Notes	Conference abstract only so scant data. Authors concluded "P is well tolerated +/- Bev but has limited monotherapy activity for rGBM."

**Reardon 2018b** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient details to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details to make a judgement
Selective reporting (reporting bias)	Unclear risk	PFS "assessed independently per cohort relative to historical benchmarks"
Other bias	Unclear risk	Conference abstract only

**Reardon 2020**
**Study characteristics**

Methods	<p>Design: Double-blind, randomized, phase II study conducted in 26 hospitals in the USA.</p> <p>Country: USA</p> <p>Accrual dates: May 2012 and 2014</p> <p>Trial reg: NCT01498328</p> <p>Funding: Celldex Therapeutics, Inc</p> <p>Declaration of interests: "D.A. Reardon is a paid consultant for Abbvie, Advantagene, Agenus, Amgen, Bayer, Bristol-Myers Squibb, Celldex, Delmar, EMD Serono, Genentech/Roche, Inovio, Merck, Merck KGaA, Monteris, Novocure, Oncurus, Oxigene, Regeneron, Stemline, and Taiho Oncology. A. Desjardins reports receiving other commercial research support from Genentech/Roche, Triphase Accelerator, Symphogen A/S, Orbus Therapeutics; holds ownership interest (including patents) in Istari Oncology; and is an unpaid consultant/advisory board member for Orbus Therapeutics and Istari Oncology. D.M. O'Rourke reports...." among others.</p>
Participants	<p>No. randomised: 73</p> <p>No. analysed: 72</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>At least 18 years of age</li> </ul>

**Reardon 2020** (Continued)

- In first or second relapse of histologically confirmed glioblastoma following standard therapy (maximum feasible resection or biopsy, radiation, and temozolomide)
- With EGFRvIII expression in primary or recurrent tumour tissue by central analysis using PCR Patients who previously received radiation and temozolomide for lower-grade glioma were permitted upon diagnosis of transformed glioblastoma.

## Exclusion criteria

- Prior receipt of bevacizumab or other VEGF- or VEGF receptor–targeting agents
- Corticosteroid requirement > 4 mg of dexamethasone per day during the week prior to entry; Karnofsky performance status < 70%
- gliomatosis cerebri, infratentorial, leptomeningeal or metastatic disease
- prior therapeutic intracerebral agents
- residual grade 2 chemotherapy or radiation-related toxicities (except alopecia and haematologic toxicity)
- salvage surgery within 4 weeks or radiation within 3 months of screening MRI.

Age: median and range in arm 1: 59 (44 to 79), in arm 2: 55 (30 to 75)

Gender: In arm 1: 53% were male, in arm 2; 59% were male.

Performance status: KPS ≥ 70.

MGMT: NR

Resection/biopsy: surgery after last relapse arm 1 = 15 (42%), arm 2 = 10 (27%)

Initial treatment details: maximum feasible resection or biopsy, radiation, and temozolomide.

Time from initial diagnosis: NR

Interventions	Arm 1: N = 36 rindopepimut + BEV Arm 2: N = 37 control (injection of keyhole limpet haemocyanin) + BEV
Outcomes	PFS, OS, objective response, SAEs
Notes	Authors concluded that "Our randomized trial supports the potential for targeted immunotherapy among patients with GBM, but the therapeutic benefit requires validation due to the small sample size and potential heterogeneity of bevacizumab response among recurrent patients with GBM."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomized to the treatment groups in a 1:1 ratio by the study sponsor using a prespecified randomization list created by a biostatistician."
Allocation concealment (selection bias)	Unclear risk	Not clearly described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators remained blinded to treatment assignments. Unblinded pharmacists who were otherwise uninvolved in study conduct obtained randomized treatment assignments and managed study treatment. Study treatments were prepared in the pharmacy and delivered to study staff in blinded, preloaded syringes. KLH was given as a control injection to produce a local reaction similar to that expected with rindopepimut to maintain the treatment blind."

**Reardon 2020** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Retrospective assessment of radiographic imaging was also performed by an independent expert review committee consisting of two neuroradiologists, with adjudication and assessment of steroid use and clinical status by a neuro-oncologist. 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	Minimal attrition with 1 patient did not receive treatment was not included in the safety analysis.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear risk	Funding and author interests noted.

**Santos 2018**
**Study characteristics**

Methods	<p>Design: non-RCT, 2-arm. Allocation methods unclear.</p> <p>Country: Brazil</p> <p>Accrual dates: NR</p> <p>Trial reg: doi.org/10.3892/ol.2017.7362</p> <p>Funding: No information on funding, however POH was formulated for delivery by inhalation and the preparation was supplied by the Multidisciplinary Laboratory of Pharmaceutical Sciences at Rio de Janeiro Federal University (Rio de Janeiro, Brazil).</p> <p>Declaration of interests: not stated</p>
Participants	<p>No. randomised: 32 enrolled</p> <p>No. analysed: 17 (3 excluded due to diet non-adherence, others excluded due to inability to finish study/death)</p> <p>Inclusion/exclusion criteria: all patients presented with relapsed GBM, had no further standard therapeutic options, were aged &gt; 18 years, had measurable contrast-enhancing tumour on magnetic resonance imaging (MRI), adequate bone marrow function, white blood cell count of <math>\geq 3000/L</math>, absolute neutrophil count of <math>\geq 1500/L</math>, platelet count of <math>\geq 100,000/L</math>, haemoglobin of <math>\geq 8.0</math> g/dL, bilirubin of <math>\geq 0.3</math> mg.</p> <p>Age: 27 to 61 years</p> <p>Gender: 7 female (40%), 10 male (60%)</p> <p>Performance status: Karnofsky performance scale of <math>\geq 70\%</math> or higher.</p> <p>MGMT: mentioned in introduction; however, not discussed in the Methods/Results section.</p> <p>Resection/biopsy: previous biopsy mentioned; however no specific information in tables or rest of text.</p> <p>Initial treatment details: conventional therapy (including surgery, chemotherapy and radiotherapy).</p> <p>Time from initial diagnosis: not reported</p>

**Santos 2018** (Continued)

Interventions	Intranasal perillyl alcohol + ketogenic diet versus intranasal perillyl alcohol + standard diet.
Outcomes	Objective response, progressive disease
Notes	Of the 32 patients enrolled only 17 were included in the analysis (9/17 in the KD/POH group and 8/15 in the standard diet/POH group); 3 patients were excluded as they did not adhere to the diet and the rest did not survive the study period. The authors reported a partial response (reduction in MRI tumour size) in 7/9 in the KD/POH group and in 2/8 patients in the control group. The study had a small sample size, high attrition and there was a lack of information on study methods.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomised. The way patients were allocated to treatment groups was not described.
Allocation concealment (selection bias)	Unclear risk	The way patients were allocated to treatment groups was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and staff would be aware of treatment arms (non-compliant patients were excluded from the study).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The observing radiologists were aware of the GBM diagnosis and follow-up data.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition as only 17/32 completed the study.
Selective reporting (reporting bias)	Unclear risk	PFS, OS and SAES were not reported.
Other bias	Low risk	None noted.

**Scorsetti 2015**
**Study characteristics**

Methods	Retrospective study of a selected cohort of patients
Participants	<p>No. analysed: 43 patients recruited consecutively.</p> <p>Inclusion/exclusion criteria: patients with MRI evidence of progressive or recurrent GMB at least 3 months after the end of radiotherapy. All patients had had open surgery resection after initial diagnosis, radiotherapy and adjuvant temozolomide. All patients had KPS greater than 70 and interval from previous treatment greater than 6 months with no multi-focal disease.</p> <p>Age: median 51 (range 27 to 80)</p> <p>Gender: Male 22/43 (51%) female 21 (49%)</p> <p>Performance status: KPS 100: 11 (26%); 90: 19 (44%); 80:2 (4%); 70: 11 (26%)</p>

**Scorsetti 2015** (Continued)

MGMT status: methylated: 18 (42%); unmethylated: 8 (19%); not known: 17 (39%)

Initial treatment details: all had surgery, radiotherapy and chemotherapy (complete resection 24 (56%); subtotal 5 (12%); partial resection 12 (28%))

Sort of recurrence: e.g. 1st, 1st and 2nd, any

Time from initial diagnosis: time to relapse from first diagnosis: less than a year 21 (49%); 12 to 24 months 13 (30%); more than 2 years 9 (21%). Median 13 months (6 to 78 months)

Patients in the 2 treatment arms were described as well matched although those undergoing re-resection and/or radiotherapy were more likely to have had later relapse (15/21 more than a year from diagnosis vs 7/22 in the chemotherapy alone arm; and those in the re-resection and/or radiotherapy groups had higher performance status at relapse 11/21 100% vs 0/22 100% in the 'chemotherapy only' arm.

Interventions	<p>Arm 1: (21 patients) combined treatment: surgery and/or radiotherapy plus chemotherapy</p> <p>Arm 2: (22 patients) chemotherapy alone</p> <p>It was not clear how many patients in the combined treatment arm had both re-resection and radiotherapy (or radiotherapy alone) with chemotherapy. Allocation to treatment modalities not clear although the conclusion recommends that treatment choice should be based on multidisciplinary evaluation.</p>
Outcomes	PFS and OR (MRI and clinical examination). Haematological toxicity and radio-necrosis.
Notes	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	A non-randomised study. This study is at high risk of selection bias. Treatment modality appeared to relate to clinical characteristics. Method of allocation not described. Patients in the 2 treatment arms were described as well matched although those undergoing re-resection and/or radiotherapy were more likely to have had later relapse (15/21 more than a year from diagnosis vs 7/22 in the chemotherapy alone arm; and those in the re-resection/ and or radiotherapy had higher performance status at relapse 11/21 100% vs 0/22 100% in the chemotherapy only arm.
Allocation concealment (selection bias)	High risk	Patients appeared to be selected for different arms based on clinical factors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding but survival outcomes may be less susceptible to assessment bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients appeared to be followed up in the selected cohort. It is not clear whether all patients treated during the recruitment period were included.
Selective reporting (reporting bias)	Unclear risk	Chemotherapy toxicity reported for all patients rather than by treatment arm.



**Scorsetti 2015** (Continued)

Other bias	Unclear risk	It was unclear how many in the combined treatment arm had both surgery and radiotherapy or radiotherapy alone.
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**Stupp 2012**

**Study characteristics**

Methods	<p>Design: Phase 3, RCT, randomised at 1:1 ratio, multicentre (28 institutions from 7 different countries)</p> <p>Country: Austria, Israel, Germany, France, Czech Republic, USA, Switzerland</p> <p>Accrual dates: September 2006 until May 2009</p> <p>Trial reg: NCT00379470</p> <p>Funding: the trial was funded and sponsored by Novocure Ltd. Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report.</p> <p>Declaration of interests: "Eilon Kirson and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company. Herwig Kostron has received honoraria from Novocure Ltd. Yoram Palti is the inventor of the Novo-TTF principle. He received consulting honoraria and travel support by Novocure Ltd. Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck &amp; Co (previously Schering-Plough). Susan Panullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck &amp; Co (previously Schering-Plough)..." among others.</p>
Participants	<p>No. randomised: 237</p> <p>No. analysed: 217</p> <p>Inclusion/exclusion criteria: adequate haematologic, renal and hepatic function. Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo peritoneal shunt).</p> <p>Age: 24 to 80</p> <p>Gender: Male 165 (70%), Female 72 (30%)</p> <p>Performance status: KPS <math>\geq</math> 70%</p> <p>MGMT: NR</p> <p>Resection/biopsy: just over 25% of patients had debulking before enrolment.</p> <p>Details of treatment: more than 80% of participants received RT and TMZ for primary treatment. More than 80% of patients had failed 2 or more prior lines of chemotherapy (second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment.</p>
Interventions	<p>Arm 1: Tumour Treatment Fields (TTF). Field intensity was set at <math>&gt; 0.7</math> V/cm (n = 120)</p> <p>Arm 2: Active control chemotherapy (n = 117). Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%).</p>
Outcomes	PFS, OS, SAEs
Notes	Many different treatments were used in the control arm, which makes interpretation of the findings difficult, especially as it is not clear whether these treatments are effective in recurrent GBM.

**Stupp 2012** (Continued)

Author conclusions "No improvement in overall survival was demonstrated, however efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible with this intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High risk for safety and QoL data. 22% attrition in the control arm for safety. QoL data were available for only 62 patients (27%)
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Suchorska 2016**

**Study characteristics**

Methods	<p>Design: Non-randomised study</p> <p>Country: Germany</p> <p>Accrual dates: NR</p> <p>Trial reg: NCT00941460</p> <p>Funding: The DIRECTOR trial (NCT 00941460) was supported by a grant from Merck Sharp and Dohme (MSD; formerly Schering-Plough) and matching-funds grant from University Hospital Zurich, Switzerland.</p> <p>Declaration of interests:</p> <p>"M.W. is an advisory board member for MSD, from which he reports receiving research grants. G.T. reports receiving a travel grant from MSD. U.H. reports receiving speakers bureau honoraria from Medac. U.S. is a consultant/advisory board member for Roche and reports receiving speakers bureau honoraria from GlaxoSmithKline and Medac. G.R. reports receiving commercial research grants from Roche and speakers bureau honoraria from Amgen and Roche. W.W. reports receiving speakers bureau honoraria from Roche, MSD, and Prime Oncology. J.C.T. is a consultant/advisory board member for Merck Serono and Roche and reports receiving speakers bureau honoraria."</p>
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**Suchorska 2016** (Continued)

Participants	<p>105 analysed.</p> <p>Study population: people with recurrent GBM taking part in the DIRECTOR trial in which they were randomised to receive 1 of 2 dose-intense TMZ regimens.</p> <p>Median age: 55 in surgery group and 59.6 in the no surgery group</p> <p>Gender: 67.6% male in the surgery group and 61.8% in the no surgery group</p> <p>Performance status: All &gt; 70</p> <p>Time to first progression: 11.5 months in the surgery group and 10.7 months in the no surgery group</p>
Interventions	<p>Arm 1 (n = 71): surgery</p> <p>Arm 2 (n = 34): no surgery</p>
Outcomes	PFS, post-recurrence survival, QoL
Notes	Extent of resection was prognostic for outcome: complete resection was associated with improved post-recurrence survival compared with incomplete resection (9.8 months vs 6.5 months).

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	A non-randomised study in which the allocated interventions may have been subject to selection bias. "Indication for surgery was commonly based on recommendations from multidisciplinary tumour boards."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Volumetric analysis of pre and post surgical MR images were performed by an experienced investigator blinded to patients' outcome"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in the analysis.
Selective reporting (reporting bias)	Low risk	None suspected.

**Taal 2014**
**Study characteristics**

Methods	<p>Design: RCT Phase 2</p> <p>Country: the Netherlands</p> <p>Accrual dates: 11 December 2009, and 10 November 2011</p> <p>Trial reg: Nederlands Trial Register (NTR1929)</p> <p>Funding: Roche Nederland and KWF Kankerbestrijding.</p> <p>Declaration of interests:</p>
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**Taal 2014** (Continued)

MJvdB has done paid consultancy for Roche, Abbvie, Celldex, Amgen, and Merck Ag; has received research grants from Roche and AbbVie; and has been on the speakers' bureau for MSD. HMO and MJT have received personal fees from Roche for consultancy. The other authors declare no competing interests.

**Participants**

No. randomised: 153

No. analysed: 148

**Inclusion criteria**

- Histologically proven glioblastoma with 1st progression after previous chemoradiotherapy with TMZ
- Documented by MRI with at least 1 bi-dimensionally measurable target lesion with 1 diameter of at least 10 mm
- Visible on 2 or more axial slices 5 mm apart
- Had not received previous chemotherapy for recurrent disease
- Had not previously received treatment with an anti-VEGF agent or nitrosoureas
- Were on a stable or decreasing dose of steroids for 7 days before the baseline MRI scan
- Had not received radiotherapy within the 3 months before the diagnosis of progression
- Had not received chemotherapy in the past 4 weeks
- Were at least 18 years of age
- Had WHO performance status of 0 to 2
- Had adequate bone marrow, renal, and hepatic function

**Exclusion criteria**

- Uncontrolled hypertension (SBP >150 mm Hg or DBP >100 mm Hg),
- Any arterial or venous thrombosis up to 6 months before registration,
- Evidence of recent haemorrhage on brain MRI,
- Substantial cardiac disease (eg, history of myocardial infarction within 6 months before inclusion or unstable angina),
- Use of therapeutic doses of oral or parenteral anticoagulants or thrombolytic drug

Age: ≥ 18 (range 24 to 77)

Gender: Approx. 59% Male 41% Female

Performance status: WHO 0 to 2

MGMT: unmethylated BEV 24, LOM 20, BEV + LOM 26; methylated BEV 18, LOM 23, BEV + LOM 21; Not done/UNK 16

Re-operation at recurrence: approx. 11%

Initial treatment details: TMZ + RT

Time from initial diagnosis: reported as since last RT. Medians were similar across groups and the range was 69 to 2087 days.

**Interventions**

Arm 1 (n = 46): lomustine (LOM) orally at a dose of 110 mg/m<sup>2</sup> on day 1 every 6 weeks with prophylactic anti-emetic drugs, for a maximum of 6 treatment cycles

Arm 2 (n= 50): bevacizumab intravenously at a dose of 10 mg/kg every 2 weeks

Arm 3 (n=52): LOM + BEV

Note: "In the combination group, lomustine was initially given at 110 mg/m<sup>2</sup> every 6 weeks, with a maximum lomustine dose of 200 mg per cycle of 6 weeks. After the pre-planned safety review, we reduced the lomustine dose for the rest of the patients in the combination group to 90 mg/m<sup>2</sup>, with a maximum lomustine dose of 160 mg per cycle of 6 weeks."

**Taal 2014** (Continued)

Outcomes	PFS, OS, SAEs, QOL
Notes	<p>The study was not powered to formally compare results between the 3 treatment groups.</p> <p>Authors concluded that: "The combination of bevacizumab and lomustine met prespecified criteria for assessment of this treatment in further phase 3 studies. However, the results in the bevacizumab alone group do not justify further studies of this treatment."</p> <p>QoL data were reported in Dirven 2015.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised by a web-based program and stratified by a
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label, although for OS this can be assumed to be low risk.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for survival and toxicity outcomes. Attrition for the QOL outcome was high because "detailed assessment of functional outcome once radiological progression has occurred is difficult".
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Tsien 2019**

**Study characteristics**

Methods	<p>Design: multi-institutional, prospective randomized phase II trial (1:1)</p> <p>Country: USA</p> <p>Accrual dates: November 2012 to April 2016</p> <p>Trial reg: RTOG 1205</p> <p>Funding: NR</p> <p>Declaration of interests: C. Tsien: Honoraria; Merck. Speaker's Bureau; Varian. Travel Expenses; Merck; RSNA Oncologic Imaging Committee. S. Pugh: Research Grant; Millennium, Pfizer-Astellas. A.P. Dickler: Research Grant; Radiation Therapy Oncology Group. Travel Expenses; Prostate Cancer Foundation; Department of Defense. J.J. Raizer: Employee; Astellas, Celldex. Stock; Celldex and Agenus. Stock Options; Exicure. M.M. Matuszak: Employee; William Beaumont Hospital. E. Lallana: Research Grant; Orbus Therapeutics, Novocure. J. Huang: Research Grant; Cantex Pharmaceuticals. Speaker's Bureau; Viewray</p>
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**Tsien 2019** (Continued)

Inc. Travel Expenses; Viewray Inc. O. Algan: None. N. Taylor: None. L. Portelance: Committee Member; NRG. J. Villano: None. J. Hamm: None. K.S. Oh: Research Grant; Merck & Co., Inc. Review and create questions for CME section of journal; IJROBP. A.N. Ali: Partner; Northwest Georgia Radiation Oncology. M.M. Kim: None. S. Lindhorst: None. M.P. Mehta: Consultant; Astra-Zeneca. Stock; Oncoceutics. Data/Clinical research; PTCOG. Protocol development; NRG Oncology.

Participants	No. randomised: 182  No. analysed: 170  Inclusion/exclusion criteria: NR  Age: NR  Gender: NR  Performance status: NR  MGMT: NR  Resection/biopsy: NR  Initial treatment details: majority of patients (80%) had previously received chemoRT.  Time from initial diagnosis: NR
Interventions	Arm 1: hypofractionated reirradiation (HFRT, 35 Gy in 10 fractions) with concurrent bevacizumab (BEV) IV 10 mg/kg q2 wks  Arm 2: Bevacizumab (IV 10 mg/kg q2 wks )
Outcomes	Median survival time, PFS rate, SAEs
Notes	Conference abstract only. Authors concluded that "Role of BEV-HFRT should be limited to small volume recurrences, especially in previously non-irradiated treatment areas at least 6 months following completion of previous RT."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient details to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to make a judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details to make a judgement.

**Tsien 2019** *(Continued)*

Selective reporting (re-reporting bias)	Unclear risk	Insufficient details to make a judgement.
Other bias	Unclear risk	Insufficient details to make a judgement.

**Twelves 2017**
**Study characteristics**

Methods	Design: Randomized Phase II trial (1:1) Country: NR Accrual dates: NR Trial reg: NCT01812603 Funding: NR Declaration of interests: NR	
Participants	No. randomised: 21 No. analysed: 21 Inclusion/exclusion criteria: NR Age: mean age was 58 years Gender: 5/12 in treatment arm, 8/9 in the placebo arm Performance status: median KPS was 90 MGMT: NR Resection/biopsy: NR Initial treatment details: Stupp protocol Time from initial diagnosis of recurrence: 3.6 weeks and 3.0 weeks for CBD:THC and placebo groups, respectively	
Interventions	Arm 1 (n = 12): CBD:THC Arm 2 (n = 9): placebo Participants in both arms received dose-intense TMZ	
Outcomes	Tolerability, toxicity, median survival	
Notes	Authors concluded that this study provides preliminary evidence that CBD:THC offers some efficacy in people with recurrent GBM when used as an adjunct to dose-intense TMZ and confirms its safety and feasibility.	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

**Twelves 2017** (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient detail to make a judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail to make a judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to make a judgement
Other bias	Unclear risk	Insufficient detail to make a judgement

**van den Bent 2018**
**Study characteristics**

Methods	Design: multicenter 3-arm comparative, randomized open label phase II trial  Country: multicountry  Accrual dates: 16 February 2015 and 1 July 2016  Trial reg: NCT02343406 / EudraCT# 2014-004438-24  Funding: this study was sponsored by AbbVie.  Declaration of interests: extensive list, page 9 of the publication
Participants	No. randomised: 260  No. analysed: 260  Inclusion criteria <ul style="list-style-type: none"> <li>• 18 years or older</li> <li>• Histologically confirmed glioblastoma, with centrally confirmed EGFR amplification,</li> <li>• Relapsing more than 3 months after the end of RT.</li> <li>• Chemotherapy had to be discontinued at least 4 weeks prior to randomization.</li> <li>• Surgery at the time of the recurrence was allowed, but required an MRI made within 48 hours following surgery.</li> <li>• Patients who were re-operated for the recurrence needed to have a bi-dimensionally measurable enhancing lesion with minimal square diameters of 10 mm on MRI, with stable or decreasing dose of steroids for 7 days prior to the baseline MR scan.</li> <li>• Adequate haematological, renal, and hepatic function,</li> <li>• For women of childbearing potential a negative pregnancy test.</li> </ul>



**van den Bent 2018** (Continued)

- To call a tumour EGFR amplified, the sample needed to show  $\geq 15\%$  tumour cells with an EGFR/chromosome enumeration probe 7 ratio of  $\geq 2$ .
- The presence of an EGFRvIII mutation was determined by a custom triplex real-time reverse-transcription quantitative PCR on RNA extracted from formalin-fixed paraffin-embedded tissue.

## Exclusion criteria

- Prior treatment with nitrosoureas, bevacizumab, or EGFR targeting agents.
- Use of enzyme inducing anti-epileptic drugs

Age: median 58.7 (range 34.9 to 82.3 yrs)

Gender: Male 167 (64.2%), Female 93 (35.8%)

Performance status: WHO PS 0: 88 (33.8%); WHO PS 1: 123 (47.3%), WHO PS 2: 49 (18.8%)

MGMT: unmethylated 113 (51.2%), methylated 126 (48.5%), missing 1 (0.4%)

Resection/biopsy/re-operation: not reported

Initial treatment details: not reported

Time from initial diagnosis: NR

Interventions	<p>Arm 1: Depatux-M 1.25 mg/kg intravenously over 30 to 40 min once every 2 weeks in combination with TMZ 150 to 200 mg/m<sup>2</sup> day 1 to 5 in 28 day cycles;</p> <p>Arm 2: Depatux-M 1.25 mg/kg intravenously over 30 to 40 min once every 2 weeks</p> <p><i>Shortly after the start of the trial, the Depatux-M start dose was decreased from 1.25 mg/kg to 1.0 mg/kg because of ocular toxicity reported in the ongoing phase I trial.</i></p> <p>Arm 3: lomustine or TMZ depending on the timing of relapse; patients who relapsed during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine 110 mg/m<sup>2</sup> (maximum dose 200 mg) on day 1 of 42-day treatment periods, whereas patients relapsing afterward were treated with TMZ 150 to 200 mg/m<sup>2</sup> on day 1 to 5 in 28-day cycles.</p>
Outcomes	OS, PFS, HRQoL, toxicity
Notes	<p>Authors concluded that "this trial suggests a role for the use of Depatux-M in combination with TMZ in EGFR amplified recurrent glioblastoma, but its findings are not supported by the companion phase III study in newly diagnosed glioblastoma. The efficacy in glioblastoma of other ADCs targeting the EGFR but with a better safety profile should be explored."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"EORTC web-based registration and randomization system"
Allocation concealment (selection bias)	Low risk	Patients were first registered and then randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	PFS assessed by independent review

**van den Bent 2018** (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Weathers 2016**
**Study characteristics**

Methods	<p>Design: randomized, 2-arm, comparative, single-centre, phase II trial with patients randomized to either treatment using a 1:1 randomization scheme. (Stratified by 1st, 2nd, or 3rd recurrence, age (<math>\leq 50</math> versus <math>&gt; 50</math> years)).</p> <p>Country: USA</p> <p>Accrual dates: January 2010 and December 2014</p> <p>Trial reg: NR</p> <p>Funding: National Institutes of Health [1R21CA152024-01] to J.D. National Institutes of Health [CCSG-P30 CA016672] to R.D.</p> <p>Declaration of interests: S.W. serves on the advisory board for Actelion. X.H. has no disclosures. D.L. has no disclosures. C.C. has consultant relationships with Actelion, DNATrix, Reata Pharma, Newlink Genetics and Cytrx Corp. M.G. has no disclosures. M.L. has no disclosures. B.O. has no disclosures. M. P-P. has no disclosures. V.P. is a consultant for Orbus Therapeutics, Foundation Medicine, Celgene, Genetech, and Merck. I. T-L. has no disclosures. R. C. has no disclosures. W. Y. is a consultant and serves on the advisory board for Actelion, DNATrix, Merck, and Novartis. J. D. serves on the advisory board for Genentech, Inc., Novartis, Celldex Therapeutics, and Foundation Medicine, Inc. J.D. serves on the DSMB for VBL Therapeutics and is a consultant for Celldex Therapeutics, OXiGENE, OmnioX, Inc. and Deciphera Pharmaceuticals. J.D. receives research support from Sanofi-Aventis, AstraZeneca, EMD-Serono, Eli Lilly, Novartis, and Deciphera Pharmaceuticals.</p>
Participants	<p>No. randomised: 71</p> <p>No. analysed: 69</p> <p>Inclusion/exclusion criteria: age <math>\geq 18</math> years, histologically confirmed glioblastoma in 1st, 2nd, or 3rd relapse, prior standard radiation for glioblastoma, prior treatment with temozolomide chemotherapy, and adequate haematologic, renal, and hepatic function. Exclusion criteria included prior treatment with an antiangiogenic agent or a nitrosurea.</p> <p>Age: 18+</p> <p>Gender: 48 Female (68%), 23 Male (32%)</p> <p>Performance status: Karnofsky performance status (KPS) <math>\geq 60</math></p> <p>MGMT: NR</p> <p>Resection/biopsy: NR</p> <p>Initial treatment details: NR</p>

**Weathers 2016** (Continued)

Time from initial diagnosis: NR

Interventions	<p>Arm 1: (N = 36) bevacizumab was given intravenously at a dose of 10 mg/kg every 2 weeks</p> <p>Arm 2: (N = 35) bevacizumab was given intravenously at a dose of 5 mg/kg every 3 weeks + lomustine was initially given at 90 mg/m<sup>2</sup> every 6 weeks but was later reduced to 75 mg/m<sup>2</sup></p>
Outcomes	OS, PFS (No HRs reported)
Notes	<p>Lomustine was initially given at 90 mg/m<sup>2</sup> every 6 weeks but was later reduced to 75 mg/m<sup>2</sup> following the occurrence of 17 grade 3 and 7 grade 4 haematologic adverse events observed in 12 patients and 27 cycles of treatment.</p> <p>After every 6-week cycle, patients underwent clinical evaluation and radiographic tumour assessment with MRI.</p> <p>Authors concluded that "The combination of low dose bevacizumab plus lomustine was not superior to standard dose bevacizumab in patients with recurrent glioblastoma. Although the study was not designed to exclusively evaluate patients at first recurrence, a strong trend towards improved PFS was seen in that subgroup for the combination of low dose bevacizumab plus lomustine."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the report.
Allocation concealment (selection bias)	Unclear risk	Not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in the report.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"scans assessed separately by treating physicians and by an independent, treatment-arm blinded, radiographic review by a neuro-radiologist based on published RANO criteria"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition. 69 out of 71 participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly reported.
Other bias	Unclear risk	Author declarations of interest noted. Trial was closed early due to futility.

**Wick 2010**
**Study characteristics**

Methods	<p>Design: phase III open-label multicentre RCT, ratio 2:1</p> <p>Countries: 14 countries including Australia, Canada, France, Germany, the Netherlands and USA.</p> <p>Accrual dates: March 2006 to August 2007</p>
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**Treatment options for progression or recurrence of glioblastoma: a network meta-analysis (Review)**

**Wick 2010** (Continued)

Funding: NR

Declaration of interests: Employment or Leadership Position: Shengyan Hong, Eli Lilly (C); Luna Musib, Eli Lilly (C); Astra M. Liepa, Eli Lilly (C); Donald E. Thornton, Eli Lilly (C) Consultant or Advisory Role: Wolfgang Wick, Eli Lilly (C); Vinay K. Puduvalli, Merck (C); Marc C. Chamberlain, Enzon (U), Genentech (U); Martin J. van den Bent, Eli Lilly (C); Lawrence M. Cher, Schering-Plough (C); Warren Mason, Eli Lilly (C); Michael Weller, Eli Lilly (C) Stock Ownership: Shengyan Hong, Eli Lilly; Luna Musib, Eli Lilly; Astra M. Liepa, Eli Lilly; Donald E. Thornton, Eli Lilly Honoraria: Vinay K. Puduvalli, Merck; Marc C. Chamberlain, Enzon, Genentech Research Funding: Vinay K. Puduvalli, Merck, Celgene, Pfizer, Eli Lilly; Lawrence M. Cher, Schering-Plough, Eli Lilly, Merck, AstraZeneca Expert Testimony: None Other Remuneration: Lawrence M. Cher, Schering-Plough

Participants	<p>Inclusion criteria included the following: 18 years of age; life expectancy 8 weeks; Karnofsky performance status (KPS) 70; histologically confirmed WHO grade 4 glioblastoma (including gliosarcomas); magnetic resonance imaging (MRI) evidence of tumour progression after radiation and chemotherapy (12 weeks must have elapsed since completion of radiotherapy or 4 weeks for chemotherapy); 2 prior chemotherapy regimens; recovery from initial surgery; and adequate organ function. Enzyme-inducing antiepileptic drugs (EIAEDs) were to be discontinued 14 days before study enrolment.</p> <p>Exclusion criteria included the following: prior enzastaurin therapy within 30 days of enrolment; treatment with any nitrosourea (including lomustine), bevacizumab, investigational drugs, or intratumoural chemotherapy; stereotactic radiosurgery; concurrent systemic anticancer therapy or anticoagulant therapy; second primary malignancy; serious concomitant systemic disorders; ECG or other clinically significant cardiac abnormalities; and pregnancy or breastfeeding.</p>
Interventions	<p>Arm 1 (n = ): 500 mg of oral enzastaurin daily (1125-mg loading dose on day 1)</p> <p>Arm 2 (n = ): 100 to 130 mg/m<sup>2</sup> of lomustine (day 1 and 6-weekly).</p>
Outcomes	PFS, OS, objective response, adverse events
Notes	<p>Enzastaurin is an oral serine/threonine kinase inhibitor that targets both the protein kinase C and the PI3K/AKT pathways 23 to induce apoptosis and suppress proliferation and tumour-induced angiogenesis.</p> <p>Tumour evaluations and neuro-radiologic exams using MRI were done after every cycle (± 5 days).</p> <p>This trial was stopped due to futility.</p> <p>Authors concluded that "Enzastaurin was well tolerated and had a better hematologic toxicity profile but did not have superior efficacy compared with lomustine in patients with recurrent glioblastoma."</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not detailed in the report.
Allocation concealment (selection bias)	Unclear risk	Not detailed in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neuroradiologic data were independently reviewed (central review) to confirm response and progression."

**Wick 2010** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients analysed.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported and study was stopped early for futility.
Other bias	Unclear risk	Funding and author interests noted.

**Wick 2014**
**Study characteristics**

Methods	<p>Design: Phase 2 RCT; ratio 1:2</p> <p>Country: Austria, Germany, Russia</p> <p>Accrual dates: December 2009 to September 2011</p> <p>Trial ID. NCT01071837</p> <p>Funding: Apogenix GmbH</p> <p>Declaration of interests: W. Wick reports receiving a commercial research grant from Boehringer Ingelheim and Roche; speaker's bureau honoraria from Prime Oncology; and is a consultant/advisory board member for Eli Lilly and Co. and Roche. B. Wiestler is a co-inventor of a patent on Neutralization of CD95 activity blocks invasion of glioblastoma cells in vivo, which is owned by the German Cancer Research Center and licensed to Apogenix. J. Debus and C. Hartmann report receiving commercial research grants from Apogenix. C. Kunz and Harald Fricke are employees of Apogenix.</p>
Participants	<p>No. randomised: 91</p> <p>No. analysed: 84</p> <p>Inclusion/exclusion criteria: adult patients with 1st or 2nd progression of a histologically confirmed glioblastoma either not being eligible for tumour resection or having macroscopic residual tumour after tumour resection, documented by contrast-enhanced magnetic resonance imaging (MRI) with the largest diameter measuring 1 cm to 4 cm and a Karnofsky performance score (KPS) 60 were eligible. No more than 2 prior therapy regimens including 1 or 2 resections, 1 or 2 chemotherapies of which one must have been temozolomide-containing, and 1 radiotherapy (completed 8 months before enrollment) were allowed.</p> <p>Age: median age 59 (25 to 79) in RT arm and 57 (20 to 73) in RT+APG101 arm</p> <p>Gender: Male 46% and 67% in arm 1 and arm 2, respectively.</p> <p>Performance status: <math>\geq 60</math></p> <p>MGMT status: methylated 57.7% and 70.6% for arms 1 and 2, respectively.</p> <p>Time from diagnosis: 20.3 mo and 23.9 mo, respectively.</p>
Interventions	<p>Arm 1 (n = 26): RT as 36 Gy in 2-Gy fractions (either stereotactic radiotherapy or image-guided)</p> <p>Arm 2 (n = 58): RT + APG101 (400 mg given weekly in an iv infusion)</p>
Outcomes	PFS, OS, adverse events, QoL

**Wick 2014** (Continued)

Notes Authors concluded that "CD95 pathway inhibition in combination with rRT is an innovative concept with clinical efficacy. It warrants further clinical development."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participant allocation was done according to an electronically generated randomization list"
Allocation concealment (selection bias)	Unclear risk	"Allocation took place by fax transmission from the CRO to the study site"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"This was an unblinded trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Biases were prevented by strict adherence to an analysis plan that was written by the statistician (K. Junge) before any analysis of the data." "Tumor response or progression was defined according to modified MacDonald criteria taking...by the local investigator and centrally."
Incomplete outcome data (attrition bias) All outcomes	Low risk	84/91 pts were evaluable for the primary endpoint
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported.
Other bias	Unclear risk	Funding and author interests noted.

**Wick 2017**
**Study characteristics**

Methods	<p>Design: Phase 3 multicentre RCT, ratio 2:1</p> <p>Countries: 8 countries including Belgium, Germany, the Netherlands, France, Switzerland.</p> <p>Accrual dates: November 2011 to December 2014</p> <p>Funding: F. Hoffmann–La Roche and EORTC Cancer Research Fund;</p> <p>Trial ID: EORTC 26101 ClinicalTrials.gov NCT01290939; Eudra-CT 2010-023218-30</p> <p>Declarations of interest: Dr. Wick reports receiving consulting fees from Merck Sharp &amp; Dohme and Celldex Therapeutics, consulting fees and lecture fees from Bristol-Myers Squibb, grant support and drugs provided for the trial from Roche and Boehringer Ingelheim, and drugs provided for the trial from Apogenix and Pfizer; Dr. Bendszus, receiving grant support from Siemens, Stryker, and Medtronic, consulting fees from Vascular Dynamics, Boehringer Ingelheim, and B. Braun, lecture fees from Teva, grant support and lecture fees from Novartis and Bayer, and grant support, consulting fees, and lecture fees from Codman Neuro and Guerbet; Dr. Taphoorn, receiving consulting fees from F. Hoffmann–La Roche; among others.</p>
Participants	<p>No. randomised: 437</p> <p>No. analysed: 437</p>

**Wick 2017** (Continued)

Included if: histologic confirmation of glioblastoma; first progression after chemoradiotherapy; at least 3 months after end of radiotherapy.

Excluded if: received prior antiangiogenic treatment or nitrosureas. Radiotherapy at a dose of no more than 65 Gy with stereotactic radiosurgery or brachytherapy was allowed if recurrence was histologically proven.

Age: median 57.7 years (21.2 to 82.3)

Gender: 60.6% male, 39.4% female

Performance status: WHO 0 to 2

MGMT status: methylated 23.8%, unmethylated 28.6% and unknown 48%

Re-operation: NR

Details of initial treatment: RT + TMZ

Time from diagnosis: NR

Interventions	Arm 1: lomustine (60mg/m <sup>2</sup> orally 6 weekly) plus bevacizumab (10 mg/kg every 2 weeks) Arm 2: lomustine (110 mg/m <sup>2</sup> every 6 weeks)
Outcomes	OS, PFS, adverse events, QOL, molecular studies
Notes	Authors concluded that "Despite somewhat prolonged progression-free survival, treatment with lomustine plus bevacizumab did not confer a survival advantage over treatment with lomustine alone in patients with progressive glioblastoma."

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The EORTC used four stratification criteria to centrally randomly assign patients who had entered the trial."
Allocation concealment (selection bias)	Unclear risk	Probably concealed but not described in the report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All the assessments and interpretations of disease status were performed locally but with continuous central quality control and independent central assessment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the primary analysis.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported.
Other bias	Unclear risk	Funding and author interests noted.

adj = adjuvant

AA = anaplastic astrocytoma  
 AE = adverse events  
 CED = cediranib  
 CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1- nitrosourea, also known as lomustine  
 CPT = irinotecan  
 DC = dendritic cell  
 ECOG = Eastern Cooperative Oncology Group  
 FOT = fotemustine  
 GBM = glioblastoma  
 GEF = gefitinib  
 HU = hydroxyurea  
 MGMT = Methyl Guanine Methyl Transferase  
 MMSE = mini mental state exam  
 NR = not reported  
 OS = overall survival  
 PFS = progression free survival  
 PS = performance status  
 QoL = quality of life  
 RT = radiotherapy  
 SAE = severe adverse event  
 TMZ = temozolomide  
 TTD = time to deterioration  
 VEGF = vascular epithelial growth factor

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

Study	Reason for exclusion
<a href="#">Abacioglu 2011</a>	This is a study of dose dense temozolomide in people with recurrent glioblastoma. This study was excluded because it was a non-comparative study, which therefore did not meet the review criteria for study design.
<a href="#">Abdel-Rahman 2015</a>	This is a systematic review of irinotecan-based salvage regimens for patients with recurrent glioblastoma multiforme (GBM).
<a href="#">ACTRN12615001072505 2015</a>	This is a study to treat raised intercranial pressure associated with brain tumours in people with oedemas/glioblastoma. We excluded it because it did not meet the reviews intervention and outcomes criteria.
<a href="#">Ahluwalia 2018</a>	This is a study of nivolumab plus standard dose bevacizumab versus nivolumab plus low dose bevacizumab in recurrent glioblastoma. We excluded it because it did not meet the review's minimum number of participants criterion.
<a href="#">Aoki 2016</a>	This is a study of temozolomide plus nimustine chemotherapy for recurrent glioblastoma. We excluded it because it was a single-arm phase I/II study.
<a href="#">Bartsch 2005</a>	This is a retrospective study of re-irradiation in people with recurrent glioblastoma, which was non-comparative.
<a href="#">Bogdahn 2011</a>	This study is a study of two different doses of trabedersen compared with standard chemotherapy for recurrent GBM or AA. We excluded it because a significant proportion of participants did not receive the standard of care (chemoradiotherapy) for the primary treatment.
<a href="#">Boiardi 2008</a>	A retrospective study of mitoxantrone added to temozolomide and re-operation for recurrent GBM. This study did not meet the review population criteria as study subjects had not received the Stupp protocol as primary treatment.



Study	Reason for exclusion
Brada 2010	This study evaluates temozolomide versus PCV among people with recurrent GBM. Participants in this study had not received the Stupp regimen for primary treatment of their GBM and therefore this study was excluded.
Brandes 2009	This is a study of fotemustine after concomitant and/or adjuvant temozolomide in people with recurrent glioblastoma. We excluded it because it was a single arm study.
Chen 2015	This retrospective study compares BEV treatment with a variety of BEV-combination treatments and non-BEV treatments. It is not clear whether patients received chemoradiotherapy as first-line treatment and the second-line treatments differed widely between groups; therefore, We excluded it due to ineligible population and diverse interventions.
Cher 2017	This is a study of tanibirumab in people with recurrent glioblastoma. We excluded it because it did not meet the review's minimum number of participants.
CTRI/2018/01/011542	This is a study protocol of mebendazole in glioblastoma.
Dixit 2015	This is a study presented in a letter which compares bevacizumab with PCV chemotherapy in a retrospective cohort of people with recurrent glioblastoma. Outcomes were neurological status and performance status. It was excluded because it included people with grade 3 and grade 4 tumours and comparison groups were not concurrent.
Duque 2017	This is a study of TVB-2640 in combination with bevacizumab in patients with first relapse of high-grade astrocytoma. We excluded it because it did not meet the criteria due to ineligible population.
Ellingson 2019	This is a conference presentation of the GLOBE study of VB111 with or without bevacizumab or bevacizumab monotherapy in people with recurrent glioblastoma. We excluded it because it is a radiographic analysis.
Fogh 2010	This is a study of hypofractionated stereotactic therapy in people with recurrent glioblastoma. We excluded it because it was a non-comparative study.
Gan 2015	This is a study of an EGFR agent called ABT-414 with or without TMZ in glioblastoma. We excluded it because it is a dose-finding study.
Gatson 2015	This is a study of rindopepimut plus bevacizumab in recurrent glioblastoma. We excluded it because the article has been retracted.
Haslund 2016	A prospective, open-label, phase II study was designed to include 175 patients with recurrent GBM in three centres in Denmark comparing ALECSAT to Bevacizumab plus Irinotecan but only 25 patients were randomised and the study was stopped due to futility.
Hong 2013	This is a retrospective study of repeated microsurgical resection versus a single re-resection in 10 vs 32 patients, respectively with GBM. Choice of surgical treatment was dependent on the surgeon's choice, only 29 of the patients received radiotherapy and temozolomide, and salvage treatments varied; we therefore considered this study to be at a high risk of bias.
Idbaih 2016	This trials is among people with recurrent grade 2 and 3 glioma therefore does not meet the review's population criteria.
Immonen 2004	This study is study of AdvHSV-tk gene therapy with intravenous ganciclovir in people with recurrent glioblastoma. We excluded it because it did not meet the review's '2005 onwards' criterion.
Ji 2016	This is an RCT of adenovirus-mediated delivery of thymidine kinase (ADV-TK) compared with "conventional treatments" in recurrent GBM patients. Only 68% of participants had chemoradiotherapy

Study	Reason for exclusion
	for the primary disease; we therefore excluded the study on patient population. Authors concluded that there was a notable improvement in PFS and OS.
Kaloshi 2015	This retrospective study of BEV+CBP vs CBP did not fulfil the population inclusion criteria of > 80% participants having had chemoradiotherapy before study treatments.
Kesari 2017	This is a post hoc analysis of the EF-14 trial among people with newly diagnosed GBM that evaluated TTF plus TMZ versus TMZ after radiotherapy. At first recurrence, 131 patients in the TTF + TMZ group chose to continue with TTF plus second-line chemotherapy therapy, 73 patients in the TMZ only group chose to receive additional second-line chemotherapy and 13 of these people crossed over to the TTF arm. The patient population in this study differs from the review population that received the Stupp protocol only prior to first recurrence.
Kinzel 2018	A non-comparative study evaluating the safety data of TTFIELDS + lomustine (CCNU).
Komotar 2010	Not a study but an editorial.
Konkel 2018	This is a study of TVB-2640 in combination with avastin versus avastin alone in patients with first relapsed AA. We excluded it because it did not meet the study criteria due to ineligible population.
Lang 2018	This is a dose-escalation, dose-finding study of an oncolytic adenovirus DNX-2401 and, as such, we excluded it on study design.
Levin 2017	This RCT compares eflornithine with lomustine versus lomustine in people with recurrent AA (grade 3 glioma); we therefore excluded it due to patient population.
Mau-Sorensen 2016	A phase 2 dose-finding study of selinexor in recurrent GBM.
Minniti 2015	This non-randomised study included patients with AA (22%) and GBM and therefore did not meet the inclusion criteria.
Muhic 2013	This is an uncontrolled study of nintedanib in people with recurrent glioblastoma.
NCT02529072 2015	This was a study of nivolumab with DC vaccines in recurrent glioblastoma. This study only had 6 participants.
NCT02852655 2016	A dose-finding study of pembrolizumab pre- and post surgery versus post-surgery only in patients with surgically resectable GBM.
NCT02866747 2016	This study is about hypofractionated stereotactic radiation therapy and durvalumab in recurrent glioblastoma. We excluded it as it was suspended on interim analysis with no data reported.
NCT03014804 2016	This study is about tumour lysate antigen vaccine and nivolumab in recurrent glioblastoma. This study was excluded because it was withdrawn with no data reported.
NCT03149575 2017	This study was about temozolomide-avastin and bevacizumab in recurrent glioblastoma. We excluded it because it was terminated due to "change in clinical development plan" and no data were reported.
Penas-Prado 2015	This is a phase 1 dose-escalation study.
Rahman 2014	This is an uncontrolled retrospective study of 42 patients with recurrent GBM, 28 who received lomustine or carmustine with BEV as second-line treatment and 14 who received this combination as third-line treatment.
Reardon 2008	This phase 2 trial was a dose-finding study that was therefore excluded on study design.

Study	Reason for exclusion
<a href="#">Ruiz-Sanchez 2012</a>	This retrospective cohort study did not have a concurrent comparison group.
<a href="#">Schmidt 2006</a>	This is a study of PCV for recurrent GBM among patients who had received radiotherapy for primary GBM. We excluded it because it is a single arm study.
<a href="#">Seystahl 2013</a>	A retrospective study of BEV vs BEV + Irinotecan in grade 2 and 3 glioma; excluded on patient population.
<a href="#">Short 2017</a>	This was a dose-finding study and therefore excluded on study design.
<a href="#">Socha 2016</a>	This retrospective study was conducted among elderly and/or frail patients, therefore did not meet the review's study population criteria.
<a href="#">Sun 2013</a>	This is a Chinese study of temozolomide versus semustine in people with recurrent glioblastoma and anaplastic astrocytoma. Data were not reported according to tumour grade and less than 80% of participants had recurrent GBM.
<a href="#">Taylor 2018</a>	This is a study of palbociclib with resection versus palbociclib without resection in people with recurrent glioblastoma. It was excluded because it was stopped early due to lack of efficacy.
<a href="#">Van den Bent 2009</a>	This negative study of erlotinib vs TMZ or LOM was excluded because it did not meet the patient population criteria, i.e. less than 80% of participants received chemoradiotherapy.
<a href="#">van den Bent 2016</a>	This is a study of temozolomide with or without bevacizumab in 1st recurrence of grade II or III glioma. We excluded it on patient population.
<a href="#">Vauleon 2012</a>	This is a retrospective study of 24 people with recurrent GBM who were treated with nitrosoureas or irinotecan and bevacizumab. This study was at a high risk of bias due to baseline differences between study groups.
<a href="#">Weller 2015</a>	This RCT was a dose-finding study comparing two TMZ schedules and therefore did not meet the study design criteria of the review.
<a href="#">Yasuda 2018</a>	This retrospective study included a mixed grade 3/4 glioma population with < 80% of participants having a diagnosis of glioblastoma; it therefore did not meet the review's population criteria.
<a href="#">Yung 2000</a>	This is a study of temozolemid vs. procarbazine in people with glioblastoma at first relapse. We excluded it because it did not meet the study criteria due to ineligible population (had radiation therapy only as initial treatment, not chemoradiation).
<a href="#">Zadeh 2018</a>	An RCT of Toca 511 and Toca FC versus standard of care in patients with recurrent high-grade glioma. Excluded because this study was terminated due to "sponsor decision".
<a href="#">Zakharia 2017</a>	This is an interim analysis of an early phase I study of of indoximod with temozolomide for adult patients with temozolomide-refractory primary malignant brain tumours.

AA = anaplastic astrocytoma  
 ALECSAT = autologous lymphoid effector cells specific against tumour cells  
 BEV = bevacizumab  
 CBP = CREB binding proteins  
 CCNU = lomustine  
 DC vaccines = dendritic cell vaccines  
 EGFR = epidermal growth factor receptor  
 GBM = glioblastoma  
 LOM = lomustine  
 OS = overall survival

PFS = progression free survival  
 PCV = procarbazine, lomustine (CCNU) and vincristine  
 RCT = randomised clinical trial  
 TTF = tumour treating fields  
 TMX = temozolomide

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

#### ACTRN12617000534381 2017

Study name	Philip 2017
Methods	Phase 2, multicentre, open-label, parallel-arm, randomised controlled trial (RCT) of STEP Care plus standard best practice cancer care versus standard best practice cancer care alone.
Participants	Participants are people with advanced cancer; high-grade glioma, breast cancer and prostate cancer.
Interventions	Early palliative "STEP" care plus best practice cancer care versus best practice cancer care alone.
Outcomes	Document the impact of "STEP" on end-of-life care, determine whether it is worth exploring further and evaluate the timing of palliative care according to carers, families and professionals.
Starting date	2017
Contact information	Jennifer.philip@svha.org.au
Notes	

#### ChiCTR1900020646 2019

Study name	Xue 2019
Methods	A phase 2 randomized controlled clinical trial of temozolomide plus apatinib in newly diagnosed high-grade glioma.
Participants	Adults with glioma
Interventions	Temozolomide and apatinib versus temozolomide alone.
Outcomes	Progression-free survival, rate of 2 year overall survival and adverse events.
Starting date	6 May 2019
Contact information	<a href="mailto:xxy0636@163.com">xxy0636@163.com</a>
Notes	NCT03741244

#### Combs 2010

Study name	NCT01166308
Methods	Open label RCT of carbon ion radiotherapy vs fractionated stereotactic radiotherapy

**Combs 2010** (Continued)

Participants	56 patients with recurrent GBM with indication for radiotherapy
Interventions	Arm 1: carbon ion radiotherapy Arm 2: fractionated stereotactic radiotherapy
Outcomes	OS, PFS
Starting date	July 2010
Contact information	Prof. Juergen Debus
Notes	Apparently completed in 2016. No results reported.

**JCOG1308C 2019**

Study name	Kobayashi 2019
Methods	A multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab.
Participants	Adults with recurrent glioblastoma and gliosarcoma.
Interventions	Bevacizumab alone versus dose-dense temozolomide (ddTMZ) and bevacizumab (BEV) sequential combination therapy.
Outcomes	Overall survival, progression-free survival, response rate and adverse events.
Starting date	22 July 2016
Contact information	kekobayashi@kki.biglobe.ne.jp
Notes	JCOG1308C

**KCT0002632 2018**

Study name	Hong 2018
Methods	Randomised, double-blinded study of efficacy and safety of low-dose temozolomide with metformin or placebo for the patients with recurrent or refractory glioblastoma.
Participants	Adults from age 19+ with recurrent or refractory glioblastoma.
Interventions	Temozolomide + metformin versus temozolomide + placebo
Outcomes	Progression-free survival, overall survival, tumour response rate
Starting date	21 November 2016
Contact information	hongyk@catholic.ac.kr
Notes	KCT0002632

**NCT01252459 2016**

Study name	GLIAA 2016
Methods	Prospective, open label, randomized (allocation 1:1), 2-arm, parallel group, phase II multi-centre trial
Participants	Adults with recurrent glioblastoma
Interventions	AA-PET based target volume delineation versus T1Gd-MRI based target volume delineation
Outcomes	Overall survival, progression-free survival, quality of life
Starting date	
Contact information	gliaa@uniklinik-freiburg.de/anca.grosu@uniklinik-freiburg.de
Notes	NCT01252459

**NCT01903330 2018**

Study name	NCT01903330
Methods	A double-blinded, randomized, Phase 2 study.
Participants	Adult patients with recurrent glioblastoma
Interventions	ERC1671 + bevacizumab versus bevacizumab + placebo
Outcomes	Adverse events, toxicity, overall survival, progression-free survival
Starting date	2017
Contact information	Tel.: +1 714 456 7032; Fax: +1 714 456 6894; dbota@uci.edu
Notes	NCT01903330

**NCT02394626 2015**

Study name	RE-SURGE
Methods	Randomized controlled comparative phase II trial on surgery for glioblastoma recurrence.
Participants	Adults with first recurrence of glioblastoma.
Interventions	Surgery followed by adjuvant second-line therapy versus second-line therapy alone
Outcomes	Overall survival, progression-free survival, morbidity of surgery
Starting date	May 2015
Contact information	Contact: Andrea Mathis+41 31 632 95 64 andrea.mathis@insel.ch

**NCT02394626 2015** *(Continued)*

Notes	NCT02394626
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**NCT02678975 2016**

Study name	DIRECT (Disulfiram REsponse as add-on to ChemoTherapy) in recurrent glioblastoma: a randomized controlled trial
Methods	Multicenter, RCT with single masking, looking at disulfiram and copper-supplement as add-on treatment in glioblastoma patients with recurrence receiving alkylating chemotherapy.
Participants	Adults with recurrent glioblastoma
Interventions	Alkylating chemotherapy + disulfiram + copper versus alkylating chemotherapy
Outcomes	Survival at 6 months, overall survival, progression-free survival, health-related quality of life
Starting date	January 2017
Contact information	asgeir.jakola@vgregion.se
Notes	NCT02678975

**NCT02715297 2018**

Study name	GlioCave
Methods	Multicentre, 2-armed, randomized, phase II study
Participants	200 adults with recurrent glioblastoma
Interventions	FET-PET-based treatment versus a T1Gd-MRI-based treatment
Outcomes	Overall survival, progression-free survival
Starting date	February 2016
Contact information	mailto:Christoph.Straube@mri.tum.de
Notes	NCT02715297

**NCT02761070 2016**

Study name	RE-GEND
Methods	A multicentre randomized Phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab
Participants	Adults with recurrent glioblastoma
Interventions	Bevacizumab monotherapy versus temozolomide plus bevacizumab

**NCT02761070 2016** *(Continued)*

Outcomes	Overall survival, progression-free survival, adverse events, complete response rate.
Starting date	11 July 2016
Contact information	mnagane@ks.kyorin-u.ac.jp
Notes	NCT02761070

**NCT02794883 2016**

Study name	Raizer 2016
Methods	Randomised, open label trial of tremelimumab and durvalumab in combination or alone in treating patients with recurrent malignant glioma
Participants	Adults with recurrent malignant glioblastoma
Interventions	Durvalumab or durvalumab + tremelimumab or tremelimumab
Outcomes	Determine T-cell safety, overall survival and progression-free survival.
Starting date	September 2016
Contact information	Not found
Notes	<a href="#">NCT02794883</a>

**NCT02942264 2016**

Study name	Wu 2016
Methods	Phase I trial of zotiraciclib (TG02) + dose-dense or metronomic temozolomide followed by randomized phase II trial of zotiraciclib (TG02) + temozolomide versus temozolomide alone in adults with recurrent anaplastic astrocytoma and glioblastoma.
Participants	Adults with recurrent anaplastic astrocytoma/glioblastoma.
Interventions	Phase I metronomic TMZ versus zotiraciclib, phase II MTD of zotiraciclib plus "winner" from phase I versus "winner" from phase I.
Outcomes	Maximum tolerated dose and progression free survival.
Starting date	14 December 2016
Contact information	Contact: Matthew R Lindsley, R.N.(240) 760-6534 matthew.lindsley@nih.gov
Notes	NCT02942264



**NCT02974621 2016**

Study name	Arrillaga-Romany 2016
Methods	A randomized Phase 2 trial of cediranib and olaparib compared to bevacizumab in patients with recurrent glioblastoma who have not received prior VEGF therapy
Participants	Patients With recurrent glioblastoma
Interventions	Cediranib maleate and olaparib compared to bevacizumab
Outcomes	Progression-free survival, safety and overall survival
Starting date	15 September 2017
Contact information	
Notes	

**NCT03025893 2019**

Study name	A Phase II/III study of high-dose, intermittent sunitinib in patients with recurrent glioblastoma multiforme (STELLAR)
Methods	Randomised, open-label
Participants	Patients with first progression of GBM
Interventions	Group 1 (experimental arm): sunitinib, 300 mg administered orally in a weekly schedule. Group 2 (control arm): lomustine 110 mg/m <sup>2</sup> , taken orally on day 1 every 6 weeks.
Outcomes	PFS, OS, AEs, HRQOL
Starting date	January 2017
Contact information	M.E. van Linde
Notes	

**NCT03149003 2018**

Study name	WIZARD201G
Methods	Phase 2, active-controlled, multicenter, open-label randomized study
Participants	Adults with recurrent or progressive glioblastoma.
Interventions	DSP-7888 dosing emulsion with bevacizumab (Bev) versus Bev alone
Outcomes	Overall survival, progression free survival and safety
Starting date	8 December 2017

**NCT03149003 2018** (Continued)

Contact information	Not found
Notes	NCT03149003

**NCT03632135 2018**

Study name	CSCRGBM
Methods	Standard chemotherapy vs. chemotherapy guided by cancer stem cell test in recurrent glioblastoma
Participants	Adults with recurrent glioblastoma
Interventions	Physician Choice treatment versus ChemoID-guided treatment
Outcomes	Overall survival, progression-free survival, tumour response and quality of life.
Starting date	15 May 2018
Contact information	Tulika.RANJAN@ahn.org
Notes	NCT03632135

**NCT03746288 2018**

Study name	Li 2018
Methods	A multicentre, randomized, open-label, controlled phase II clinical trial to evaluate the efficacy and safety of CAN008 combined with re-irradiation (rRT) for treating patients with recurrent glioblastoma
Participants	Adults with recurrent glioblastoma
Interventions	CAN008 + radiotherapy versus radiotherapy
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response
Starting date	20 November 2018
Contact information	neure55@126.com
Notes	NCT03746288

**NCT03970447 2019b**

Study name	GBM AGILE
Methods	GBM AGILE: global adaptive trial master protocol: an international, seamless phase II/III response adaptive randomization platform trial designed to evaluate multiple regimens in newly diagnosed and recurrent GBM.

**NCT03970447 2019b** *(Continued)*

Participants	Adults with recently diagnosed or recurrent GBM.
Interventions	Arm 1 ND GBM: regorafenib + TMZ, recurrent GBM: regorafenib. Arm 2 ND GBM: XRT, TMZ, maintenance therapy. Recurrent GBM: Lomustine
Outcomes	Overall survival, progression-free survival, tumour response.
Starting date	30 July 2019
Contact information	Contact: Rachel Rosenstein-Sisson <a href="mailto:RRosenstein.Sisson%40GCAResearch.org?subject=NC-T03970447">mailto:RRosenstein.Sisson%40GCAResearch.org?subject=NC-T03970447</a> , GCAR-7213, A Trial to Evaluate Multiple Regimens in Newly Diagnosed and Recurrent Glioblastoma
Notes	NCT03970447

**NCT04003649 2019**

Study name	Badie 2019
Methods	A phase 1, randomised, open-label clinical trial.
Participants	Adult patients with resectable recurrent glioblastoma
Interventions	Nivolumab, ipilimumab, IL13Ralpha2 CAR T cells versus nivolumab, IL13Ra2 CAR T cells
Outcomes	Adverse events, toxicity, overall survival, progression free survival and feasibility
Starting date	November 23, 2018
Contact information	GliomaCarT@coh.org
Notes	<a href="#">NCT04003649</a>

AA-PET = Amino acid positive emission tomography

AE = adverse events

FET-PET = type of amino acid positive emission tomography

GBM = glioblastoma multiforme

HRQOL = health-related quality of live

OS = overall survival

PFS = progression free survival

RCT = randomised controlled trial

VEGF = vascular endothelial growth factor

## ADDITIONAL TABLES

**Table 1. Median survival of participants in included studies**

Study ID	No. participants	No. of recurrences	Comparison	Median PFS (months)	Median OS (months)	Study design	Comment
<b>First recurrence</b>							
Azoulay 2017	183	1st	I: Re-operation	NR	9.8	NRS	Patients selected for different arms based on clinical factors therefore a high risk of selection bias.
			C: No re-operation		5.0		
Batchelor 2013	325	1st	I: CED	3.0	8.0	Phase 3	CED did not significantly improve survival.
			I: CED+LOM	4.1	9.4		
			C: LOM	2.7	9.8		
Brandes 2016b	91	1st	I: BEV	3.4	7.3	Phase 2	Investigators concluded that single-agent BEV "may have a role".
			C: FOT	3.5	8.7		
Brandes 2018	123	1st	I: BEV+LOM	2.3	6.4	Phase 2	Terminated early due to high drop-out rate during first-line treatment.
			C: LOM	1.8	5.5		
Brandes 2016a	119	1st	I: GAL+LOM	1.8	6.7	Phase 2	Investigators concluded that GAL failed to demonstrate activity.
			C: LOM	1.9	7.5		
Brown 2016	38	1st	I: CED+GEF	3.6	7.2	Phase 2	Study was underpowered.
			C: CED	2.8	5.5		
Cloughesy 2017	129	1st	I: ONA+BEV	3.9	8.8	Phase 3	No evidence of clinical benefit with addition of ONA
			C: BEV	2.9	12.6		
Dresemann 2010	240	1st	I: IMA+HU	1.4	NR	Phase 3	No clinically meaningful differences.
			C: HU	1.4			
Lombardi 2019	119	1st	I: REG	2.0	7.4	Phase 2	Considered by investigators to have potential for further study.
			C: LOM	1.9	5.6		

**Table 1. Median survival of participants in included studies** (Continued)

Kunwar 2010	296	1st	I: cintredekin besudotox C: gliadel wafers	NR	9.1 8.8	Phase 3	No survival difference but higher risk of pulmonary embolism with cintredekin besudotox (P = 0.014).
Narita 2019	88	1st	I: PPV C: Placebo	NR	8.4 8.0	Phase 3	Did not meet primary endpoint and PPV shortened the OS in certain patients.
Omuro 2018	20	1st	I: NIV C: NIV+IPI	1.9 1.5	10.4 9.2	Phase 2	NIV was better tolerated than NIV+IPI
Puduvalli 2018	74	1st	I: BEV+VOR C: BEV	3.7 3.9	7.8 9.3	Phase 2	No clinical benefit with BEV+VOR. Does not warrant further investigation.
Reardon 2015b	78	1st	I: AFA+TMZ I: AFA C: TMZ	1.5 1.0 1.9	8.0 9.8 10.6	Phase 2	Investigators concluded that afatinib had limited single agent activity.
Scorsetti 2015	43	1st	I: Re-operation C: No re-operation	15 5	17 6	NRS	Patients selected for different arms based on clinical factors therefore a high risk of selection bias.
Suchorska 2016	93	1st	I: re-operation C: no re-operation	2.0 1.8	11.4 9.8	NRS	Patients selected for different arms based on clinical factors therefore a high risk of selection bias. Complete resection was associated with improved survival compared with incomplete resection.
Taal 2014	153	1st	I: LOM I: BEV+LOM C: BEV	1.0 4.0 3.0	8.0 12.0 8.0	Phase 2	BEV+LOM met investigator criteria for further evaluation in phase 3 studies. Single agent BEV was found to have low activity.
Twelves 2017	21	1st	I: CBD:THC C: placebo	- -	18.3 12.3		All patients received dose intense TMZ. 1 year survival was 83% and 56% in the CBD:THC and placebo groups, respectively.
van den Bent 2018	260	1st	I: ABT414+TMZ	2.7	9.6	Phase 2	ABT414 had insufficient single-agent activity.

**Table 1. Median survival of participants in included studies** (Continued)

			I: ABT414	1.9	7.9		
			C: TMZ or LOM	1.9	8.2		
<a href="#">Wick 2017</a>	437	1st	I: LOM+BEV	4.2	9.1	Phase 3	No OS benefit with combination.
			C: LOM	1.5	8.6		
<b>Any, second or subsequent recurrence</b>							
<a href="#">Bloch 2017</a>	90	1st or 2nd (% not reported)	I: HSPPC-96+BEV	NR	7.5	Phase 2	Terminated for futility after interim analysis.
			C: BEV		10.7		
<a href="#">Cuncannon 2019</a>	43	2nd or 3rd relapse	I: BEV	NR	6.0	NRS	Patients selected for different arms based on patient choice therefore high risk of selection bias.
			C: BSC		1.0		
<a href="#">Friedman 2009</a>	167	1st and 2nd (< 20%)	I: BEV+IRI	5.6	8.7	Phase 2	No survival benefit with combination.
			C: BEV	4.2	9.2		
<a href="#">Reardon 2018a</a>	80	1st and 2nd (% not reported)	I: PEM	NR	8.8	Phase 2	Investigators reported that there was no monotherapy activity.
			C: PEM+BEV		10.3		
<a href="#">Reardon 2018b</a>	48	1st and 2nd (33%)	I: TNB	0.7	11.4	NRS	Accrual to TNB was discontinued early due to lack of monotherapy activity.
			C: TNB+BEV	3.6	9.5		
<a href="#">Cloughesy 2018</a>	256	1st and 2nd (27%)	I: VB111+BEV	3.4	6.8	Phase 3	VB111+BEV failed to improve outcomes
			C: BEV	3.7	7.9		
<a href="#">Duerinck 2018</a>	79	Any	I: AXI	2.9	6.3	Phase 2	No indication that AXI+LOM improves results.
			C: AXI+LOM	3.0	6.7		
<a href="#">Field 2015</a>	122	Any (33% 2nd or subsequent)	I: BEV+CAB	3.5	6.9	Phase 2	Adding CAB resulted in more toxicity without additional clinical benefit.
			C: BEV	3.5	7.5		
<a href="#">Galanis 2017</a>	101	2nd or later	I: TRC105+BEV	2.9	10.0	Phase 2	Investigators reported no significant survival difference with TRC105.
			C: BEV	3.2	7.4		

**Table 1. Median survival of participants in included studies** (Continued)

Galanis 2019	121	Any (% not reported)	I: DAS+BEV	3.2	7.3	Phase 2	DAS+BEV did not significantly improve clinical outcomes.
			C: BEV	3.2	7.7		
Gilbert 2017	117	Any (% not reported)	I: BEV+TMZ	4.7	9.4	Phase 2	Both arms surpassed predetermined efficacy thresholds.
			C: BEV+IRI	4.1	7.7		
Heiland 2016	43	3rd	I: BEV	2.3	4.1	NRS	Investigators concluded that last-line therapy with BEV/LOM results in a longer PFS and OS compared to BEV only.
			C: BEV+LOM	6.1	6.6		
Modh 2018	34	"median of 3"	I: FSRS + BEV	5.3	7.1	RCT	Investigators concluded that FSRS in heavily pretreated patients with recurrent malignant glioma is feasible and improves local control and PFS
			C: Chemo+BEV	1.8	4.8		
Reardon 2011	23	"heavily pre-treated"	I: ETO+BEV	1.9	4.4	Phase 2	Investigators concluded that metronomic ETO or TMZ is ineffective administered with BEV in this context.
Santos 2018	32	Unclear	I: IPA + ketogenic diet	NR	NR	NRS	Investigators concluded that results on ketogenic diet were encouraging.
			C: IPA + regular diet				
Stupp 2012	237	Any (88% 2nd or later)	I: TTF	2.2	6.6	Phase 3	No improvement in survival but toxicity and QOL favoured TTF.
			C: BPC	2.1	6.0		
Tsien 2019	170	NR	I: BEV+RT	NR	10.1	Phase 2	BEV +RT was associated with improved 6-month PFS (54% vs 29%).
			C: BEV		9.7		
Weathers 2016	69	1st (68%), 2nd, and 3rd	I: LOM+BEV (low dose)	4.3	9.6	Phase 2	Median PFS for 1st recurrence (47 pts) was 5.0 mths vs 3.2 mths, respectively; median OS was 13.1 mths vs 8.8 mths, respectively.
			C: BEV	4.1	8.3		
Wick 2010	266	1st and 2nd (25%)	I: ENZ	1.5	6.6	Phase 3	Terminated early due to futility.
			C: LOM	1.6	7.1		

**Table 1. Median survival of participants in included studies** (Continued)

Wick 2014	84	1st and 2nd/3rd (29%)	I: APG101+RT C: RT	4.5 2.5	11.5 11.5	Phase 2	Investigators concluded that APG101 had potential for further clinical development.
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BEV = bevacizumab  
 BPC = Best Physician's Care  
 BSC = Best supportive care  
 CAB = carboplatin  
 CBD:THC = cannabidiol:delta-9-tetrahydrocannabinol  
 CED = cediranib  
 DAS = dasatinib  
 ENZ = enzastaurine  
 ETO = etoposide  
 HU = hydroxyurea  
 IMA = imatinib  
 IPA = intranasal perillyl alcohol  
 IRI = irinotecan  
 IPI = ipilimumab  
 LOM = lomustine  
 NIV = nivolumab  
 PEM = pembrolizumab  
 PPV = personalised peptide vaccine  
 RT = radiotherapy  
 ONA = onartuzumab  
 TTF = tumour-treating fields  
 TNB = trebananib  
 FSRH = fractionated stereotactic radiotherapy  
 TMZ = temozolomide

**Table 2. Overall survival: League table showing HR and 95% CI estimates for all intervention comparisons**

LOM	ABT414	ABT414_TMZ	BEV	BEV_IRI	BEV_LOM	BEV_ONA	CED	CED_LOM	FOT	REG
<b>LOM</b>	0.96 (0.69,1.34)	0.66 (0.47,0.92)	1.22 (0.84,1.76)	1.16 (0.71,1.88)	0.91 (0.75,1.10)	1.76 (0.94,3.30)	1.43 (0.97,2.12)	1.15 (0.76,1.74)	0.89 (0.51,1.57)	0.50 (0.33,0.76)
1.04 (0.75,1.45)	<b>ABT414</b>	0.68 (0.49,0.95)	1.27 (0.77,2.08)	1.20 (0.67,2.17)	0.95 (0.64,1.39)	1.83 (0.90,3.73)	1.49 (0.89,2.50)	1.20 (0.71,2.03)	0.93 (0.48,1.79)	0.52 (0.31,0.89)
1.52 (1.09,2.12)	1.46 (1.05,2.04)	<b>ABT414_TMZ</b>	1.85 (1.13,3.04)	1.76 (0.98,3.17)	1.38 (0.94,2.03)	2.68 (1.32,5.46)	2.18 (1.30,3.65)	1.75 (1.03,2.97)	1.36 (0.70,2.62)	0.76 (0.45,1.30)





**Table 2. Overall survival: League table showing HR and 95% CI estimates for all intervention comparisons** (Continued)

0.82 (0.57,1.19)	0.79 (0.48,1.30)	0.54 (0.33,0.89)	<b>BEV</b>	0.95 (0.70,1.30)	0.75 (0.52,1.08)	1.45 (0.87,2.41)	1.18 (0.69,2.02)	0.95 (0.54,1.64)	0.73 (0.48,1.13)	0.41 (0.24,0.72)
0.86 (0.53,1.40)	0.83 (0.46,1.49)	0.57 (0.32,1.02)	1.05 (0.77,1.44)	<b>BEV_IRI</b>	0.79 (0.48,1.28)	1.52 (0.84,2.77)	1.24 (0.67,2.31)	0.99 (0.53,1.88)	0.77 (0.45,1.31)	0.43 (0.23,0.82)
1.10 (0.91,1.33)	1.06 (0.72,1.55)	0.72 (0.49,1.06)	1.34 (0.92,1.94)	1.27 (0.78,2.07)	<b>BEV_LOM</b>	1.94 (1.03,3.64)	1.58 (1.02,2.44)	1.27 (0.80,1.99)	0.98 (0.56,1.73)	0.55 (0.35,0.87)
0.57 (0.30,1.07)	0.55 (0.27,1.11)	0.37 (0.18,0.76)	0.69 (0.41,1.15)	0.66 (0.36,1.20)	0.52 (0.27,0.97)	<b>BEV_ONA</b>	0.81 (0.39,1.71)	0.65 (0.31,1.39)	0.51 (0.26,0.99)	0.28 (0.13,0.60)
0.70 (0.47,1.03)	0.67 (0.40,1.12)	0.46 (0.27,0.77)	0.85 (0.50,1.45)	0.81 (0.43,1.50)	0.63 (0.41,0.98)	1.23 (0.59,2.58)	<b>CED</b>	0.80 (0.54,1.20)	0.62 (0.31,1.24)	0.35 (0.20,0.62)
0.87 (0.58,1.31)	0.84 (0.49,1.42)	0.57 (0.34,0.97)	1.06 (0.61,1.84)	1.01 (0.53,1.90)	0.79 (0.50,1.24)	1.53 (0.72,3.24)	1.25 (0.83,1.86)	<b>CED_LOM</b>	0.78 (0.38,1.56)	0.44 (0.24,0.78)
1.12 (0.64,1.98)	1.08 (0.56,2.08)	0.74 (0.38,1.42)	1.36 (0.89,2.10)	1.30 (0.76,2.21)	1.02 (0.58,1.80)	1.97 (1.01,3.85)	1.61 (0.81,3.20)	1.29 (0.64,2.60)	<b>FOT</b>	0.56 (0.28,1.13)
1.99 (1.32,3.01)	1.92 (1.13,3.25)	1.31 (0.77,2.22)	2.42 (1.40,4.21)	2.31 (1.22,4.35)	1.81 (1.15,2.85)	3.51 (1.66,7.44)	2.86 (1.62,5.04)	2.29 (1.28,4.10)	1.78 (0.88,3.58)	<b>REG</b>

ABT414 = depatux-m  
BEV = bevacizumab  
CED = cediranib  
IRI = irinotecan  
LOM = lomustine  
ONA = onartuzumab

**Table 3. Progression-free survival: League table showing HR and 95% CI estimates for all intervention comparisons**

LOM	BEV	BEV_IRI	BEV_LOM	BEV_ONA	REG
<b>LOM</b>	0.90 (0.58,1.38)	0.80 (0.44,1.45)	0.57 (0.44,0.74)	0.98 (0.51,1.87)	0.65 (0.42,1.01)
1.12 (0.72,1.72)	<b>BEV</b>	0.90 (0.60,1.34)	0.64 (0.41,0.99)	1.09 (0.67,1.77)	0.73 (0.39,1.35)
1.25 (0.69,2.25)	1.12 (0.75,1.67)	<b>BEV_IRI</b>	0.71 (0.39,1.28)	1.22 (0.65,2.28)	0.81 (0.39,1.69)
1.75 (1.36,2.26)	1.57 (1.02,2.43)	1.41 (0.78,2.55)	<b>BEV_LOM</b>	1.71 (0.89,3.29)	1.14 (0.68,1.90)
1.02 (0.53,1.96)	0.92 (0.57,1.49)	0.82 (0.44,1.54)	0.58 (0.30,1.12)	<b>BEV_ONA</b>	0.67 (0.30,1.46)
1.54 (0.99,2.40)	1.38 (0.74,2.57)	1.24 (0.59,2.59)	0.88 (0.53,1.46)	1.50 (0.68,3.30)	<b>REG</b>

BEV = bevacizumab  
 CED = cediranib  
 IRI = irinotecan  
 LOM = lomustine  
 ONA = onartuzumab  
 REG = regorafenib

**Table 4. Severe adverse events for treatments compared with lomustine: League table with effect estimates and 95% CIs**

LOM	BEVLOM	CED	CEDGET	CEDLOM	REG
<b>LOM</b>	2.51 (1.72,3.66)	1.00 (0.54,1.85)	2.46 (0.46,13.26)	2.51 (1.29,4.90)	1.90 (0.92,3.95)
0.40 (0.27,0.58)	<b>BEVLOM</b>	0.40 (0.19,0.82)	0.98 (0.17,5.50)	1.00 (0.46,2.15)	0.76 (0.33,1.72)
1.00 (0.54,1.85)	2.51 (1.22,5.17)	<b>CED</b>	2.46 (0.51,11.80)	2.51 (1.43,4.42)	1.90 (0.73,4.94)
0.41 (0.08,2.19)	1.02 (0.18,5.73)	0.41 (0.08,1.95)	<b>CEDGET</b>	1.02 (0.19,5.40)	0.77 (0.12,4.84)
0.40 (0.20,0.78)	1.00 (0.46,2.15)	0.40 (0.23,0.70)	0.98 (0.19,5.18)	<b>CEDLOM</b>	0.76 (0.28,2.03)
0.53 (0.25,1.09)	1.32 (0.58,3.00)	0.53 (0.20,1.36)	1.29 (0.21,8.10)	1.32 (0.49,3.54)	<b>REG</b>

BEV = bevacizumab  
 CED = cediranib  
 GET = getitinib  
 LOM = lomustine  
 REG = regorafenib

**Table 5. Severe adverse events for treatments compared with bevacizumab: League table with effect estimates and 95% CIs**

BEV	BEVCAB	BEVDAS	BEVIRI	BEVONA	BEVTRC105	BEVVB111	FOM	HSPPCBEV
<b>BEV</b>	1.27 (0.61,2.66)	1.52 (0.69,3.34)	2.22 (1.18,4.18)	1.17 (0.57,2.39)	6.86 (2.55,18.41)	3.77 (2.25,6.33)	0.44 (0.11,1.72)	1.01 (0.33,3.10)
0.79 (0.38,1.64)	<b>BEVCAB</b>	1.19 (0.41,3.51)	1.75 (0.66,4.61)	0.92 (0.33,2.57)	5.39 (1.57,18.47)	2.97 (1.21,7.29)	0.35 (0.07,1.63)	0.79 (0.21,3.03)
0.66 (0.30,1.45)	0.84 (0.29,2.46)	<b>BEVDAS</b>	1.46 (0.53,4.02)	0.77 (0.27,2.23)	4.51 (1.28,15.96)	2.48 (0.97,6.37)	0.29 (0.06,1.40)	0.66 (0.17,2.62)
0.45 (0.24,0.85)	0.57 (0.22,1.51)	0.68 (0.25,1.88)	<b>BEVIRI</b>	0.53 (0.20,1.37)	3.09 (0.95,9.97)	1.70 (0.75,3.84)	0.20 (0.04,0.89)	0.45 (0.13,1.65)
0.85 (0.42,1.75)	1.09 (0.39,3.03)	1.30 (0.45,3.76)	1.90 (0.73,4.93)	<b>BEVONA</b>	5.86 (1.73,19.82)	3.22 (1.33,7.79)	0.38 (0.08,1.75)	0.86 (0.23,3.26)
0.15 (0.05,0.39)	0.19 (0.05,0.64)	0.22 (0.06,0.78)	0.32 (0.10,1.05)	0.17 (0.05,0.58)	<b>BEVTRC105</b>	0.55 (0.18,1.68)	0.06 (0.01,0.35)	0.15 (0.03,0.66)
0.26 (0.16,0.44)	0.34 (0.14,0.83)	0.40 (0.16,1.03)	0.59 (0.26,1.33)	0.31 (0.13,0.75)	1.82 (0.60,5.54)	<b>BEVVB111</b>	0.12 (0.03,0.50)	0.27 (0.08,0.92)
2.26 (0.58,8.80)	2.88 (0.61,13.49)	3.44 (0.72,16.52)	5.03 (1.12,22.49)	2.65 (0.57,12.28)	15.51 (2.89,83.17)	8.54 (2.00,36.51)	<b>FOM</b>	2.28 (0.39,13.29)
0.99 (0.32,3.04)	1.26 (0.33,4.82)	1.51 (0.38,5.93)	2.20 (0.61,7.98)	1.16 (0.31,4.39)	6.80 (1.52,30.30)	3.74 (1.09,12.86)	0.44 (0.08,2.55)	<b>HSPPCBEV</b>

BEV = bevacizumab  
 CAB = carboplatin  
 DAS = desatinib  
 IRI = irinotecan  
 FOM = fotemustine  
 HSPCC = HSPCC-96 vaccine  
 ONA = onartuzumab  
 TRC105 = carotuximab

## APPENDICES

### Appendix 1. CENTRAL Search Strategy

- #1 MeSH descriptor: [Astrocytoma] this term only
- #2 MeSH descriptor: [Glioblastoma] this term only
- #3 glioblastom\* or GBM\* or astrocytom\* or gliosarcom\*
- #4 #1 or #2 or #3
- #5 MeSH descriptor: [Neoplasm Recurrence, Local] this term only
- #6 recurren\* or return\* or relapse\*
- #7 #5 or #6
- #9 #4 and #7

### Appendix 2. MEDLINE Search Strategy

*Intervention MEDLINE search:*

1. astrocytoma/
2. glioblastoma/
3. (glioblastom\* or GBM\* or astrocytom\* or gliosarcom\*).mp.
4. 1 or 2 or 3
5. neoplasm recurrence, local/
6. (recurren\* or return\* or relapse\*).mp.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. clinical trials as topic.sh.
14. randomly.ab.
15. trial.ti.
16. (before adj3 after adj3 (study or studies)).mp.
17. (CBA adj (study or studies)).mp.
18. interrupted time series.mp.
19. exp Cohort Studies/
20. (cohort\* or prospective\* or retrospective\*).mp.
21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. (animals not (humans and animals)).sh.
23. 21 not 22
24. 8 and 23

#### Key:

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

pt = publication type

ab = abstract

fs = floating subheading

sh = subject heading

*Economic MEDLINE search:*

1. astrocytoma/
2. glioblastoma/
3. (glioblastom\* or GBM\* or astrocytom\* or gliosarcom\*).mp.
4. 1 or 2 or 3
5. neoplasm recurrence, local/
6. (recurren\* or return\* or relapse\*).mp.
7. 5 or 6
8. 4 and 7
9. economics/
10. exp "costs and cost analysis"/
11. economics, dental/
12. exp "economics, hospital"/

13. economics, medical/
14. economics, nursing/
15. economics, pharmaceutical/
16. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab.
17. (expenditure\$ not energy).ti,ab.
18. (value adj1 money).ti,ab.
19. budget\$.ti,ab.
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. ((energy or oxygen) adj cost).ti,ab.
22. (metabolic adj cost).ti,ab.
23. ((energy or oxygen) adj expenditure).ti,ab.
24. 21 or 22 or 23
25. 20 not 24
26. letter.pt.
27. editorial.pt.
28. historical article.pt.
29. 26 or 27 or 28
30. 25 not 29
31. Animals/
32. Humans/
33. 32 not (32 and 33)
34. 30 not 33
35. 8 and 34
36. (2015\* or 2016\* or 2017\* or 2018\* or 2019\*).ed.
37. 35 and 36

**Key:**

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

pt = publication type

ab = abstract

fs = floating subheading

sh = subject heading

**Appendix 3. Embase Search Strategy**

*Intervention Embase search:*

1. astrocytoma/
2. glioblastoma/
3. (glioblastom\* or GBM\* or astrocytom\* or gliosarcom\*).mp.
4. 1 or 2 or 3
5. tumor recurrence/
6. (recurren\* or return\* or relapse\*).mp.
7. 5 or 6
8. 4 and 7
9. crossover procedure/
10. double-blind procedure/
11. randomized controlled trial/
12. single-blind procedure/
13. random\*.mp.
14. factorial\*.mp.
15. (crossover\* or cross over\* or cross-over\*).mp.
16. placebo\*.mp.
17. (double\* adj blind\*).mp.
18. (singl\* adj blind\*).mp.
19. assign\*.mp.
20. allocat\*.mp.
21. volunteer\*.mp.
22. (before adj3 after adj3 (study or studies)).mp.
23. (CBA adj (study or studies)).mp.
24. interrupted time series.mp.
25. exp Cohort Studies/
26. (cohort\* or prospective\* or retrospective\*).mp.

27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26  
28. 8 and 27

**Key:**

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier  
pt = publication type  
ab = abstract  
fs = floating subheading  
sh = subject heading

*Economic Embase search:*

1. astrocytoma/
2. glioblastoma/
3. (glioblastom\* or GBM\* or astrocytom\* or gliosarcom\*).mp.
4. 1 or 2 or 3
5. tumor recurrence/
6. (recurren\* or return\* or relapse\*).mp.
7. 5 or 6
8. 4 and 7
9. Health Economics/
10. exp Economic Evaluation/
11. exp Health Care Cost/
12. pharmacoeconomics/
13. 9 or 10 or 11 or 12
14. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab.
15. (expenditure\$ not energy).ti,ab.
16. (value adj2 money).ti,ab.
17. budget\$.ti,ab.
18. 14 or 15 or 16 or 17
19. 13 or 18
20. letter.pt.
21. editorial.pt.
22. note.pt.
23. 20 or 21 or 22
24. 19 not 23
25. (metabolic adj cost).ti,ab.
26. ((energy or oxygen) adj cost).ti,ab.
27. ((energy or oxygen) adj expenditure).ti,ab.
28. 25 or 26 or 27
29. 24 not 28
30. 8 and 29
31. (2015\* or 2016\* or 2017\* or 2018\* or 2019\*).dd.
32. 30 and 31

**Key:**

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier  
pt = publication type  
ab = abstract  
fs = floating subheading  
sh = subject heading

**WHAT'S NEW**

Date	Event	Description
4 May 2021	Amended	Text amended

## HISTORY

Protocol first published: Issue 4, 2020

Review first published: Issue 12, 2020

## CONTRIBUTIONS OF AUTHORS

TL performed study selection, data extraction and wrote the first draft of the review. ER performed study selection, data extraction and conducted the initial analyses. CM provided clinical guidance and contributed to the text of the review, AK and TR contributed the economic component of the review, SJ provided clinical guidance. All authors advised on and approved the final version of the review.

## DECLARATIONS OF INTEREST

Catherine McBain: none declared

Theresa Lawrie: none declared

Ewelina Rogozinska: none declared

Ashleigh Kernohan: none declared

Tomos Robinson: none declared

Sarah Jefferies: none declared

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- NIHR 16/144 Cochrane Programme Grant Scheme, UK, UK

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol included an additional secondary outcome 'seizures'. We obtained scant data for this outcome, did not attempt to synthesise these data, and decided to remove the outcome from the review.