



Salvage therapies for recurrent grade 4 IDH-wildtype glioma: a BRAIN Registry analysis of real-world treatment patterns

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Abstract

Purpose The prognosis for patients with glioblastoma after failure of first-line therapy is poor. Despite this, the standard of care for patients with recurrent disease is not well-defined. Here we report on the use of salvage therapies in glioblastoma using real-world data.

Methods Data were extracted from the BRAIN Registry for patients diagnosed with glioblastoma (Grade 4, IDH wild-type) between 09/2019 and 01/2024. Only patients who received salvage therapies following a documented date of recurrence/progression were included. Relevant descriptive and intergroup statistics were used, with survival calculated using Kaplan-Meier and Cox regression used for multivariate analyses.

Results 275 patients were identified. Median age was 61 (range:23–88) years, with 56% being ECOG 0–1 at recurrence. Median time to progression was 7.6 months with 65% recurring/progressing during first-line therapy. Systemic therapy (85%) was most utilised with 67% receiving single-agent bevacizumab. Outcomes in this subgroup were similar to clinical trial data. 29% patients underwent re-resection with 58% of these then receiving systemic treatment. Compared with no surgery, patients who underwent re-resection were younger ($p=0.02$), of better performance status ($p=0.006$) and more likely to have recurred post completing first-line therapy ($p=0.001$). Few patients ($n=9$) received re-irradiation with median of 15 months between radiation events. Median post-progression survival (PPS) was 9.5 months. After adjustment for confounders, there was no difference in PPS for patients who underwent re-resection versus systemic therapy alone ($p=0.242$). The survival differences observed between treatment modalities likely reflect patient factors influencing treatment selection and were impacted by small subgroup sizes.

Conclusion Systemic therapy is most utilised in the salvage setting, predominantly bevacizumab. Certain patient characteristics were associated with re-resection. Re-irradiation was rarely used.

Clinical trial number ACTRN12618001959268.

Keywords Glioblastoma · Recurrence · Treatment patterns · Systemic therapy · Surgery · Radiotherapy

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumour in adults [1]. The current standard of care for patients with newly diagnosed GBM is maximal safe surgical resection followed by radiotherapy with concomitant and post-radiation temozolomide (TMZ) [2]. Despite optimal treatment, most patients inevitably recur, with over

70% of patients experiencing disease recurrence or progression within 12 months of diagnosis [2]. Following failure of first-line therapy, salvage treatment options for recurrent GBM (rGBM) have limited efficacy [3, 4]. Treatment selection is informed by patient and tumour characteristics, with options including systemic therapy, re-resection, re-irradiation, combined modality therapy or supportive care alone [5, 6].

Extended author information available on the last page of the article

Systemic therapy options for rGBM include bevacizumab (BEV), TMZ rechallenge, and nitrosureas such as lomustine, with none proven to impact overall survival [3, 7]. As such international guidelines recommend participation in clinical trials where available [5–7].

Re-resection has been suggested to improve survival outcomes [8, 9], but such data comes from retrospective analyses and thus potentially confounded by selection bias [10]. Salvage radiotherapy may be appropriate for some patients with rGBM, particularly those of good performance status in whom the minimum interval from the previous radiotherapy course is 6 months [11]. Similarly to re-resection, there is a paucity of data from large, randomised controlled studies to support its use, with the recommendation for re-irradiation made based on individual decision-making following multidisciplinary discussion [4, 11].

Given that the standard of care is not well-defined, the management approach for rGBM, particularly systemic therapy use, varies in population-based studies [12–16]. To better inform treatment selection this study aimed to describe of the patterns of salvage therapy use and outcomes for patients with rGBM in Australia using data from a multi-centre, translational brain cancer registry.

Methods

Data sources and variables

Data were extracted from the BRAIN registry (Brain Registry Australia: INnovation and translation) for adult patients (≥ 18 years) diagnosed with GBM (World Health Organisation Tumour Grade 4, IDH wild-type glioma) between 01/09/2019 and 30/01/2024. The BRAIN registry captures comprehensive clinical data for consecutive patients diagnosed with brain tumours at twenty participating sites across Australia (ACTRN12618001959268) [17].

Data obtained included demographics, tumour characteristics, treatment received in first and subsequent lines, extent of surgical resection, receipt of radiotherapy and/or systemic therapy and survival. O⁶-methylguanine-DNA methyltransferase promoter (MGMTp) status was captured where available.

Patients were classified according to treatment received following first disease progression: systemic therapy alone, re-resection with or without post-operative therapy and re-irradiation with or without systemic therapy. Only patients who had treatment data recorded after the date of disease progression or recurrence were included in this analysis. Patients who only received best supportive care after first disease progression were not included.

Overall survival (OS) was defined as the time from diagnosis to death from any cause. Time to progression (TTP) was defined as the time from diagnosis to first progression. Post-progression survival (PPS) was calculated from time of first progression to death. The time from first progression to confirmed second progression or death was defined as progression-free survival (PFS). The date of last known follow-up was used for censoring for all time-to-event analyses.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics for Windows, Version 30.0. Relevant descriptive and intergroup statistics were used to compare variables across treatment groups with Chi-square and Fisher's exact tests used for categorical variables and the independent-samples Kruskal-Wallis test for continuous variables. Time-to-event and survival analyses were undertaken using Kaplan-Meier estimates with Cox proportional hazards model for multivariate analyses. Variables incorporated in multivariate analyses were selected on clinical grounds. Two-sided *P*-values < 0.05 were considered statistically significant.

Subgroup analysis was undertaken of patients who received BEV monotherapy, using the inclusion and exclusion criteria from the CABARET trial (ACTRN12610000915055) [18].

Results

A total of 788 patients with WHO Tumour Grade 4, IDH wild-type glioma were identified from the BRAIN registry. Of these, 440 patients had documented disease progression. 142 patients received best supportive care alone following first disease progression and were excluded from analysis. 275 patients received salvage therapy and were eligible for inclusion in this analysis (Fig. 1).

The patient and clinical characteristics are outlined in Table 1. In the overall population, the median age was 61 years (range:23–88 years) and 64% (176/275) were male. At initial diagnosis, 215 patients (78%) had either gross macroscopic resection or subtotal resection. Most patients (254/275, 92%) received post-operative radiotherapy with concurrent TMZ, with 70% (193/275) also receiving adjuvant TMZ. The median duration of post-radiation TMZ was 4.8 months (range:0.2–14.1). 118 patients (43%) were MGMTp unmethylated, whereas 80 patients (29%) were MGMTp methylated. MGMTp status was unknown in 77 patients (28%).

Median TTP for initial therapy in the overall population was 7.6 months (95% CI:6.8–8.3), with 65% (178/275)

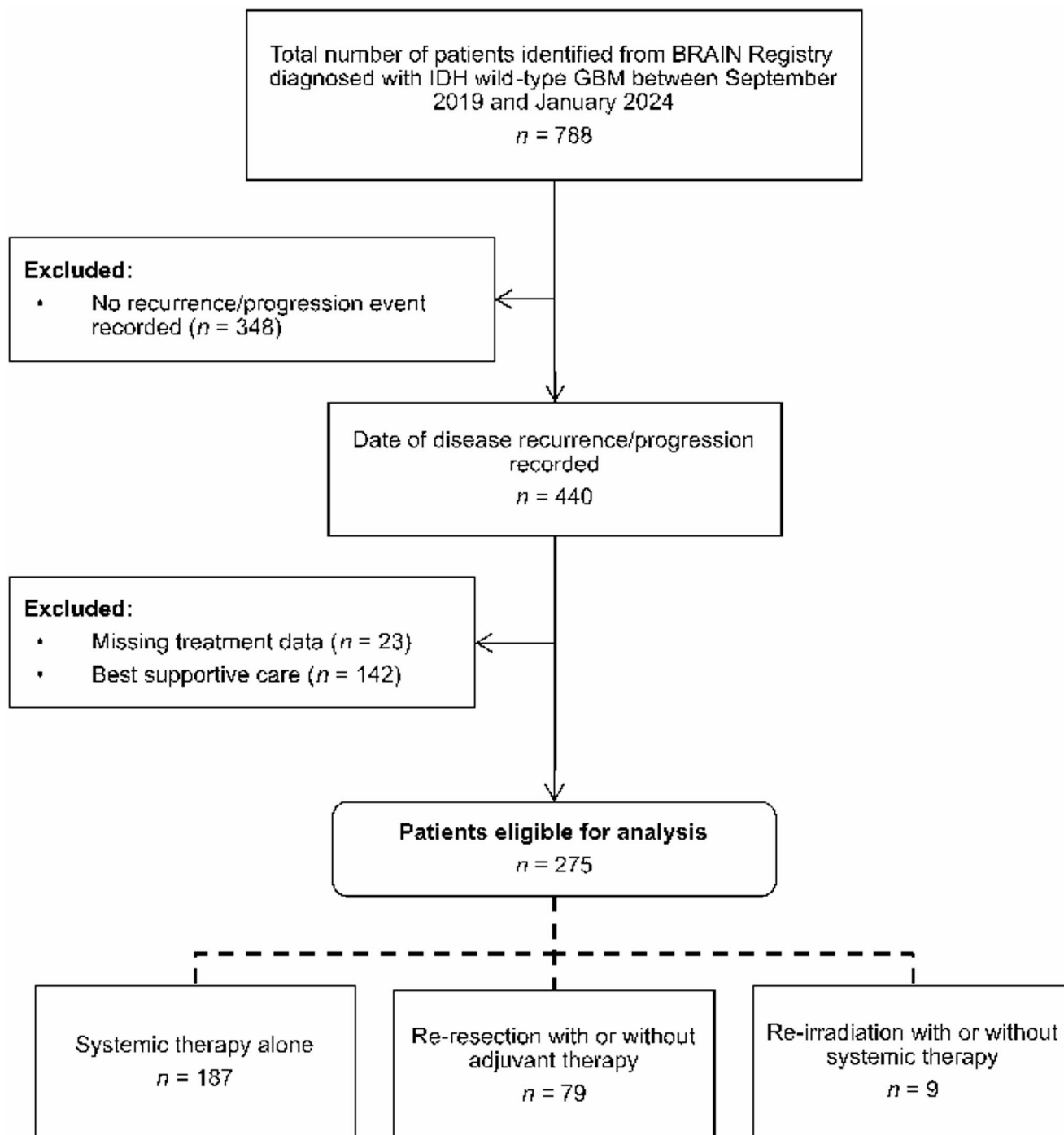


Fig. 1 - Overview of study schema

recurring during first-line therapy (Supplementary Table 1). At the time of first progression, 56% (155/275) of patients were of good performance status with an Eastern Cooperative Group (ECOG) score of ≤ 1 .

Compared with patients who progressed after completion of first-line therapy, those who progressed during first-line therapy were more likely to be MGMTp unmethylated (49

vs. 31%, $p=0.003$) and to have had incomplete resection or biopsy at initial diagnosis (63 vs. 58%, $p=0.027$).

Of patients with rGBM that were actively treated, most received only one further therapy (58%, 160/275). The sequence of salvage treatments used following first, second and third progression are presented in Fig. 2.

Table 1 Baseline characteristics according to salvage therapy received after first recurrence/progression

Characteristic	Overall population (<i>n</i> =275)	Systemic therapy (<i>n</i> =187)	Re-resection +/- post-operative therapy (<i>n</i> =79)	Re-irradiation +/- systemic therapy (<i>n</i> =9)	<i>P</i> value
Age (years)					
Median (range)	61 (23–88)	62 (23–88)	59 (23–79)	66 (43–84)	0.049
Gender (%)					
Male	176 (64)	116 (62)	54 (68)	6 (67)	0.631
Female	99 (36)	71 (38)	25 (32)	3 (33)	
ECOG at progression/recurrence (%)					
≤ 1	155 (56)	94 (50)	56 (71)	5 (56)	0.021
> 1	79 (29)	63 (34)	13 (17)	3 (33)	
Unknown	41 (15)	30 (16)	10 (13)	1 (11)	
Extent of primary surgery (%)					
Gross macroscopic resection	100 (36)	57 (31)	38 (48)	5 (56)	0.056
Subtotal resection (50–95%)	115 (42)	80 (43)	33 (42)	2 (22)	
Partial resection (<50%)	8 (3)	7 (4)	1 (1)	0	
Biopsy	43 (16)	36 (19)	6 (8)	2 (22)	
Unknown	9 (3)	7 (4)	1 (1)	0	
MGMTp status (%)					
Unmethylated	118 (43)	77 (41)	38 (48)	3 (33)	0.094
Methylated	80 (29)	54 (29)	20 (25)	6 (67)	
Unknown	77 (28)	56 (30)	21 (27)	0 (0)	
Adjuvant treatment prior to progression/recurrence (%)					
Concurrent RT+TMZ with adjuvant TMZ	193 (70)	127 (68)	62 (79)	4 (44)	0.112
Concurrent RT+TMZ	61 (22)	46 (25)	12 (15)	3 (33)	<0.001
Radiotherapy alone	19 (7)	13 (7)	4 (5)	2 (22)	
Unknown	2 (1)	1 (1)	1 (1)	0	
Adjuvant radiotherapy dose (%)					
<40 Gy	17 (6)	13 (7)	1 (1)	3 (33)	
40–59 Gy	61 (22)	51 (27)	8 (10)	2 (22)	0.460
≥60 Gy	181 (66)	112 (60)	65 (82)	4 (44)	
Unknown	16 (6)	11 (6)	5 (6)	0	
Duration of adjuvant TMZ (%)					
≤3 months	48 (25)	36 (28)	12 (19)	0	<0.001
3–6 months	92(48)	57 (45)	31 (50)	4 (100)	
>6 months	48 (25)	31 (24)	17 (27)	0	
Unknown	5 (3)	3 (2)	2 (3)	0	
Timing of first progression/recurrence (%)					
During first-line therapy	178 (65)	139 (74)	38 (48)	1 (11)	<0.001
After first-line therapy	95 (35)	47 (25)	40 (51)	8 (89)	
Unknown	2 (1)	1 (1)	1 (1)	0	
Time from diagnosis to first progression/recurrence (months)					
Median (range)	7.6 (1.1–57.1)	6.7 (1.2–57.1)	8.9 (1.1–41.4)	14.9 (3.5–29.3)	<0.001
95% CI	6.8–8.3	5.8–7.6	7.4–10.4	12.4–17.4	
Number of lines of salvage therapy (%)					
1	160 (58)	125 (67)	31 (39)	4 (44)	<0.001
2	85 (31)	53 (28)	29 (37)	3 (33)	
3	23 (8)	8 (4)	14 (18)	1 (11)	
4	7 (3)	1 (1)	5 (6)	1 (11)	

Systemic therapy received after first progression/recurrence (%) *n* = 235

Table 1 (continued)

Characteristic	Overall population (<i>n</i> =275)	Systemic therapy (<i>n</i> =187)	Re-resection +/- post-operative therapy (<i>n</i> =79)	Re-irradiation +/- sys-temic therapy (<i>n</i> =9)	<i>P</i> value
BEV	157 (67)	140 (75)	15 (33)	2 (67)	<0.001
TMZ continued	24 (10)	15 (8)	9 (20)	0	
TMZ rechallenge	21 (9)	8 (4)	12 (27)	1 (33)	
BEV and TMZ	10 (4)	8 (4)	2 (4)	0	
BEV and CCNU	8 (3)	6 (3)	2 (4)	0	
CCNU	5 (2)	4 (2)	1 (2)	0	
Other	10 (4)	6 (3)	4 (9)	0	
Extent of re-resection (%) <i>n</i> =79					
Gross macroscopic resection	-	-	22 (28)	-	-
Subtotal resection (50–95%)	-	-	47 (59)	-	
Partial resection (<50%)	-	-	3 (4)	-	
Unknown	-	-	7 (9)	-	

ECOG, Eastern Cooperative Oncology Group performance status; MGMTp, O6-methylguanine-DNA methyltransferase promoter; RT, radiotherapy; BEV, bevacizumab; TMZ, temozolomide; CCNU, lomustine

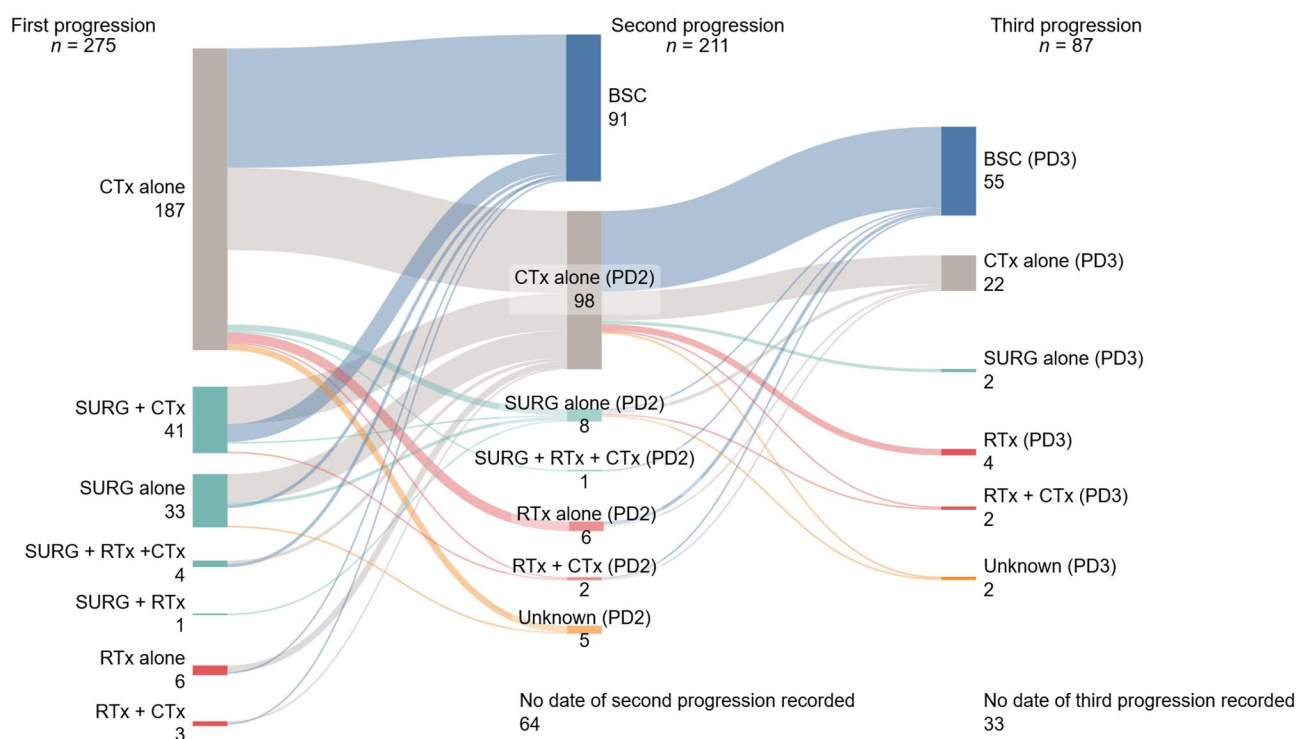


Fig. 2 Sankey diagram outlining salvage treatments received after first, second and third progression. CTx, systemic therapy; SURG, re-resection; RTx, radiotherapy; BSC, best supportive care; PD2, second progression; PD3, third progression

Systemic therapy

Systemic therapy was the most common treatment modality utilised at first progression (187/275, 68%). Of those who received systemic therapy alone, 75% (140/187) received single agent BEV with a median duration of BEV monotherapy of 4.2 months (range:0.2–33.0). There were no significant differences in the duration of BEV for those who progressed during versus following first-line therapy

(median 4.3 vs. 3.5 months, $p=0.765$). Forty-two patients received third-line treatment following progression on BEV, most commonly lomustine as monotherapy (40%, 17/42).

TMZ was continued in 15 patients who progressed during first-line therapy at a median of 3.0 months from diagnosis. Median PFS in this subgroup was 3.6 months (95% CI:1.5–5.7), with most patients subsequently receiving BEV (9/15, 60%).

TMZ was rechallenged in 8 patients, all but one of whom were MGMTp methylated. Although this subgroup had a median TTP on initial therapy of 17.3 months (95% CI:14.0–20.5), the median PFS for TMZ rechallenge was 3.1 months (95% CI:2.9–3.4).

Molecular-targeted therapies, predominately accessed through a clinical trial, were infrequently utilised. Only 3% of patients (8/275) received targeted therapy in any line in the salvage setting, the most common target being the Epidermal Growth Factor Receptor (EGFR). Similarly, few patients (16/275, 6%) participated in a clinical trial in any line of treatment in the salvage setting for rGBM.

Re-resection

Re-resection was undertaken in 79 patients (29%) at a median time of 9.8 months (range:1.2–41.5) from primary surgery. Compared with those who received other systemic therapy or radiotherapy, patients who underwent surgery for rGBM were younger (median age 59 vs. 62 years, $p=0.018$) and had better performance status (ECOG $\leq$ 1: 71 vs. 51%, $p=0.006$). This cohort were also more likely to have had gross macroscopic resection at initial surgery (48 vs. 32%, $p=0.029$) and to have recurred after completion of first-line therapy (51 vs. 28%, $p=0.001$).

Following re-resection, 46 patients (58%) received post-operative treatment, most commonly systemic therapy (45/46). BEV, either as monotherapy or in combination with TMZ, lomustine and/or radiotherapy (19/46, 41%), was most frequently utilised (Table 1).

Radiotherapy

Few patients received salvage radiotherapy. Of the 14 patients who underwent re-irradiation following first progression, 6 (2%) had radiotherapy alone, 5 (2%) had radiotherapy following re-resection and 3 (1%) received radiotherapy with systemic therapy. A further fifteen patients received radiotherapy in the second- or third-line salvage setting. Overall, for patients who received salvage radiotherapy in any line of treatment for rGBM, the median treatment dose was 35 Gy (range:8–40) in 10 fractions (range:1–15). The median time between initial and salvage radiation events was 15 months (range:1.7–41.4).

Treatment outcomes

Median OS from initial diagnosis was 17.8 months (95% CI:16.7–19.0). The 1-, 2- and 3-year survival probabilities were 81% (222/275), 22% (61/275) and 6% (16/175) respectively.

Median PPS after first disease progression was 9.5 months (95% CI:8.6–10.4). ECOG performance status at the time of recurrence ($p=0.029$) and MGMTp status ($p=0.019$) were both significant predictors of PPS on univariate analysis. There were no differences in PPS associated with age (<65 vs. $\geq$ 65 years, $p=0.640$), gender ($p=0.829$), extent of primary surgery ($p=0.802$) or timing of recurrence (during vs. following first-line therapy, $p=0.998$).

Figure 3 demonstrates the Kaplan Meier survival curve for PPS according to salvage therapy received after first disease progression. Median PPS for patients who underwent re-resection was 11.4 months (95% CI:9.2–13.7), compared with 9.0 months (95% CI:7.8–10.2) for those who received systemic therapy and 5.0 months (95% CI:4.7–5.3) for those who had radiotherapy. There was a difference observed in PPS according to salvage therapy modality received, with patients who had re-resection ($p=0.004$) or systemic therapy ($p=0.028$) having longer PPS compared with those who received salvage radiotherapy. Multivariate analysis with adjustment for confounders (Table 2) similarly demonstrated worse survival in the salvage radiotherapy group compared with the re-resection and systemic therapy groups with adjusted hazard ratios (HR) of 2.73 (95% CI:1.27–5.9, $p=0.010$) and 2.25 (95% CI:1.08–4.7, $p=0.031$) respectively. Notably, there was no significant difference in PPS between the re-resection and systemic therapy groups on multivariate analysis ($p=0.232$). Similar results were seen when the salvage radiotherapy group were excluded from this analysis (Supplementary Table S2).

Subgroup analysis

A subgroup analysis was undertaken using key eligibility criteria for the CABARET trial [18]. This phase II randomised clinical trial recruited participants from 18 Australian sites to receive either carboplatin and BEV or BEV monotherapy for rGBM [18]. To reflect the BEV monotherapy arm of the CABARET trial, this subgroup included patients who had received BEV for either first or subsequent recurrence after previous treatment with radiotherapy and TMZ (either concurrently or in combination). Patients with an ECOG score greater than 2, or who had progressed within 12 weeks of initial radiotherapy were excluded. Ultimately, 110 patients were eligible for this analysis, most of whom had received BEV after first disease recurrence (75%, 83/110).

In this subgroup, the median PFS on BEV monotherapy was 4.4 months (95% CI:3.5–5.3) with a 6-month PFS of 32%. This compares to a median PFS in the BEV monotherapy arm of the CABARET trial of 3.5 months (95% CI:1.9–3.7), with a 6-month PFS of 18% [18]. The median OS in this subgroup was comparable to the CABARET trial at 7.6 months (95% CI:6.1–9.0) [18].

Fig. 3 Kaplan Meier analysis of post-progression survival (PPS) by salvage therapy received after first disease progression

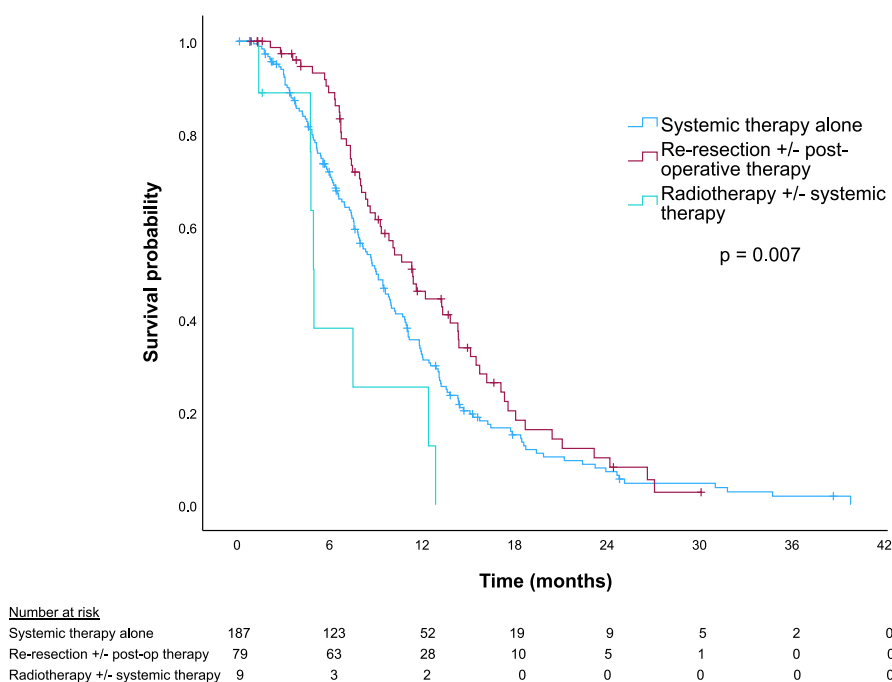


Table 2 Multivariate Cox regression analysis of post-progression survival in patients with WHO Tumour Grade 4, IDH wild-type glioma

Variable	Hazard Ratio (95% CI)	P-value
Age (years)		
<65	1.00	
≥65	1.09 (0.82–1.45)	0.557
ECOG at recurrence		
0–1	1.00	
>1	1.38 (1.00–1.89)	0.045
Unknown	1.29 (0.88–1.91)	0.196
MGMTp status		
Methylated	1.00	
Unmethylated	1.65 (1.18–2.32)	0.003
Unknown	1.31 (0.91–1.87)	0.145
Salvage therapy		
Re-resection +/- post-operative therapy	1.00	
Systemic therapy	1.21 (0.88–1.67)	0.232
Radiotherapy +/- systemic therapy	2.73 (1.27–5.9)	0.010

Variables selected on clinical grounds. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; MGMTp, O6-methylguanine-DNA methyltransferase promoter

Discussion

To our knowledge, this is the largest retrospective analysis to describe the patterns of care and outcomes for patients with rGBM in a contemporary Australian population. As there is no universally established standard of care for rGBM, analyses of real-world datasets provide valuable

insight into modern treatment patterns, sequencing and outcomes in clinical practice.

In this study of 275 patients who received salvage therapy for rGBM, systemic therapy was the most utilised treatment modality. In total, 85% of patients received systemic therapy either alone (68%) or in combination with surgery and/or radiotherapy (17%). After second and third progression, treatment selection in our population was varied, which is reflective of the paucity of evidence regarding treatment efficacy in later-line settings [3–5].

In our population, the median PPS was 9.5 months which is within the range reported in population-based studies in the post-Stupp era [12–16]. There was a difference observed in PPS according to salvage therapy modality received, favouring surgery and systemic therapy over radiotherapy. However, this observed difference likely reflects the small size of the radiotherapy group and the impact of potential confounding factors influencing treatment selection. Although attempts were made to mitigate selection bias through multivariate analysis, the inferiority of radiotherapy cannot be assumed from this data.

There was no significant difference in PPS on multivariate analysis between patients who underwent re-resection versus those who received systemic therapy alone. Improved functioning and survival outcomes with resection for rGBM have been previously reported [8–10]. However, similar to other studies [10, 19, 20], patients in our re-resection population had more favourable prognostic factors which could have contributed to the observed survival

advantage. Notably, these patients were younger, had better performance status at the time of recurrence, were more likely to have had gross macroscopic resection at initial surgery and have recurred after completion of first-line therapy. Given this, the survival impact of re-resection remains uncertain. Data from prospective randomised studies, such as the RESURGE trial (NCT02394626) will provide further insight into the survival and functional impact of re-resection [21].

Although multiple systemic agents have been studied in patients with rGBM, none have been consistently proven to prolong overall survival in this setting [3–5]. BEV was approved for use in rGBM by Australia's regulatory authority, the Therapeutic Goods Association, in 2010 after the response rates and PFS of two phase II trials [22, 23] were compared with pooled historical data [24]. A subsequent phase III trial demonstrated improved PFS with the combination of BEV and lomustine, compared to lomustine alone, however no OS benefit was shown [25]. Several combination partners for BEV have been studied, none of which have been demonstrated to improve OS in rGBM [26–28]. Although BEV has been shown to reduce steroid use and the side effects from radiotherapy in some studies [28], it is currently not authorised for use in rGBM by the European Medicines Agency [3, 5]. The latest European Association for Neuro-Oncology (EANO) guidelines [5, 29] list lomustine as an appropriate standard of care for rGBM, due to its activity when used as the comparator in multiple randomised controlled trials [25–27, 30].

Due to differences in drug approval and access internationally, systemic treatment selection in rGBM varies in population-based studies, which complicates the comparison of real-world outcomes [12–16]. In our study, BEV was the most used agent for rGBM. This in part reflects the accessibility to BEV for this indication in Australia, following its listing for the treatment of relapsed or refractory GBM on the Pharmaceutical Benefits Scheme (PBS) in August 2019 [31]. The PBS is an Australian Government scheme through which approved medications are subsidised for eligible patients [32]. Notably, lomustine is not PBS-listed for rGBM patients in Australia which contributes to the infrequent use of this agent in our population. Although many contemporary trials continue to utilise lomustine as the control arm for rGBM [33], this does not reflect the real-world practice in our population. In addition to limiting the applicability of trial findings to routine practice, this may also pose a challenge for regulatory approval and reimbursement of novel therapies for rGBM in Australia.

The real-world outcomes for patients who received BEV for rGBM in our study were compared with those from the CABARET trial [18]. The BEV monotherapy arm of this study was selected as comparator for our analysis as it is

the largest cohort of BEV-treated rGBM patients from an Australian trial population to date. In comparison, our BEV-treated patients had comparable median OS (7.6 vs. 7.5 months), but a longer median PFS (4.4 vs. 3.5 months) and higher 6-month PFS (32% vs. 18%), potentially due to less frequent imaging in a real-world population. The complexity of radiological assessments in BEV-treated patients, and recent acknowledgement of entities such as BEV-induced coagulative necrosis [34], have prompted multiple updates to the Response Assessment in Neuro-Oncology (RANO) criteria, including the modified RANO criteria (mRANO) and RANO 2.0 [35, 36]. These changes may have also contributed to the numerically longer PFS observed in our population compared with the CABARET cohort. Additionally, the more widespread uptake of advanced imaging techniques such as dynamic susceptibility MRI, may have contributed to the more accurate assessment of treatment-related change from true progression in the real-world setting and longer durations of BEV therapy [37]. Furthermore, the CABARET population were also more heavily pre-treated, with 31% receiving BEV as third- or later-line therapy [18], compared with 25% in our study, which may also account for shorter time to progression. Overall, our data supports ongoing use of BEV in this setting.

Although international guidelines recommend participation in clinical trials as the preferred option for eligible patients, few in our cohort were enrolled in a clinical trial [5–7]. This reflects the continuing limited number of clinical trial options for patients with rGBM in Australia during our study period, as well as the potential impact of the COVID-19 pandemic, which is considered to have had a negative impact on cancer clinical trials globally [38, 39]. Beyond trial availability, the limited use of comprehensive tumour sequencing and the exclusion of patients who have previously received anti-angiogenic agents such as BEV [40] also contribute to low rates of clinical trial participation. Whilst the implementation of the nationwide precision medicine initiative, Precision Oncology Screening Platform Enabling Clinical Trials (PrOSPeCT), in 2023 has improved access to genomic profiling for patients with newly diagnosed or rGBM [41], further research is required to determine whether this translates to improved trial participation and clinical outcomes in this population.

Despite improvements in the understanding of the molecular pathogenesis of GBM and the utility of tumour sequencing, there have been only modest advancements in the development of effective targeted therapies for rGBM [7]. In addition to the challenges posed by the intrinsic aspects of glioma biology, the lack of efficient clinical trial infrastructure to evaluate novel therapies in a rare tumour remains a barrier to progress [42]. Adaptive platform trials such as GBM AGILE (Adaptive, Global, Innovative

Learning Environment) have been designed to address these barriers by allowing simultaneous assessment of multiple therapeutics [43]. There is also increasing interest in the integration of external control data in novel clinical trials [44]. Externally augmented clinical trial designs in which an external control group consisting of a dataset of pre-treatment covariates and patient outcomes, can contextualise data from single-arm studies and reduce sample sizes [44]. Although randomised controlled trials remain the gold-standard, leveraging high-quality real-world data from established registries, such as the BRAIN registry, has the potential to improve decision-making and support drug development [44].

This study has several limitations. Firstly, its retrospective design introduces the potential for selection and confounding biases. Although we attempted to adjust for confounding factors on multivariate analysis, other factors which may have influenced decisions regarding salvage therapy, including tumour extent and volume, were not readily available in our dataset. Secondly, our analysis relied on the completeness of documentation. Documentation of ECOG at recurrence was missing in 15% of patients. Similarly, MGMTp status was not recorded in 28% of our cohort, although it is unclear whether this is due to this not being performed (testing is not routine in Australia) or incomplete data. Thirdly, the small subgroup sizes, particularly of those who received radiotherapy and systemic therapy agents other than BEV, limits the accurate analyses of outcomes in these cohorts. Finally, data regarding treatment safety and toxicity were not analysed in this study. Hence, we cannot comment on the tolerability of salvage therapies in our population nor the impact of different treatments on the quality-of-life and function of patients with rGBM. Additionally, as this study included only those who received salvage therapy for rGBM, the outcomes described apply only to those who were actively treated and do not reflect the outcomes or experiences of those who received supportive care alone.

Conclusion

This retrospective study provides insight into the salvage therapy use for rGBM in a contemporary Australian population. Systemic therapy, predominantly BEV, was most commonly utilised. Subgroup analysis of this cohort demonstrated similar outcomes to trial data, albeit with longer median PFS in the real-world setting due to the challenges of radiological assessment of disease progression in BEV-treated patients. Despite differences in the demographics of those who underwent re-resection compared with those who

received systemic therapy, no statistically significant difference in PPS was observed.

Given the lack of superiority of one treatment modality over another, treatment selection for rGBM remains individualised. Future prospective studies should incorporate patient-reported outcomes and functional parameters to improve our understanding of the overall benefits of salvage treatment in this population, beyond conventional survival metrics.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11060-026-05717-x>.

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Data availability The de-identified data generated and analysed during the current study are available from the corresponding author, on reasonable request.

Declarations

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. The BRAIN registry (Brain Registry Australia: INnovation and translation) has ethics approval by the Melbourne Health Ethics Committee (Date: 2018/Ref No: HREC/44314/MH-2018) and is registered on the Australia New Zealand Clinical Trials Registry (registration number: ACTRN12618001959268). A waiver of consent model was approved by the Human Ethics and Research Committee.

Competing interests The authors declare no competing interests.

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