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Buparlisib plus carboplatin or lomustine in patients with recurrent glioblastoma: a phase Ib/II, open-label, multicentre, randomised study

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ABSTRACT

Background Glioblastoma relapse is associated with activation of phosphatidylinositol 3-kinase (PI3K) signalling pathway. In preclinical studies, the pan-PI3K inhibitor buparlisib showed antitumour activity in glioma models.

Methods This was a two-part, multicentre, phase Ib/II study in patients with recurrent glioblastoma pretreated with radiotherapy and temozolomide standard of care. Patients received buparlisib (80 mg or 100 mg once daily) plus carboplatin (area under the curve (AUC)=5 every 3 weeks), or buparlisib (60 mg once daily) plus lomustine (100 mg/m^2 every 6 weeks). The primary endpoint was to determine the maximum tolerable dose (MTD) and/or recommended phase II dose of buparlisib plus carboplatin or lomustine.

Results Between 28 February 2014 and 7 July 2016, 35 patients were enrolled and treated with buparlisib plus carboplatin (n=17; buparlisib (80 mg) plus carboplatin, n=3; and buparlisib (100 mg) plus carboplatin, n=14), or buparlisib (60 mg) plus lomustine (n=18). The MTD of buparlisib was determined to be 100 mg per day in combination with carboplatin at an AUC of 5 every 3 weeks. The MTD of buparlisib in combination with lomustine could not be determined as it did not satisfy the MTD criteria per the Bayesian logistic regression model.

Conclusion The overall safety profile of buparlisib remained unchanged, and no new or unexpected safety findings were reported in this study. Preliminary assessment for both combinations did not demonstrate sufficient antitumour activity compared with historical data on single-agent carboplatin or lomustine.

Trial registration number NCT01934361.

Key questions

What is already known about this subject?

- Glioblastoma (GBM) is the most common and most aggressive malignant primary brain tumor in adults, with poor survival rates. Bevacizumab, an anti–vascular endothelial growth factor antibody, has improved progression-free survival in recurrent GBM (rGBM), but without any prolongation of overall survival.
- A high unmet medical need in rGBM treatment still remains, and the molecular basis of the recurrence process in GBM is still poorly understood.

What does this study add?

- Here, we present results of the phase Ib/II, open-label, multicenter, randomized study of buparlisib plus carboplatin or lomustine in patients with recurrent glioblastoma.
- Preliminary assessment for both combinations did not demonstrate sufficient anti-tumor activity compared with historical data on single-agent carboplatin or lomustine.

How might this impact on clinical practice?

- The modest outcomes observed in the current study are consistent with those reported for rGBM and further highlight the challenges of treating rGBM.

INTRODUCTION

Glioblastoma (GBM) is the most common and most aggressive malignant primary brain tumour in adults, with poor survival rates.[1–5] The current standard of care (SoC) for patients with newly diagnosed GBM includes tumour resection followed by radiotherapy (RT) and chemotherapy (CT; temozolomide (TMZ)).[6–8]

GBM has an unfavourable prognosis mainly due to its high propensity for tumour recurrence, with a median survival of 12–15 months.[9 10] Recurrence is common, with 75% of patients with GBM experiencing disease progression within 2 years of diagnosis and less than 10% surviving for 5 years after diagnosis.[1 2 11 12] Bevacizumab, an anti-vascular endothelial growth factor antibody, has improved progression-free survival (PFS) in recurrent GBM (rGBM), but without any prolongation of overall survival.[13] A high unmet medical need in rGBM treatment

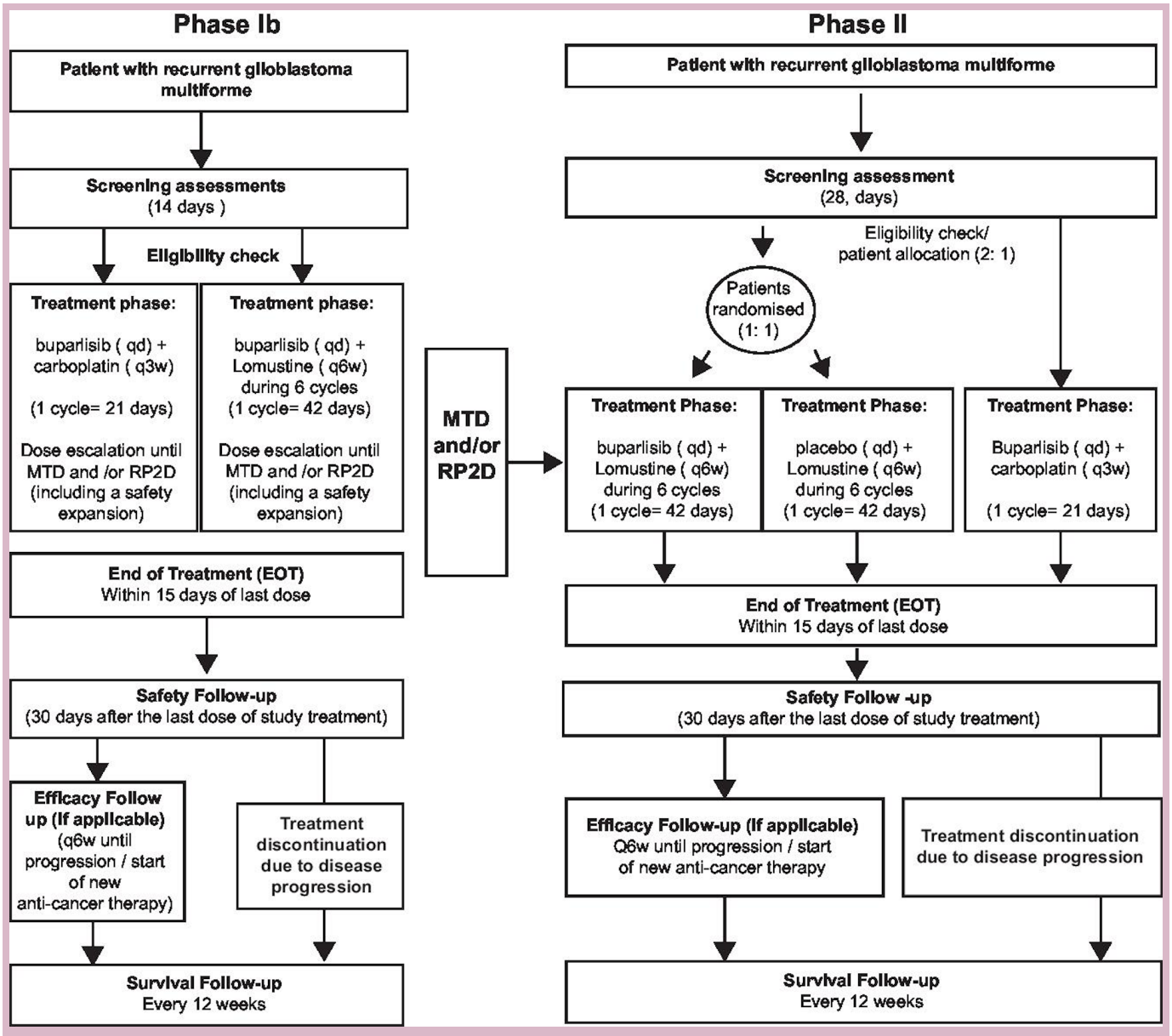

Figure 1 Study design. MTD, maximum tolerated dose; qd, once daily; q3w, once every 3 weeks; q6w, once every 6 weeks; RP2D, recommended phase II dose.

remains, and the molecular basis of the recurrence process in GBM is still poorly understood.[14] Preclinical data suggest that activation of the phosphatidylinositol 3-kinase (PI3K) signalling pathway is one of the key factors contributing to GBM relapse.[15] The PI3K pathway was found to be frequently altered in GBM, with up to 90% of GBM tumours having an activated PI3K pathway.[16–18] Therefore, GBM represents a disease with a compelling biological rationale for treatment with PI3K inhibitors. We hypothesise that combining chemotherapeutic agents used for GBM treatment with a PI3K inhibitor may confer a clinical benefit to patients with rGBM.

Buparlisib is a potent and highly specific oral pan-class I PI3K inhibitor of all class 1 isoforms.[19] Buparlisib has also been shown to cross the blood–brain barrier, accumulate in the brain tissue of non-tumour-bearing rats, and efficiently downregulate tissue phospho-S6 and phospho-AKT.[20] Buparlisib has also shown preclinical efficacy in various PI3K pathway-hyperactivated cancer models, including GBM.[21–24]

Here, we report the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of buparlisib in combination with carboplatin or lomustine and the safety and preliminary antitumour activity of these combinations in patients with rGBM.

PATIENTS AND METHODS

Study design and participants

This was a two-part, multicentre, phase Ib/II study in patients with rGBM pretreated with RT and TMZ SoC. In the phase Ib part of the study, approximately 15–22 evaluable patients per treatment arm were planned to be enrolled to determine the MTD and/or RP2D of oral

Table 1 Patient disposition by treatment arm

Disposition reason, n (%)	Buparlisib+carboplatin			
	Buparlisib (80 mg)+carboplatin	Buparlisib (100 mg)+carboplatin	All patients	Buparlisib (60 mg) + lomustine
Patients enrolled, n	3	14	17	18
Treated	3 (100)	14 (100)	17 (100)	18 (100)
Patients treated				
End of treatment	3 (100)	14 (100)	17 (100)	18 (100)
Primary reason for end of treatment				
Adverse event	0	2 (14.3)	2 (11.8)	3 (16.7)
Death	–	–	–	1 (5.6)
Progressive disease	3 (100)	12 (85.7)	15 (88.2)	14 (77.8)
Post-treatment follow-up after end of treatment				
Not applicable*	3 (100)	12 (85.7)	15 (88.2)	15 (83.3)
Patients no longer being followed for post-treatment follow-up	0	2 (14.3)	2 (11.8)	3 (16.7)
Primary reason for discontinuation of post-treatment follow-up				
Progressive disease	0	2 (14.3)	2 (11.8)	1 (5.6)
Death	–	1† (7.1)	1 (5.9)	1 (5.6)
Withdrawal of consent	–	–	–	1 (5.6)

Percentage is based on 'n'.
*Patients who withdrew consent from the study, died or decided not to attend the post-treatment efficacy follow-up at the end of treatment evaluation.
†Deaths occurred up to 30 days after last dose of study treatment.

buparlisib administered once daily in combination with carboplatin or with lomustine based on dose-limiting toxicities (DLTs) using a Bayesian logistic regression model (BLRM) with overdose control (figure 1).

Eligible patients were aged 18 years or older with rGBM pretreated with RT and TMZ SoC. Patients must have had at least one measurable and/or non-measurable lesion as per the Response Assessment in Neuro-Oncology (RANO) criteria,[25] must have recovered (to grade ≤1) from all clinically significant toxicities related to prior antineoplastic therapies, must have had a Karnofsky Performance Status (KPS) ≥70%, and must have had adequate organ and bone marrow functions. PI3K expression status was not an inclusion criterion and testing isocitrate dehydrogenase (IDH) mutations or O6-methylguanine-DNA methyltransferase (MGMT) methylation status was not planned.

Patients were excluded if they had received previous treatment with PI3K pathway inhibitors: lomustine or carboplatin for newly diagnosed GBM or rGBM, or antineoplastic treatment for rGBM. Patients who had received more than one line of cytotoxic CT, patients with a history of or having an active cardiac disease, patients with grade ≥3 anxiety, patients with a Generalized Anxiety Disorder-7 (GAD-7) mood scale score ≥15, and patients with a score ≥12 on the Patient Health Questionnaire-9 (PHQ-9) were not permitted.

Written informed consent was obtained from all patients.

Outcomes

The primary endpoint in phase Ib (dose escalation part) was to determine the MTD and/or RP2D of buparlisib plus carboplatin/lomustine combinations in patients with rGBM whose disease had progressed after SoC (RT with TMZ in combination and adjuvant), regardless of PI3K pathway activation status. The secondary endpoints were to evaluate the safety and tolerability of buparlisib plus carboplatin/lomustine combinations and to assess the preliminary antitumour activity of buparlisib plus carboplatin/lomustine combinations in patients with rGBM whose disease had progressed after SoC, regardless of PI3K pathway activation status.

Assessments

Contrast MRI scans and clinical factors were evaluated based on investigator assessment at baseline within 28 days before the start of treatment and subsequently every 6 weeks from treatment start until progression of disease or until start of another antineoplastic treatment or death, whichever occurred earlier. Tumour response and progression were assessed using the RANO working group-updated response assessment criteria for high-grade gliomas.[25]

Table 2 Patient demographics and other baseline characteristics by treatment arm

Characteristics	Buparlisib (80 mg)+carboplatin (n=3)	Buparlisib (100 mg)+carboplatin (n=14)	All patients (buparlisib+carboplatin) (n=17)	Buparlisib (60 mg)+lomustine (n=18)
Age, median (range), years	54.0 (35.0–55.0)	57.0 (29.0–67.0)	55.0 (29.0–67.0)	58.0 (35.0–73.0)
<65 years, n (%)	3 (100)	11 (78.6)	14 (82.4)	13 (72.2)
≥65 years, n (%)	0	3 (21.4)	3 (17.6)	5 (27.8)
Sex, n (%)				
Male	3 (100)	10 (71.4)	13 (76.5)	13 (72.2)
Female	0	4 (28.6)	4 (23.5)	5 (27.8)
Race, n (%)				
Caucasian	2 (66.7)	12 (85.7)	14 (82.4)	14 (77.8)
Asian	1 (33.3)	0	1 (5.9)	1 (5.6)
Other	0	1 (7.1)	1 (5.9)	1 (5.6)
Unknown	0	1 (7.1)	1 (5.9)	2 (11.1)
Karnofsky Performance Status, n (%)				
100	1 (33.3)	2 (14.3)	3 (17.6)	1 (5.6)
90	1 (33.3)	2 (14.3)	3 (17.6)	12 (66.7)
80	1 (33.3)	6 (42.9)	7 (41.2)	2 (11.1)
70	0	4 (28.6)	4 (23.5)	3 (16.7)
Primary site of cancer, n (%)				
Brain	3 (100)	12 (85.7)	15 (88.2)	17 (94.4)
CNS: supratentorial	0	2 (14.3)	2 (11.8)	1 (5.6)
Type of lesions at baseline, n (%)				
T1 target only	0	10 (71.4)	10 (58.8)	9 (50.0)
Non-target T1/T2/FLAIR only	0	0	0	2 (11.1)
Both	3 (100)	4 (28.6)	7 (41.2)	7 (38.9)
Time from initial diagnosis to first recurrence/progression, n (%)				
<6 months	1 (33.3)	3 (21.4)	4 (23.5)	2 (11.1)
6 to <12 months	2 (66.7)	5 (35.7)	7 (41.2)	12 (66.7)
12 to <24 months	0	4 (28.6)	4 (23.5)	1 (5.6)
≥24 months	0	2 (14.3)	2 (11.8)	3 (16.7)
Time since most recent relapse/progression, n (%)				
<3 months	3 (100)	13 (92.9)	16 (94.1)	17 (94.4)
3 to <6 months	0	1 (7.1)	1 (5.9)	1 (5.6)

CNS, central nervous system; FLAIR, fluid attenuated inversion recovery.

Safety was monitored by occurrence of adverse events (AEs), physical examination, evaluation of vital signs, weight, KPS, ECG and cardiac imaging, and laboratory evaluations including glucose monitoring. Patient-rated mood was assessed using GAD-7 and PHQ-9.

Statistical considerations

Determination of the MTD/RP2D of each combination treatment was based on a synthesis of all relevant data available from all dose levels evaluated continuously during the phase Ib part, including safety information, data on DLTs, and all Common Terminology Criteria for Adverse Events grade ≥2 toxicity data during cycle 1 from evaluable patients.

The full analysis set consisted of all patients who received at least one dose of study treatment (buparlisib and/or carboplatin for the buparlisib plus carboplatin arm; buparlisib and/or lomustine for the buparlisib plus lomustine arm). The safety set (SS) included all patients who had received at least one dose of study treatment and had at least one postbaseline safety assessment. All patients from the SS who either met the minimum exposure criteria and had sufficient safety evaluations or had experienced a DLT during the first cycle were included in

Table 3 Best overall response as per local investigator assessment per RANO criteria, by treatment

	Buparlisib (80 mg)+carboplatin (n=3)	Buparlisib (100 mg)+carboplatin (n=14)	Buparlisib (60 mg)+lomustine (n=18)
Patients with measurable enhancing T1 lesion at baseline, n (%)	3 (100)	14 (100)	16 (88.9)
Patients with non-measurable, non-enhancing T2/FLAIR lesion at baseline, n (%)	2 (66.7)	3 (21.4)	6 (33.3)
Best overall response, n (%)			
Complete response (CR)	0	0	0
Partial response (PR)	1 (33.3)	0	0
Stable disease (SD)	0	3 (21.4)	2 (11.1)
Progressive disease (PD)	2 (66.7)	11 (78.6)	14 (77.8)
Unknown	0	0	2 (11.1)
Overall response rate (ORR)*, n (%) (95% CI)	1 (33.3) (0.8 to 90.6)	0 (0.0 to 23.2)	0 (0.0 to 18.5)
Disease control rate (DCR)†, n (%) (95% CI)	1 (33.3) (0.8 to 90.6)	3 (21.4) (4.7 to 50.8)	2 (11.1) (1.4 to 34.7)

*ORR includes CR+PR
†DCR includes CR+PR+SD.
FLAIR, fluid attenuated inversion recovery; RANO, Response Assessment in Neuro-Oncology.

the dose-determining set and contributed to dose escalation decisions.

For the buparlisib plus carboplatin phase Ib arm, the minimum exposure criteria during the first cycle were at least 16 of the 21 full daily planned doses of buparlisib and the full carboplatin dose of 5 AUC (area under the curve) for 21 days. For the buparlisib plus lomustine phase Ib arm, the minimum exposure criteria during the first cycle were at least 32 of the 42 full daily planned doses of buparlisib and at least one dose of 100 mg/m^2 of lomustine.

An adaptive BLRM dose escalation with overdose control was used to guide the recommended dose for the next cohort of patients. MTD and/or RP2D was defined as the highest drug dosage that did not cause, with a posterior probability greater than 25%, a DLT in more than 35% of the treated patients during the first cycle of treatment.

RESULTS

Patient characteristics

Between 28 February 2014 and 7 July 2016, 35 patients were enrolled and treated with either the combination of buparlisib plus carboplatin (n=17; buparlisib (80 mg) plus carboplatin (AUC 5), n=3; and buparlisib (100 mg) plus carboplatin (AUC 5), n=14), or buparlisib plus lomustine (n=18; buparlisib (60 mg) plus lomustine 100 mg/m^2). The primary reason for end of treatment in both the buparlisib plus carboplatin arm and the buparlisib plus lomustine arm was disease progression (88.2% and 77.8%, respectively) (table 1).

The median age of the patients was 55 years in the buparlisib plus carboplatin arm and 58 years in the buparlisib plus lomustine arm. The majority of the patients in both arms were Caucasians, reflecting the countries that participated in this study. Overall, 76.5% of patients in the buparlisib plus carboplatin arm vs 83.3% of patients in the buparlisib plus lomustine arm had a KPS ≥80%. At baseline, 58.8% of patients in the buparlisib plus carboplatin arm and 50% of patients in the buparlisib plus lomustine arm had only T1 target lesions. In both arms, majority of the patients had their first recurrence/progression within 12 months of initial diagnosis. Time since the most recent relapse/progression was less than 3 months in 94.1% of patients in the buparlisib plus carboplatin arm and 94.4% of patients in the buparlisib plus lomustine arm (table 2).

Efficacy and MTD

The starting dose of buparlisib was 80 mg once daily in combination with carboplatin (at an AUC of 5 every 3 weeks); the starting dose of buparlisib was reduced to 60 mg once daily for potential increased myelotoxicity in combination with lomustine (at 100 mg/m^2 every 6 weeks).

The MTD of buparlisib in combination with carboplatin at an AUC of 5 every 3 weeks was confirmed to be 100 mg per day. No dose of buparlisib in combination with lomustine arm satisfied the criteria for confirmation of MTD.

Assessment for both combinations (buparlisib plus carboplatin or lomustine) demonstrated no enough antitumour activity compared with historical data with single-agent carboplatin or lomustine. The median PFS was 1.4 months (95% CI 1.1 to 1.6) in the buparlisib plus carboplatin arm and 1.3 months (95% CI 1.2 to 1.4) in the buparlisib plus lomustine arm. In the 80 mg buparlisib dose level plus carboplatin, the overall response rate and disease control rate (DCR) were 33.3% (95% CI 0.8 to 90.6) each; one patient had a long-lasting partial response (PR; 15.1 months). In the 100 mg buparlisib dose level plus carboplatin, the DCR was 21.4% (95% CI 4.7 to 50.8); no patient had a complete response (CR) or PR. In the 60 mg buparlisib dose level plus lomustine, the

Table 4 Most frequent on-treatment adverse events, regardless of study treatment relationship (all grade incidence ≥15% in any arm)

Buparlisib+carboplatin arm

	Buparlisib (80 mg)+carboplatin (n=3)		Buparlisib (100 mg)+carboplatin (n=14)		All patients (buparlisib+carboplatin) (n=17)	
Preferred term, n (%)	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**
Headache	2 (66.7)	0	7 (50.0)	0	9 (52.9)	0
Fatigue	3 (100)	0	5 (35.7)	1 (7.1)	8 (47.1)	1 (5.9)
Nausea	2 (66.7)	0	6 (42.9)	0	8 (47.1)	0
Thrombocytopaenia	0	0	6 (42.9)	0	6 (35.3)	0
Constipation	1 (33.3)	0	4 (28.6)	0	5 (29.4)	0
Depression	1 (33.3)	0	4 (28.6)	1 (7.1)	5 (29.4)	1 (5.9)
Diarrhoea	0	0	5 (35.7)	0	5 (29.4)	0
Insomnia	2 (66.7)	0	3 (21.4)	0	5 (29.4)	0
Neutropaenia	0	0	5 (35.7)	1 (7.1)	5 (29.4)	1 (5.9)
Decreased platelet count	1 (33.3)	0	4 (28.6)	3 (21.4)	5 (29.4)	3 (17.6)
Decreased appetite	0	0	4 (28.6)	0	4 (23.5)	0
Hyperglycaemia	1 (33.3)	0	3 (21.4)	0	4 (23.5)	0
Hypertension	1 (33.3)	0	3 (21.4)	1 (7.1)	4 (23.5)	1 (5.9)
Decreased neutrophil count	1 (33.3)	1 (33.3)	3 (21.4)	2 (14.3)	4 (23.5)	3 (17.6)
Vomiting	1 (33.3)	0	3 (21.4)	0	4 (23.5)	0
Decreased white cell count	1 (33.3)	0	3 (21.4)	1 (7.1)	4 (23.5)	1 (5.9)
Anxiety	1 (33.3)	0	2 (14.3)	0	3 (17.6)	0
Hiccups	1 (33.3)	0	2 (14.3)	0	3 (17.6)	0
Pruritus	2 (66.7)	0	1 (7.1)	0	3 (17.6)	0
Somnolence	1 (33.3)	0	2 (14.3)	0	3 (17.6)	0
Dehydration	1 (33.3)	1 (33.3)	1 (7.1)	0	2 (11.8)	1 (5.9)
Hypokalaemia	0	0	2 (14.3)	2 (14.3)	2 (11.8)	2 (11.8)
Lymphopaenia	0	0	2 (14.3)	2 (14.3)	2 (11.8)	2 (11.8)
Myalgia	1 (33.3)	0	1 (7.1)	0	2 (11.8)	0
Seizure	1 (33.3)	0	1 (7.1)	1 (7.1)	2 (11.8)	1 (5.9)
Urinary tract infection	1 (33.3)	0	1 (7.1)	0	2 (11.8)	0

Buparlisib+lomustine arm

Preferred term, n (%)	**Buparlisib (60 mg)+lomustine (n=18)**	
	All grades	**Grades 3/4**
Fatigue	8 (44.4)	1 (5.6)
Nausea	8 (44.4)	0
Decreased platelet count	8 (44.4)	2 (11.1)
Anaemia	6 (33.3)	1 (5.6)
Confusional state	5 (27.8)	0
Depression	5 (27.8)	1 (5.6)
Headache	5 (27.8)	0
Anxiety	4 (22.2)	0
Hypertension	4 (22.2)	1 (5.6)
Hypokalaemia	4 (22.2)	2 (11.1)
Insomnia	4 (22.2)	0
Neutropaenia	4 (22.2)	2 (11.1)
Thrombocytopaenia	4 (22.2)	4 (22.2)

Continued

Table 4 Continued

Buparlisib+lomustine arm		
Preferred term, n (%)	Buparlisib (60 mg)+lomustine (n=18)	
	All grades	Grades 3/4
Decreased white cell count	4 (22.2)	2 (11.1)
Increased alanine aminotransferase	3 (16.7)	1 (5.6)
Asthenia	3 (16.7)	0
Constipation	3 (16.7)	0
Diarrhoea	3 (16.7)	0
Gastro-oesophageal reflux disease	3 (16.7)	0
Hyperglycaemia	3 (16.7)	1 (5.6)
Memory impairment	3 (16.7)	0
Decreased neutrophil count	3 (16.7)	1 (5.6)
Seizure	3 (16.7)	1 (5.6)
Somnolence	3 (16.7)	0

DCR was 11.1% (95% CI 1.4 to 34.7) and no patient had a CR or PR (table 3).

Preliminary assessment indicated no enough antitumour activity compared with historical data with single-agent carboplatin or lomustine. Based on the overall challenging safety profile and no enough antitumour activity observed in this phase of the study, no additional patients were enrolled and the phase II part of the study was not conducted.

Safety

The median duration of exposure to study treatment was 47 days (range: 42–798 days) in the 80 mg buparlisib dose level plus carboplatin and 42 days (range: 21–259 days) in the 100 mg buparlisib dose level plus carboplatin. The median duration of exposure to study treatment was 42 days (range: 15–231 days) in the 60 mg buparlisib plus lomustine arm.

In the buparlisib plus carboplatin arm, DLTs were reported in three patients, all in the 100 mg buparlisib dose level, including one event of decreased neutrophil count (grade 4), one event of anxiety disorder (grade 4) and one event of suicidal ideation (grade 2). In the buparlisib plus lomustine arm, five patients reported DLTs, including one event of thrombocytopaenia (grade 4), one event of fatigue (grade 3), one event of decreased platelet count (grade 4), two events of depression (one grade 2 and one grade 3) and one event of pneumonitis (grade 3).

The most common any-grade AEs in the buparlisib plus carboplatin arm were headache (52.9%), fatigue and nausea (47.1% each), and thrombocytopaenia (35.3%). The most common grade 3/4 AEs were decreased neutrophil count and decreased platelet count (17.6% each) and hypokalaemia and lymphopaenia (11.8% each). In the buparlisib plus lomustine arm, the most common any-grade AEs were fatigue, nausea, and decreased platelet count (44.4% each) and anaemia (33.3%). The most common grade 3/4 AEs were thrombocytopaenia (22.2%) and increased gamma-glutamyltransferase, hypokalaemia, decreased lymphocyte count, neutropaenia, decreased platelet count and decreased white cell count (11.1% each) (table 4).

Buparlisib dose was reduced due to AEs in one (33.3%) patient in the 80 mg buparlisib plus carboplatin dose level, three (21.4%) patients in the 100 mg buparlisib plus carboplatin dose level, and one (5.6%) patient in the buparlisib plus lomustine arm. Buparlisib dose interruptions due to AEs occurred in one (33.3%), six (42.9%) and seven (38.9%) patients in the 80 mg buparlisib plus carboplatin dose level, the 100 mg buparlisib plus carboplatin dose level, and the buparlisib plus lomustine arm, respectively (table 5).

Two on-treatment deaths due to disease progression were reported, one each in the buparlisib plus carboplatin arm and in the buparlisib plus lomustine arm.

Patient-reported mood assessments

In both the buparlisib plus carboplatin arm and the buparlisib plus lomustine arm, the majority of the patients reported a shift from baseline to the mild depression severity category post baseline (score: 5–9) on PHQ-9. No patient reported a score in the severe depression severity category (score: 20–27) (table 6).

For PHQ-9 question 9 regarding suicidal thoughts, all patients in the 80 mg buparlisib dose level plus carboplatin (100%), most of the patients in the 100 mg buparlisib plus carboplatin dose level (78.6%), and in the buparlisib (60 mg) plus lomustine arm (72.2%) had a worst post-baseline score of 0 (not at all), which was the same as their baseline score. One patient reported a worst postbaseline score of 1 (several days) and one patient reported a score of 2 (more than half the days) in the 100 mg buparlisib plus carboplatin dose level. Three patients reported a score of 1 and one patient reported a score of 3 (nearly every day) in the buparlisib plus lomustine arm.

Table 5 Dose reductions and interruptions of study drug

	Buparlisib*		Carboplatin†		Buparlisib*	Lomustine‡
	Buparlisib (80 mg) + carboplatin (n=3)	Buparlisib (100 mg) + carboplatin (n=14)	Buparlisib (80 mg) + carboplatin (n=3)	Buparlisib (100 mg) + carboplatin (n=14)	Buparlisib (60 mg) + lomustine (n=18)	Buparlisib (60 mg) + lomustine (n=18)
Reductions, n (%)						
Number of patients requiring dose reduction§						
0	2 (66.7)	11 (78.6)	2 (66.7)	13 (92.9)	17 (94.4)	18 (100)
1	1 (33.3)	3 (21.4)	1 (33.3)	1 (7.1)	1 (5.6)	0
2	0	0	0	0	0	0
≥3	0	0	0	0	0	0
Number of patients with at least one dose reduction by reason¶	1 (33.3)	3 (21.4)	1 (33.3)	1 (7.1)	1 (5.6)	0
Adverse event	1 (33.3)	3 (21.4)	1 (33.3)	1 (7.1)	1 (5.6)	0
Interruptions, n (%)						
Number of patients with dose interruption§						
0	2 (66.7)	8 (57.1)	2 (66.7)	13 (92.9)	11 (61.1)	17 (94.4)
1	0	4 (28.6)	1 (33.3)	1 (7.1)	5 (27.8)	1 (5.6)
2	0	0	0	0	1 (5.6)	0
≥3	1 (33.3)	2 (14.3)	0	0	1 (5.6)	0
Number of patients with at least one dose interruption by reason¶	1 (33.3)	6 (42.9)	1 (33.3)	1 (7.1)	7 (38.9)	1 (5.6)
Adverse event	1 (33.3)	6 (42.9)	1 (33.3)	1 (7.1)	7 (38.9)	1 (5.6)
Dosing error/technical problems	1 (33.3)	0	0	0	1 (5.6)	0
Number of patients with permanent discontinuation by reason, n (%)	3 (100)	14 (100)	3 (100)	14 (100)	18 (100)	18 (100)
Adverse event	0	3 (21.4)	0	2 (14.3)	3 (16.7)	3 (16.7)
Physician decision	0	0	1 (33.3)	0	–	–
Death	–	–	–	–	1 (5.6)	1 (5.6)
Progressive disease	3 (100)	11 (78.6)	2 (66.7)	12 (85.7)	14 (77.8)	14 (77.8)

Percentage is based on 'n'.
*Denotes the study drug buparlisib
†Denotes the study drug carboplatin
‡Denotes the study drug lomustine.
§A patient with multiple occurrences of the reason for dose reduction or interruption is counted only once in that category
¶A patient with multiple reasons for dose reduction or interruption is counted only once in the total row (ie, 'number of patients with at least one dose reduction/interruption by reason')

For the GAD-7 questionnaire, in the buparlisib plus carboplatin arm, eight patients had no shift from baseline (seven patients remained at none and one at mild). Eight patients shifted to a worse category (one patient in the 80 mg buparlisib dose level from none to mild and seven in the 100 mg buparlisib dose level: four from none to mild, one from none to moderate, one from mild to moderate, and one from mild to severe). One patient in the 100 mg buparlisib dose level shifted from mild at baseline to none post baseline. In the buparlisib plus lomustine arm, seven patients remained at the same category as at baseline (five patients at none and two at mild), six patients shifted to a worse category (five patients from none to mild, and one from none to moderate), three patients shifted from mild at baseline to none post baseline, and one from severe to mild (table 7).

DISCUSSION

The purposes of this study were to determine the MTD and/or RP2D for the combination of buparlisib plus carboplatin or lomustine and to assess the tolerability and the preliminary antitumour activity of the combinations in patients with rGBM. The MTD of buparlisib was established as 100 mg per day in combination with carboplatin at an AUC of 5 every 3 weeks. The MTD of buparlisib in combination with lomustine 100 mg/m^2 every 6 weeks could not be determined as it did not satisfy the MTD

Table 6 Shift from baseline to worst postbaseline depression severity on PHQ-9

	Baseline category		Worst postbaseline category				
			None	Mild	Moderate	Severe	Missing
Treatment	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)
Buparlisib (80 mg)+ carboplatin (n=3)	None	3 (100)	1 (33.3)	2 (66.7)	0	0	0
	Mild	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Total	3 (100)	1 (33.3)	2 (66.7)	0	0	0
Buparlisib (100 mg)+ carboplatin (n=14)	None	8 (57.1)	2 (25.0)	2 (25.0)	4 (50.0)	0	0
	Mild	4 (28.6)	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (25.0)
	Moderate	2 (14.3)	0	2 (100)	0	0	0
	Severe	0	0	0	0	0	0
	Total	14 (100)	3 (21.4)	5 (35.7)	5 (35.7)	0	1 (7.1)
Buparlisib (60 mg)+ lomustine (n=18)	None	10 (55.6)	4 (40.0)	4 (40.0)	2 (20.0)	0	0
	Mild	5 (27.8)	0	3 (60.0)	2 (40.0)	0	0
	Moderate	3 (16.7)	0	2 (66.7)	0	0	1 (33.3)
	Severe	0	0	0	0	0	0
	Total	18 (100)	4 (22.2)	9 (50.0)	4 (22.2)	0	1 (5.6)

Grades based on severity: normal (severity: none, score: 0–4), mild (score 5–9), moderate (score 10–19) and severe (score 20–27).
PHQ-9, Patient Health Questionnaire-9.

criteria per the BLRM. Overall, rapid disease progression was observed with both the combinations, thus limiting study treatment exposure. The median PFS was 1.4 months in the buparlisib plus carboplatin arm and 1.3 months in the buparlisib plus lomustine arm. Only one patient (in the buparlisib plus carboplatin arm) had a PR lasting 15.1 months, and most patients had progressive disease as the best response. All except one patient in the study had AEs suspected to be related to the study treatment. Based on the overall safety profile and preliminary

Table 7 Shift from baseline to worst postbaseline anxiety severity on GAD-7

	Baseline category		Worst postbaseline category				
			None	Mild	Moderate	Severe	Missing
Treatment	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)
Buparlisib (80 mg)+ carboplatin (n=3)	None	3 (100)	2 (66.7)	1 (33.3)	0	0	0
	Mild	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Total	3 (100)	2 (66.7)	1 (33.3)	0	0	0
Buparlisib (100 mg)+ carboplatin (n=14)	None	11 (78.6)	5 (45.5)	4 (36.4)	1 (9.1)	1 (9.1)	0
	Mild	3 (21.4)	1 (33.3)	1 (33.3)	1 (33.3)	0	0
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Total	14 (100)	6 (42.9)	5 (35.7)	2 (14.3)	1 (7.1)	0
Buparlisib (60 mg)+ lomustine (n=18)	None	12 (66.7)	5 (41.7)	5 (41.7)	1 (8.3)	0	1 (8.3)
	Mild	5 (27.8)	3 (60.0)	2 (40.0)	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	1 (5.6)	0	1 (100)	0	0	0
	Total	18 (100)	8 (44.4)	8 (44.4)	1 (5.6)	0	1 (5.6)

Grades based on severity: normal (severity: none, score: 0–4), mild (score: 5–9)
GAD-7, Generalized Anxiety Disorder-7.

antitumour activity observed in this study, the phase II part of the study was not conducted. Moreover, due to the small number of patients, low response rate and short duration of treatment, no conclusion can be drawn on the relationship between response and PI3K activation status.

The modest outcomes observed in the current study are consistent with those reported for rGBM and further highlight the challenges of treating rGBM.

Several pan-PI3K inhibitors, including buparlisib, pictilisib and CLR457, have been evaluated for their clinical efficacy in a variety of tumours. However, most of the studies assessing these agents have demonstrated a modest improvement in efficacy outcomes accompanied by a challenging toxicity profile. In a phase III trial in patients with hormone receptor-positive breast cancer, buparlisib in combination with fulvestrant showed that the addition of a PI3K inhibitor improved outcomes; however, toxicities in the buparlisib arm limited the treatment duration and intensity.[26 27] Similarly, pictilisib also demonstrated a modest efficacy improvement in combination with an aromatase inhibitor in hormone receptor-positive breast cancer, but the clinical activity was limited by the challenging toxicity profile.[28] CLR457, evaluated in solid tumours, demonstrated limited antitumour activity and poor tolerability, leading to termination of its clinical development.[29] Overall, data from the current study and from previous studies of pan-PI3K inhibitors highlight the challenges of achieving a meaningful clinical benefit when targeting all class I PI3K isoforms.

The current study demonstrated that, with the dose levels studied, neither buparlisib plus carboplatin nor buparlisib plus lomustine significantly improved antitumour activity compared with historical data on single-agent carboplatin or lomustine.

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Data availability statement Data are available upon reasonable request. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com.

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