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Phase I, open-label, multicentre study of buparlisib in combination with temozolomide or with concomitant radiation therapy and temozolomide in patients with newly diagnosed glioblastoma

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ABSTRACT

Background Most glioblastoma tumours exhibit intrinsic phosphatidylinositol 3-kinase (PI3K) pathway activation. Preclinical in vitro and in vivo models suggest that buparlisib (an oral pan-PI3K inhibitor) can have an effect on glioblastoma directly and by enhancing the activity of radiation and of temozolomide.

Methods This was a phase I, two-stage, multicentre, open-label, dose-escalation study of buparlisib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma. In stage I, patients who completed the concomitant phase of combination of temozolomide and radiation prior to study entry received buparlisib in combination with temozolomide. In stage II, patients received buparlisib in combination with temozolomide and radiotherapy in the concomitant phase and temozolomide in the adjuvant treatment phase. The primary objective was to estimate the maximum tolerated dose (MTD) of buparlisib when combined with the approved first-line treatment of temozolomide and radiotherapy.

Results The MTD of buparlisib in combination with temozolomide at stage I (adjuvant phase only) was 80 mg/day, which was used as the starting dose in stage II. The MTD of buparlisib in combination with temozolomide and radiotherapy in stage II (concomitant + adjuvant phase) was not determined due to the observed dose-limitingtoxicities and treatment discontinuations due to adverse events (AEs). In stage I, the most commonly reported AEs were nausea (72.7%) and fatigue (59.1%). In stage II, the most commonly reported AEs were fatigue and nausea (56.3% each). No on-treatment deaths were reported during the study.

Conclusion Considering that the primary objective of estimating the MTD was not achieved in addition to the observed challenging safety profile of buparlisib in combination with radiotherapy and temozolomide, Novartis decided not to pursue the development of buparlisib in newly diagnosed glioblastoma.

Trial registration number
ClinicalTrials.govidentifier: NCT01473901.

Key questions

What is already known about this subject?

- Glioblastoma comprises a highly heterogeneous group of invasive malignant brain tumours. The current standard of care, which consists of concomitant radiotherapy and temozolomide followed by adjuvant temozolomide monotherapy for up to 6 months, combined with tumour-treating fields offers limited efficacy, and almost all patients experience recurrent disease.

What does this study add?

- Here, we present results of the phase I, two-stage, multicentre, open-label, dose-escalation study of buparlisib in combination with temozolomide or with concomitant radiation therapy and temozolomide in adult patients (age ≥18 years) with newly diagnosed glioblastoma. This study illustrates the difficulty encountered when targeted therapies are combined with radiation therapy and temozolomide. Overlapping toxicities often prevent the targeted therapy from being administered at the full single-agent dose, potentially reducing the effectiveness of the combinations.

How might this impact on clinical practice?

- Based on the result of this and other studies, clinical trials with novel agents in newly diagnosed glioblastomas are being conducted in a subset of glioblastoma patients with unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) without temozolomide, enabling the agent of interest to be administered at the full single-agent dose.

INTRODUCTION

Glioblastoma comprises a highly heterogeneous group of invasive malignant brain tumours.[1] The current standard of care, which consists of concomitant radiotherapy

and temozolomide (TMZ) followed by adjuvant TMZ monotherapy for up to 6 months, combined with tumour-treating fields offers limited efficacy, and almost all patients experience recurrent disease.[2 3]

Most glioblastoma tumours exhibit activation of the intrinsic phosphatidylinositol 3-kinase (PI3K) pathway, commonly through phosphatase and tensin homologue (*PTEN*) alteration, and this activation is associated with a dependence on PI3K signalling for cell survival and proliferation.[4 5]

Studies in preclinical in vitro and in vivo models suggest that buparlisib (a potent and highly specific oral pan-class I PI3K inhibitor) can have an effect on glioblastoma directly and by enhancing the activity of radiation and of TMZ.[6–9] Buparlisib has 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 phosphor AKT.[10] A recent study in patients with recurrent glioblastoma who were pretreated with buparlisib prior to surgery also demonstrated good penetration across the blood-brain barrier, with a tumour-to-plasma ratio of 1.[11] However, single-agent efficacy was limited. Potentially, buparlisib may be more effective when combined with standard radiation therapy and TMZ chemotherapy in patients with newly diagnosed glioblastoma.

Here, we report the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of buparlisib in combination with TMZ or with concomitant radiation therapy and TMZ, the safety and preliminary antitumour activity of these combinations in patients with newly diagnosed glioblastoma.

METHODS

Study design and participants

This was a phase I, two-stage, multicentre, open-label, dose-escalation study conducted in adult patients (age ≥18 years) with newly diagnosed glioblastoma. Patients with primary glioblastoma or patients whose previously existing lower-grade glioma underwent transformation were eligible.

Stage I of the study included patients who completed concomitant TMZ-radiotherapy prior to study entry to estimate the MTD of buparlisib combined with TMZ in adjuvant treatment of glioblastoma. Buparlisib dose escalation was evaluated sequentially in adjuvant cycle 1 (A1) and in adjuvant cycle 2 (A2). Stage II included patients who had received only surgery prior to study entry to estimate the MTD/RP2D of buparlisib in the concomitant phase (TMZ-radiotherapy; C), A1, A2 and beyond (cycle 3 +) (figure 1).

Patients enrolled into stage I must have received at least 75% of planned radiotherapy (60 Gy) with TMZ treatment during the concomitant phase; had an absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L and no occurrence of common toxicity criteria grade ≥2 non-haematological toxicity (except for alopecia, nausea and vomiting) during the concomitant phase; and completed TMZ therapy in the concomitant phase 4 to 6 weeks prior to enrolment. Patients enrolled into stage II were required to have completed primary glioblastoma resection 2to 6 weeks prior to enrolment. Patients must have recovered from the definitive surgical procedure for glioblastoma.

In stage I, a minimum of six evaluable patients must have completed the combination treatment in adjuvant phase A1 and A2 sequentially, with a minimum of 60 mg/day buparlisib demonstrated as tolerable in treatment phase A1, before the initiation of stage II. In stage II, a minimum of nine evaluable patients (including those in the earlier dose-escalation cohorts) must have completed the combination treatment in the concomitant phase (C), adjuvant phase cycle 1 (A1) and adjuvant phase cycle 2 (A2) sequentially, demonstrating the tolerability of the dose sequence, in order to confirm the RP2D and/or MTD, which was to be declared when a minimum of three evaluable patients completed the dose sequence and shown it was tolerable.

The concomitant phase was of 42 days duration during which the patients received buparlisib in combination with TMZ (75 mg/m^2/day) and radiotherapy (60 Gy in 30 fractions), followed by a rest phase of 4 to 6 weeks duration. In the adjuvant phase, patients received buparlisib in combination with TMZ for 12 cycles or until disease progression or death, withdrawal of consent and start of another antineoplastic treatment whichever occurred first.

This study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all the patients.

Objectives

The primary objective of the study was to estimate the MTD and/RP2D of buparlisib in three sequential treatment phases (C, A1 and A2), in combination with the approved first-line treatment of radiotherapy and TMZ in patients with newly diagnosed glioblastoma. Secondary endpoints included safety profile and tolerability of the combination regimens; antitumour activity, including the objective response rate (ORR), progression-free survival and overall survival, in patients with newly diagnosed glioblastoma after surgery; pharmacokinetic (PK) profile and potential drug-drug interaction of buparlisib and TMZ in the combination.

Assessments

In stage I, dose-limiting toxicity (DLT) was assessed only in treatment phase A1 and treatment phase A2. In stage II, DLT was assessed in treatment phase C, up to 21 days after the last administration of buparlisib or completion of cranial irradiation (whichever is later) during the rest period, in treatment phase A1 and in treatment phase A2 as per stage I.

In the concomitant phase, contrast MRI scans were to be performed at the end of rest period (+/−7 days) before starting the study treatment in the adjuvant phase. In the

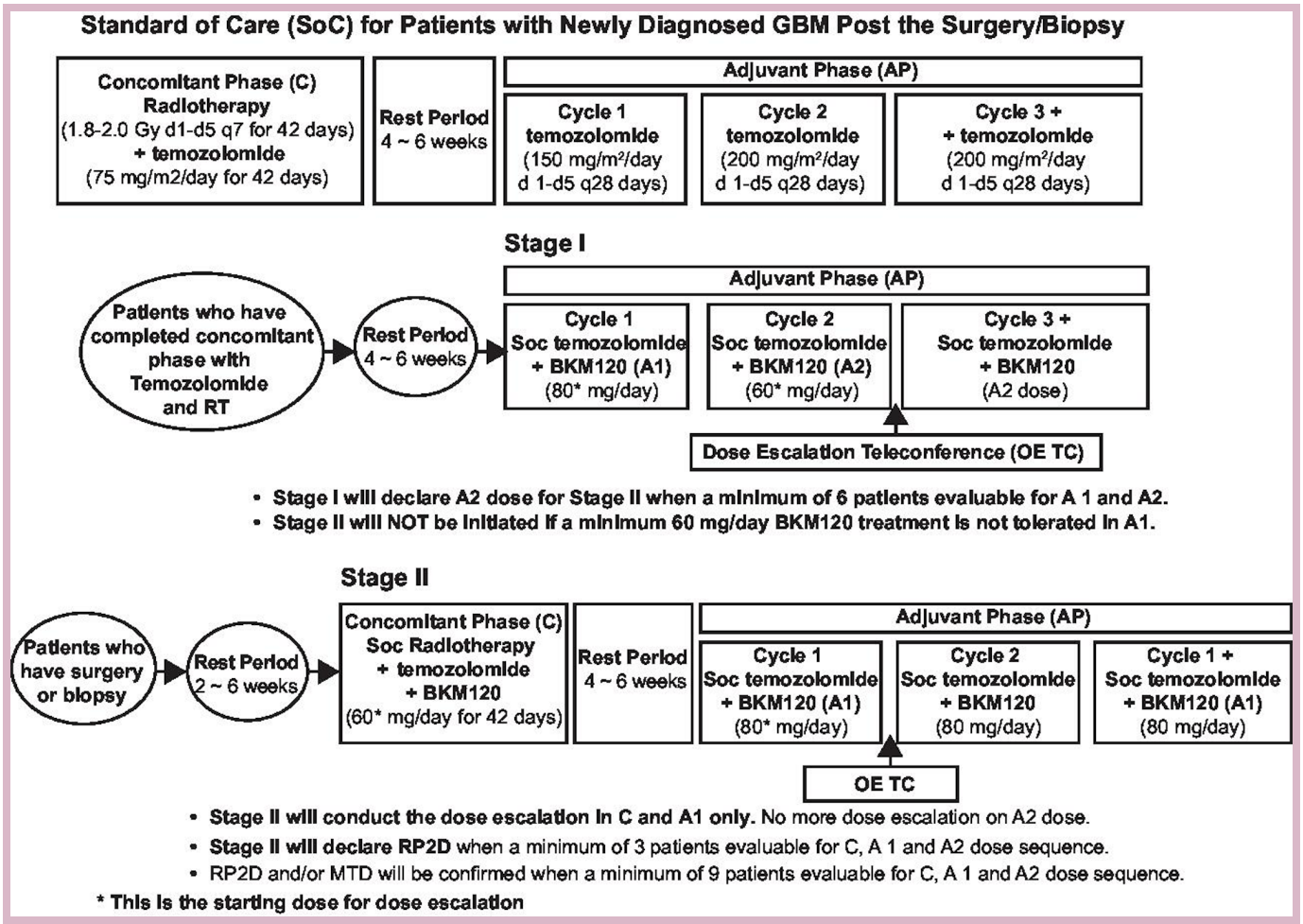

Figure 1 Study design. BKM120, buparlisib; GBM, glioblastoma multiforme; MTD, maximum tolerated dose; q,every; RP2D, recommended phase II dose; RT, radiotherapy.

adjuvant phase, contrast MRI scans were to be performed at screening and every 8 weeks (+/−7 days) from the start of study treatment until disease progression, withdrawal of consent, start of another antineoplastic therapy or death, whichever occurred first.

Tumour response and progression were assessed using the Response Assessment in Neuro-Oncology Working Group updated response assessment criteria for high-grade gliomas.[12]

Safety was monitored by physical examination, vital signs, weight, Karnofsky Performance Scale (KPS) evaluation, ECG, cardiac imaging, laboratory evaluations, including glucose monitoring, and assessment of patient self-rating mood questionnaires, as well as collecting all adverse events (AEs) and serious AEs (SAEs) along with their severity and relationship to study drug and pregnancies. Patient-rated mood was assessed using the patient self-rating questionnaires for depression (Patient Health Questionnaire-9 (PHQ-9)) and anxiety (Generalised Anxiety Disorder 7-item (GAD-7) scale).

Statistical considerations

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control was used to guide dose escalation and determine the MTD/RP2D of buparlisib in combination with the standard of care, TMZ with radiotherapy. The adaptive BLRM provided an estimate of the risk of observing the DLT in each treatment phase and for the buparlisib study dose separately, as well as an estimate of cumulative toxicity across treatment phases. A clinical synthesis of the available toxicity information, PK and efficacy information, as well as the recommendations from the Bayesian model were used to determine the dose sequence to be tested in the next cohort.

The MTD was defined as the highest buparlisib dose not causing medically unacceptable toxicity, in each treatment phase. For each treatment phase, the BLRM provided an estimate of the highest dose of buparlisib not exceeding the MTD, by determining the dose with the maximum probability of targeted toxicity (DLT rate between 16% and 35%).

Stage II of this study (concomitant + adjuvant phase) represents the standard of care for patients with newly diagnosed glioblastoma. The purpose of stage I was to estimate the MTD/DLT of buparlisib in the adjuvant phase and is accordingly considered supportive. Therefore, the

Table 1 Patient disposition (full analysis set)

Reason for disposition, n (%)	Concomitant + adjuvant (stage II) n=16	Adjuvant (stage I) n=22
End of treatment	16 (100)	22 (100)
Primary reason for end of treatment		
Adverse event(s)	11 (68.8)	7 (31.8)
Administrative problems	2 (12.5)	2 (9.1)
Disease progression	3 (18.8)	13 (59.1)
Patients no longer being followed for study evaluation	16 (100)	22 (100)
Primary reason for study evaluation completion		
Adverse events	0	1 (4.5)
Subject withdrew consent	1 (6.3)	1 (4.5)
Administrative problems	2 (12.5)	2 (9.1)
Death	1 (6.3)	2 (9.1)
Disease progression	10 (62.5)	16 (72.7)
Follow-up phase completed as per protocol	2 (12.5)	0

results are presented in the order of stage II followed by stage I.

RESULTS

Patient characteristics

A total of 38 patients with newly diagnosed glioblastoma were enrolled in this study: 22 in stage II (concomitant + adjuvant phase) and 16 in stage I (adjuvant phase) (table 1). Six patients who were enrolled in stage II did not receive buparlisib in the concomitant phase and were therefore included in the assessment of stage I (where no administration of buparlisib was scheduled). Of the 16 remaining patients in stage II, five patients each were included at the 40 mg/day and 40i mg/day intermittent dose levels and six patients were included at the 60 mg/day dose level. Of the 22 patients who were considered in stage I, five were at the 80/60 mg/day dose level, 15 at the 80/80 mg/day dose level and two at the 80/not-determined (ND) mg/day dose level.

Stage II (concomitant + adjuvant phase): The median age of patients was 50.5 years (range: 32 to 71 years), and 18.8% of patients were aged ≥65 years; 62.5% of patients were male. Nearly all patients were Caucasian (93.8%), and all patients had a KPS score ≥80 (table 2). The median time since initial diagnosis of glioblastoma was 1.1 months (range: 1 to 4 months). At baseline, 50% of patients had measurable disease and 25% had no lesion. Of 16 patients in stage II, five patients (31.3%) had PI3K pathway activated status and eight patients (50%) had non-activated status. Activation of the pathway was caused by PTEN mutations in four patients (25%), while it was caused by loss of PTEN expression and phosphatidylinositol 4, 5-bisphosphate 3-kinase (PIK3CA) mutations in one patient each (6.3%).

Stage I (adjuvant phase only): The median age of patients was 61 years (range: 49 to 72 years) and 27.3% of patients were aged ≥65 years; 77.3% of patients were male. All patients were Caucasian and 95.5% of patients had a KPS score ≥80 (table 2). Prior to study entry, all patients had surgery and had received TMZ treatment with radiotherapy (concomitant phase), as per protocol. The median time since initial diagnosis of glioblastoma was 3.5 months (range: 1 to 5 months). At baseline, 77.3% of patients had measurable disease, while 4.5% of patients had no lesion. Of the 22 patients in stage I, eight (36.4%) had PI3K pathway activated status and 11 (50%) had non-activated status. Activation of the pathway was caused by *PTEN* mutations in five patients (22.7%), loss of *PTEN* expression in two patients (9.1%) and *PIK3CA* mutation in one (4.5%) patient.

Efficacy and MTD

The MTD for buparlisib in combination with TMZ in stage I (adjuvant phase cycles 1 and 2 only) was identified as 80 mg/day, which was used as the starting dose for the adjuvant phase in stage II. The MTD for buparlisib in the combination phase (with TMZ and radiotherapy) in stage II was ND, as unacceptable DLTs were observed with all schedules and doses investigated (buparlisib 40 mg/day, 60 mg/day and 40 mg/day intermittent dosing (5 days on and 2 days off)). In addition, especially in the combination phase, the challenging safety profile of buparlisib led to a high rate of study treatment discontinuation prior to the adjuvant phase due to AEs. This led to a short treatment duration, which may have contributed to the observed lack of antitumour activity. In stage II vs stage I, dose reductions occurred in 18.8% vs 40.9% of patients and dose interruptions in 43.8% vs 77.3% of patients, respectively. All patients discontinued study treatment, mainly due to AEs (68.8% vs 31.8%) and disease progression (18.8% vs 59.1%) (table 1).

Of 16 patients in stage II, complete response (CR) was observed in one patient at the 40 mg/day dose level and partial response (PR) was observed in one patient at the 40i mg/day dose level. The ORR was 12.5% and the overall disease control rate (DCR) was 68.8%. Of 22 patients in stage I, none of the patients had CR or PR, and the overall DCR was 81.8% (table 3).

Safety

The overall safety and tolerability profile of buparlisib was consistent with that of prior studies, and buparlisib showed similar class effects of PI3K inhibitors.

In stage II, the most commonly reported AEs were fatigue and nausea (56.3% each). Grade 3 or 4 AEs

Table 2 Patient demographics and other baseline characteristics

Demographic variable	Concomitant + adjuvant (stage II) n=16	Adjuvant (stage I) n=22	All patients n=38
Age, median (range), years	50.5 (32 to 71)	61.0 (49 to 72)	53.5 (32 to 72)
Sex, n (%)			
Female	6 (37.5)	5 (22.7)	11 (28.9)
Male	10 (62.5)	17 (77.3)	27 (71.1)
Race, n (%)			
Caucasian	15 (93.8)	22 (100.0)	37 (97.4)
Asian	1 (6.3)	0	1 (2.6)
Karnofsky performance status, n (%)			
100	8 (50.0)	5 (22.7)	13 (34.2)
90	6 (37.5)	8 (36.4)	14 (36.8)
80	2 (12.5)	8 (36.4)	10 (26.3)
70	0	1 (4.5)	1 (2.6)
Primary site of cancer, n (%)			
CNS: supratentorial	12 (75.0)	14 (63.6)	26 (68.4)
CNS: infratentorial	2 (12.5)	1 (4.5)	3 (7.9)
Other	2 (12.5)	7 (31.8)	9 (23.7)
Histological grade, n (%)			
Poorly differentiated	3 (18.8)	3 (13.6)	6 (15.8)
Undifferentiated	7 (43.8)	9 (40.9)	16 (42.1)
Unknown	6 (37.5)	10 (45.5)	16 (42.1)
Time since initial diagnosis of glioblastoma, median (range), months	1.1 (1 to 4)	3.5 (1 to 5)	1.7 (1 to 5)
Type of lesions at baseline			
Target lesion – measurable enhancing lesion (T1)	8 (50.0)	17 (77.3)	25 (65.8)
Non-target lesion – non-measurable enhancing lesion (T1)	2 (12.5)	3 (13.6)	5 (13.2)
Non-target lesion – non-enhancing lesion (T2/FLAIR)	2 (12.5)	1 (4.5)	3 (7.9)
No lesion	4 (25.0)	1 (4.5)	5 (13.2)
Prior surgery			
Yes	16 (100.0)	22 (100.0)	38 (100.0)

CNS, central nervous system; T2/FLAIR, T2-weighted-fluid-attenuated inversion recovery.

reported in 93.8% of patients were mainly decreased lymphocyte count, thrombocytopenia and decreased neutrophil count (31.3% each), followed by hyperglycaemia and increased amylase (12.5% each) (table 4). In stage I, the most commonly reported AEs were nausea (72.7%) and fatigue (59.1%). Grade 3 or 4 AEs reported in 77.3% of patients were mainly hyperglycaemia and thrombocytopenia (18.2% each), followed by decreased platelet count, cognitive disorder and confusional state (13.6% each) (table 4).

At least one AE suspected to be study treatment related was reported in 93.8% of patients in stage II and in all patients in stage I. The AEs suspected to be study treatment related in ≥30% of patients in stage II were nausea, fatigue (43.8% each), decreased lymphocyte count, thrombocytopenia (37.5% each), alopecia, hyperglycaemia and decreased neutrophil count (31.3% each), while in stage I, these were nausea (59.1%), fatigue (45.5%), hyperglycaemia (40.9%), decreased platelet count and thrombocytopenia (36.4% of patients each).

In stage II, SAEs were reported in eight (50%) patients, with thrombocytopenia (12.5%) being the most frequently reported SAE. In stage I, SAEs were reported in 12 (54.5%) patients, with aphasia and seizure (13.6% each) being the most frequently reported SAEs.

Mood disorder events were reported in 62.5% of patients (12.5% of patients had grade 3 events; no grade 4 events were observed) in stage II and 68.2% of patients

Table 3 Best overall response summary using the RANO criteria (investigator assessment)

	Concomitant + adjuvant (stage II)	Adjuvant (stage I)
	n=16, n (%)	n=22, n (%)
Patients without disease at baseline*	4 (25.0)	1 (4.5)
Patients with measurable disease at baseline	8 (50.0)	17 (77.3)
Patients with non-measurable disease only at baseline (non-measurable enhancing lesion T1 and/or non-enhancing T2/FLAIR lesion only)	4 (25.0)	4 (18.2)
Best overall response		
CR	1 (6.3)	0
PR	1 (6.3)	0
SD	9 (56.3)	18 (81.8)
PD	2 (12.5)	3 (13.6)
Non-evaluable	2 (12.5)	1 (4.5)
Unknown	1 (6.3)	0
ORR: CR+PR	2 (12.5) (95% CI: 1.6 to 38.3)	0
DCR: CR+PR+SD	11 (68.8) (95% CI: 41.3 to 89.0)	18 (81.8) (95% CI: 59.7 to 94.8)

*Patients who had complete resection of the tumour.
CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; T2/FLAIR, T2-weighted-fluid-attenuated inversion recovery.

in stage I, of which grade 4 suicidal ideation event was noted in one patient.

During stage II, DLTs were reported in nine patients (60%). Onset of increased lipase (n=2), decreased platelet count (n=1) and altered mood (n=1) were reported in the concomitant phase; onset of thrombocytopenia (n=4) was reported in three patients in the concomitant phase and one patient in the A2 phase, while onset of hyperglycaemia (n=1) was reported in the A2 phase.

During stage I, DLTs were reported in six patients (27.3%). Onset of hyperglycaemia (n=1), anxiety (n=1) and confusional state (n=1) were reported in the A1 phase, while onset of thrombocytopenia (n=1), increased blood glucose (n=1) and depression and altered mood (n=1) were reported in the A2 phase.

No on-treatment deaths were reported during the study.

Patient-reported mood assessments

In stage II, 10 patients (62.6%) reported a worsening in the post-baseline PHQ-9 questionnaire score; seven patients shifted from none-to-mild category, one patient shifted from none-to-moderate category and two patients shifted from mild-to-moderate category. In stage I, 12 patients (54.5%) reported a worsening in the post-baseline PHQ-9 questionnaire score; six patients shifted from none-to-mild category, four patients shifted from none-to-moderate category, one patient shifted from mild-to-moderate category and one patient shifted from mild-to-severe category. For PHQ-9 regarding suicidal thoughts, shift from 0 to 1 (several days) was noted in three patients and shift from 0 to 3 (nearly every day) was noted in one patient.

In stage II, three patients (18.8%) reported a worsening in the GAD-7 anxiety scale, with all three shifting from none-to-mild category. In stage I, nine patients (41%) reported a worsening in the post-baseline GAD-7 anxiety scale; six patients shifted from none-to-mild category, one patient shifted from none-to-moderate category and two patients shifted from none-to-severe category.

DISCUSSION

The MTD/RP2D for buparlisib in combination with TMZ in stage I was identified as 80 mg/day and was used as the starting dose for the adjuvant phase in stage II. The MTD/RP2D of buparlisib given concomitantly with radiotherapy and TMZ in the concomitant phase (stage II) could not be determined because of the challenging safety profile of buparlisib and the high rate of study treatment discontinuation due to AEs in this setting at all doses and schedules tested. This resulted in the observed short duration of treatment at stage II that may also have in turn contributed to the observed lack of antitumour activity in this study.

Considering the limited to modest efficacy results of buparlisib in different studies in different indications, particularly in large phase III studies in breast cancer, and the challenging yet manageable safety profile of

Table 4 All grade and grade 3/4 adverse events regardless of study treatment relationship, with at least 25% incidence (safety set)

	Concomitant + adjuvant (stage II), n=16		Adjuvant (stage I), n=22	
Adverse event	**All grades, N (%)**	**Grade 3 or 4, N (%)**	**All grades, N (%)**	**Grade 3 or 4, N (%)**
Fatigue	9 (56.3)	1 (6.3)	13 (59.1)	0
Nausea	9 (56.3)	0	16 (72.7)	0
Alopecia	6 (37.5)	0	–	–
Anxiety	6 (37.5)	1 (6.3)	7 (31.8)	1 (4.5)
Decreased appetite	6 (37.5)	0	9 (40.9)	0
Depression	6 (37.5)	0	–	–
Lymphocyte count decreased	6 (37.5)	5 (31.3)	–	–
Thrombocytopenia	6 (37.5)	5 (31.3)	8 (36.4)	4 (18.2)
Blood bilirubin increased	5 (31.3)	0	–	–
Hyperglycaemia	5 (31.3)	2 (12.5)	11 (50.0)	4 (18.2)
Neutrophil count decreased	5 (31.3)	5 (31.3)	–	–
Alanine aminotransferase increased	4 (25.0)	1 (6.3)	–	–
Amylase increased	4 (25.0)	2 (12.5)	–	–
Aspartate aminotransferase increased	4 (25.0)	1 (6.3)	–	–
Asthenia	4 (25.0)	0	7 (31.8)	2 (9.1)
Constipation	4 (25.0)	0	8 (36.4)	0
Diarrhoea	4 (25.0)	0	–	–
Dry skin	4 (25.0)	0	–	–
Headache	4 (25.0)	0	7 (31.8)	0
Platelet count decreased	4 (25.0)	1 (6.3)	8 (36.4)	3 (13.6)
Rash	4 (25.0)	0	–	–
Vomiting	4 (25.0)	0	9 (40.9)	0
Cognitive disorder	–	–	6 (27.3)	3 (13.6)
Gait disturbance	–	–	6 (27.3)	1 (4.5)
Muscular weakness	–	–	6 (27.3)	0
Weight decreased	–	–	6 (27.3)	0

buparlisib, Novartis decided not to pursue further development of buparlisib. Accordingly, this study was terminated early.

This study illustrates the difficulty encountered when targeted therapies are combined with radiation therapy and TMZ. Overlapping toxicities often prevent the targeted therapy from being administered at the full single-agent dose, potentially reducing the effectiveness of the combinations. Based on the result of this and other studies, clinical trials with novel agents in newly diagnosed glioblastomas are being conducted in a subset of glioblastoma patients with unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) without TMZ, enabling the agent of interest to be administered at the full single-agent dose.[13]

Ongoing studies with several new agents, including checkpoint inhibitors and chimeric antigen receptor T-cells (CAR-T), may help identify clinically relevant treatment options for patients with glioblastoma.

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Competing interests PYW reports research support from Agios, AstraZeneca, Beigene, Eli Lily, Genentech/Roche, Karyopharm, Kazia, MediciNova, Merck, Novartis, Oncoceutics, Sanofi-Aventis and VBI Vaccines; participated on advisory boards for Abbvie, Agios, AstraZeneca, Blue Earth Diagnostics, Eli Lilly, Genentech/Roche, Karyopharm, Kiyatec, Puma, Vascular Biogenics, Taiho, Deciphera, VBI Vaccines and Tocagen; speaker for Merck and Prime Oncology. JAR reports grants from Novartis and Bayer; personal fees from Novartis, MSD, PEPTOMYC, Eli Lilly and Bayer outside the submitted work. VD is an employee of Novartis Pharma SAS and holds Novartis stock options. DM is an employee of Novartis Pharma AG and holds Novartis stock options. ME-H is an employee of Novartis Pharmaceuticals Corporation and holds Novartis stock options. WM, JTB, JDG and MR have nothing to disclose.

Patient consent for publication Written informed consent was obtained from all the patients.

Ethics approval The study has received approval from the Office for Research – The Royal Melbourne Hospital in Australia, University Health Network Research Ethics Board in Canada, Hamilton Integrated Research Ethics Board in Canada, Hospital Universitari Vall d'Hebron in Spain and Office for Human Research Studies Dana-Farber Cancer Institute in USA. The study has also undergone review by UT MD Anderson Cancer Center and Western Institutional Review Board in USA.

Provenance and peer review Not commissioned; externally peer reviewed.

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 is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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