Sponsor

Novartis

Generic Drug Name

Buparlisib

Trial Indication(s)

Newly diagnosed glioblastoma

Protocol Number

CBKM120E2101

Protocol Title

A Phase I, two-stage, multi-center, open-label dose-escalation study of BKM120 in combination with adjuvant temozolomide and with concomitant radiation therapy and temozolomide in patients with newly diagnosed glioblastoma (GBM)

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

30-Dec-2011 to 17-May-2017

Reason for Termination (If applicable)

The primary objective of determining the MTD at Stage II was not achieved in addition to the challenging safety profile of buparlisib in combination of chemotherapy and radiation leading to high rate of study treatment discontinuation due to AEs. This contributed to the observed short duration of treatment at Stage II that may also have contributed to the non-promising tumor activity seen in the study. Based on this, Novartis decided not to pursue the development of buparlisib in newly diagnosed GBM indication. Additionally, based on the results of other studies in different indications, particularly in the Phase III studies in breast cancer, Novartis decided not to pursue further development of buparlisib. Accordingly, this study was terminated early.

Study Design/Methodology

Two-stage, multi-center, open label, dose escalation study to estimate the MTD and/or RP2D of buparlisib in combination with the standard of care, temozolomide with radiotherapy, in patients with newly diagnosed GBM.

In Stage I, patients who completed concomitant phase of combination of temozolomide and radiation prior to study entry were to receive buparlisib in combination with temozolomide in the study in the adjuvant treatment phase: in Cycle 1 (treatment phase A1), then Cycle 2 (treatment phase A2) and beyond (Cycle 3+). In Stage II, patients were to receive buparlisib in combination with temozolomide and radiotherapy in the concomitant phase (treatment phase C) and in combination with temozolomide in the adjuvant treatment phase. Patients enrolled in Stage II received only surgery prior to study entry.

Centers

8 centers in 4 countries: Australia (1), Canada (2), Spain (2), USA (3)

Objectives:

Primary objective

- To estimate the MTD and/RP2D of buparlisib in three sequential treatment phases (C, A1 and A2), when combined with the approved first line treatment of temozolomide-radiotherapy in patients with newly diagnosed glioblastoma GBM

Secondary objective(s)

- To characterize the safety profile and tolerability of combination regimens
- To assess anti-tumor activity for patients with newly diagnosed GBM after surgery based on objective response rate (ORR)
- To assess anti-tumor activity for patients with newly diagnosed GBM after surgery based on progression-free survival (PFS)
- To assess anti-tumor activity for patients with newly diagnosed GBM after surgery based on overall survival (OS)
- To characterize the pharmacokinetic (PK) profile and potential drug-drug interaction of buparlisib and temozolomide in the combination

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug used was buparlisib. Buparlisib was supplied as 10 mg and 50 mg hard gelatin capsules, packaged in bottles, and was given orally on a flat scale of mg/day. Temozolomide was supplied commercially (except for Spain) as 5 mg, 20 mg, 100 mg, 140 mg, 180 mg or 250 mg capsules, packaged in bottles, and was given orally based on patient's body surface area.

The duration of concomitant phase was 42-day during which patients were to receive buparlisib in combination with temozolomide (75 mg/m2/day) and radiotherapy (60 Gy in 30 fractions), followed by a rest phase of 4 to 6 weeks. In the adjuvant phase, patients were to receive buparlisib in combination with temozolomide for 12 cycles; buparlisib was to be continued beyond 12 adjuvant cycles until the patient discontinued due to disease progression, intolerable toxicity, withdrawal of consent, starting another antineoplastic therapy, or death, whichever occurred first.

Statistical Methods

An adaptive Bayesian logistic regression model (BLRM) with overdose control (EWOC) was used to guide dose escalation and determine the MTD/RP2D of buparlisib in combination with the standard of care, temozolomide with radiotherapy.

At each decision time point, Novartis called a dose escalation teleconference. The adaptive BLRM provided an estimate of the risk of observing DLT in each treatment phase and buparlisib study dose separately, as well as an estimate of the cumulative toxicity. A clinical synthesis of the available toxicity information, PK, and efficacy information as well as the recommendations from the Bayesian model was used to determine the dose sequence to be tested in next cohort.

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

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patient is ≥ 18 years of age on the day of consent signature
- Patient with histologically demonstrated, previously untreated glioblastoma
- Patient may have received initial treatment for GBM as follows:
  - For patients enrolled into Stage I, they must have received at least 75% of planned radiotherapy (60 Gy) with temozolomide treatment during the concomitant phase have documentation that the patient's absolute neutrophil count (ANC) is ≥ 1.5 x 109/L, platelet count is ≥ 100 x 109/L, and there was no Common Toxicity Criteria grade 2 or above non hematological toxicity (except for alopecia, nausea, vomiting) during the concomitant phase treatment be within ≥ 4 weeks but ≤ 6 weeks following the completion of temozolomide in the concomitant phase
  - For patients enrolled into Stage II, they must be within ≥ 2 weeks but ≤ 6 weeks after primary GBM resection/biopsy The patient must have recovered from the definitive surgical procedure for GBM
- Patient is able to be assessed by periodic dynamic contrast enhanced magnetic resonance imaging scan
- Patient has Karnofsky performance status >= 60
- Patient has adequate bone marrow and organ function

Exclusion Criteria:

- Patient has received previous treatment with PI3K and/or mTOR inhibitors for GBM or for pre-existing neoplasm transformed to GBM. Patient has received any prior anti-neoplastic therapy for BKM, except for the treatment allowed in inclusion criteria
- Patient has any tumor progression after definitive GBM resection/ biopsy, except for the transformation from previous low grade glioma. Patient with a concurrent malignancy or malignancy within 3 years of study enrollment (with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer)
- Patient who had not recovered to grade 1 or better from any adverse events (except alopecia, nausea, vomiting) related to previous antineoplastic therapy before screening procedures are initiated, as allowed in inclusion criteria
- Patient has any of the following baseline mood disorders (not attributable to GBM) as judged by the Investigator or a Psychiatrist, or meets the cut-off score of ≥ 12 in the PHQ- 9 or a cut-off of ≥ 15 in the GAD-7 mood scale for reasons not attributable to GBM; or selects a positive response of '1, 2, 3' to question number 9 regarding potential for suicidal thoughts or ideation in the PHQ-9 (independent of the total score of the PHQ-9)
- Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others)
- Active severe personality disorders (defined according to DSM-IV). Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.
- ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 3 anxiety
- Patient who is concurrently using any other approved or investigational anti-neoplastic agent
- Patient who has undergone the following invasive procedures: Major surgical procedure, open biopsy or significant traumatic injury < 14 days prior to starting study drug or has not recovered from side effects of such therapy, anticipation of need for invasive surgical procedure during the course of the study, biopsy within 7 days prior to starting study drug
- Patient has poorly controlled diabetes mellitus (HbA1c > 8%)
- Patient is currently receiving increasing or chronic treatment with corticosteroids or another immunosuppressive agent

- Patient is currently receiving an enzyme inducing anti-epileptic drug (EIAED). The patient must have discontinued EIAED therapy for at least two weeks prior to starting study drug. Non-enzyme inducing anti-epileptic medication is allowed, except those listed in the protocol

Participant Flow Table

Stage II (Concomitant + Adjuvant phase)

Patient disposition for all patients in the Concomitant + Adjuvant phase by buparlisib dose sequence (Full analysis set)

Phase: Concomitant + Adjuvant	Buparlisib 40 mg/d	Buparlisib 60 mg/d	Buparlisib 40i mg/d	All patients
	N=5	N=6	N = 5	N=16
Disposition Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients treated				
End of treatment	5 (100)	6 (100)	5 (100)	16 (100)
Primary reason for end of treatment				
Adverse Event(s)	3 (60.0)	6 (100)	2 (40.0)	11 (68.8)
Administrative problems	0	0	2 (40.0)	2 (12.5)
Disease progression	2 (40.0)	0	1 (20.0)	3 (18.8)
Study evaluation after end of treatment				
Patients no longer being followed for study evaluation	5 (100)	6 (100)	5 (100)	16 (100)
Primary reason for study evaluation completion				
Adverse Events	0	0	0	0
Subject withdrew consent	0	1 (16.7)	0	1 (6.3)
Administrative problems	0	0	2 (40.0)	2 (12.5)
Death[1]	0	1 (16.7)	0	1 (6.3)
Disease progression	5 (100)	3 (50.0)	2 (40.0)	10 (62.5)
Follow-up phase completed as per protocol[2]	0	1 (16.7)	1 (20.0)	2 (12.5)

Buparlisib Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i"
Percentage is based on N.
[1] One patient in the 60 mg/d dose level died 75 days after the last date of study treatment due to the study indication (glioblastoma).
[2] Completion of imaging follow-up of 18 months post first dose of buparlisib for patients who discontinued from study treatment due to the reasons other than disease progression, starting another antineoplastic therapy, or death.

Stage I (Adjuvant phase only)

Patient disposition for all patients in the Adjuvant phase by buparlisib dose sequence (Full analysis set)

Phase: Adjuvant	Buparlisib 80/60 mg/d	Buparlisib 80/80 mg/d	Buparlisib 80/ND mg/d	All patients
	N=5	N=15	N=2	N=22
Disposition Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients treated				
End of treatment	5 (100)	15 (100)	2 (100)	22 (100)
Primary reason for end of treatment				
Adverse Event(s)	2 (40.0)	3 (20.0)	2 (100)	7 (31.8)
Administrative problems	0	2 (13.3)	0	2 (9.1)
Disease progression	3 (60.0)	10 (66.7)	0	13 (59.1)
Study evaluation after end of treatment				
Patients no longer being followed for study evaluation	5 (100)	15 (100)	2 (100)	22 (100)
Primary reason for study evaluation completion				
Adverse Events	1 (20.0)	0	0	1 (4.5)
Subject withdrew consent	0	1 (6.7)	0	1 (4.5)
Administrative problems	0	2 (13.3)	0	2 (9.1)
Death[1]	0	1 (6.7)	1 (50.0)	2 (9.1)
Disease progression	4 (80.0)	11 (73.3)	1 (50.0)	16 (72.7)
Follow-up phase completed as per protocol[2]	0	0	0	0

"ND" indicates no buparlisib dose was administered in that phase
Percentage is based on N.
[1] One patient in the 80/80 mg/d dose level died 112 days after the last date of study treatment and one patient in the 80/ND mg/d dose level died 157 days after the last date of study treatment; both patients died due to the study indication (glioblastoma).
[2] Completion of imaging follow-up of 18 months post first dose of buparlisib for patients who discontinued from study treatment due to the reasons other than disease progression, starting another antineoplastic therapy, or death.

Baseline Characteristics
Stage II (Concomitant + Adjuvant phase)

Demographics at Baseline, for all patients in the Concomitant + Adjuvant phase by buparlisib dose sequence (Full analysis set)

Demographic Variable	BKM120 40 mg/d N=5 n (%)	BKM120 60 mg/d N=6 n (%)	BKM120 40i mg/d N=5 n (%)
Age (Years)			
n	5	6	5
Mean	46.4	56.7	48.6
SD	11.08	14.71	7.80
Median	43.0	59.5	46.0
Minimum	33	32	40
Maximum	61	71	61
Age category (Years) - n (%)			
<65	5 (100)	3 (50.0)	5 (100)
≥ 65	0	3 (50.0)	0
Sex-n (%)			
Female	2 (40.0)	1 (16.7)	3 (60.0)
Male	3 (60.0)	5 (83.3)	2 (40.0)
Race-n (%)			
Caucasian	5 (100)	5 (83.3)	5 (100)
Asian	0	1 (16.7)	0
Ethnicity-n (%)			
Hispanic/Latino	1 (20.0)	1 (16.7)	1 (20.0)
Indian (Indian subcontinent)	0	1 (16.7)	0
Mixed ethnicity	1 (20.0)	0	0
Other	3 (60.0)	4 (66.7)	4 (80.0)

Demographic Variable	BKM120 40 mg/d N=5 n (%)	BKM120 60 mg/d N=6 n (%)	BKM120 40i mg/d N=5 n (%)
Body surface area (m^2)			
n	5	6	5
Mean	2.0	2.0	1.9
SD	0.12	0.22	0.25
Median	2.0	2.0	1.9
Minimum	2	2	2
Maximum	2	2	2
Body mass index (kg/m^2)			
n	5	6	5
Mean	27.6	28.6	27.5
SD	4.46	6.61	5.75
Median	28.0	28.7	29.4
Minimum	23	21	20
Maximum	32	39	34
Karnofsky performance status-n (%)			
100	3 (60.0)	3 (50.0)	2 (40.0)
90	2 (40.0)	1 (16.7)	3 (60.0)
80	0	2 (33.3)	0
70	0	0	0

Stage I (Adjuvant phase)

Demographics at Baseline, for all patients in the Adjuvant phase by buparlisib dose sequence (Full analysis set)

Demographic Variable	BKM120 80/60 mg/d N=5 n (%)	BKM120 80/80 mg/d N=15 n (%)	BKM120 80/ND mg/d N=2 n (%)
Age (Years)			
n	5	15	2
Mean	58.8	58.9	61.5
SD	9.20	7.73	3.54
Median	56.0	63.0	61.5
Minimum	49	50	59
Maximum	72	68	64
Age category (Years) - n (%)			
<65	4 (80.0)	10 (66.7)	2 (100)
≥ 65	1 (20.0)	5 (33.3)	0
Sex-n (%)			
Female	2 (40.0)	2 (13.3)	1 (50.0)
Male	3 (60.0)	13 (86.7)	1 (50.0)
Race-n (%)			
Caucasian	5 (100)	15 (100)	2 (100)
Asian	0	0	0
Ethnicity-n (%)			
Hispanic/Latino	1 (20.0)	2 (13.3)	1 (50.0)
Indian (Indian subcontinent)	0	0	0
Mixed ethnicity	0	0	0
Other	4 (80.0)	13 (86.7)	1 (50.0)

Demographic Variable	BKM120 80/60 mg/d N=5 n (%)	BKM120 80/80 mg/d N=15 n (%)	BKM120 80/ND mg/d N=2 n (%)
Body surface area (m^2)			
n	5	15	2
Mean	1.7	2.0	1.9
SD	0.27	0.23	0.28
Median	1.8	2.1	1.9
Minimum	1	2	2
Maximum	2	2	2
Body mass index (kg/m^2)			
n	5	15	2
Mean	26.0	27.2	27.4
SD	5.08	3.89	0.28
Median	26.9	26.5	27.4
Minimum	18	20	27
Maximum	31	34	28
Karnofsky performance status-n (%)			
100	1 (20.0)	4 (26.7)	0
90	3 (60.0)	5 (33.3)	0
80	0	6 (40.0)	2 (100)
70	1 (20.0)	0	0

Weight and height are taken from any vital signs evaluation performed on or before the first day of treatment.
BSA: Body surface area is calculated using the Mosteller formula.
BSA (m^2) = sqrt(wt(kg)×ht(cm)/3600).
BMI (kg/m^2) = weight(kg)/(height(m)^2).
BSA and BMI are calculated based on raw data assessments.

Stage I (Adjuvant phase) + Stage II (Concomitant + Adjuvant Phase)

Demographics at Baseline, for all patients by buparlisib study phase (Full analysis set)

Demographic Variable	Concomitant + Adjuvant Phase C/A1/A2 N=16 n (%)	Adjuvant Phase A1/A2 N=22 n (%)	All Patients N=38 n (%)
Age (Years)			
n	16	22	38
Mean	50.9	59.1	55.7
SD	11.95	7.56	10.35
Median	50.5	61.0	53.5
Minimum	32	49	32
Maximum	71	72	72
Age category (Years) - n (%)			
<65	13 (81.3)	16 (72.7)	29 (76.3)
≥ 65	3 (18.8)	6 (27.3)	9 (23.7)
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)	37 (97.4)
Asian	1 (6.3)	0	1 (2.6)
Ethnicity-n (%)			
Hispanic/Latino	3 (18.8)	4 (18.2)	7 (18.4)
Indian (Indian subcontinent)	1 (6.3)	0	1 (2.6)
Mixed ethnicity	1 (6.3)	0	1 (2.6)

Demographic Variable	Concomitant + Adjuvant Phase C/A1/A2 N=16 n (%)	Adjuvant Phase A1/A2 N=22 n (%)	All Patients N=38 n (%)
Other	11 (68.8)	18 (81.8)	29 (76.3)
Body surface area (m^2)			
n	16	22	38
Mean	2.0	2.0	2.0
SD	0.21	0.26	0.24
Median	2.0	2.0	2.0
Minimum	2	1	1
Maximum	2	2	2
Body mass index (kg/m^2)			
n	16	22	38
Mean	28.0	26.9	27.4
SD	5.39	3.92	4.55
Median	28.7	27.1	27.2
Minimum	20	18	18
Maximum	39	34	39
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)

Weight and height are taken from any vital signs evaluation performed on or before the first day of treatment.
BSA: Body surface area is calculated using the Mosteller formula.
BSA (m^2) = sqrt(wt(kg)×ht(cm)/3600).
BMI (kg/m^2) = weight(kg)/(height(m)^2).
BSA and BMI are calculated based on raw data assessments.

Summary of Efficacy

Primary Outcome Result(s)

Determination of maximum tolerated dose

Summary of posterior distribution of DLT rates at time of MTD confirmation, Concomitant phase (Dose determining set)

	Posterior probabilities that Pr(DLT) is in interval							
Buparlisib Intermittent dose (mg/day)	**Under-dosing [0.0,0.16)**	**Targeted toxicity [0.16,0.35)**	**Excessive toxicity [0.35,1.0]**	**Quantiles**				
				Mean	**SD**	**2.50%**	**50.00%**	**97.50%**
Buparlisib=0	0.493	0.422	0.085	0.176	0.115	0.009	0.162	0.428
Buparlisib =40	0.133	0.685	0.182	0.263	0.095	0.106	0.254	0.473
Buparlisib =60	0.061	0.655	0.284	0.298	0.097	0.133	0.291	0.508
Buparlisib =80	0.027	0.560	0.413	0.334	0.101	0.158	0.327	0.546

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, in the 42-day concomitant phase and up to 21 days following the last administrations of buparlisib or completion of cranial irradiation, whichever date is later; if a full course of cranial irradiation cannot be completed, the evaluation period for DLTs will end 21 days following the final date of radiation therapy.

Summary of posterior distribution of DLT rates at time of MTD confirmation, Adjuvant phase cycle 1 (Dose determining set)

	Posterior probabilities that Pr(DLT) is in interval							
Buparlisib	**Under-dosing**	**Targeted toxicity**	**Excessive toxicity**			**Quantiles**		
Dose (mg/day)	**[0.0,0.16)**	**[0.16,0.35)**	**[0.35,1.0]**	**Mean**	**SD**	**2.50%**	**50.00%**	**97.50%**
Buparlisib=0	0.983	0.016	0.000	0.053	0.035	0.012	0.043	0.145
Buparlisib =20	0.975	0.025	0.000	0.068	0.037	0.019	0.060	0.160
Buparlisib =40	0.940	0.060	0.000	0.089	0.040	0.029	0.082	0.185
Buparlisib =60	0.820	0.180	0.000	0.118	0.047	0.046	0.112	0.227
Buparlisib =80	0.558	0.435	0.007	0.159	0.064	0.059	0.150	0.304
Buparlisib =100	0.358	0.557	0.085	0.208	0.097	0.064	0.193	0.433

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, during the entire 28 days of Cycle 1 in adjuvant phase.

Summary of posterior distribution of DLT rates at time of MTD confirmation, Adjuvant phase cycle 2 (Dose determining set)

	Posterior probabilities that Pr(DLT) is in interval							
Buparlisib dose (mg/day)	**Under-dosing [0.0,0.16)**	**Targeted toxicity [0.16,0.35)**	**Excessive toxicity [0.35,1.0]**	**Mean**	**SD**	**Quantiles 2.50%**	**50.00%**	**97.50%**
Buparlisib=0	0.937	0.059	0.004	0.066	0.057	0.011	0.050	0.218
Buparlisib=20	0.581	0.401	0.018	0.157	0.076	0.042	0.144	0.333
Buparlisib =40	0.366	0.606	0.028	0.192	0.073	0.074	0.184	0.354
Buparlisib =60	0.189	0.737	0.074	0.230	0.077	0.104	0.222	0.398
Buparlisib =80	0.114	0.680	0.207	0.272	0.095	0.113	0.263	0.479
Buparlisib =100	0.098	0.537	0.365	0.315	0.126	0.108	0.303	0.591

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, during the entire 28 days of Cycle 2 in the adjuvant phase.

Dose-limiting toxicities by primary system organ class, preferred term and study phase and BKM120 dose sequence (Dose determining set)

Stage II (Concomitant + Adjuvant phase)

Phase: Concomitant+Adjuvant

Primary system organ class Preferred term	BKM120 40 mg/d N=5 n (%)	BKM120 60 mg/d N=5 n (%)	BKM120 40i mg/d N=5 n (%)	All patients N=15 n (%)
-Any primary system organ class				
-Total	4 (80.0)	3 (60.0)	2 (40.0)	9 (60.0)
Blood and lymphatic system disorders				
-Total	1 (20.0)	3 (60.0)	0	4 (26.7)
Thrombocytopenia	1 (20.0)	3 (60.0)	0	4 (26.7)
Investigations				
-Total	2 (40.0)	0	1 (20.0)	3 (20.0)
Lipase increased	2 (40.0)	0	0	2 (13.3)
Platelet count decreased	0	0	1 (20.0)	1 (6.7)
Metabolism and nutrition disorders				

Phase: Concomitant+Adjuvant

Primary system organ class Preferred term	BKM120 40 mg/d N=5 n (%)	BKM120 60 mg/d N=5 n (%)	BKM120 40i mg/d N=5 n (%)	All patients N=15 n (%)
-Total	1 (20.0)	0	0	1 (6.7)
Hyperglycaemia	1 (20.0)	0	0	1 (6.7)
Psychiatric disorders				
-Total	0	0	1 (20.0)	1 (6.7)
Mood altered	0	0	1 (20.0)	1 (6.7)

- BKM Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i"; "ND" indicates no BKM120 dose was administered in that phase.
- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All patients' column.
- A patient with multiple occurrences of an DLTs under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

Dose-limiting toxicities by primary system organ class, preferred term and study phase and BKM120 dose sequence (Dose determining set)

Stage I (Adjuvant phase only)

Phase: Adjuvant

Primary system organ class Preferred term	BKM120 80/60 mg/d N=5 n (%)	BKM120 80/80 mg/d N=15 n (%)	BKM120 80/ND mg/d N=2 n (%)	All patients N=22 n (%)
-Any primary system organ class				
-Total	1 (20.0)	3 (20.0)	2 (100)	6 (27.3)
Blood and lymphatic system disorders				
-Total	0	1 (6.7)	0	1 (4.5)
Thrombocytopenia	0	1 (6.7)	0	1 (4.5)
Investigations				
-Total	0	1 (6.7)	0	1 (4.5)
Blood glucose increased	0	1 (6.7)	0	1 (4.5)
Metabolism and nutrition disorders				
-Total	1 (20.0)	0	0	1 (4.5)

Phase: Adjuvant

Primary system organ class Preferred term	BKM120 80/60 mg/d N=5 n (%)	BKM120 80/80 mg/d N=15 n (%)	BKM120 80/ND mg/d N=2 n (%)	All patients N=22 n (%)
Hyperglycaemia	1 (20.0)	0	0	1 (4.5)
Psychiatric disorders				
-Total	0	1 (6.7)	2 (100)	3 (13.6)
Anxiety	0	0	1 (50.0)	1 (4.5)
Confusional state	0	0	1 (50.0)	1 (4.5)
Depression	0	1 (6.7)	0	1 (4.5)
Mood altered	0	1 (6.7)	0	1 (4.5)

- BKM Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i"; "ND" indicates no BKM120 dose was administered in that phase.
- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All patients' column.
- A patient with multiple occurrences of an DLTs under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

Secondary Outcome Result(s)

Overall response rate

Stage II (Concomitant + Adjuvant phase)

Best overall response summary as per Investigator review, using RANO criteria, in the Concomitant + Adjuvant phase by buparlisib dose sequence (Full Analysis Set)

Phase: Concomitant + Adjuvant

	Buparlisib 40 mg/d N=5		Buparlisib 60 mg/d N=6		Buparlisib 40i mg/d N=5		All patients N=16	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients without disease at baseline*	1 (20.0)		0		3 (60.0)		4 (25.0)	
Patients with measurable disease at baseline	3 (60.0)		4 (66.7)		1 (20.0)		8 (50.0)	
Patients with non-measurable disease only at baseline (non-measurable enhancing lesion T1, and/or nonenhancing T2/FLAIR lesion only)	1 (20.0)		2 (33.3)		1 (20.0)		4 (25.0)	
Best overall response								
Complete Response (CR)	1 (20.0)		0		0		1 (6.3)	
Partial Response (PR)	0		0		1 (20.0)		1 (6.3)	
Stable Disease (SD)	2 (40.0)		6 (100)		1 (20.0)		9 (56.3)	
Progressive Disease (PD)	1 (20.0)		0		1 (20.0)		2 (12.5)	
Non-evaluable[1]	0		0		2 (40.0)		2 (12.5)	
Unknown	1 (20.0)		0		0		1 (6.3)	
Overall Response Rate (ORR: CR+PR)	1 (20.0)	(0.5 - 71.6)	0		1 (20.0)	(0.5 - 71.6)	2 (12.5)	(1.6 - 38.3)

Buparlisib Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i";
N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using exact binomial 95% confidence interval.*Patients who underwent complete resection of the tumor.
[1] The patients who had no disease at baseline, are reported as “non-evaluable” if they didn’t experience disease progression. Their responses were recorded as “UNK” in the eCRF if no PD.

Stage I (Adjuvant phase only)

Best overall response summary as per Investigator review, using RANO criteria, in the Adjuvant phase by buparlisib dose sequence (Full Analysis Set)

Phase: Adjuvant

	Buparlisib 80/60 mg/d N=5		Buparlisib 80/80 mg/d N=15		Buparlisib 80/ND mg/d N=2		All patients N=22	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients without disease at baseline*	0		1 (6.7)		0		1 (4.5)	
Patients with measurable disease at baseline	3 (60.0)		12 (80.0)		2 (100.0)		17 (77.3)	
Patients with non-measurable disease only at baseline (non-measurable enhancing lesion T1, and/or nonenhancing T2/FLAIR lesion only)	2 (40.0)		2 (13.3)		0		4 (18.2)	
Best overall response								
Complete Response (CR)	0		0		0		0	
Partial Response (PR)	0		0		0		0	
Stable Disease (SD)	4 (80.0)		12 (80.0)		2 (100)		18 (81.8)	
Progressive Disease (PD)	1 (20.0)		2 (13.3)		0		3 (13.6)	
Non-evaluable[1]	0		1 (6.7)		0		1 (4.5)	
Unknown	0		0		0		0	
Overall Response Rate (ORR: CR+PR)	0		0		0		0	

"ND" indicates no buparlisib dose was administered in that phase.
N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using exact binomial 95% confidence interval.*Patients who underwent complete resection of the tumor.
[1] The patients who had no disease at baseline, are reported as “non-evaluable”, if they didn’t experience disease progression. Their responses were recorded as “UNK” in the eCRF if no PD.

Summary of Safety

Safety Results

Stage II (Concomitant + Adjuvant phase)

All and grade 3/4 adverse events regardless of study treatment relationship by system organ class in the Concomitant + Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Concomitant+Adjuvant

	Buparlisib 40 mg/d N=5		Buparlisib 60 mg/d N=6		Buparlisib 40i mg/d N=5		All patients N=16	
Primary System organ class	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Total	5(100)	4(80.0)	6(100)	6(100)	5(100)	5(100)	16(100)	15(93.8)
Blood and lymphatic system disorders	1(20.0)	1(20.0)	4(66.7)	3(50.0)	2(40.0)	2(40.0)	7(43.8)	6(37.5)
Cardiac disorders	1(20.0)	0	0	0	1(20.0)	0	2(12.5)	0
Ear and labyrinth disorders	1(20.0)	0	0	0	2(40.0)	0	3(18.8)	0
Eye disorders	1(20.0)	0	1(16.7)	0	1(20.0)	0	3(18.8)	0
Gastrointestinal disorders	4(80.0)	0	5(83.3)	0	4(80.0)	0	13(81.3)	0
General disorders and administration site conditions	4(80.0)	0	6(100)	0	5(100)	1(20.0)	15(93.8)	1(6.3)
Infections and infestations	0	0	2(33.3)	0	4(80.0)	2(40.0)	6(37.5)	2(12.5)
Injury, poisoning and procedural complications	1(20.0)	0	1(16.7)	0	2(40.0)	0	4(25.0)	0
Investigations	5(100)	3(60.0)	5(83.3)	3(50.0)	4(80.0)	4(80.0)	14(87.5)	10(62.5)
Metabolism and nutrition disorders	2(40.0)	1(20.0)	5(83.3)	1(16.7)	3(60.0)	0	10(62.5)	2(12.5)
Musculoskeletal and connective tissue disorders	1(20.0)	0	2(33.3)	0	0	0	3(18.8)	0
Nervous system disorders	2(40.0)	0	6(100)	2(33.3)	3(60.0)	0	11(68.8)	2(12.5)
Psychiatric disorders	3(60.0)	0	4(66.7)	2(33.3)	3(60.0)	1(20.0)	10(62.5)	3(18.8)
Renal and urinary disorders	0	0	0	0	1(20.0)	0	1(6.3)	0

Phase: Concomitant+Adjuvant								
	Buparlisib 40 mg/d N=5		Buparlisib 60 mg/d N=6		Buparlisib 40i mg/d N=5		All patients N=16	
Primary System organ class	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Respiratory, thoracic and mediastinal disorders	2(40.0)	0	2(33.3)	1(16.7)	2(40.0)	0	6(37.5)	1(6.3)
Skin and subcutaneous tissue disorders	3(60.0)	0	3(50.0)	0	5(100)	1(20.0)	11(68.8)	1(6.3)

Buparlisib Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i";
Primary system organ classes are presented alphabetically
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.
MedDRA Version 20.0 has been used for the reporting.

Stage I (Adjuvant phase only)

All and grade 3/4 adverse events regardless of study treatment relationship by system organ class in the Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Adjuvant								
	Buparlisib 80/60 mg/d N=5		Buparlisib 80/80 mg/d N=15		Buparlisib 80/ND mg/d N=2		All patients N=22	
Primary System organ Class	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	5(100)	4(80.0)	15(100)	11(73.3)	2(100)	2(100)	22(100)	17(77.3)
Blood and lymphatic system disorders	2(40.0)	2(40.0)	6(40.0)	3(20.0)	0	0	8(36.4)	5(22.7)
Ear and labyrinth disorders	0	0	3(20.0)	0	0	0	3(13.6)	0
Eye disorders	0	0	3(20.0)	0	0	0	3(13.6)	0
Gastrointestinal disorders	5(100)	0	14(93.3)	0	2(100)	0	21(95.5)	0
General disorders and administration site conditions	3(60.0)	0	14(93.3)	2(13.3)	2(100)	1(50.0)	19(86.4)	3(13.6)
Infections and infestations	1(20.0)	1(20.0)	7(46.7)	0	1(50.0)	1(50.0)	9(40.9)	2(9.1)

Phase: Adjuvant

Primary System organ Class	Buparlisib 80/60 mg/d N=5		Buparlisib 80/80 mg/d N=15		Buparlisib 80/ND mg/d N=2		All patients N=22	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Injury, poisoning and procedural complications	0	0	6(40.0)	0	0	0	6(27.3)	0
Investigations	1(20.0)	1(20.0)	10(66.7)	4(26.7)	1(50.0)	0	12(54.5)	5(22.7)
Metabolism and nutrition disorders	3(60.0)	3(60.0)	13(86.7)	2(13.3)	0	0	16(72.7)	5(22.7)
Musculoskeletal and connective tissue disorders	2(40.0)	0	7(46.7)	0	1(50.0)	0	10(45.5)	0
Nervous system disorders	4(80.0)	2(40.0)	13(86.7)	5(33.3)	2(100)	0	19(86.4)	7(31.8)
Psychiatric disorders	3(60.0)	0	12(80.0)	3(20.0)	2(100)	2(100)	17(77.3)	5(22.7)
Renal and urinary disorders	1(20.0)	0	3(20.0)	1(6.7)	0	0	4(18.2)	1(4.5)
Respiratory, thoracic and mediastinal disorders	0	0	4(26.7)	0	0	0	4(18.2)	0
Skin and subcutaneous tissue disorders	3(60.0)	0	7(46.7)	1(6.7)	1(50.0)	0	11(50.0)	1(4.5)
Vascular disorders	0	0	4(26.7)	0	0	0	4(18.2)	0

"ND" indicates no buparlisib dose was administered in that phase.
Primary system organ classes are presented alphabetically
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.
MedDRA Version 20.0 has been used for the reporting.

Stage II (Concomitant + Adjuvant phase)

All and grade 3/4 adverse events regardless of study treatment relationship with at least 20% incidence by preferred term in the Concomitant + Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Concomitant + Adjuvant

	Buparlisib 40 mg/d N=5		Buparlisib 60 mg/d N=6		Buparlisib 40i mg/d N=5		All patients N=16	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4

Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	5 (100)	4 (80.0)	6 (100)	6 (100)	5 (100)	5 (100)	16 (100)	15 (93.8)
Fatigue	2 (40.0)	0	3 (50.0)	0	4 (80.0)	1 (20.0)	9 (56.3)	1 (6.3)
Nausea	4 (80.0)	0	2 (33.3)	0	3 (60.0)	0	9 (56.3)	0
Alopecia	2 (40.0)	0	1 (16.7)	0	3 (60.0)	0	6 (37.5)	0
Anxiety	1 (20.0)	0	3 (50.0)	1 (16.7)	2 (40.0)	0	6 (37.5)	1 (6.3)
Decreased appetite	1 (20.0)	0	3 (50.0)	0	2 (40.0)	0	6 (37.5)	0
Depression	3 (60.0)	0	2 (33.3)	0	1 (20.0)	0	6 (37.5)	0
Lymphocyte count decreased	0	0	2 (33.3)	2 (33.3)	4 (80.0)	3 (60.0)	6 (37.5)	5 (31.3)
Thrombocytopenia	1 (20.0)	1 (20.0)	4 (66.7)	3 (50.0)	1 (20.0)	1 (20.0)	6 (37.5)	5 (31.3)
Blood bilirubin increased	2 (40.0)	0	1 (16.7)	0	2 (40.0)	0	5 (31.3)	0
Hyperglycaemia	2 (40.0)	1 (20.0)	3 (50.0)	1 (16.7)	0	0	5 (31.3)	2 (12.5)
Neutrophil count decreased	1 (20.0)	1 (20.0)	2 (33.3)	2 (33.3)	2 (40.0)	2 (40.0)	5 (31.3)	5 (31.3)
Alanine aminotransferase increased	0	0	2 (33.3)	1 (16.7)	2 (40.0)	0	4 (25.0)	1 (6.3)
Amylase increased	2 (40.0)	2 (40.0)	0	0	2 (40.0)	0	4 (25.0)	2 (12.5)
Aspartate aminotransferase increased	1 (20.0)	0	2 (33.3)	1 (16.7)	1 (20.0)	0	4 (25.0)	1 (6.3)
Asthenia	2 (40.0)	0	1 (16.7)	0	1 (20.0)	0	4 (25.0)	0
Constipation	0	0	3 (50.0)	0	1 (20.0)	0	4 (25.0)	0
Diarrhoea	1 (20.0)	0	1 (16.7)	0	2 (40.0)	0	4 (25.0)	0
Dry skin	1 (20.0)	0	1 (16.7)	0	2 (40.0)	0	4 (25.0)	0
Headache	1 (20.0)	0	1 (16.7)	0	2 (40.0)	0	4 (25.0)	0
Platelet count decreased	0	0	0	0	4 (80.0)	1 (20.0)	4 (25.0)	1 (6.3)
Rash	1 (20.0)	0	2 (33.3)	0	1 (20.0)	0	4 (25.0)	0
Vomiting	1 (20.0)	0	2 (33.3)	0	1 (20.0)	0	4 (25.0)	0

Buparlisib Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i";
Preferred terms are sorted in descending frequency, as reported in the 'All grades' under the ‘All patients’ column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.
MedDRA Version 20.0 has been used for the reporting.

Stage I (Adjuvant phase only)

All and grade 3/4 adverse events regardless of study treatment relationship with at least 20% incidence by preferred term in the Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Adjuvant

	Buparlisib 80/60 mg/d N=5		Buparlisib 80/80 mg/d N=15		Buparlisib 80/ND mg/d N=2		All patients N=22	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Total	5 (100)	4 (80.0)	15 (100)	11 (73.3)	2 (100)	2 (100)	22 (100)	17 (77.3)
Nausea	4 (80.0)	0	11 (73.3)	0	1 (50.0)	0	16 (72.7)	0
Fatigue	2 (40.0)	0	11 (73.3)	0	0	0	13 (59.1)	0
Hyperglycaemia	2 (40.0)	2 (40.0)	9 (60.0)	2 (13.3)	0	0	11 (50.0)	4 (18.2)
Decreased appetite	0	0	9 (60.0)	0	0	0	9 (40.9)	0
Vomiting	2 (40.0)	0	6 (40.0)	0	1 (50.0)	0	9 (40.9)	0
Constipation	1 (20.0)	0	6 (40.0)	0	1 (50.0)	0	8 (36.4)	0
Platelet count decreased	1 (20.0)	0	7 (46.7)	3 (20.0)	0	0	8 (36.4)	3 (13.6)
Thrombocytopenia	2 (40.0)	2 (40.0)	6 (40.0)	2 (13.3)	0	0	8 (36.4)	4 (18.2)
Anxiety	2 (40.0)	0	4 (26.7)	0	1 (50.0)	1 (50.0)	7 (31.8)	1 (4.5)
Asthenia	1 (20.0)	0	4 (26.7)	1 (6.7)	2 (100)	1 (50.0)	7 (31.8)	2 (9.1)
Headache	0	0	7 (46.7)	0	0	0	7 (31.8)	0
Cognitive disorder	1 (20.0)	1 (20.0)	4 (26.7)	2 (13.3)	1 (50.0)	0	6 (27.3)	3 (13.6)
Gait disturbance	0	0	6 (40.0)	1 (6.7)	0	0	6 (27.3)	1 (4.5)
Muscular weakness	1 (20.0)	0	4 (26.7)	0	1 (50.0)	0	6 (27.3)	0
Weight decreased	0	0	6 (40.0)	0	0	0	6 (27.3)	0
Aphasia	2 (40.0)	1 (20.0)	3 (20.0)	1 (6.7)	0	0	5 (22.7)	2 (9.1)
Confusional state	0	0	4 (26.7)	2 (13.3)	1 (50.0)	1 (50.0)	5 (22.7)	3 (13.6)
Depression	1 (20.0)	0	4 (26.7)	1 (6.7)	0	0	5 (22.7)	1 (4.5)
Dizziness	1 (20.0)	0	3 (20.0)	0	1 (50.0)	0	5 (22.7)	0

Phase: Adjuvant

	Buparlisib 80/60 mg/d N=5		Buparlisib 80/80 mg/d N=15		Buparlisib 80/ND mg/d N=2		All patients N=22	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Insomnia	0	0	4 (26.7)	0	1 (50.0)	0	5 (22.7)	0
Lymphocyte count decreased	0	0	5 (33.3)	2 (13.3)	0	0	5 (22.7)	2 (9.1)
Memory impairment	0	0	5 (33.3)	0	0	0	5 (22.7)	0
Rash	1 (20.0)	0	4 (26.7)	0	0	0	5 (22.7)	0

"ND" indicates no Buparlisib dose was administered in that phase.
Preferred terms are sorted in descending frequency, as reported in the 'All grades' under the ‘All patients’ column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.
MedDRA Version 20.0 has been used for the reporting.

Stage II (Concomitant + Adjuvant phase)

All deaths reported in the Concomitant + Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Concomitant +Adjuvant				
	Buparlisib 40 mg/d	Buparlisib 60 mg/d	Buparlisib 40i mg/d	All patients
Primary system organ class	N=5	N=6	N=5	N=16
Principal cause of death	n (%)	n (%)	n (%)	n (%)
Any primary system organ class				
Total	3 (60.0)	4 (66.7)	1 (20.0)	8 (50.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total	3 (60.0)	4 (66.7)	1 (20.0)	8 (50.0)
Glioblastoma	3 (60.0)	4 (66.7)	1 (20.0)	8 (50.0)

Buparlisib Dose Sequence: Intermittent dosing is presented by the dose level and suffix "i";
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the 'All patients' column.
All deaths during the study are included.

Stage I (Adjuvant phase only)

All deaths reported in the Adjuvant phase by buparlisib dose sequence (Safety set)

Phase: Adjuvant

Primary system organ class Principal cause of death	Buparlisib 80/60 mg/d N=5 n (%)	Buparlisib 80/80 mg/d N=15 n (%)	Buparlisib 80/ND mg/d N=2 n (%)	All patients N=22 n (%)
Any primary system organ class				
Total	5 (100)	13 (86.7)	2 (100)	20 (90.9)
Injury, poisoning and procedural complications				
Total	0	1 (6.7)	0	1 (4.5)
Respiratory fume inhalation disorder	0	1 (6.7)	0	1 (4.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total	5 (100)	12 (80.0)	2 (100)	19 (86.4)
Glioblastoma	5 (100)	12 (80.0)	2 (100)	19 (86.4)

"ND" indicates no buparlisib dose was administered in that phase.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the ‘All patients’ column.
All deaths during the study are included.

Other Relevant Findings

None

Conclusion:

The study did not meet its primary objective; the MTD for buparlisib in combination with temozolomide and radiotherapy in the Concomitant + Adjuvant phase was not achieved. The maximum explored dose was 60 mg/d in the Concomitant phase. This was not possible due to the observed DLT with all schedules and doses investigated in addition to the challenging safety profile of buparlisib in combination with temozolomide and radiotherapy. This resulted in low number of patient in the A1 and A2 parts of Stage II as well by the short duration of exposure at Stage II compared to Stage I. The tolerable dose for buparlisib in combination with temozolomide in Stage I (Adjuvant phase only) of the study was determined as 80 mg/d.

Overall, safety profile of buparlisib is challenging yet manageable; no new or unexpected findings were reported in this study. Considering the primary objective of estimating the MTD not being achieved; in addition the observed safety profile of buparlisib in combination with radiotherapy and temozolomide leading to high rate of study treatment discontinuation due to AEs which contributed to short duration of treatment at Stage II. This may have contributed to non-promising tumor activity. Accordingly, Novartis decided not to pursue the development of buparlisib in newly diagnosed GBM indication.

Date of Clinical Trial Report

28-Nov-2017