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Sponsor

Novartis

Generic Drug Name

Buparlisib

Trial Indication(s)

Recurrent glioblastoma multiforme (GBM)

Protocol Number

CBKM120E2102; EudraCT no. 2013-003129-27

Protocol Title

A Phase Ib/II multicenter study of buparlisib plus carboplatin or lomustine in patients with recurrent glioblastoma multiforme (GBM)

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase Ib/II

Study Start/End Dates

28-Feb-2014 to 07-Jul-2016

Reason for Termination

Not Applicable

Study Design/Methodology

This study was a two-part, multi-center, Phase Ib/Phase II study in patients with recurrent GBM pre treated with radiotherapy (RT) and temozolomide（TMZ) standard of care (SoC).

Phase Ib (Dose-escalation part)

Phase Ib part of the study was designed to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of oral 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. It was planned to enroll 15 to 22 patients per treatment arm during the phase Ib.

Only buparlisib doses were escalated during the Phase Ib part of study. For the first cohort, the starting dose of buparlisib was at 80 mg once daily in combination with carboplatin given at a fixed dose of AUC=5 every 3 weeks and was 60 mg once daily in combination with lomustine at a fixed dose of 100 mg/m² every 6 weeks. The buparlisib dose was to be adjusted in each arm for the later cohorts following the recommendation of an adaptive BLRM for dose escalation with overdose control (EWOC) until MTD/RP2D was defined.

Phase II

A preliminary assessment for both combinations (buparlisib plus carboplatin or lomustine) demonstrated that there was not enough antitumor activity compared to historical data with single agent carboplatin or lomustine. Based on the overall safety profile, and preliminary anti-tumor activity observed in this study, Novartis decided that no additional patients will be enrolled into this study. As a consequence, the Phase II part of the study was not conducted.

Centers

Twelve centers in 6 countries: Belgium (1), France (3), Canada (1), Australia (2), USA (3), Spain (2).

Objectives:

Primary objective:

Primary objective was to determine the maximum tolerate dose (MTD) and/or RP2D of buparlisib plus carboplatin/lomustine in patients with recurrent GBM who have progressed after SoC (RT with TMZ in combination and adjuvant) regardless of PI3K pathway activation status.

Secondary objective:

To assess safety and tolerability of buparlisib plus carboplatin/lomustine combinations, to assess preliminary anti-tumor activity of buparlisib plus carboplatin/lomustine combinations in patients with recurrent GBM who have progressed after SoC regardless of PI3K pathway activation status.

Test Product, Dose, and Mode of Administration

The investigational drug used was buparlisib. The commercially available drugs carboplatin or lomustine were used in combination with buparlisib. Novartis Drug Supply Management or its designee provided buparlisib as 10 mg and 50 mg hard gelatin capsules in bottles packaged as individual patient supply. Carboplatin and lomustine were supplied as the commercially available drug, including generic formulations in each participating country.

Statistical Methods

Determination of the MTD/RP2D of each combination treatment was based on a synthesis of all relevant data available from all dose levels evaluated during the study including safety information, DLTs, all common terminology criteria for adverse events (CTCAE) grade ≥ 2 toxicity data during Cycle 1 from evaluable patients. The recommended dose for the next cohort of subjects was guided by the adaptive 5-parameter BLRM with overdose control (EWOC) principle.

The MTD is the dose with the highest probability of being in the targeted toxicity range (e.g. DLT rate between 16%-35%) among the doses fulfilling the overdose criteria (e.g. less than 25% chance of excessive toxicity). The use of EWOC principles limits the risk that a potential dose will exceed the MTD.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Adult patients ≥ 18 years with recurrent GBM previously treated with RT and TMZ.
- Patient had at least one measurable and/or non-measurable lesion as per response assessment in neuro-oncology (RANO) criteria.
- Patient had recovered (to Grade ≤1) from all clinically significant toxicities related to prior antineoplastic therapies.
- Patient had Karnofsky performance status (KPS) ≥ 70%. Patient had adequate organ and bone marrow functions. Patient had tumor tissues available.

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Participant Flow Table

Patient disposition by treatment arm– Carboplatin arm (Full analysis set)

Disposition Reason	Buparlisib 80 mg + Carboplatin N=3 n (%)	Buparlisib 100 mg + Carboplatin N=14 n (%)	All patients N=17 n (%)
Patients enrolled			
Treated	3 (100)	14 (100)	17 (100)
Patients treated			
End of treatment	3 (100)	14 (100)	17 (100)
Primary reason for end of treatment			
Adverse event	0	2 (14.3)	2 (11.8)
Progressive disease	3 (100)	12 (85.7)	15 (88.2)
Post Treatment follow-up after End of Treatment			
*Not applicable	3 (100)	12 (85.7)	15 (88.2)
Patients no longer being followed for post treatment follow-up	0	2 (14.3)	2 (11.8)
Primary reason for discontinuation of post treatment follow-up			
Progressive disease	0	2 (14.3)	2 (11.8)

-* Patients who withdrew consent from the study, died or decided not to go to post treatment efficacy follow-up at the end of treatment evaluation.
Percentage is based on N

Patient disposition by treatment arm – Lomustine arm (Full analysis set)

Disposition Reason	Buparlisib 60 mg + Lomustine N=18 n (%)
Patients enrolled	
Treated	18 (100)
Patients treated	
End of treatment	18 (100)
Primary reason for end of treatment	
Adverse event	3 (16.7)
Death	1 (5.6)
Progressive disease	14 (77.8)
Post Treatment follow-up after End of Treatment	
*Not applicable	15 (83.3)
Patients no longer being followed for post treatment follow-up	3 (16.7)
Primary reason for discontinuation of post treatment follow- up	
Death	1 (5.6)
Progressive disease	1 (5.6)
Subject/guardian decision	1 (5.6)

-* Patients who withdrew consent from the study, died or decided not to go to post treatment efficacy follow-up at the end of treatment evaluation.
Percentage is based on N

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Baseline Characteristics

Demographic summary, by treatment – Carboplatin arm (Full analysis set)

Demographic Variable	Buparlisib 80 mg + Carboplatin N=3	Buparlisib 100 mg + Carboplatin N=14	All patients N=17
Age -n (%)			
<65 years	3 (100)	11 (78.6)	14 (82.4)
≥65 years	0	3 (21.4)	3 (17.6)
Age (Years)			
Mean	48.0	55.9	54.5
SD	11.27	10.24	10.52
Minimum	35.0	29.0	29.0
Median	54.0	57.0	55.0
Maximum	55.0	67.0	67.0
Sex -n (%)			
Male	3 (100)	10 (71.4)	13 (76.5)
Female	0	4 (28.6)	4 (23.5)
Race -n (%)			
Caucasian	2 (66.7)	12 (85.7)	14 (82.4)
Black	1 (33.3)	0	1 (5.9)
Other	0	1 (7.1)	1 (5.9)
Unknown	0	1 (7.1)	1 (5.9)
Ethnicity -n (%)			
Other	3 (100)	8 (57.1)	11 (64.7)
Not reported	0	2 (14.3)	2 (11.8)
Unknown	0	4 (28.6)	4 (23.5)
BSA (m^2)			
Mean	2.3	2.0	2.0
SD	0.06	0.28	0.29
Minimum	2.2	1.4	1.4
Median	2.3	2.0	2.1
Maximum	2.4	2.5	2.5
BMI (kg/m^2)			
Mean	31.6	26.8	27.6
SD	3.10	4.51	4.63
Minimum	29.2	18.9	18.9
Median	30.5	25.6	26.2
Maximum	35.2	37.8	37.8
Karnofsky performance status -n (%)			
100	1 (33.3)	2 (14.3)	3 (17.6)
90	1 (33.3)	2 (14.3)	3 (17.6)
80	1 (33.3)	6 (42.9)	7 (41.2)
70	0	4 (28.6)	4 (23.5)

- BSA: Body surface area is calculated using the Mosteller formula.
- BSA (m^2) = square root of (wt(kg)×ht(cm)/3600)
- Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**^{2})

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Demographic summary, by treatment – Lomustine arm (Full analysis set)

Demographic Variable	Buparlisib 60 mg + Lomustine N=18
Age -n (%)	
<65 years	13 (72.2)
≥65 years	5 (27.8)
Age (Years)	
Mean	55.4
SD	11.98
Minimum	35.0
Median	58.0
Maximum	73.0
Sex -n (%)	
Male	13 (72.2)
Female	5 (27.8)
Race -n (%)	
Caucasian	14 (77.8)
Asian	1 (5.6)
Other	1 (5.6)
Unknown	2 (11.1)
Ethnicity -n (%)	
Russian	1 (5.6)
Southeast Asian	1 (5.6)
Other	13 (72.2)
Unknown	3 (16.7)
BSA (m^2)	
Mean	1.9
SD	0.17
Minimum	1.5
Median	2.0
Maximum	2.2
BMI (kg/m^2)	
Mean	26.9
SD	4.50
Minimum	20.2
Median	26.0
Maximum	37.1
Karnofsky performance status -n (%)	
100	1 (5.6)
90	12 (66.7)
80	2 (11.1)
70	3 (16.7)

- BSA: Body surface area is calculated using the Mosteller formula.
- BSA (m^2) = square root of (wt(kg)×ht(cm)/3600)
- Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**^{2})

Summary of Efficacy and MTD

Primary Outcome Results

Determination of MTD/RP2D

Summary of posterior distribution of DLT rates at time of MTD/RP2D declaration - Carboplatin arm (Dose Determining Set)

Buparlisib dose (mg/day)	Posterior probabilities that Pr(DLT) is in interval			Quantiles				
	[0.0,0.16)	[0.16,0.35)	[0.35,1.0]	Mean	SD	2.50%	50.00%	97.50%
Buparlisib=60	0.384	0.609	0.007	0.180	0.055	0.089	0.175	0.303
Buparlisib=80	0.260	0.718	0.022	0.204	0.064	0.098	0.199	0.346
Buparlisib=100	0.170	0.740	0.090	0.236	0.080	0.104	0.228	0.411

Dose limiting toxicities during Cycle 1 by primary system organ class, preferred term - carboplatin arm (Dose-determining Set)

Primary system organ class Preferred Term	Buparlisib 80 mg + Carboplatin N=3 n (%)	Buparlisib 100 mg + Carboplatin N=13 n (%)	All patients N=16 n (%)
Any Primary system organ class			
Total	0	3 (23.1)	3 (18.8)
Investigations			
Total	0	1 (7.7)	1 (6.3)
Neutrophil count decreased	0	1 (7.7)	1 (6.3)
Psychiatric disorders			
Total	0	2 (15.4)	2 (12.5)
Anxiety disorder	0	1 (7.7)	1 (6.3)
Suicidal ideation	0	1 (7.7)	1 (6.3)

- A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment.

- A subject with multiple DLTs within a primary system organ class is counted only once in the total row.

- Primary system organ classes are presented in alphabetical order; preferred terms are listed within system organ classes in order of descending frequency of AEs in the total column.

- DLTs up to 21 days after the first dose of study treatment are included

Summary of posterior distribution of DLT rates at time of MTD/RP2D declaration – Lomustine arm (Dose-determining set)

Buparlisib dose (mg/day)	Posterior probabilities that Pr(DLT) is in interval			Quantiles				
	[0.0,0.16)	[0.16,0.35)	[0.35,1.0]	Mean	SD	2.50%	50.00%	97.50%
BKM120=60	0.028	0.609	0.363	0.322	0.094	0.156	0.316	0.523
BKM120=80	0.020	0.378	0.602	0.388	0.123	0.168	0.383	0.639
BKM120=100	0.019	0.240	0.741	0.460	0.155	0.174	0.458	0.764

Dose limiting toxicities during Cycle 1 by primary system organ class, preferred term - Lomustine arm (Dose-determining Set)

Primary system organ class Preferred Term	Buparlisib 60 mg + Lomustine N=12 n (%)
Any Primary system organ class	
Total	5 (41.7)
Blood and lymphatic system disorders	
Total	1 (8.3)
Thrombocytopenia	1 (8.3)
General disorders and administration site conditions	
Total	1 (8.3)
Fatigue	1 (8.3)
Investigations	
Total	1 (8.3)
Platelet count decreased	1 (8.3)
Psychiatric disorders	
Total	2 (16.7)
Depression	2 (16.7)
Respiratory, thoracic and mediastinal disorders	
Total	1 (8.3)
Pneumonitis	1 (8.3)

- A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment.

- A subject with multiple DLTs within a primary system organ class is counted only once in the total row.

- Primary system organ classes are presented in alphabetical order; preferred terms are listed Within system organ classes in order of descending frequency of AEs in the total column.

- DLTs up to 42 days after the first dose of study treatment are included

Secondary Outcome Results

Progression Free Survival (months) as per Investigator review by buparlisib dose and combination – Carboplatin arm (Full analysis set)

	Buparlisib 80mg + Carboplatin N=3	Buparlisib 100mg + Carboplatin N=14	All patients N=17
n/N (%)	3/3 (100)	14/14 (100)	17/17 (100)
Percentiles (95% CI) [1]:			
25%	1.1 (1.1;26.2)	1.2 (0.5;1.4)	1.2 (0.5;1.3)
Median	1.1 (1.1;26.2)	1.4 (1.2;1.6)	1.4 (1.1;1.6)
75%	26.2 (1.1;26.2)	1.6 (1.4;8.5)	1.6 (1.4;8.5)
% Event free probability estimates (95% CI) [2]:			
1.5 Months	33.3 (0.9;77.4)	28.6 (8.8;52.4)	29.4 (10.7;51.1)
3 Months	33.3 (0.9;77.4)	21.4 (5.2;44.8)	23.5 (7.3;44.9)
6 Months	33.3 (0.9;77.4)	7.1 (0.5;27.5)	11.8 (2.0;31.2)
9 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
12 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
15 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
18 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
21 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
24 Months	33.3 (0.9;77.4)	0 (NA;NA)	5.9 (0.4;23.5)
27 Months	0 (NA;NA)	0 (NA;NA)	0 (NA;NA)

[1]- Calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

[2]- Estimated probability that a patient will remain event-free up to the specified time point.

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment arms;

Greenwood formula is used for CIs of KM estimates.

- n: Total number of events included in the analysis.

- N: Total number of patients included in the analysis.

Progression Free Survival (months) as per Investigator review by buparlisib dose and combination – Lomustine arm (Full analysis set)

	Buparlisib 60mg + Lomustine N=18
n/N (%)	17/18 (94.4)
Median time to censoring	8.3
Percentiles (95% CI) [1]:	
25%	1.2 (0.5;1.3)
Median	1.3 (1.2;1.4)
75%	1.6 (1.3;5.5)
% Event free probability estimates (95% CI) [2]**:**	
1.5 Months	27.8 (10.1;48.9)
3 Months	16.7 (4.1;36.5)
6 Months	5.6 (0.4;22.4)
9 Months	NA (NA; NA)

[1]- Calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

[2]- Estimated probability that a patient will remain event-free up to the specified time point.

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups;

Greenwood formula is used for CIs of KM estimates.

- n: Total number of events included in the analysis.

- N: Total number of patients included in the analysis.

Best overall response summary table as per local Investigator assessment per RANO criteria, by treatment – Carboplatin arm (Full analysis set)

	Buparlisib 80 mg + Carboplatin N=3		Buparlisib 100 mg + Carboplatin N=14	
	n (%)	(95% CI)[1]	n (%)	(95% CI)[1]
Patients with measurable enhancing T1 lesion at baseline	3 (100)	-	14 (100)	-
Patients with non-measurable non-enhancing T2/FLAIR lesion at baseline	2 (66.7)	-	3 (21.4)	-
Best overall response				
Complete Response (CR)	0	-	0	-
Partial Response (PR)	1 (33.3)	-	0	-
Stable Disease (SD)	0	-	3 (21.4)	-
Progressive Disease (PD)	2 (66.7)	-	11 (78.6)	-
Unknown (UNK)	0	-	0	-
Overall Response Rate (ORR)*	1 (33.3)	(0.8, 90.6)	0	(0.0, 23.2)
Disease Control Rate (DCR)**	1 (33.3)	(0.8, 90.6)	3 (21.4)	(4.7, 50.8)

* ORR includes CR+PR.

** DCR includes CR+PR+SD.

[1]- The 95% CI for the frequency distribution of each variable were computed using exact binomial 95% confidence interval.

Best overall response summary table as per local Investigator assessment per RANO criteria, by treatment – Lomustine arm (Full analysis set)

	Buparlisib 60 mg + Lomustine N=18	
	n (%)	(95% CI)[1]
Patients with measurable enhancing T1 lesion at baseline	16 (88.9)	
Patients with non-measurable non-enhancing T2/FLAIR lesion at baseline	6 (33.3)	
Best overall response		
Complete Response (CR)	0	
Partial Response (PR)	0	
Stable Disease (SD)	2 (11.1)	
Progressive Disease (PD)	14 (77.8)	
Unknown (UNK)	2 (11.1)	
Overall Response Rate (ORR)*	0	(0.0, 18.5)
Disease Control Rate (DCR)**	2 (11.1)	(1.4, 34.7)

* ORR includes CR+PR

** DCR includes CR+PR+SD

[1]- The 95% CI for the frequency distribution of each variable were computed using exact binomial 95% confidence interval

Summary of Safety

Adverse events regardless of study treatment relationship, by primary system organ class, overall and grade 3/4 - Carboplatin arm (Safety set)

	Buparlisib 80 mg + Carboplatin N=3		Buparlisib 100 mg + Carboplatin N=14		All patients N=17	
	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	3 (100)	2 (66.7)	14 (100)	11 (78.6)	17 (100)	13 (76.5)
Gastrointestinal disorders	2 (66.7)	0	11 (78.6)	0	13 (76.5)	0
General disorders and administration site conditions	3 (100)	0	9 (64.3)	2 (14.3)	12 (70.6)	2 (11.8)
Nervous system disorders	2 (66.7)	0	10 (71.4)	1 (7.1)	12 (70.6)	1 (5.9)
Psychiatric disorders	3 (100)	0	9 (64.3)	1 (7.1)	12 (70.6)	1 (5.9)
Investigations	2 (66.7)	2 (66.7)	7 (50.0)	3 (21.4)	9 (52.9)	5 (29.4)
Metabolism and nutrition disorders	1 (33.3)	1 (33.3)	7 (50.0)	2 (14.3)	8 (47.1)	3 (17.6)
Blood and lymphatic system disorders	0	0	6 (42.9)	3 (21.4)	6 (35.3)	3 (17.6)
Vascular disorders	2 (66.7)	1 (33.3)	4 (28.6)	1 (7.1)	6 (35.3)	2 (11.8)
Infections and infestations	2 (66.7)	0	3 (21.4)	0	5 (29.4)	0
Skin and subcutaneous tissue disorders	2 (66.7)	0	3 (21.4)	1 (7.1)	5 (29.4)	1 (5.9)
Respiratory, thoracic and mediastinal disorders	2 (66.7)	0	2 (14.3)	0	4 (23.5)	0
Eye disorders	1 (33.3)	0	1 (7.1)	0	2 (11.8)	0
Musculoskeletal and connective tissue disorders	1 (33.3)	0	1 (7.1)	0	2 (11.8)	0
Renal and urinary disorders	1 (33.3)	1 (33.3)	1 (7.1)	0	2 (11.8)	1 (5.9)
Congenital, familial and genetic disorders	0	0	1 (7.1)	0	1 (5.9)	0
Hepatobiliary disorders	1 (33.3)	0	0	0	1 (5.9)	0
Injury, poisoning and procedural complications	0	0	1 (7.1)	0	1 (5.9)	0

- Primary system organ classes are sorted in descending frequency, as reported in the all grades column of 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 adverse events within a primary system organ class is counted only once in the total row.

- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Adverse events regardless of study treatment relationship, by primary system organ class, overall and grade 3/4 – Lomustine arm (Safety set)

	Buparlisib 60 mg + Lomustine N=18	
	All grades	Grades 3/4
Primary system organ class	n (%)	n (%)
Total	18 (100)	14 (77.8)
General disorders and administration site conditions	14 (77.8)	2 (11.1)
Nervous system disorders	13 (72.2)	4 (22.2)
Psychiatric disorders	12 (66.7)	2 (11.1)
Blood and lymphatic system disorders	11 (61.1)	5 (27.8)
Gastrointestinal disorders	11 (61.1)	1 (5.6)
Investigations	11 (61.1)	8 (44.4)
Metabolism and nutrition disorders	7 (38.9)	2 (11.1)
Infections and infestations	5 (27.8)	1 (5.6)
Skin and subcutaneous tissue disorders	5 (27.8)	0
Vascular disorders	5 (27.8)	2 (11.1)
Renal and urinary disorders	4 (22.2)	1 (5.6)
Cardiac disorders	3 (16.7)	0
Eye disorders	3 (16.7)	0
Musculoskeletal and connective tissue disorders	3 (16.7)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (11.1)	1 (5.6)
Ear and labyrinth disorders	1 (5.6)	1 (5.6)
Reproductive system and breast disorders	1 (5.6)	0

- Primary system organ classes are sorted in descending frequency, as reported in the All grades column of 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 adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Most frequent on-treatment adverse events regardless of study treatment relationship, with at least 10% incidence of all grade events in either arm by preferred term, grade 3/4 and treatment– Carboplatin arm (Safety set)

	Buparlisib 80 mg + Carboplatin		Buparlisib 100 mg + Carboplatin		All patients	
	N=3		N=14		N=17	
	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	3 (100)	2 (66.7)	14 (100)	11 (78.6)	17 (100)	13 (76.5)
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
Thrombocytopenia	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
Neutropenia	0	0	5 (35.7)	1 (7.1)	5 (29.4)	1 (5.9)
Platelet count decreased	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)
Neutrophil count decreased	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
White blood cell count decreased	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)
Lymphopenia	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)
Suicidal ideation	0	0	2 (14.3)	1 (7.1)	2 (11.8)	1 (5.9)
Urinary tract infection	1 (33.3)	0	1 (7.1)	0	2 (11.8)	0

- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.

- Preferred terms are sorted in descending frequency, as reported in the All grades column.

Most frequent on-treatment adverse events regardless of study treatment relationship, with at least 10% incidence of all grade events in either arm by preferred term, grade 3/4 and treatment– Lomustine arm (Safety set)

	Buparlisib 60 mg + Lomustine N=18	
Preferred term	**All grades n (%)**	**Grades 3/4 n (%)**
-Total	18 (100)	14 (77.8)
Fatigue	8 (44.4)	1 (5.6)
Nausea	8 (44.4)	0
Platelet count decreased	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
Neutropenia	4 (22.2)	2 (11.1)
Thrombocytopenia	4 (22.2)	4 (22.2)
White blood cell count decreased	4 (22.2)	2 (11.1)
Alanine aminotransferase increased	3 (16.7)	1 (5.6)
Asthenia	3 (16.7)	0
Constipation	3 (16.7)	0
Diarrhoea	3 (16.7)	0
Gastrooesophageal reflux disease	3 (16.7)	0
Hyperglycaemia	3 (16.7)	1 (5.6)
Memory impairment	3 (16.7)	0
Neutrophil count decreased	3 (16.7)	1 (5.6)
Seizure	3 (16.7)	1 (5.6)
Somnolence	3 (16.7)	0
Anhedonia	2 (11.1)	0
Aspartate aminotransferase increased	2 (11.1)	1 (5.6)
Cough	2 (11.1)	0
Decreased appetite	2 (11.1)	0
Gamma-glutamyltransferase increased	2 (11.1)	2 (11.1)
General physical health deterioration	2 (11.1)	1 (5.6)
Irritability	2 (11.1)	0
Lymphocyte count decreased	2 (11.1)	2 (11.1)
Lymphopenia	2 (11.1)	1 (5.6)
Muscular weakness	2 (11.1)	1 (5.6)
Petechiae	2 (11.1)	0
Sinus tachycardia	2 (11.1)	0

Preferred term	Buparlisib 60 mg + Lomustine N=18 All grades n (%)	Buparlisib 60 mg + Lomustine N=18 Grades 3/4 n (%)
Upper respiratory tract infection	2 (11.1)	0
Urinary incontinence	2 (11.1)	0
Vomiting	2 (11.1)	0

- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.
- Preferred terms are sorted in descending frequency, as reported in the All grades column.

Summary of deaths and adverse events by treatment – Carboplatin arm (Safety set)

	Buparlisib 80 mg + Carboplatin	Buparlisib 100 mg + Carboplatin	All patients
	N=3	N=14	N=17
	n (%)	n (%)	n (%)
Patients with at least one AE	3 (100)	14 (100)	17 (100)
Patients with at least one SAE	1 (33.3)	4 (28.6)	5 (29.4)
Patients who died	0	1 (7.1)	1 (5.9)
Patients who discontinued from study treatment due to AEs	0	3 (21.4)	3 (17.6)
Patients who discontinued from study treatment due to SAEs	0	1 (7.1)	1 (5.9)
Patients who discontinued from study treatment due to non-serious AEs	0	2 (14.3)	2 (11.8)

- Only deaths and AEs occurring during the treatment or within 30 days of the last study medication are reported

Summary of deaths and adverse events by treatment – Lomustine arm (Safety set)

	Buparlisib 60 mg + Lomustine
	N=18
	n (%)
Patients with at least one AE	18 (100)
Patients with at least one SAE	4 (22.2)
Patients who died	1 (5.6)
Patients who discontinued from study treatment due to AEs	3 (16.7)
Patients who discontinued from study treatment due to SAEs	2 (11.1)
Patients who discontinued from study treatment due to non-serious AEs	1 (5.6)

- Only deaths and AEs occurring during the treatment or within 30 days of the last study medication are reported

Other Relevant Findings

None

Conclusion:

The overall safety profile of buparlisib remained unchanged and no new or unexpected findings were reported in this study. A preliminary assessment for both combinations (buparlisib plus carboplatin or lomustine) did not demonstrate sufficient antitumor activity compared to historical data with single agent carboplatin or lomustine. After careful evaluation of ongoing study data, it was concluded that available data did not support the conduct of the phase II part.

Date of Clinical Trial Report

20-Feb-2017