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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Sonidegib and Buparlisib

Trial Indication(s)

Solid tumors

Protocol Number

CLDE225X2114

Protocol Title

A Phase Ib, multi-center, open-label, dose escalation study of oral LDE225 in combination with BKM120 in patients with advanced solid tumors.

Clinical Trial Phase

Phase IB

Phase of Drug Development

Phase III

Study Start/End Dates

04-Jul-2012 to 15-Apr-2015

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, open-label, dose-finding, Phase Ib study to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) for the combination of sonidegib plus buparlisib. This was followed by an expansion part to further assess safety and preliminary efficacy of the combination in patients with advanced solid tumors that were frequently associated with dysregulated hedgehog (Hh) and/or phosphatidylinositol-3-kinase (PI3K) pathways, specifically triple negative metastatic breast cancer (MBC), hormone receptor positive (ER+/PR+ and Her2-) MBC, advanced pancreatic adenocarcinoma, metastatic colorectal cancer (CRC) and recurrent glioblastoma multiforme (GBM)

The patients received daily oral doses of sonidegib and buparlisib. The starting dose for the dose escalation part was 400 mg qd of sonidegib and 60 mg qd of buparlisib. A Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) was used to guide dose escalation. Dose escalation was continued until identification of the MTD or PK futility (defined as no significant increase in exposure despite administration of increasing doses) was encountered, and at least six eligible patients were required at the dose declared to be the MTD/RDE.

Once the MTD/RDE for the combination therapy was determined, approximately 75 patients were planned to be enrolled in the dose expansion part of the study to further assess safety and preliminary efficacy of the combination in patients with advanced solid tumors. There was no fixed treatment duration; patients were treated until documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the Investigator, or premature termination of the study.

Centers

23 centers in 8 countries: Australia (1), Belgium (1), Canada (1), Germany (1), Italy (2), Spain (2), United Kingdom (2), United States of America (13)

Publication

None

Objectives:

Primary objective: To determine a combination MTD and/or RDE of sonidegib and buparlisib when co-administered orally in patients with advanced solid tumors (specifically, MBC, advanced pancreatic adenocarcinoma, metastatic CRC and recurrent GBM).

Secondary objectives:

- To characterize the safety and tolerability of continuous daily co-administration of sonidegib and buparlisib.
- To assess the preliminary antitumor activity of combination therapy with sonidegib and buparlisib.
- To characterize the single and multiple dose pharmacokinetic (PK) of sonidegib and buparlisib following co-administration

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

Sonidegib capsules for oral administration were supplied to the Investigators at dose strengths of 200 mg. Buparlisib capsules for oral administration were supplied at dose strengths of 10 mg and 50 mg.

Statistical Methods

MTD/RDE: Estimation of MTD and/or RDE in the dose-escalation phase of the study was based upon the estimation of the probability of DLTs. A 5-parameter BLRM with EWOC was used during the dose escalation phase for the combination treatment for recommendation of MTD and/or RDE. The dose limiting toxicities (DLTs) were summarized based on dose determining set, by primary system organ class and preferred term for each dose cohort, and summary of posterior distribution of DLT rates was also provided.

Efficacy: The Objective response rate (ORR) and early progression rate (EPR) at six months were used to evaluate preliminary efficacy of the combination therapy. Efficacy analyses were based on Full analysis set (FAS). Summary of data was presented by different tumor types.

The ORR was defined as the proportion of patients with confirmed best overall response of CR or PR. ORR was summarized in terms of percentage rates with 95% confidence intervals. The EPR was defined as the proportion of GBM patients with progressive disease within 6 months of the start of treatment. The EPR included all patients who at 6 months did not had an overall lesion response of stable disease (SD), partial response (PR) or complete response (CR). Patients with an unknown (UNK) assessment and no PD before, were not be counted as early progressors in the analysis but were be included in the denominator of the EPR rate.

Safety: All safety analyses were based on safety set. The assessment of safety was based mainly on the frequency and severity of adverse events (AEs) and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs) were considered as appropriate. The safety summary tables included only on-treatment assessments (from day of start of study treatment to 30 days following the last date of study treatment) and were presented by dose and for all patients. The AEs were coded using MedDRA version in effect at the time of database lock and were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Number and percentage of patients was described according to Patient Health Questionnaire (PHQ-9) total score severity classifications (None: 0-4, Mild: 5-9, Moderate: 10-19, Severe: 20-27). Shift tables (from Baseline to worst post-baseline total score) based on the classification of severity were produced for assessments of the PHQ-9.

Number and percentage of patients was described according to General Anxiety Disorder Assessment (GAD-7) total score severity classifications (None: 0-4, Mild: 5-9, Moderate: 10-14, Severe: ≥15). Shift tables (from Baseline to worst post-baseline total score) based on the classification of severity as specified above were produced.

Pharmacokinetics: Plasma concentrations and PK parameters of sonidegib and buparlisib were summarized using descriptive statistics. Descriptive statistics (mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric CV%, median, and range) were presented for all parameters for each dose cohort for each compound. When a geometric mean was presented, it was stated as such. Only median values and ranges were given for Tmax. Summary data was presented by dose cohort.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria: The patients meeting following criteria were included:

- Male or female adult patients, who had histologically/cytologically confirmed diagnosis of the following advanced tumors that had progressed despite standard therapy or that had no available established treatments: triple negative MBC, hormone receptor positive (ER+/PR+ and Her2-) MBC, advanced pancreatic adenocarcinoma, metastatic CRC, gastric/gastroesophageal junction cancer and recurrent GBM.
- Patients who had measurable disease as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for non-GBM tumors and by Revised Assessment in Neuro-Oncology (RANO) criteria for GBM
- Patients who had adequate bone marrow and organ function, recurrent GBM patient who had a Karnofsky performance status (KPS) score ≥ 70
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (only applied to patients enrolled under the original and Amendment 1 protocol versions) and 0-1 (only applied to patients enrolled under Amendment 2 and any later protocol versions).

Key exclusion criteria: The patients meeting following criteria were excluded:

- History of hypersensitivity to sonidegib, buparlisib or to drugs of similar chemical classes.
- Patient had received previous treatment with PI3K inhibitors and/or smoothened inhibitors.
- Patients with recurrent GBM who had received radiotherapy within 3 months of initiating study treatment.
- Patients with primary central nervous system (CNS) tumor (except recurrent GBM), uncontrolled or symptomatic CNS metastasis. However, patients with controlled, asymptomatic or with resected CNS metastases with no radiological evidence of disease or with stable brain metastasis with no progression (as shown by 2 computed tomography or magnetic resonance imaging scans spaced at least 3 months apart) were eligible for the study.
- Patients who were planning on embarking on new physical activities, such as strenuous exercise, that could result in significant increases in plasma CK levels while on study treatment.
- Patients who required the use of warfarin.

- Patient who had a score ≥ 12 on the PHQ-9, who selected responses of "1", "2" or "3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation, who had a GAD-7 mood scale score ≥ 15, who had ≥ Common Terminology CTCAE grade 3 anxiety, clinically significant abnormal electrocardiogram (ECG), who had a left ventricular ejection fraction (LVEF) <50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO), who was receiving treatment with QT prolonging medication known to have a risk to induce Torsades de Pointes, and the treatment could not be discontinued or switched to a different medication 7 days prior to starting the study and for the duration of the study.

Participant Flow Table

Patient disposition by treatment (FAS)

	LDE400 +BKM60 N=6 n (%)	LDE800 +BKM60 N=7 n (%)	LDE400 +BKM80 N=89 n (%)	LDE400 +BKM100 N=9 n (%)	LDE200 +BKM100 N=9 n (%)	All Patients N=120 n (%)
Patients						
Treated	6 (100.0)	7 (100.0)	89 (100.0)	9 (100.0)	9 (100.0)	120 (100.0)
End of treatment	6 (100.0)	7 (100.0)	89 (100.0)	9 (100.0)	9 (100.0)	120 (100.0)
End of study	3 (50.0)	5 (71.4)	45 (50.6)	5 (55.6)	3 (33.3)	61 (50.8)
Primary reason for end of treatment						
Progressive disease	3 (50.0)	4 (57.1)	60 (67.4)	6 (66.7)	6 (66.7)	79 (65.8)
Adverse event	0	2 (28.6)	15 (16.9)	3 (33.3)	1 (11.1)	21 (17.5)
Subject/guardian decision	2 (33.3)	0	9 (10.1)	0	1 (11.1)	12 (10.0)
Death	1 (16.7)	1 (14.3)	3 (3.4)	0	1 (11.1)	6 (5.0)
Non-compliance with study treatment	0	0	1 (1.1)	0	0	1 (0.8)
Physician decision	0	0	1 (1.1)	0	0	1 (0.8)
Study evaluation after the end of treatment phase						
Patients continuing to be followed for study evaluation	3 (50.0)	5 (71.4)	45 (50.6)	5 (55.6)	3 (33.3)	61 (50.8)

	LDE400 +BKM60 N=6 n (%)	LDE800 +BKM60 N=7 n (%)	LDE400 +BKM80 N=89 n (%)	LDE400 +BKM100 N=9 n (%)	LDE200 +BKM100 N=9 n (%)	All Patients N=120 n (%)
Patients no longer being followed for study evaluation	3 (50.0)	2 (28.6)	44 (49.4)	4 (44.4)	6 (66.7)	59 (49.2)
Primary reason for study evaluation completion						
Death	1 (16.7)	2 (28.6)	18 (20.2)	2 (22.2)	2 (22.2)	25 (20.8)
Completed	2 (33.3)	2 (28.6)	10 (11.2)	2 (22.2)	1 (11.1)	17 (14.2)
Lost to follow-up	0	0	7 (7.9)	1 (11.1)	0	8 (6.7)
Lack of efficacy	0	1 (14.3)	5 (5.6)	0	0	6 (5.0)
Adverse Event	0	0	2 (2.2)	0	0	2 (1.7)
New therapy for study indication	0	0	2 (2.2)	0	0	2 (1.7)
Non-compliance with study treatment	0	0	1 (1.1)	0	0	1 (0.8)

Percentage is based on N.

Patient disposition by tumor type (FAS)

	GBM N=30 n (%)	BC I N=12 n (%)	BC II N=17 n (%)	BC III N=4 n (%)	Gastric N=14 n (%)	CRC N=30 n (%)	Pancreatic N=13 n (%)	All patients N=120 n (%)
Patients enrolled								
Treated	30 (100)	12 (100)	17 (100)	4 (100)	14 (100)	30 (100)	13 (100)	120 (100)
Patients Treated								
End of treatment	30 (100)	12 (100)	17 (100)	4 (100)	14 (100)	30 (100)	13 (100)	120 (100)
End of study	10 (33.3)	7 (58.3)	9 (52.9)	3 (75.0)	11 (78.6)	16 (53.3)	5 (38.5)	61 (50.8)
Primary reason for end of treatment								
Progressive disease	23 (76.7)	10 (83.3)	8 (47.1)	0	9 (64.3)	20 (66.7)	9 (69.2)	79 (65.8)
Adverse event	5 (16.7)	0	5 (29.4)	2 (50.0)	3 (21.4)	5 (16.7)	1 (7.7)	21 (17.5)

	GBM N=30 n (%)	BC I N=12 n (%)	BC II N=17 n (%)	BC III N=4 n (%)	Gastric N=14 n (%)	CRC N=30 n (%)	Pancreatic N=13 n (%)	All patients N=120 n (%)
Subject/guardian decision	0	1 (8.3)	3 (17.6)	1 (25.0)	1 (14.3)	3 (10.0)	2 (15.4)	12 (10.0)
Death	1 (3.3)	0	1 (5.9)	1 (25.0)	0	2 (6.7)	1 (7.7)	6 (5.0)
Non-compliance with study treatment	1 (3.3)	0	0	0	0	0	0	1 (0.8)
Physician decision	0	1 (8.3)	0	0	0	0	0	1 (0.8)
Study evaluation after end of treatment								
Patients continuing to be followed for study evaluation	10 (33.3)	7 (58.3)	9 (52.9)	3 (75.0)	11 (78.6)	16 (53.3)	5 (38.5)	61 (50.8)
Patients no longer being followed for study evaluation	20 (66.7)	5 (41.7)	8 (47.1)	1 (25.0)	3 (21.4)	14 (46.7)	8 (61.5)	59 (49.2)
Primary reason for study evaluation completion								
Death	7 (23.3)	2 (16.7)	3 (17.6)	1 (25.0)	5 (35.7)	4 (13.3)	3 (23.1)	25 (20.8)
Completed	0	1 (8.3)	2 (11.8)	1 (25.0)	4 (28.6)	8 (26.7)	1 (7.7)	17 (14.2)
Lack of efficacy	0	2 (16.7)	1 (5.9)	1 (25.0)	0	1 (3.3)	1 (7.7)	6 (5.0)
Adverse event	0	0	1 (5.9)	0	1 (7.1)	0	0	2 (1.7)
New therapy for study indication	0	0	2 (11.8)	0	0	0	0	2 (1.7)
Non-compliance with study treatment	1 (3.3)	0	0	0	0	0	0	1 (0.8)

GBM=Glioblastoma multiforme, BC=Breast cancer, CRC=Colorectal cancer.

Percentage is based on N.

BC I = triple negative metastatic breast cancer; BC II = hormone receptor positive (ER+/PR+, and Her2-) metastatic breast cancer; BC III = metastatic breast cancer with unknown subtype.

Baseline Characteristics

Demographics by treatment (FAS)

	LDE 400+ BKM60 N=6 n (%)	LDE 800+ BKM60 N=7 n (%)	LDE 400+ BKM80 N=89 n (%)	LDE 400+ BKM100 N=9 n (%)	LDE 200+ BKM100 N=9 n (%)	All patients N=120 n (%)
Age (years)						
n	6	7	89	9	9	120
Mean	57.8	66.0	56.5	55.6	48.4	56.4
SD	9.24	6.66	11.04	9.41	12.76	11.10
Median	61.5	63.0	57.0	55.0	49.0	57.0
Min	40.0	60.0	20.0	41.0	20.0	20.0
Max	65.0	78.0	76.0	68.0	63.0	78.0
Age category (years) - n (%)						
<65	5 (83.3)	4 (57.1)	67 (75.3)	7 (77.8)	9 (100)	92 (76.7)
≥ 65	1 (16.7)	3 (42.9)	22 (24.7)	2 (22.2)	0	28 (23.3)
Sex - n (%)						
Female	3 (50.0)	3 (42.9)	46 (51.7)	7 (77.8)	5 (55.6)	64 (53.3)
Male	3 (50.0)	4 (57.1)	43 (48.3)	2 (22.2)	4 (44.4)	56 (46.7)
Race - n (%)						
Caucasian	5 (83.3)	7 (100)	81 (91.0)	8 (88.9)	8 (88.9)	109 (90.8)
Asian	1 (16.7)	0	3 (3.4)	0	0	4 (3.3)
Black	0	0	2 (2.2)	1 (11.1)	0	3 (2.5)
Other	0	0	2 (2.2)	0	1 (11.1)	3 (2.5)
Pacific Islander	0	0	1 (1.1)	0	0	1 (0.8)
Weight (Kg)						
n	6	7	89	9	9	120

Mean	72.1	69.3	72.5	72.5	69.3	72.0
SD	13.94	16.46	18.21	24.54	7.46	17.67
Median	70.4	68.6	69.0	67.2	67.6	68.7
Min	56.0	55.0	46.3	40.0	62.5	40.0
Max	96.5	100.6	146.0	128.0	86.6	146.0
Height (cm)						
n	6	7	86	9	9	117
Mean	165.8	165.0	169.2	163.9	166.3	168.1
SD	9.78	11.43	10.20	12.33	6.73	10.20
Median	163.7	159.0	167.5	165.0	166.5	166.5
Min	156.0	153.0	149.0	140.5	158.1	140.5
Max	178.7	182.0	200.1	180.0	178.3	200.1
Karnofsky performance status n (%) (GBM patients)						
100	0	0	1 (1.1)	0	0	1 (0.8)
90	1 (16.7)	0	11 (12.4)	0	1 (11.1)	13 (10.8)
80	1 (16.7)	0	8 (9.0)	0	0	9 (7.5)
70	0	0	2 (2.2)	0	1 (11.1)	3 (2.5)
Missing	0	0	3 (3.4)	0	1 (11.1)	4 (3.3)
Not applicable	4 (66.7)	7 (100)	64 (71.9)	9 (100)	6 (66.7)	90 (75.0)
ECOG performance status n (%) (non-GBM patients)						
0	1 (16.7)	7 (100)	25 (28.1)	5 (55.6)	1 (11.1)	39 (32.5)
1	3 (50.0)	0	39 (43.8)	3 (33.3)	5 (55.6)	50 (41.7)
2	0	0	0	1 (11.1)	0	1 (0.8)
Not applicable	2 (33.3)	0	25 (28.1)	0	3 (33.3)	30 (25.0)

SD=Standard deviation

Karnofsky performance status: 100%: Normal; no complaints; 90%: Able to carry on normal activity; minor signs or symptoms of disease; 80%: Normal activity with effort;

some signs or symptoms of disease; 70%: Cares for self; unable to carry on normal activity or work; <70: Unable to work.

ECOG performance status: 0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Summary of Efficacy

Primary Outcome Result(s)

Summary of posterior distribution of DLT rates (Dose determining set)

BKM120=60mg	Posterior probabilities (%) that Pr(DLT) is in interval:				
	[0, 0.16)	[0.16, 0.33)	[0.33-1]	Mean	SD
200 mg LDE225	0.570	0.423	0.008	0.156	0.059
400 mg LDE225	0.378	0.597	0.024	0.186	0.064
800 mg LDE225	0.097	0.620	0.284	0.282	0.105
BKM120=80 mg					
200 mg LDE225	0.271	0.700	0.029	0.201	0.061
400 mg LDE225	0.137	0.792	0.071	0.229	0.065
800 mg LDE225	0.033	0.545	0.422	0.322	0.106
BKM120=100 mg					
200 mg LDE225	0.113	0.750	0.138	0.247	0.076
400 mg LDE225	0.053	0.723	0.224	0.275	0.078
800 mg LDE225	0.020	0.403	0.578	0.364	0.117

Secondary Outcome Result(s)

Best overall response by tumor type (FAS)

	GBM N=30 n (%)	BC I N=12 n (%)	BC II N=17 n (%)	BC III N=4 n (%)	Gastric N=14 n (%)	CRC N=30 n (%)	Pancreatic N=13 n (%)	All patients N=120 n (%)
Best overall response								
CR	0	0	0	0	0	0	0	0
PR	1 (3.3)	1 (8.3)	0	0	0	0	0	2 (1.7)
SD	6 (20.0)	2 (16.7)	3 (17.6)	1 (25.0)	6 (42.9)	10 (33.3)	3 (23.1)	31 (25.8)
PD	22 (73.3)	7 (58.3)	10 (58.8)	2 (50.0)	5 (35.7)	16 (53.3)	6 (46.2)	68 (56.7)
Unknown	1 (3.3)	2 (16.7)	4 (23.5)	1 (25.0)	3 (21.4)	4 (13.3)	4 (30.8)	19 (15.8)
Overall response rate (ORR: CR+PR)								
	1 (3.3)	1 (8.3)	0	0	0	0	0	2 (1.7)
95% CI for ORR (%)	[0.1, 17.2]	[0.2, 38.5]	[0.0, 19.5]	[0.0, 60.2]	[0.0, 23.2]	[0.0, 11.6]	[0.0, 24.7]	[0.2, 5.9]
EPR (GBM only)								
	22 (73.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
95% CI for EPR (%)	[54.1, 87.7]	N/A	N/A	N/A	N/A	N/A	N/A	N/A

GBM=Glioblastoma multiforme, BC=Breast cancer, CRC=Colorectal cancer, EPR=Early progression rate, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, N/A=Not applicable

BC I = triple negative metastatic breast cancer; BC II = hormone receptor positive (ER+/PR+, and Her2-) metastatic breast cancer; BC III = metastatic breast cancer with unknown subtype

N: The total number of patients in each tumor type group. It is the denominator for percentage (%) calculation.

EPR is the proportion of patients with best overall response being progressive disease within 6 months of the start of treatment.

Summary of PK parameters for sonidegib by treatment for Cycle 1 Day 1 and Cycle 4 Day 1 (PAS)

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
		Visit Cycle 1 Day 1				
LDE 400+BKM 60 (N=6)	N	6	6	6	-	1
	Mean (SD)	3420 (3040)	384 (274)	N/A	-	123
	CV% mean	89.0	71.4	N/A	-	-
	Geo-mean	2600	306	N/A	-	123
	CV% geo-mean	91.7	87.4	N/A	-	-
	Median	2250	285	2.01	-	123
	[Min; Max]	[951; 9270]	[118; 759]	[2.00; 6.17]	-	[123; 123]
LDE 800+BKM 60 (N=7)	N	6	7	7	-	-
	Mean (SD)	4090 (3950)	477 (297)	N/A	-	-
	CV% mean	96.4	62.4	N/A	-	-
	Geo-mean	2990	401	N/A	-	-
	CV% geo-mean	103	72.7	N/A	-	-
	Median	2660	404	2.00	-	-
	[Min; Max]	[873; 11900]	[137; 980]	[1.98; 7.00]	-	-
LDE 400+BKM 100 (N=9)	N	8	9	9	-	3
	Mean (SD)	2140 (2010)	244 (213)	N/A	-	129 (106)
	CV% mean	93.9	87.4	N/A	-	82.4
	Geo-mean	1490	169	N/A	-	104
	CV% geo-mean	111	116	N/A	-	90.2
	Median	1130	172	4.00	-	76.4
	[Min; Max]	[494; 5890]	[53.9; 646]	[1.00; 6.98]	-	[59.2; 251]
LDE 400+BKM 80 (N=29)	N	25	28	28	-	13
	Mean (SD)	2540 (1640)	303 (227)	N/A	-	229 (240)
	CV% mean	64.8	75.0	N/A	-	105

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
	Geo-mean	2050	225	N/A	-	166
	CV% geo-mean	80.1	102	N/A	-	89.0
	Median	2060	250	3.00	-	166
	[Min; Max]	[348; 7140]	[24.7; 896]	[1.03; 24.0]	-	[65.5; 940]
LDE 200+BKM 100 (N=9)	N	8	9	9	-	1
	Mean (SD)	1240 (1330)	146 (163)	N/A	-	275
	CV% mean	108	111	N/A	-	
	Geo-mean	870	102	N/A	-	275
	CV% geo-mean	104	103	N/A	-	
	Median	763	109	2.00	-	275
	[Min; Max]	[226; 4420]	[27.8; 568]	[2.00; 6.02]	-	[275; 275]
		Visit : Cycle 4 Day 1				
LDE 800+BKM 60 (N=7)	N	1	1	1	1	1
	Mean (SD)	81300	4110	N/A	29.7	9.84
	CV% mean	N/A	N/A	N/A	N/A	N/A
	Geo-mean	81300	4110	N/A	29.7	9.84
	CV% geo-mean	N/A	N/A	N/A	N/A	N/A
	Median	81300	4110	1.00	29.7	9.84
	[Min; Max]	[81300; 81300]	[4110; 4110]	[1.00; 1.00]	[29.7; 29.7]	[9.84; 9.84]
LDE 400+BKM 100 (N=9)	n	1	2	2	1	1
	Mean (SD)	12500	779 (164)	N/A	16.0	32.0
	CV% mean	N/A	21.1	N/A	N/A	
	Geo-mean	12500	770	N/A	16.0	32.0
	CV% geo-mean	N/A	21.5	N/A	N/A	
	Median	12500	779	0.985	16.0	32.0
	[Min; Max]	[12500; 12500]	[663; 895]	[0; 1.97]	[16.0; 16.0]	[32.0; 32.0]

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
LDE 400+BKM 80 (N=29)	n	4	5	5	4	4
	Mean (SD)	32200 (5850)	1640 (837)	N/A	24.0 (31.7)	12.7 (2.49)
	CV% mean	18.2	51.0	N/A	132	19.5
	Geo-mean	31800	1440	N/A	13.3	12.6
	CV% geo-mean	19.0	66.6	N/A	175	19.0
	Median	32700	1580	3.88	9.92	12.3
	[Min; Max]	[24800; 38800]	[543; 2900]	[1.83; 22.2]	[4.77; 71.2]	[10.3; 16.2]
LDE 200+BKM 100 (N=9)	n	1	1	1	1	1
	Mean (SD)	5380	261	N/A	8.51	37.2
	CV% mean	N/A	N/A	N/A	N/A	N/A
	Geo-mean	5380	261	N/A	8.51	37.2
	CV% geo-mean	N/A	N/A	N/A	N/A	N/A
	Median	5380	261	4.47	8.51	37.2
	[Min; Max]	[5380; 5380]	[261; 261]	[4.47; 4.47]	[8.51; 8.51]	[37.2; 37.2]

N/A=Not applicable

Summary of PK parameters for buparlisib by treatment for Cycle 1 Day 1 and Cycle 4 Day 1 (PAS)

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
		Visit Cycle 1 Day 1				
LDE 400+BKM 60 (N=6)	n	6	6	6	-	1
	Mean (SD)	3620 (1240)	346 (112)	N/A	-	-
	CV% mean	34.2	32.5	N/A	-	-
	Geo-mean	3460	332	N/A	-	-
	CV% geo-mean	33.7	30.5	N/A	-	-
	Median	3350	300	1.95	-	-

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
	[Min; Max]	[2180; 5790]	[238; 544]	[1.00; 2.02]	-	-
LDE 800+BKM 60 (N=7)	n	7	7	7	-	-
	Mean (SD)	4300 (856)	494 (139)	N/A	-	-
	CV% mean	19.9	28.2	N/A	-	-
	Geo-mean	4220	477	N/A	-	-
	CV% geo-mean	22.4	29.8	N/A	-	-
	Median	4620	511	1.93	-	-
	[Min; Max]	[2840; 5160]	[324; 673]	[0.580; 2.00]	-	-
LDE 400+BKM 100 (N=9)	n	8	9	9	-	-
	Mean (SD)	5970 (1350)	578 (225)	N/A	-	-
	CV% mean	22.6	39.0	N/A	-	-
	Geo-mean	5810	539	N/A	-	-
	CV% geo-mean	26.0	41.9	N/A	-	-
	Median	6140	587	2.00	-	-
	[Min; Max]	[3480; 7550]	[274; 1010]	[0.980; 5.95]	-	-
LDE 400+BKM 80 (N=29)	n	25	28	28	-	1
	Mean (SD)	4400 (1260)	485 (167)	N/A	-	18.7
	CV% mean	28.6	34.5	N/A	-	N/A
	Geo-mean	4210	460	N/A	-	18.7
	CV% geo-mean	32.0	33.5	N/A	-	N/A
	Median	4350	457	1.99	-	18.7
	[Min; Max]	[1610; 7260]	[231; 955]	[0.470; 8.00]	-	[18.7; 18.7]
LDE 200+BKM 100 (N=9)	n	8	9	9	-	-
	Mean (SD)	5670 (1870)	745 (420)	N/A	-	-
	CV% mean	33.0	56.4	N/A	-	-
	Geo-mean	5390	630	N/A	-	-

Treatment	Statistics	AUC 0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Racc (fold)	CL/F (L/hr)
	CV% geo-mean	36.0	73.1	N/A	-	-
	Median	6180	735	2.00	-	-
	[Min; Max]	[3330; 8650]	[213; 1500]	[0.580; 2.00]	-	-
			Visit Cycle 4 Day 1			
LDE 400+BKM 80 (N=29)	n	3	3	3	3	3
	Mean (SD)	12000 (1760)	954 (285)	N/A	2.09 (0.186)	6.76 (0.934)
	CV% mean	14.7	29.9	N/A	8.90	13.8
	Geo-mean	11900	926	N/A	2.08	6.71
	CV% geo-mean	14.4	30.3	N/A	8.81	14.4
	Median	11400	904	1.17	2.04	7.01
	[Min; Max]	[10600; 14000]	[697; 1260]	[1.05; 3.88]	[1.93; 2.29]	[5.72; 7.54]
LDE 200+BKM 100 (N=9)	n	1	1	1	1	1
	Mean (SD)	10400	604	N/A	2.64	9.65
	CV% mean	N/A	N/A	N/A		
	Geo-mean	10400	604	N/A	2.64	9.65
	CV% geo-mean	N/A	N/A	N/A		
	Median	10400	604	0.670	2.64	9.65
	[Min; Max]	[10400; 10400]	[604; 604]	[0.670; 0.670]	[2.64; 2.64]	[9.65; 9.65]

N/A=Not applicable

Summary of Safety

Safety Results

Dose limiting toxicity

Dose limiting toxicities by primary system organ class, preferred term and treatment (Dose Determining set)

System organ class Preferred term	LDE400+ BKM60 N=4 n (%)	LDE800+ BKM60 N=5 n (%)	LDE400+ BKM80 N=7 n (%)	LDE400+ BKM100 N=9 n (%)	LDE200+ BKM100 N=4 n (%)	All patients N=29 n (%)
Any primary SOC	**0**	**2 (40.0)**	**1 (14.3)**	**3 (33.3)**	**1 (25.0)**	**7 (24.1)**
Investigations	**0**	**2 (40.0)**	**1 (14.3)**	**1 (11.1)**	**1 (25.0)**	**5 (17.2)**
Blood creatine phosphokinase increased	0	2 (40.0)	1 (14.3)	0	0	3 (10.3)
Alanine aminotransferase increased	0	0	0	1 (11.1)	1 (25.0)	2 (6.9)
Aspartate aminotransferase increased	0	1 (20.0)	0	1 (11.1)	0	2 (6.9)
Metabolism and nutrition disorders	**0**	**1 (20.0)**	**0**	**0**	**0**	**1 (3.4)**
Decreased appetite	0	1 (20.0)	0	0	0	1 (3.4)
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**2 (22.2)**	**0**	**2 (6.9)**
Photosensitivity reaction	0	0	0	1 (11.1)	0	1 (3.4)
Rash maculo-papular	0	0	0	1 (11.1)	0	1 (3.4)

SOC: System organ class, DLT: Dose limiting toxicity
Primary SOCs are presented alphabetically; preferred terms are sorted Within primary SOC in descending frequency, as reported in the all patients column.
A patient with multiple occurrences of a DLT is counted only once in the AE category for that treatment.
A patient with multiple occurrences of a DLT is counted only once in the total row.

Adverse events by system organ class

Adverse events, regardless of study drug relationship, by primary system organ class and treatment (Safety set)

Primary System organ class	LDE400+ BKM60 N=6 n (%)	LDE800+ BKM60 N=7 n (%)	LDE400+ BKM80 N=89 n (%)	LDE400+ BKM100 N=9 n (%)	LDE200+ BKM100 N=9 n (%)	All patients N=120 n (%)

Primary System organ class	LDE400+ BKM60 N=6 n (%)	LDE800+ BKM60 N=7 n (%)	LDE400+ BKM80 N=89 n (%)	LDE400+ BKM100 N=9 n (%)	LDE200+ BKM100 N=9 n (%)	All patients N=120 n (%)
Any primary SOC	**6 (100)**	**7 (100)**	**87 (97.8)**	**9 (100)**	**8 (88.9)**	**117 (97.5)**
Investigations	2 (33.3)	7 (100)	59 (66.3)	9 (100)	5 (55.6)	82 (68.3)
Gastrointestinal disorders	2 (33.3)	6 (85.7)	61 (68.5)	7 (77.8)	4 (44.4)	80 (66.7)
General disorders and administration site conditions	2 (33.3)	5 (71.4)	57 (64.0)	6 (66.7)	4 (44.4)	74 (61.7)
Metabolism and nutrition disorders	2 (33.3)	7 (100)	47 (52.8)	7 (77.8)	5 (55.6)	68 (56.7)
Nervous system disorders	6 (100)	3 (42.9)	41 (46.1)	2 (22.2)	4 (44.4)	56 (46.7)
Musculoskeletal and connective tissue disorders	4 (66.7)	4 (57.1)	39 (43.8)	4 (44.4)	2 (22.2)	53 (44.2)
Skin and subcutaneous tissue disorders	4 (66.7)	4 (57.1)	29 (32.6)	4 (44.4)	1 (11.1)	42 (35.0)
Psychiatric disorders	4 (66.7)	5 (71.4)	23 (25.8)	4 (44.4)	3 (33.3)	39 (32.5)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	2 (28.6)	25 (28.1)	4 (44.4)	2 (22.2)	34 (28.3)
Infections and infestations	2 (33.3)	4 (57.1)	13 (14.6)	2 (22.2)	0	21 (17.5)
Blood and lymphatic system disorders	1 (16.7)	0	14 (15.7)	3 (33.3)	1 (11.1)	19 (15.8)
Eye disorders	0	1 (14.3)	7 (7.9)	3 (33.3)	0	11 (9.2)
Hepatobiliary disorders	0	2 (28.6)	5 (5.6)	1 (11.1)	0	8 (6.7)
Injury, poisoning and procedural complications	1 (16.7)	0	6 (6.7)	0	1 (11.1)	8 (6.7)
Renal and urinary disorders	1 (16.7)	0	6 (6.7)	1 (11.1)	0	8 (6.7)
Vascular disorders	0	1 (14.3)	5 (5.6)	1 (11.1)	0	7 (5.8)
Reproductive system and breast disorders	0	1 (14.3)	3 (3.4)	1 (11.1)	0	5 (4.2)
Ear and labyrinth disorders	0	0	2 (2.2)	1 (11.1)	0	3 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (3.4)	0	0	3 (2.5)
Cardiac disorders	0	0	1 (1.1)	0	0	1 (0.8)

Primary System organ class	LDE400+ BKM60 N=6 n (%)	LDE800+ BKM60 N=7 n (%)	LDE400+ BKM80 N=89 n (%)	LDE400+ BKM100 N=9 n (%)	LDE200+ BKM100 N=9 n (%)	All patients N=120 n (%)

SOC: System organ class

Primary SOC are presented in descending frequency of all patients column.

A patient with multiple occurrences of an AE under one treatment was counted only once In the AE category for that treatment.

A patient with multiple AEs within a primary SOC was counted only once in the total row.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events (with incidence of greater than or equal to 10% of patients in all patients column), regardless of study drug relationship, by preferred term and treatment (Safety set)

	LDE400+ BKM60 N=6		LDE800+ BKM60 N=7		LDE400+ BKM80 N=89		LDE400+ BKM100 N=9		LDE200+ BKM100 N=9		All patients N=120	
	All grades	Grade 3/4	All grades	Grade 3/4	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 (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	**6 (100)**	**3 (50.0)**	**7 (100)**	**7 (100)**	**87 (97.8)**	**62 (69.7)**	**9 (100)**	**8 (88.9)**	**8 (88.9)**	**4 (44.4)**	**117 (97.5)**	**84 (70.0)**
AST increased	1 (16.7)	1 (16.7)	4 (57.1)	3 (42.9)	35 (39.3)	13 (14.6)	7 (77.8)	4 (44.4)	5 (55.6)	2 (22.2)	52 (43.3)	23 (19.2)
ALT increased	1 (16.7)	1 (16.7)	3 (42.9)	3 (42.9)	33 (37.1)	21 (23.6)	6 (66.7)	4 (44.4)	5 (55.6)	3 (33.3)	48 (40.0)	32 (26.7)
Fatigue	2 (33.3)	0	4 (57.1)	1 (14.3)	30 (33.7)	6 (6.7)	4 (44.4)	0	4 (44.4)	1 (11.1)	44 (36.7)	8 (6.7)
Decreased appetite	2 (33.3)	0	5 (71.4)	2 (28.6)	28 (31.5)	0	5 (55.6)	0	3 (33.3)	0	43 (35.8)	2 (1.7)
Nausea	0	0	4 (57.1)	2 (28.6)	31 (34.8)	3 (3.4)	2 (22.2)	0	4 (44.4)	0	41 (34.2)	5 (4.2)
Diarrhoea	1 (16.7)	1 (16.7)	3 (42.9)	0	26 (29.2)	0	3 (33.3)	0	2 (22.2)	0	35 (29.2)	1 (0.8)

	LDE400+ BKM60 N=6		LDE800+ BKM60 N=7		LDE400+ BKM80 N=89		LDE400+ BKM100 N=9		LDE200+ BKM100 N=9		All patients N=120	
	All grades	Grade 3/4	All grades	Grade 3/4	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 (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Blood creatine phosphokinase increased	0	0	4 (57.1)	4 (57.1)	25 (28.1)	9 (10.1)	4 (44.4)	2 (22.2)	0	0	33 (27.5)	15 (12.5)
Vomiting	0	0	3 (42.9)	1 (14.3)	26 (29.2)	3 (3.4)	3 (33.3)	0	1 (11.1)	0	33 (27.5)	4 (3.3)
Hyperglycaemia	1 (16.7)	1 (16.7)	4 (57.1)	2 (28.6)	19 (21.3)	4 (4.5)	4 (44.4)	0	2 (22.2)	0	30 (25.0)	7 (5.8)
Abdominal pain	1 (16.7)	0	0	0	15 (16.9)	5 (5.6)	0	0	1 (11.1)	0	17 (14.2)	5 (4.2)
Dysgeusia	2 (33.3)	0	2 (28.6)	0	10 (11.2)	0	1 (11.1)	0	2 (22.2)	0	17 (14.2)	0
Muscle spasms	1 (16.7)	0	1 (14.3)	0	13 (14.6)	0	2 (22.2)	0	0	0	17 (14.2)	0
Weight decreased	0	0	3 (42.9)	0	9 (10.1)	0	3 (33.3)	0	1 (11.1)	0	16 (13.3)	0
Constipation	1 (16.7)	0	3 (42.9)	0	9 (10.1)	2 (2.2)	2 (22.2)	0	0	0	15 (12.5)	2 (1.7)
Cough	1 (16.7)	0	1 (14.3)	0	11 (12.4)	0	2 (22.2)	0	0	0	15 (12.5)	0
Asthenia	0	0	1 (14.3)	0	13 (14.6)	1 (1.1)	0	0	0	0	14 (11.7)	1 (0.8)
Blood alkaline phosphatase increased	0	0	1 (14.3)	1 (14.3)	10 (11.2)	1 (1.1)	1 (11.1)	0	2 (22.2)	2 (22.2)	14 (11.7)	4 (3.3)
Stomatitis	1 (16.7)	0	1 (14.3)	0	8 (9.0)	0	3 (33.3)	0	1 (11.1)	0	14 (11.7)	0
Anaemia	0	0	0	0	12 (13.5)	2 (2.2)	1 (11.1)	0	0	0	13 (10.8)	2 (1.7)
Depression	1 (16.7)	0	2 (28.6)	0	8 (9.0)	1 (1.1)	2 (22.2)	0	0	0	13 (10.8)	1 (0.8)
Headache	3 (50.0)	1 (16.7)	0	0	7 (7.9)	0	1 (11.1)	0	1 (11.1)	0	12 (10.0)	1 (0.8)

	LDE400+ BKM60 N=6		LDE800+ BKM60 N=7		LDE400+ BKM80 N=89		LDE400+ BKM100 N=9		LDE200+ BKM100 N=9		All patients N=120	
	All grades	Grade 3/4	All grades	Grade 3/4	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 (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

AST=aspartate aminotransferase, ALT: alanine aminotransferase

Preferred terms are presented in descending frequency of all grades column, as reported in the all patients group.

A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

A patient with multiple AEs within a SOC was counted only once in the total row.

One AE of pyrexia with missing grade was included.

Serious Adverse Events and Deaths

	LDE400+ BKM60 N=6 n (%)	LDE800+ BKM60 N=7 n (%)	LDE400+ BKM80 N=89 n (%)	LDE400+ BKM100 N=9 n (%)	LDE200+ BKM100 N=9 n (%)	All patients N=120 n (%)
No. (%) of subjects with AE(s)	6 (100)	7 (100)	87 (97.8)	9 (100)	8 (88.9)	117 (97.5)
Number (%) of subjects with serious or other significant events						
Death	3 (50.0)	3 (42.9)	40 (44.9)	5 (55.6)	5 (55.6)	56 (46.7)
SAEs	2 (33.3)	5 (71.4)	31 (34.8)	0	2 (22.2)	40 (33.3)
Discontinued due to AEs	0	3 (42.9)	18 (20.2)	2 (22.2)	1 (11.1)	24 (20.0)

Other Relevant Findings

None.

Conclusion:

- The study met its primary objective and sonidegib 400 mg in combination with buparlisib 80 mg when co-administered orally was established as the RDE in patients with advanced solid tumors (specifically, metastatic breast cancer, advanced pancreatic adenocarcinoma, metastatic CRC and recurrent GBM).
- The safety and tolerability profile of sonidegib plus buparlisib combination observed in the current study was consistent with prior experience and with the expected safety profile as single agents in an advanced oncology setting.
- The efficacy results from this study suggested that the combination of sonidegib and buparlisib failed to corroborate the expected strong synergistic activity on tumor cell inhibition of the Hh and/PI3K signaling pathways.
- No obvious drug-drug interactions between sonidegib and buparlisib were observed in the dose expansion level.

Date of Clinical Trial Report

11-Jan-2016