Sponsor

Novartis

Generic Drug Name

Buparlisib

Trial Indication(s)

Advanced breast cancer or advanced carcinomas with squamous cell histology (including non-small cell lung cancer (NSCLC), squamous cell cancer of the head and neck (SCCHN), and esophageal)

Protocol Number

CBKM120Z2102

Protocol Title

Phase I study of buparlisib, administered orally in adult Chinese patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

16-Jul-2012 to 04-Apr-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I, open-label, dose-escalation and dose expansion study in which buparlisib was administered once daily in Chinese patients with advanced breast cancer or advanced carcinomas with squamous cell histology (including NSCLC, SCCHN, and esophageal) whose disease had progressed on (or those that had not been able to tolerate) standard therapy, or for whom no standard therapy existed.

The starting dose for the escalation period was 80 mg/day. Two dose levels were tested in this study: 80 mg/day and 100 mg/day. Patients were treated until disease progression, unacceptable toxicity, investigator's decision to discontinue treatment, or patient refusal.

A minimum of 3 evaluable patients were to be enrolled into each cohort of the dose escalation phase and at least 6 evaluable patients at the recommended phase II dose/maximum tolerated dose (RP2D/MTD). All evaluable patients included in each dose cohort were to be assessed for decision making on dose escalation. Before a dose level could be declared to be the RP2D/MTD, at least 9 evaluable patients were required to be treated, with at least 6 evaluable patients treated at the RP2D/MTD dose level for one treatment cycle.

Once the RP2D/MTD was declared, the RP2D/MTD cohort was expanded to enroll at least 21 additional patients to obtain a total of at least 30 patients. Overall, including both the dose-escalation phase and the dose expansion phase, approximately 15 patients were to be treated with buparlisib at 80 mg/day and approximately 15 patients were to be treated with buparlisib at 100 mg/day.

A cohort could be expanded at any dose level below the RP2D/MTD for further elaboration of safety, pharmacokinetic (PK) and/or pharmacodynamic parameters as required.

Centers

Three centers in China

Publication

None

Objectives:

The primary objective was to determine the RP2D/MTD of buparlisib as a single agent when administered orally to adult Chinese patients with advanced solid tumors.

The secondary objectives were:

- To assess the tolerability and safety of buparlisib
- To characterize the PK profile of oral buparlisib
- To obtain preliminary evidence of efficacy of buparlisib

Objectives were completed as planned.

Test Product, Doses, and Mode of Administration

Buparlisib was supplied as hard gelatin capsules at dose strengths of 10 mg and 50 mg. Buparlisib was dosed orally on a flat scale of mg/day and was not adjusted to body weight or body surface area. A complete treatment cycle was defined as 28 days of once daily continuous treatment with buparlisib. The starting dose was 80 mg/day given at approximately the same time each day in the morning. Buparlisib was to be ingested with a

glass of water, one hour following a light breakfast and patients were not allowed to eat for 2 hours following the administration of buparlisib.

Statistical Methods

Determination of RP2D/MTD: The primary objective of the dose escalation part of the study was to determine the RP2D/MTD of the single agent buparlisib. An adaptive Bayesian logistic regression model using the escalation with overdose control (EWOC) principle guided dose escalation. All relevant information available about the dose-toxicity relationship of single agent buparlisib from studies BKM120X2101 and BKM120X1101 was summarized in prior distributions. This prior distribution was then updated after each cohort of patients with the dose limiting toxicity (DLT) data from the current trial. Once updated, a dose recommendation was based on posterior summaries for each dose, including the mean, median, standard deviation, 95%-confidence interval (CI), and the probability that the true DLT rate for each tested dose lay in one of the following categories:

- [0,16%] under-dosing
- [16%, 33%] targeted toxicity
- [33%,60%] excessive toxicity

Following the EWOC principle, after each cohort of patients, the recommended dose was the one with the highest posterior probability of DLT in the target level [16%, 33%] among the doses fulfilling the overdose criterion that there was less than 25% chance of either excessive or unacceptable toxicity. The recommendations of the Bayesian logistic regression model were shared with the clinical trial team and investigators at each planned Dose Escalation Teleconference.

The DLT assessment was performed using the safety set, which consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The dose-determining set consisted of all patients from the safety set who, in Cycle 1, either met the minimum exposure criterion and had sufficient safety evaluations, or discontinued due to DLT.

Efficacy: The full analysis set (FAS – which consisted of all patients who received at least one dose of study drug) was used for these analyses. The best overall response as per investigator evaluation according to response evaluation criteria in solid tumors (RECIST) version 1.1 was summarized. Overall response rate (ORR) was summarized along with 95% CI. In addition, time to progression per RECIST v1.1 was summarized using Kaplan-Meier estimates.

Safety: The assessment of safety was based mainly on the frequency of adverse events (AEs) and on the number of laboratory values that fell outside of pre-determined ranges using CTCAE v4.03. Other safety data (e.g. electrocardiogram, vital signs, and special tests) and questionnaires were considered as appropriate. All safety results were presented based on the safety set.

Pharmacokinetics: Summary of PK parameters and plasma concentrations during Cycle 1 on Day 1, Day 8, and Day 28 were presented to characterize PKs of buparlisib. Descriptive graphical plots of individual plasma concentration, time profiles and trough concentrations were generated. Descriptive statistics were presented for all parameters for each dose cohort. The PK analysis set (PAS) was used for these analyses, consisting of all patients who received at least one dose of study drug and had at least one post-baseline pharmacokinetic assessment.

Biomarkers: All biomarker sample results obtained were listed by patient. Biomarkers obtained at baseline and post baseline were summarized by descriptive statistics by dose level if feasible. The FAS was used for these analyses.

The data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK measurements.

Cohorts treated at the same dose level were pooled into treatment groups. All analyses, summaries, listings and figures were performed by treatment group unless otherwise specified.

The analysis of the study data was based on all patients' data up to the time when the last patient had completed at least four cycles of treatment or discontinued the study.

Study Population: Key Inclusion/ Exclusion Criteria

Inclusion criteria

- Patients with histologically-confirmed, advanced unresectable breast cancer or advanced carcinoma with squamous cell histology (including NSCLC, SCCHN, and esophageal) who have progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy exists
- Patient must provide a representative archival or fresh tumor biopsy for shipping to a Novartis designated laboratory for profiling. Note: one block or ≥ 15 unstained slides is required to determine the PI3K activation status. Whenever possible ≥ 20 unstained slides is preferred.
- Patient has measurable and/or non-measurable disease as per RECIST v1.1 guidelines for solid tumors
- Patient is an adult (female or male) ≥ 18 years of age on the day of consent signature
- Patient has an ECOG performance status (ECOG PS) ≤ 2

Exclusion criteria

- Patient has received previous treatment with a PI3K inhibitor
- Patient has symptomatic central nervous system (CNS) metastases
    - Patients with asymptomatic CNS metastases may participate in this trial. The patient must have completed any prior local treatment for CNS metastases ≥ 14 days prior to the start of study treatment (including radiotherapy and/or surgery). If the patient is receiving ongoing corticosteroid therapy, the following criteria must be met:

  - The patient must be receiving a stable or decreasing dose ≤ dexamethasone 4 mg/day or equivalent anti-inflammatory potency of another corticosteroid
  - The dose of corticosteroid may not have been escalated for at least 14 days before the start of study treatment
- Patient is currently receiving increasing or chronic treatment with corticosteroids (>dexamethasone 4 mg or equivalent anti-inflammatory potency of another corticosteroid) or another immunosuppressive agent.
  - Note: Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular) are allowed. Patients with previously treated and asymptomatic brain metastases, are permitted to use corticosteroids as per specific protocol criteria
- Patient is currently receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated. Switching to a different medication prior to starting study treatment is allowed.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient Disposition by Dose Level (FAS)

Disposition reason	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Patients treated			
Treatment ongoing	0	0	0
End of treatment	15 (100.0)	17 (100.0)	32 (100.0)
Primary reason for end of treatment phase			
Progressive disease	9 (60.0)	11 (64.7)	20 (62.5)
Subject/guardian decision	3 (20.0)	3 (17.6)	6 (18.8)
Adverse event	1 (6.7)	3 (17.6)	4 (12.5)
Death	2 (13.3)	0	2 (6.3)

Percentage based on N

Baseline Characteristics

Demographic Summary by Dose Level (FAS)

Demographic Variable	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Age group			
<45	3 (20.0)	7 (41.2)	10 (31.3)
45 to <65	9 (60.0)	9 (52.9)	18 (56.3)
≥ 65	3 (20.0)	1 (5.9)	4 (12.5)
Age (years)			
Mean (SD)	53.8 (12.47)	48.5 (14.65)	51.0 (13.72)
Median	54.0	51.0	52.0
Min; max	31; 75	24; 72	24; 75
Sex			
Male	7 (46.7)	7 (41.2)	14 (43.8)
Female	8 (53.3)	10 (58.8)	18 (56.3)
Race			
Asian	15 (100.0)	17 (100.0)	32 (100.0)
Ethnicity			
East Asian	15 (100.0)	17 (100.0)	32 (100.0)
Weight (kg)			
Mean (SD)	59.2 (9.03)	59.5 (9.08)	59.4 (8.91)
Median	62.0	61.0	61.5
Min; max	35; 71	39; 82	35; 82
Height (cm)			
Mean (SD)	161.9 (7.90)	161.9 (8.21)	161.9 (7.93)
Median	163.0	161.0	162.0
Min; max	148; 175	150; 176	148; 176
Body surface area (m^2)			
Mean (SD)	1.63 (0.137)	1.63 (0.153)	1.63 (0.144)
Median	1.67	1.65	1.65
Min; max	1.2; 1.8	1.3; 1.9	1.2; 1.9
Body mass index (kg/m^2)			
Mean (SD)	22.76 (4.181)	22.67 (2.839)	22.71 (3.472)

Demographic Variable	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Median	24.00	22.04	22.80
Min; max	13.7; 28.3	17.3; 30.1	13.7; 30.1
ECOG performance status			
0	0	1 (5.9)	1 (3.1)
1	13 (86.7)	15 (88.2)	28 (87.5)
2	2 (13.3)	1 (5.9)	3 (9.4)
Missing	0	0	0

Weight and height are taken from screening vital signs evaluations
Body Mass Index: BMI [kg/m^2]=weight[kg]/(height[m]**2)
Body Surface Area (Mosteller): BSA(m^2)= v(wt(kg)xht(cm)/3600)

Disease History by Dose Level (FAS)

Disease history	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Primary site of cancer			
Breast	3 (20.0)	7 (41.2)	10 (31.3)
Head and neck	3 (20.0)	4 (23.5)	7 (21.9)
Lung	9 (60.0)	6 (35.3)	15 (46.9)
Histological grade			
Well differentiated	0	1 (5.9)	1 (3.1)
Moderately differentiated	6 (40.0)	7 (41.2)	13 (40.6)
Poorly differentiated	2 (13.3)	5 (29.4)	7 (21.9)
Undifferentiated	3 (20.0)	3 (17.6)	6 (18.8)
Unknown	4 (26.7)	1 (5.9)	5 (15.6)
Metastatic site of cancer			
Lung	10 (66.7)	10 (58.8)	20 (62.5)
Liver	9 (60.0)	6 (35.3)	15 (46.9)
Pulmonary lymph nodes	7 (46.7)	7 (41.2)	14 (43.8)
Bone	5 (33.3)	5 (29.4)	10 (31.3)
Pleura	5 (33.3)	5 (29.4)	10 (31.3)
Thoracic lymph nodes	5 (33.3)	5 (29.4)	10 (31.3)
Other lymph nodes	6 (40.0)	1 (5.9)	7 (21.9)

Disease history	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Pleural effusion (malignant)	1 (6.7)	5 (29.4)	6 (18.8)
Axillary lymph nodes	0	5 (29.4)	5 (15.6)
Supraclavicular lymph nodes	4 (26.7)	1 (5.9)	5 (15.6)
Adrenal	2 (13.3)	1 (5.9)	3 (9.4)
Cervical lymph nodes	0	1 (5.9)	1 (3.1)
Chest wall	0	1 (5.9)	1 (3.1)
Chest wall nodules	0	1 (5.9)	1 (3.1)
Mesenteric lymph nodes	1 (6.7)	0	1 (3.1)
Para-aortic lymph nodes	1 (6.7)	0	1 (3.1)
Retroperitoneal lymph nodes	1 (6.7)	0	1 (3.1)
Spleen	0	1 (5.9)	1 (3.1)
Stage at initial diagnosis			
Stage IA	1 (6.7)	1 (5.9)	2 (6.3)
Stage II	0	1 (5.9)	1 (3.1)
Stage IIB	1 (6.7)	2 (11.8)	3 (9.4)
Stage III	1 (6.7)	1 (5.9)	2 (6.3)
Stage IIIA	2 (13.3)	5 (29.4)	7 (21.9)
Stage IIIB	2 (13.3)	1 (5.9)	3 (9.4)
Stage IIIC	0	1 (5.9)	1 (3.1)
Stage IV	8 (53.3)	4 (23.5)	12 (37.5)
Stage IVA	0	1 (5.9)	1 (3.1)
Stage at study entry			
Stage IIIB	1 (6.7)	1 (5.9)	2 (6.3)
Stage IV	12 (80.0)	10 (58.8)	22 (68.8)
Stage IVB	2 (13.3)	6 (35.3)	8 (25.0)
Types of lesions at Baseline			
Non-target only	0	4 (23.5)	4 (12.5)
Both target and non-target	15 (100)	13 (76.5)	28 (87.5)
Time from initial diagnosis to first recurrence /progression (months)			
<3	0	1 (5.9)	1 (3.1)
3 to <6	2 (13.3)	2 (11.8)	4 (12.5)

Disease history	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
6 to <12	9 (60.0)	5 (29.4)	14 (43.8)
≥ 12	4 (26.7)	9 (52.9)	13 (40.6)
Time since most recent relapse/progression (months)			
<3	14 (93.3)	15 (88.2)	29 (90.6)
3 to <6	0	0	0
6 to <12	1 (6.7)	1 (5.9)	2 (6.3)
≥ 12	0	1 (5.9)	1 (3.1)

PI3K Pathway Activation Status by Dose Level at Study Entry (FAS)

PI3K activation status	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
PIK3CA Mutation			
Yes	1 (6.7)	2 (11.8)	3 (9.4)
No	9 (60.0)	12 (70.6)	21 (65.6)
Unknown	1 (6.7)	2 (11.8)	3 (9.4)
Missing	4 (26.7)	1 (5.9)	5 (15.6)
PTEN Negative			
Yes	2 (13.3)	3 (17.6)	5 (15.6)
No	9 (60.0)	13 (76.5)	22 (68.8)
Unknown	0	0	0
Missing	4 (26.7)	1 (5.9)	5 (15.6)
PI3K activation status			
Yes	2 (13.3)	5 (29.4)	7 (21.9)
No PIK3CA mutation or PTEN loss detected	8 (53.3)	9 (52.9)	17 (53.1)
Unknown	1 (6.7)	2 (11.8)	3 (9.4)
Missing	4 (26.7)	1 (5.9)	5 (15.6)

Missing pathway status = damaged samples not suitable for analysis

Primary Outcome Results

In total, five patients experienced DLTs during the dose escalation and dose expansion period: three DLTs of hyperglycemia and one DLT of depression in the 80 mg group and one DLT of hyperglycemia in the 100 mg group

Summary of Posterior Distribution of DLT Rates at Time of MTD Declaration (DDS)

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Buparlisib Dose (mg/day)	**[0-0.16)**	**[0.16-0.33)**	**[0.33-1]**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
60	0.851	0.143	0.006	0.093	0.068	0.006	0.078	0.265
80	0.728	0.257	0.016	0.127	0.074	0.025	0.114	0.306
100	0.512	0.432	0.056	0.172	0.087	0.041	0.157	0.373
120	0.343	0.484	0.172	0.224	0.123	0.051	0.201	0.525

Recommended dose is the one with the highest posterior probability of DLT in the target interval [0.16,0.33] among the doses fulfilling the overdose criterion that the posterior probability is less than 25% in the excessive toxicity interval [0.33,1]

Summary of Posterior Distribution of DLT Rates at End of Study (DDS)

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Buparlisib Dose (mg/day)	**[0-0.16)**	**[0.16-0.33)**	**[0.33-1]**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
60	0.760	0.237	0.003	0.122	0.059	0.028	0.114	0.259
80	0.564	0.426	0.009	0.156	0.062	0.057	0.149	0.297
100	0.349	0.612	0.039	0.192	0.071	0.075	0.185	0.351
120	0.237	0.632	0.131	0.229	0.091	0.085	0.216	0.438

Recommended dose was the one with the highest posterior probability of DLT in the target interval [0.16,0.33] among the doses fulfilling the overdose criterion that the posterior probability was less than 25% in the excessive toxicity interval [0.33,1]

Summary of Efficacy

Best Overall Response Summary as per Investigator by Dose Level (Full Analysis Set)

Best overall response	Buparlisib 80 mg N=15 n (%) (95% CI)	Buparlisib 100 mg N=17 n (%) (95% CI)	Total N=32 n (%) (95% CI)
Patients with measurable disease at baseline	15 (100)	13 (76.5)	28 (87.5)
Patients with non-measurable disease only at baseline	0	4 (23.5)	4 (12.5)
Best overall response			
Complete response	0	0	0
Partial response	0	0	0
Stable disease	2 (13.3)	8 (47.1)	10 (31.3)
Progressive disease	7 (46.7)	5 (29.4)	12 (37.5)
Non-CR/Non-PD	0	1 (5.9)	1 (3.1)
Unknown	6 (40.0)	3 (17.6)	9 (28.1)
Not assessed	0	0	0
Overall response rate (ORR:CR+PR)	0	0	0
Disease control rate (DCR: CR+PR+SD+Non-CR/Non-PD)	2 (13.3) (1.7, 40.5)	9 (52.9) (27.8, 77.0)	11 (34.4) (18.6, 53.2)

N: The total number of patients in the dose level. 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 Clopper-Pearson method if there was sufficient data.

Secondary Outcome Results

Summary of Primary PK Parameters Cycle 1 Day 1 (Pharmacokinetic Analysis Set)

Treatment	Statistics	Tmax (hr)	Cmax (ng/mL)	AUC0-24 (ng.hr/mL)
Buparlisib 80 mg	N	15	15	15
	Mean (SD)	1.02 (0.483; 8.00)	838 (422)	7000 (2230)
Buparlisib 100 mg	N	17	17	17
	Mean (SD)	1.00 (0.500; 4.00)	994 (344)	8770 (2260)

Mean (SD) except for Tmax: Median (Min – Max)
Patients with at least 7 days of daily dosing prior to the PK assessments were included in the summary statistics of C1D8 and C1D28

Summary of Primary PK Parameters Cycle 1 Day 8 (Pharmacokinetic Analysis Set)

Treatment	Statistics	Tmax (hr)	Cmax (ng/mL)	AUC0-24 (ng.hr/mL)	T1/2,acc (hr)	Racc
Buparlisib 80 mg	N	14	14	14	14	14
	Mean (SD)	1.00 (0.50;6.00)	1470 (476)	18000 (6260)	36.7 (13.5)	2.75 (0.796)
Buparlisib 100 mg	N	16	16	16	16	16
	Mean (SD)	1.73 (0.50;4.00)	1980 (493)	22500 (5680)	36.0 (10.8)	2.70 (0.637)

Mean (SD) except for Tmax: Median (Min – Max)
Patients with at least 7 days of daily dosing prior to the PK assessments were included in the summary statistics of C1D8 and C1D28

Summary of Primary PK Parameters Cycle 1 Day 28 (Pharmacokinetic Analysis Set)

Treatment	Statistics	Tmax (hr)	Cmax (ng/mL)	AUC0-24 (ng.hr/mL)	T1/2,acc (hr)	Racc
Buparlisib 80 mg	N	9	9	9	9	9
	Mean (SD)	1.00 (0.50;3.87)	1330 (443)	18000 (4260)	39.3 (8.6)	2.90 (0.510)
Buparlisib 100 mg	N	13	13	13	13	13
	Mean (SD)	1.50 (0.50;4.00)	1880 (520)	22400 (6340)	38.3 (13.3)	2.84 (0.777)

Mean (SD) except for Tmax: Median (Min – Max)
Patients with at least 7 days of daily dosing prior to the PK assessments were included in the summary statistics of C1D8 and C1D28

Summary of Safety

Safety Results

Treatment-emergent Adverse Events Irrespective of Causality by Primary System Organ Class (Buparlisib 80 mg) (Safety set)

	Buparlisib 80 mg N=15					
Primary SOC	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Any primary SOC	1 (6.7)	3 (20.0)	8 (53.3)	3 (20.0)	11 (73.3)	15 (100)
Metabolism and nutrition disorders	2 (13.3)	6 (40.0)	6 (40.0)	0	6 (40.0)	14 (93.3)
Investigations	6 (40.0)	1 (6.7)	2 (13.3)	1 (6.7)	3 (20.0)	10 (66.7)
Psychiatric disorders	2 (13.3)	6 (40.0)	1 (6.7)	0	1 (6.7)	9 (60.0)
General disorders and administration site conditions	4 (26.7)	2 (13.3)	1 (6.7)	1 (6.7)	2 (13.3)	8 (53.3)
Respiratory, thoracic and mediastinal disorders	0	4 (26.7)	0	2 (13.3)	2 (13.3)	6 (40.0)
Infections and infestations	3 (20.0)	0	1 (6.7)	0	1 (6.7)	4 (26.7)
Gastrointestinal disorders	3 (20.0)	0	0	0	0	3 (20.0)
Nervous system disorders	3 (20.0)	0	0	0	0	3 (20.0)
Skin and subcutaneous tissue disorders	2 (13.3)	1 (6.7)	0	0	0	3 (20.0)
Blood and lymphatic system disorders	0	0	2 (13.3)	0	2 (13.3)	2 (13.3)
Musculoskeletal and connective tissue disorders	1 (6.7)	0	1 (6.7)	0	1 (6.7)	2 (13.3)
Cardiac disorders	1 (6.7)	0	0	0	0	1 (6.7)

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.

Treatment-emergent Adverse Events Irrespective of Causality by Primary System Organ Class (Buparlisib 100 mg) (Safety set)

	Buparlisib 100 mg N=17					
Primary SOC	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Any primary SOC	2 (11.8)	3 (17.6)	8 (47.1)	4 (23.5)	12 (70.6)	17 (100)
Investigations	8 (47.1)	1 (5.9)	4 (23.5)	1 (5.9)	5 (29.4)	14 (82.4)
Metabolism and nutrition disorders	3 (17.6)	7 (41.2)	3 (17.6)	1 (5.9)	4 (23.5)	14 (82.4)
Gastrointestinal disorders	5 (29.4)	2 (11.8)	2 (11.8)	0	2 (11.8)	9 (52.9)
Blood and lymphatic system disorders	3 (17.6)	3 (17.6)	1 (5.9)	1 (5.9)	2 (11.8)	8 (47.1)
Psychiatric disorders	5 (29.4)	1 (5.9)	1 (5.9)	0	1 (5.9)	7 (41.2)
Respiratory, thoracic and mediastinal disorders	1 (5.9)	2 (11.8)	3 (17.6)	1 (5.9)	4 (23.5)	7 (41.2)
General disorders and administration site conditions	2 (11.8)	4 (23.5)	0	0	0	6 (35.3)
Skin and subcutaneous tissue disorders	1 (5.9)	4 (23.5)	0	0	0	5 (29.4)
Infections and infestations	1 (5.9)	2 (11.8)	0	1 (5.9)	1 (5.9)	4 (23.5)
Musculoskeletal and connective tissue disorders	1 (5.9)	2 (11.8)	1 (5.9)	0	1 (5.9)	4 (23.5)
Cardiac disorders	1 (5.9)	1 (5.9)	0	0	0	2 (11.8)
Nervous system disorders	1 (5.9)	0	1 (5.9)	0	1 (5.9)	2 (11.8)

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 (>10%) Treatment-emergent Adverse Events, Regardless of Causality, Overall by Preferred Term n (%) (Buparlisib 80 mg) (Safety set)

	Buparlisib 80 mg N=15				
Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**
Total	**1 (6.7)**	**3 (20.0)**	**8 (53.3)**	**3 (20.0)**	**15 (100)**
Hyperglycaemia	6 (40.0)	3 (20.0)	2 (13.3)	0	11 (73.3)
Hypoalbuminaemia	1 (6.7)	4 (26.7)	1 (6.7)	0	6 (40.0)
Alanine aminotransferase increased	3 (20.0)	1 (6.7)	1 (6.7)	0	5 (33.3)
Anxiety	2 (13.3)	3 (20.0)	0	0	5 (33.3)
Depression	1 (6.7)	3 (20.0)	1 (6.7)	0	5 (33.3)
Fatigue	3 (20.0)	1 (6.7)	0	1 (6.7)	5 (33.3)
Aspartate aminotransferase increased	3 (20.0)	0	1 (6.7)	0	4 (26.7)
Blood alkaline phosphatase increased	3 (20.0)	1 (6.7)	0	0	4 (26.7)

Preferred term	Buparlisib 80 mg N=15 Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Blood bilirubin increased	2 (13.3)	2 (13.3)	0	0	4 (26.7)
Cough	0	4 (26.7)	0	0	4 (26.7)
Decreased appetite	3 (20.0)	0	1 (6.7)	0	4 (26.7)
Hypokalaemia	3 (20.0)	0	1 (6.7)	0	4 (26.7)
Hyponatraemia	3 (20.0)	0	1 (6.7)	0	4 (26.7)
Dyspnoea	0	2 (13.3)	0	1 (6.7)	3 (20.0)
Gamma-glutamyltransferase increased	0	0	2 (13.3)	1 (6.7)	3 (20.0)
Haemoptysis	1 (6.7)	1 (6.7)	0	1 (6.7)	3 (20.0)
Hypocalcaemia	2 (13.3)	1 (6.7)	0	0	3 (20.0)
Vomiting	3 (20.0)	0	0	0	3 (20.0)
Anaemia	0	0	2 (13.3)	0	2 (13.3)
Bilirubin conjugated increased	2 (13.3)	0	0	0	2 (13.3)
Blood lactate dehydrogenase increased	2 (13.3)	0	0	0	2 (13.3)
Blood triglycerides increased	2 (13.3)	0	0	0	2 (13.3)
Insulin c-peptide increased	2 (13.3)	0	0	0	2 (13.3)
Nasopharyngitis	2 (13.3)	0	0	0	2 (13.3)
Pneumonia	1 (6.7)	0	1 (6.7)	0	2 (13.3)
Pruritus	1 (6.7)	1 (6.7)	0	0	2 (13.3)
Pyrexia	1 (6.7)	0	1 (6.7)	0	2 (13.3)

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 was counted only once in the total row.

Most Frequently Reported (>10%) Treatment-emergent Adverse Events, Regardless of Causality, Overall by Preferred Term n (%) (Buparlisib 100 mg) (Safety set)

Preferred term	Buparlisib 100 mg N=17 Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Total	**2 (11.8)**	**3 (17.6)**	**8 (47.1)**	**4 (23.5)**	**17 (100)**
Alanine aminotransferase increased	7 (41.2)	0	2 (11.8)	0	9 (52.9)
Aspartate aminotransferase increased	6 (35.3)	1 (5.9)	1 (5.9)	1 (5.9)	9 (52.9)
Hyperglycaemia	4 (23.5)	3 (17.6)	1 (5.9)	0	8 (47.1)
Anaemia	3 (17.6)	2 (11.8)	1 (5.9)	0	6 (35.3)
Decreased appetite	4 (23.5)	2 (11.8)	0	0	6 (35.3)
Hyponatraemia	2 (11.8)	0	2 (11.8)	1 (5.9)	5 (29.4)

Preferred term	Buparlisib 100 mg N=17 Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Gamma-glutamyltransferase increased	1 (5.9)	0	2 (11.8)	1 (5.9)	4 (23.5)
Hypocalcaemia	3 (17.6)	1 (5.9)	0	0	4 (23.5)
Diarrhoea	1 (5.9)	1 (5.9)	1 (5.9)	0	3 (17.6)
Dyspnoea	0	1 (5.9)	2 (11.8)	0	3 (17.6)
Hypoalbuminaemia	1 (5.9)	2 (11.8)	0	0	3 (17.6)
Insomnia	3 (17.6)	0	0	0	3 (17.6)
Nausea	3 (17.6)	0	0	0	3 (17.6)
Rash	2 (11.8)	1 (5.9)	0	0	3 (17.6)
Anxiety	0	1 (5.9)	1 (5.9)	0	2 (11.8)
Asthenia	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Bilirubin conjugated increased	1 (5.9)	0	1 (5.9)	0	2 (11.8)
Blood albumin decreased	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Blood bilirubin increased	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Blood glucose increased	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Blood lactate dehydrogenase increased	0	1 (5.9)	0	1 (5.9)	2 (11.8)
C-reactive protein increased	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Constipation	2 (11.8)	0	0	0	2 (11.8)
Fatigue	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Haemoptysis	2 (11.8)	0	0	0	2 (11.8)
Hypoglycaemia	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Hypokalaemia	2 (11.8)	0	0	0	2 (11.8)
Insulin c-peptide increased	2 (11.8)	0	0	0	2 (11.8)
Mood altered	2 (11.8)	0	0	0	2 (11.8)
Mouth ulceration	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Platelet count decreased	0	1 (5.9)	1 (5.9)	0	2 (11.8)

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 was counted only once in the total row.

Treatment-emergent Deaths

Primary system organ class Preferred term	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Any primary SOC			
Total	4 (26.7)	4 (23.5)	8 (25.0)
General disorders and administrative site conditions	2 (13.3)	1 (5.9)	3 (9.4)

Primary system organ class Preferred term	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Disease progression	2 (13.3)	1 (5.9)	3 (9.4)
Infections and infestations	0	1 (5.9)	1 (3.1)
Pneumonia	0	1 (5.9)	1 (3.1)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	1 (6.7)	1 (5.9)	2 (6.3)
Lung neoplasm malignant	1 (6.7)	0	1 (3.1)
Neoplasm progression	0	1 (5.9)	1 (3.1)
Respiratory, thoracic and mediastinal disorders	1 (6.7)	1 (5.9)	2 (6.3)
Haemoptysis	1 (6.7)	0	1 (3.1)
Respiratory failure	0	1 (5.9)	1 (3.1)

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.

Treatment-emergent Serious Adverse Events Irrespective of Causality by Primary System Organ Class and Preferred Term (Buparlisib 80 mg) (Safety set)

	Buparlisib 80 mg N=15					
Primary SOC Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Any primary SOC						
Total	0	1 (6.7)	1 (6.7)	2 (13.3)	3 (20.0)	4 (26.7)
Infections and infestations						
Total	0	0	1 (6.7)	0	1 (6.7)	1 (6.7)
Pneumonia	0	0	1 (6.7)	0	1 (6.7)	1 (6.7)
Respiratory, thoracic and mediastinal disorders						
Total	0	1 (6.7)	0	2 (13.3)	2 (13.3)	3 (20.0)
Dyspnoea	0	1 (6.7)	0	1 (6.7)	1 (6.7)	2 (13.3)
Haemoptysis	0	0	0	1 (6.7)	1 (6.7)	1 (6.7)

Only on-treatment AEs are reported
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 AEs within a primary SOC was counted only once in the total row.

Treatment-emergent Serious Adverse Events Irrespective of Causality by Primary System organ Class and Preferred term (Buparlisib 100 mg) (Safety set)

	Buparlisib 100 mg N=17					
Primary SOC Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Any primary SOC						
Total	0	1 (5.9)	1 (5.9)	2 (11.8)	3 (17.6)	4 (23.5)
Blood and lymphatic system disorders						
Total	0	0	1 (5.9)	0	1 (5.9)	1 (5.9)
Thrombocytopenia	0	0	1 (5.9)	0	1 (5.9)	1 (5.9)
Infections and infestations						
Total	0	1 (5.9)	0	1 (5.9)	1 (5.9)	2 (11.8)
Pneumonia	0	0	0	1 (5.9)	1 (5.9)	1 (5.9)
Pulmonary tuberculosis	0	1 (5.9)	0	0	0	1 (5.9)
Psychiatric disorders						
Total	0	0	1 (5.9)	0	1 (5.9)	1 (5.9)
Suicide attempt	0	0	1 (5.9)	0	1 (5.9)	1 (5.9)
Respiratory, thoracic and mediastinal disorders						
Total	0	1 (5.9)	0	1 (5.9)	1 (5.9)	2 (11.8)
Pneumonitis	0	1 (5.9)	0	0	0	1 (5.9)
Respiratory failure	0	0	0	1 (5.9)	1 (5.9)	1 (5.9)

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 AEs within a primary SOC was counted only once in the total row.

Other Relevant Findings

Adverse Events per Specific Safety Event Category (SEC) (Safety set)

Adverse events per specific event category	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
Any risk total	13 (86.7)	16 (94.1)	29 (90.6)
Asthenia, fatigue total	5 (33.3)	4 (23.5)	9 (28.1)
Asthenic conditions (HLT)	5 (33.3)	4 (23.5)	9 (28.1)
Hyperglycemia (narrow) (SEC) total	11 (73.3)	10 (58.8)	21 (65.6)
Hyperglycaemia/new onset diabetes mellitus (SMQ) (narrow)	11 (73.3)	10 (58.8)	21 (65.6)
Hypersensitivity, rash (including DRESS, photosensitivity) total	1 (6.7)	4 (23.5)	5 (15.6)
Hypersensitivity (SMQ) (narrow)	1 (6.7)	4 (23.5)	5 (15.6)
Liver toxicity total	7 (46.7)	11 (64.7)	18 (56.3)
Liver related investigations, signs and symptoms (SMQ) (narrow)	7 (46.7)	11 (64.7)	18 (56.3)
Mood disorders (SEC) total	2 (13.3)	3 (17.6)	5 (15.6)
Mood disorders and disturbances NEC (HLGT)	2 (13.3)	2 (11.8)	4 (12.5)
Suicidal and self-injurious behaviours NEC (HLGT)	0	1 (5.9)	1 (3.1)
Nausea, vomiting, diarrhea (SEC) total	3 (20.0)	6 (35.3)	9 (28.1)
Nausea and vomiting symptoms (HLT)	3 (20.0)	3 (17.6)	6 (18.8)
Diarrhoea (excl infective) (HLT)	1 (6.7)	3 (17.6)	4 (12.5)
Pneumonitis total	0	1 (5.9)	1 (3.1)
Interstitial lung disease (SMQ) (narrow)	0	1 (5.9)	1 (3.1)
QTc prolongation total	1 (6.7)	0	1 (3.1)
Torsade de pointes/QT prolongation (SMQ) (broad)	1 (6.7)	0	1 (3.1)

MedDRA term levels: HLGT=high –level group terms; HLT=high-level terms; SMQ=Standardized MedDRA Queries
DRESS: drug reaction with eosinophilia
NEC: Not elsewhere classified

Number and Percentage of Patients with Notable ECG Values (Safety set)

	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
QTcF (ms)			
New >450	1/15 (6.7)	1/17 (5.9)	2/32 (6.3)
New >480	1/15 (6.7)	0	1/32 (3.1)
New >500	1/15 (6.7)	0	1/32 (3.1)
Increase from Baseline >30 ms	3/15 (20.0)	4/17 (23.5)	7/32 (21.9)
Increase from Baseline >60 ms	1/15 (6.7)	0	1/32 (3.1)

	Buparlisib 80 mg N=15 n (%)	Buparlisib 100 mg N=17 n (%)	Total N=32 n (%)
QT (ms)			
New >450	0	0	0
New >480	0	0	0
New >500	0	0	0
Increase from Baseline >30 ms	5/15 (33.3)	8/17 (47.1)	13/32 (40.6)
Increase from Baseline >60 ms	2/15 (13.3)	1/17 (5.9)	3/32 (9.4)
PR (ms)			
Increase from Baseline >25% and to a value of >200	0	1/17 (5.9)	1/32 (3.1)
QRS (ms)			
Increase from Baseline >25% and to a value of >110	1/15 (6.7)	0	1/32 (3.1)

n: Number of patients who met for a designated criterion
m: Number of patients at risk for a designated change with a non-missing value at Baseline and post-baseline
N: Total number of patients in the dose level in this analysis set
All scheduled and unscheduled visits were included in this output.

Shift from Baseline to Worst Post-baseline Score in Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder Assessment (GAD-7) (Safety set)

		PHQ-9 questionnaire					
		Baseline	Worst post- baseline value				
			1	2	3	4	Missing
Treatment		n (%)	n (%)	n (%)	n (%)	n (%)	n
Buparlisib 80 mg	1	7 (46.7)	3 (20.0)	1 (6.7)	0	1 (6.7)	2 (13.3)
	2	7 (46.7)	1 (6.7)	2 (13.3)	4 (26.7)	0	0
	3	1 (6.7)	0	0	1 (6.7)	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	15 (100.0)	4 (26.7)	3 (20.0)	5 (33.3)	1 (6.7)	2 (13.3)
Buparlisib 100 mg	1	12 (70.6)	6 (35.3)	5 (29.4)	1 (5.9)	0	0
	2	5 (29.4)	3 (17.6)	0	1 (5.9)	0	1 (5.9)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	17 (100.0)	9 (52.9)	5 (29.4)	2 (11.8)	0	1 (5.9)
Total	1	19 (59.4)	9 (28.1)	6 (18.8)	1 (3.1)	1 (3.1)	2 (6.3)

	2	12 (37.5)	4 (12.5)	2 (6.3)	5 (15.6)	0	1 (3.1)
	3	1 (3.1)	0	0	1 (3.1)	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	32 (100.0)	13 (40.6)	8 (25.0)	7 (21.9)	1 (3.1)	3 (9.4)
			GAD-7 questionnaire				
Buparlisib 80 mg	1	10 (66.7)	5 (33.3)	2 (13.3)	1 (6.7)	0	2 (13.3)
	2	4 (26.7)	0	3 (20.0)	1 (6.7)	0	0
	3	1 (6.7)	0	0	1 (6.7)	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	15 (100.0)	5 (33.3)	5 (33.3)	3 (20.0)	0	2 (13.3)
Buparlisib 100 mg	1	15 (88.2)	11 (64.7)	2 (11.8)	2 (11.8)	0	0
	2	2 (11.8)	0	1 (5.9)	0	0	1 (5.9)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	17 (100.0)	11 (64.7)	3 (17.6)	2 (11.8)	0	1 (5.9)
Total	1	25 (78.1)	16 (50.0)	4 (12.5)	3 (9.4)	0	2 (6.3)
	2	6 (18.8)	0	4 (12.5)	1 (3.1)	0	1 (3.1)
	3	1 (3.1)	0	0	1 (3.1)	0	0
	4	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	32 (100.0)	16 (50.0)	8 (25.0)	5 (15.6)	0	3 (9.4)

% is based on all evaluable patients with both baseline and post baseline scales available
PHQ-9, category 1=0-4, category 2=5-9, category 3=10-19, category 4=20-27
GAD-7, category 1=0-4, category 2=5-9, category 3=10-14, category 4=>=15
Observation time points with any missing answer are not used unless the total scores are already classified as category 4 at post-treatment

Conclusion:

The MTD/RP2D of single agent buparlisib in Chinese patients has been confirmed as 100 mg daily.

With a fast absorption and a long terminal half-life, the exposure of buparlisib at the doses of 80 and 100 mg in Chinese patients was found to be comparable to its PK in the Caucasian and Japanese patients.

No patient achieved a complete response (CR) or partial response (PR) during the study. Eleven patients (34.4%) had a best overall response of stable disease or Non-CR/Non-PD of which the majority were patients in buparlisib 100 mg arm (nine patients, 28.1%). The disease control rate was 52.9% in the 100 mg arm and 13.3% in the 80 mg arm.

The overall safety profile of buparlisib in Chinese patients was similar to what was reported in a previous study in Western and Japanese patients.

Date of Clinical Trial Report

19-Dec-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

30-Mar-2015

Date of Latest Update

Reason for Update