Sponsor

Novartis

Generic Drug Name

BEZ235 granule

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Protocol Number

CBEZ235A1101

Title

A phase I study of BEZ235, administered orally in adult Japanese patients with advanced solid tumors

Study Phase

Phase I

Study Start/End Dates

06-Oct-2010 to 03-Jul-2013

Study Design/Methodology

This study was a phase I, multi-center, open-label dose escalation study in which BEZ235 was to be administered orally as a single agent on a continuous once daily or twice daily dosing schedule. The starting dose level for first cycle (28 days) was set as 400 mg/day qd and a standard 3+3 method for dose escalation was used to establish the MTD of BEZ235. Decisions regarding dose escalation were based on the safety profile, and particularly on DLTs, observed in the first cycle of treatment for each patient.

Centers

2 centers in Japan

Publication

None

Objectives

Primary objective

To determine the MTD of BEZ235 as a single agent when administered orally to adult Japanese patients, with advanced solid tumors, which have progressed despite standard therapy or for whom no standard anticancer therapy exists.

Secondary objectives

The following secondary objectives were investigated for both the once daily and twice daily regimens:

- To assess the safety and tolerability of BEZ235 in Japanese patients.
- To characterize the PK profiles of oral BEZ235 in Japanese patients.
- To evaluate preliminary efficacy of BEZ235 in Japanese patients.
- To assess treatment effect on PI3K/mTOR pathway pharmacodynamic biomarkers.
- To assess molecular status of markers related to the PI3K/mTOR pathway and PK of BEZ235.
- To assess changes in cellular physiology by [^{18}F]-FDG-PET in patients who fulfill the eligible criteria for PET assessments.
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Test Product (s), Dose(s), and Mode(s) of Administration

BEZ235 granules were supplied at dose strengths of 200 mg and 400 mg. Following are the batch numbers of investigational product used.

Study drug and strength	Formulation control number	Batch number
BEZ235 granule 200 mg	7007710.001	H786DG
BEZ235 granule 200 mg	7007710.001	H857KG
BEZ235 granule 400 mg	7007713.001	H787DG
BEZ235 granule 400 mg	7007713.001	H838HG

Statistical Methods

The assessment of safety was based mainly on the frequency of dose limiting toxicities, other adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, and special tests) were considered as appropriate. All safety data were summarized by dose cohort and listed. All safety results were presented based on the safety set.

Objective response rate, the duration of overall response (CR or PR) and of overall complete response (CR) and progression-free survival were assessed by RECIST and summarized in terms of percentage rates with 95% confidence intervals for each stratum.

Study Population: Inclusion/Exclusion Criteria and Demographics

The target population included adult patients with advanced solid malignancies whose disease has progressed despite standard therapy or for whom no standard therapy exists.

Key inclusion criteria: at least one measurable lesion as defined by RECIST for solid tumors; age ≥ 20 years; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2; life expectancy of at least 12 weeks.

Participant Flow

Patient disposition – qd (Full Analysis Set)

	BEZ235 once daily					
Disposition Reasons	**400 mg qd N=3 n (%)**	**800 mg qd N=3 n (%)**	**1000 mg qd N=8 n (%)**	**1200 mg qd N=6 n (%)**	**1400 mg qd N=7 n (%)**	**All patients N=27 n (%)**
Treatment Discontinued	3 (100.0)	3 (100.0)	8 (100.0)	6 (100.0)	7 (100.0)	27(100.0)
Adverse event(s)	0	0	2 (25.0)	1 (16.7)	3 (42.9)	6 (22.2)
Subject withdrew consent	1 (33.3)	0	1 (12.5)	2 (33.3)	1 (14.3)	5 (18.5)
Disease progression	2 (66.7)	3 (100.0)	5 (62.5)	3 (50.0)	3 (42.9)	16 (59.3)

Patient disposition – bid (Full Analysis Set)

	BEZ235 twice daily
Disposition Reasons	**400 mg bid N=8 n (%)**
Treatment Discontinued	8 (100.0)
Adverse event(s)	1 (12.5)
Disease progression	7 (87.5)

Baseline Characteristics

Demographic characteristics – qd (Full Analysis Set)

	BEZ235 once daily					
Demographic Variable	400 mg qd N=3	800 mg qd N=3	1000 mg qd N=8	1200 mg qd N=6	1400 mg qd N=7	All patients N=27
Age (Years)						
n	3	3	8	6	7	27
Mean	62.0	65.7	54.4	60.5	55.7	58.2
SD	8.89	7.23	13.08	11.57	14.02	11.95
Median	65.0	62.0	58.5	64.5	55.0	62.0
Minimum	52.0	61.0	31.0	37.0	38.0	31.0
Maximum	69.0	74.0	70.0	67.0	74.0	74.0
Sex -n (%)						
Male	0	2 (66.7)	8 (100.0)	4 (66.7)	2 (28.6)	16 (59.3)
Female	3 (100.0)	1 (33.3)	0	2 (33.3)	5 (71.4)	11 (40.7)
Weight (kg)						
n	3	3	8	6	7	27
Mean	55.4	55.1	64.4	61.9	51.9	58.6
SD	13.28	1.47	10.92	9.34	8.65	10.36
Median	53.2	55.6	62.1	60.0	52.4	56.2
Minimum	43.3	53.4	50.2	53.5	39.7	39.7
Maximum	69.6	56.2	83.3	76.5	64.7	83.3
ECOG PS -n (%)						
0	2 (66.7)	0	4 (50.0)	3 (50.0)	2 (28.6)	11 (40.7)
1	1 (33.3)	3 (100.0)	4 (50.0)	3 (50.0)	5 (71.4)	16 (59.3)

Table Error! No text of specified style in document.**-1 Demographic characteristics – bid (Full Analysis Set)**

	BEZ235 twice daily
Demographic Variable	**400 mg bid N=8**
Age (Years)	
n	8
Mean	52.5
SD	13.35
Median	50.0
Minimum	36.0
Maximum	74.0
Sex -n (%)	
Male	4 (50.0)
Female	4 (50.0)
Weight (kg)	

Demographic Variable	BEZ235 twice daily 400 mg bid N=8
n	8
Mean	58.4
SD	16.72
Median	56.9
Minimum	43.8
Maximum	96.2
ECOG PS -n (%)	
0	3 (37.5)
1	5 (62.5)

Outcome Measures

Summary of Efficacy

Efficacy Results

Best overall response – qd (Full Analysis Set)

Best response	BEZ235 once daily 400 mg qd N=3 n (%)	800 mg qd N=3 n (%)	1000 mg qd N=8 n (%)	1200 mg qd N=6 n (%)	1400 mg qd N=7 n (%)	All patients N=27 n (%)
Objective response (CR+PR)	0	0	0	0	0	0
Complete Response (CR)	0	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0	0
Stable Disease (SD)	1 (33.3)	3(100.0)	3 (37.5)	3 (50.0)	4 (57.1)	14 (51.9)
Progressive Disease (PD)	1 (33.3)	0	5 (62.5)	2 (33.3)	2 (28.6)	10 (37.0)
Unknown (UNK)	1 (33.3)	0	0	1 (16.7)	1 (14.3)	3 (11.1)

Best overall response – bid (Full Analysis Set)

Best response	BEZ235 twice daily 400 mg bid N=8 n (%)
Objective response (CR+PR)	0
-Complete Response (CR)	0
-Partial Response (PR)	0
Stable Disease (SD)	2 (25.0)
Progressive Disease (PD)	5 (62.5)
Unknown (UNK)	1 (12.5)

Summary of Safety

Safety Results

Adverse Events by System Organ Class (At least 20%) – qd (Safety Set)

	BEZ235 once daily					
System Organ Class	400 mg qd N=3 n (%)	800 mg qd N=3 n (%)	1000 mg qd N=8 n (%)	1200 mg qd N=6 n (%)	1400 mg qd N=7 n (%)	All patients N=27 n (%)
-Any primary system organ class	3 (100.0)	3 (100.0)	8 (100.0)	6 (100.0)	7 (100.0)	27 (100.0)
Gastrointestinal disorders	3 (100.0)	3 (100.0)	8 (100.0)	6 (100.0)	7 (100.0)	27 (100.0)
Metabolism and nutrition disorders	2 (66.7)	3 (100.0)	7 (87.5)	6 (100.0)	7 (100.0)	25 (92.6)
Skin and subcutaneous tissue disorders	1 (33.3)	3 (100.0)	6 (75.0)	4 (66.7)	7 (100.0)	21 (77.8)
General disorders and administration site conditions	1 (33.3)	2 (66.7)	6 (75.0)	5 (83.3)	4 (57.1)	18 (66.7)
Blood and lymphatic system disorders	2 (66.7)	1 (33.3)	5 (62.5)	2 (33.3)	7 (100.0)	17 (63.0)
Infections and infestations	0	2 (66.7)	5 (62.5)	4 (66.7)	3 (42.9)	14 (51.9)
Investigations	2 (66.7)	2 (66.7)	2 (25.0)	3 (50.0)	5 (71.4)	14 (51.9)
Nervous system disorders	0	2 (66.7)	3 (37.5)	4 (66.7)	2 (28.6)	11 (40.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (66.7)	2 (66.7)	2 (25.0)	1 (16.7)	0	7 (25.9)

AE with 20% or higher incidence by SOC in All Patients are shown.

Adverse Events by System Organ Class (At least 20%) – bid (Safety Set)

	BEZ235 twice daily
System Organ Class	400 mg bid N=8 n (%)
-Any primary system organ class	8 (100.0)
Gastrointestinal disorders	8 (100.0)
Blood and lymphatic system disorders	7 (87.5)
Investigations	7 (87.5)
Metabolism and nutrition disorders	7 (87.5)
Skin and subcutaneous tissue disorders	7 (87.5)
General disorders and administration site conditions	6 (75.0)
Infections and infestations	5 (62.5)
Psychiatric disorders	5 (62.5)
Respiratory, thoracic and mediastinal disorders	4 (50.0)

System Organ Class	BEZ235 twice daily 400 mg bid N=8 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (37.5)
Musculoskeletal and connective tissue disorders	2 (25.0)

AE with 20% or higher incidence by SOC in All Patients are shown.

Most Frequently Reported AEs Overall by Preferred Term (At least 20%) –qd (Safety Set)

Preferred Term	BEZ235 once daily 400 mg qd N=3 n (%)	800 mg qd N=3 n (%)	1000 mg qd N=8 n (%)	1200 mg qd N=6 n (%)	1400 mg qd N=7 n (%)	All patients N=27 n (%)
-Total	3 (100.0)	3 (100.0)	8 (100.0)	6 (100.0)	7 (100.0)	27 (100.0)
Diarrhoea	2 (66.7)	3 (100.0)	7 (87.5)	6 (100.0)	7 (100.0)	25 (92.6)
Decreased appetite	2 (66.7)	3 (100.0)	7 (87.5)	6 (100.0)	6 (85.7)	24 (88.9)
Nausea	3 (100.0)	1 (33.3)	7 (87.5)	5 (83.3)	6 (85.7)	22 (81.5)
Stomatitis	2 (66.7)	2 (66.7)	3 (37.5)	6 (100.0)	5 (71.4)	18 (66.7)
Vomiting	2 (66.7)	1 (33.3)	4 (50.0)	5 (83.3)	5 (71.4)	17 (63.0)
Fatigue	1 (33.3)	2 (66.7)	6 (75.0)	4 (66.7)	4 (57.1)	17 (63.0)
Rash	1 (33.3)	0	5 (62.5)	1 (16.7)	4 (57.1)	11 (40.7)
Lymphopenia	2 (66.7)	1 (33.3)	2 (25.0)	1 (16.7)	4 (57.1)	10 (37.0)
Neutropenia	0	1 (33.3)	1 (12.5)	2 (33.3)	4 (57.1)	8 (29.6)
Thrombocytopenia	0	1 (33.3)	4 (50.0)	0	3 (42.9)	8 (29.6)
Dysgeusia	0	1 (33.3)	2 (25.0)	3 (50.0)	2 (28.6)	8 (29.6)
Cancer pain	2 (66.7)	2 (66.7)	2 (25.0)	1 (16.7)	0	7 (25.9)
Leukopenia	0	1 (33.3)	2 (25.0)	1 (16.7)	2 (28.6)	6 (22.2)
Pyrexia	1 (33.3)	1 (33.3)	2 (25.0)	2 (33.3)	0	6 (22.2)
Alanine aminotransferase increased	2 (66.7)	0	0	1 (16.7)	3 (42.9)	6 (22.2)
Blood alkaline phosphatase increased	1 (33.3)	0	2 (25.0)	1 (16.7)	2 (28.6)	6 (22.2)

AE with 20% or higher incidence by PT in All Patients are shown.

Most Frequently Reported AEs Overall by Preferred Term (At least 20%) –bid (Safety Set)

Preferred term	BEZ235 twice daily 400 mg bid N=8 n (%)
-Total	8 (100.0)
Diarrhoea	7 (87.5)
Nausea	7 (87.5)
Decreased appetite	7 (87.5)
Thrombocytopenia	5 (62.5)
Stomatitis	5 (62.5)
Fatigue	5 (62.5)
Lymphopenia	4 (50.0)
Vomiting	4 (50.0)
Alanine aminotransferase increased	4 (50.0)
Aspartate aminotransferase increased	4 (50.0)
Haemoglobin decreased	4 (50.0)
Hypoalbuminaemia	4 (50.0)
Insomnia	4 (50.0)
Dry skin	4 (50.0)
Rash	4 (50.0)
Cheilitis	3 (37.5)
Dysphagia	3 (37.5)
Blood creatinine increased	3 (37.5)
Cancer pain	3 (37.5)
Malaise	2 (25.0)
Pyrexia	2 (25.0)
Urinary tract infection	2 (25.0)
Blood alkaline phosphatase increased	2 (25.0)
Gamma-glutamyltransferase increased	2 (25.0)
Hyperkalaemia	2 (25.0)
Hyponatraemia	2 (25.0)
Anxiety	2 (25.0)

AE with 20% or higher incidence by PT are shown.

Death, other serious or clinically significant adverse events- (Safety Set)

	BEZ235 once daily						BEZ235 twice daily
	400 mg qd N=3 n (%)	800 mg qd N=3 n (%)	1000 mg qd N=8 n (%)	1200 mg qd N=6 n (%)	1400 mg qd N=7 n (%)	All patients N=27 n (%)	400 mg bid N=8 n (%)
Death	0	0	0	0	0	0	0
SAEs	2 (66.7)	0	3 (37.5)	2 (33.3)	1(14.3)	8 (29.6)	1 (12.5)
AEs leading to discontinuation	1 (33.3)	0	2 (25.0)	1 (16.7)	3 (42.9)	7 (25.9)	1 (12.5)
AEs requiring dose interruption or reduction	2 (66.7)	0	5 (62.5)	6 (100)	6 (85.7)	19 (70.4)	7 (87.5)

Other Relevant Findings

None

Date of Clinical Trial Report

02 April 2014

Date Inclusion on Novartis Clinical Trial Results Database

15 April 15, 2014

Date of Latest Update