Sponsor

Novartis

Generic Drug Name

BKM120

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Protocol Number

CBKM120X1101

Title

A Phase I study of BKM120, administered orally in adult Japanese patients with advanced solid tumors

Phase of Development

Phase I

Study Start/End Dates

05-Oct-2009 to 08-Oct-2011

Study Design/Methodology

The study was an open-label, multicenter Phase I dose-escalation study in adult patients with advanced solid tumors whose disease had progressed despite standard therapy or for whom no standard anticancer therapy existed. Oral BKM120 was administered once daily on a continuous schedule and a treatment cycle consisted of 28 days.

Fifteen patients were planned to be enrolled for the Bayesian model to have reasonable operating characteristics relating to its Maximum Tolerated Dose (MTD) recommendation and six patients were planned to be enrolled at the MTD level.

A total of fifteen patients were enrolled into this study and received at least one dose of BKM120: three patients in the 25 mg/day cohort, three patients in the 50 mg/day cohort, and nine patients in the 100 mg/day cohort.

Duration of treatment: A treatment cycle consisted of 28 days.

Centres

National Cancer Center Hospital East and Nagoya University Hospital

Publication

None

Outcome measures

Primary outcome measure(s)

Maximum Tolerated Dose (MTD) - Determination of the MTD was based upon the estimation of the dose dependent incidence rate of dose limiting toxicity (DLT) in Cycle 1 in patients of the dose-determining set.

Secondary outcome measure(s)

Efficacy:

- Efficacy assessments using Response Evaluation Criteria In Solid Tumors (RECIST) guidelines were done by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan.
- Tumor markers were to be assessed at the discretion of the investigator, only if measurable levels at baseline.

Safety:

- Incidence rate of DLT was the primary variable for safety and tolerability assessment.
- Other safety assessments: Frequency and type of adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiogram (ECG), patient-reported outcomes, cardiac imaging (multiple gated acquisition [MUGA] or echocardiogram [ECHO]), physical examination, height and body weight.

Bioanalytics:

- PK parameters of BKM120 were evaluated based on concentration of BKM120 in plasma.
- Biomarkers in tumor, skin, and blood were assessed.

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

BKM120 2.5-mg, 10-mg, and 50-mg hard gelatin capsules.

Oral BKM120 was administered once daily on a continuous schedule. The starting dose level for Cycle 1 was set as 25 mg/day. Cycle 1 doses were to be administered according to the dose-escalation schedule. Dose-escalation or dose-reduction was to continue until MTD was reached.

Statistical Methods

The predicted MTD was the actually administered dose with the highest posterior probability of DLT in the target interval [16%, 33%) among the dose fulfilling the overdose criteria. The determination of MTD was based on the final predicted MTD, but

also took into account further available safety and tolerability information.

Unless otherwise noted, the other safety and efficacy analyses were conducted by dose cohort. For continuous variables, descriptive statistics (n, Mean, standard deviation [SD], Median, Min, Max) were used. For discrete variables, the number and percentage of patients or events were presented. All data were listed appropriately. No statistical hypothesis testing was conducted.

No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Patients aged 20 years old and above
- Patients with histologically-confirmed, advanced unresectable solid tumors who had progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy existed
- At least one measurable or non-measurable lesion as defined by RECIST guidelines
- Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2

Exclusion criteria:

- History of primary central nervous system tumors or brain metastases or who had signs/symptoms attributable to brain metastases and had not been assessed with radiologic imaging to rule out the presence of brain metastases
- Prior treatment with a PI3K inhibitor
- Known clinically significant chronic liver disease (active or history of Hepatitis B virus or Hepatitis C virus [positive HBsAg, HBcAb, or HCVAb]), renal disease or pancreatitis
- Patients with any peripheral neuropathy ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 2
- Patients with the following mood disorders:
  - Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others)
  - ≥CTCAE grade 3 anxiety
- Concurrent severe and/or uncontrolled medical conditions- impaired cardiac function or clinically significant cardiac diseases, clinically manifest diabetes mellitus, history of gestational diabetes mellitus, or steroid-induced diabetes mellitus, active or uncontrolled infection
- Patients who were currently receiving treatment with medication that had the potential to prolong the QT interval or inducing Torsades de Pointes, and the treatment could not either be discontinued or switched to a different medication prior to starting study drug
- Patients who were currently receiving treatment with warfarin potassium or any other coumarin-derivative anticoagulants

- Patients who had received corticosteroids ≤ 2 weeks systemically prior to starting study drug or who had not recovered from the side effects of such treatment

Participant Flow

Patient disposition (FAS)

	25 mg/day N=3 n (%)	50 mg/day N=3 n (%)	100 mg/day N=9 n (%)	All N=15 n (%)
Treatment ongoing	0	0	0	0
Discontinued	3(100.0)	3(100.0)	9(100.0)	15(100.0)
Adverse event(s)	2(66.7)	0	3(33.3)	5(33.3)
Abnormal laboratory value(s)	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0
Subject withdrew consent	0	0	0	0
Lost to follow-up	0	0	0	0
Administrative problems	0	0	0	0
Death*	0	0	0	0
Disease progression	1(33.3)	3(100.0)	6(66.7)	10(66.7)
Protocol deviation	0	0	0	0

*: Death includes only those patients who discontinued the study due to death.

Baseline Characteristics

Demographic and baseline characteristics (FAS)

Demographic variable	25 mg/day N=3	50 mg/day N=3	100 mg/day N=9	All N=15
Age (Years)				
Mean (SD)	59.0(13.00)	45.0(22.07)	56.9(12.93)	54.9(14.71)
Median	66.0	47.0	58.0	58.0
Min-Max	44-67	22-66	35-71	22-71
Sex, n (%)				
Male	2(66.7)	3(100.0)	7(77.8)	12(80.0)
Female	1(33.3)	0	2(22.2)	3(20.0)
BSA* (m2)				
Mean (SD)	1.68(0.205)	1.72(0.155)	1.65(0.217)	1.67(0.192)
Median	1.74	1.80	1.69	1.73
Min-Max	1.4- 1.8	1.5- 1.8	1.3- 1.9	1.3- 1.9
ECOG performance status, n (%)				
0	3(100.0)	2(66.7)	5(55.6)	10(66.7)
1	0	1(33.3)	4(44.4)	5(33.3)
2	0	0	0	0

* BSA (m^2) = 234.94 x Height(cm)**0.422 x Weight(kg)**0.515 / 10000

Outcome measures

Primary Outcome Result(s)

MTD

DLTs were assessed in fifteen patients in the dose-determining set. One patient in the 100 mg/day cohort experienced a DLT (grade 4 abnormal of liver function) on C1D28 which led to temporary interruption of the study medication followed by discontinuation due to disease progression. This DLT resolved approximately one month after the onset.

The recommended dose was determined to be 100 mg/day. Posterior probabilities of DLT rates being in the targeted toxicity [16%, 33%), excessive toxicity [33%, 60%), and unacceptable toxicity [60%, 100%] range at 100 mg/day were 24.6%, 1.9%, and 0.0%, respectively.

The posterior distribution of DLT rates indicated that doses from 120 to 150 mg/day also satisfied the overdose criteria for recommended. Nevertheless, all principal investigators and the Novartis agreed to recommend the dose of 100 mg/day without further dose escalation to determine MTD, taking into account the clinical information such as hyperglycemia, mood alteration, and increased transaminases.

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

Dose (mg/day)	Posterior probabilities (%) that the probability of DLT is in interval:						Quantile		
	0-0.16	0.16-0.33	0.33-0.60	0.60-1	Mean	SD	2.5%	50%	97.5%
25	99.6	0.4	0.0	0.0	2.1	2.8	0.0	1.0	10.1
50	97.6	2.4	0.0	0.0	4.4	4.2	0.1	3.1	15.9
100	73.5	24.6	1.9	0.0	12.2	7.9	1.8	10.6	31.3
120	55.5	35.8	8.4	0.3	16.9	10.8	2.6	14.6	43.2
140	41.6	38.9	17.2	2.2	21.9	14.6	3.2	18.6	58.8
150	36.8	38.6	20.4	4.2	24.4	16.4	3.5	20.5	66.6
160	32.9	37.5	23.0	6.5	26.9	18.2	3.8	22.5	73.1
170	29.8	36.2	24.9	9.1	29.2	19.7	4.1	24.4	78.8

Secondary Outcome Result(s)

Best overall response

Best overall response	25 mg/day N=3 n (%)	50 mg/day N=3 n (%)	100 mg/day N=9 n (%)	All N=15 n (%)
Complete response (CR)	0	0	0	0
Partial response (PR)	0	0	0	0
Stable disease (SD)	2(66.7)	1(33.3)	3*(33.3)	6*(40.0)
Progressive disease (PD)	1(33.3)	2(66.7)	4(44.4)	7(46.7)
Unknown (UNK)	0	0	2(22.2)	2(13.3)
Overall response	0	0	0	0
Disease control (CR+PR+SD)	2(66.7)	1(33.3)	3(33.3)	6(40.0)

* Including one unconfirmed PR

Pharmacokinetic

Summary of PK parameters of BKM120 (PK analysis set)

PK parameter	25 mg/day			50 mg/day			100 mg/day		
	C1D1	C1D8	C1D28	C1D1	C1D8	C1D28	C1D1	C1D8	C1D28
Tmax (hr)									
n	3	3	3	3	3	3	9	7	9
Median	1.00	1.00	1.00	1.02	1.10	1.50	1.50	1.02	2.98
Min-Max	1.000-1.000	1.000-3.000	1.000-4.000	0.500-2.000	1.000-4.000	1.050-2.000	0.483-2.120	0.500-4.070	1.000-4.050
Cmax (ng/mL)									
n	3	3	3	3	3	3	9	7	9
Mean (SD)	289 (45.0)	549 (275.0)	530 (131.0)	595 (212.0)	738 (221.0)	767 (121.0)	1080 (331.0)	1930 (560.0)	1790 (503.0)
AUClast (hr·ng/mL)									
n	3	3	3	3	3	3	9	7	9
Mean (SD)	2060 (475)	4640 (1230)	6800 (3040)	3840 (830)	9540 (3180)	11400 (3330)	8800 (1530)	24300 (6200)	25100 (8010)
AUC0-24 (hr·ng/mL)									
n	3	3	3	3	3	3	9	7	9
Mean (SD)	2060 (474)	4640 (1230)	6800 (3040)	3830 (834)	9550 (3200)	11400 (3320)	8800 (1530)	24300 (6190)	25000 (7950)
T1/2 (hr)									
n	2	1	NA	NA	NA	NA	4	3	2
Mean (SD)	36.8 (9.20)	43.8(-)					30.6 (9.62)	39.5 (25.20)	41.8 (16.90)
Racc									
n	NA	3	3	NA	3	3	NA	7	9
Mean (SD)		2.25 (0.150)	3.20 (0.673)		2.58 (1.160)	3.09 (1.290)		2.78 (0.655)	2.87 (0.829)

Safety Results

Adverse Events by System Organ Class (SOC) (Safety Population)

AEs observed in 3 or more patients (≥15% of all patients) regardless of study drug relationship by primary SOC and preferred term (PT) (Safety set)

	All grades				Grade 3/4			
System organ class Preferred term	25 mg/day N=3 n (%)	50 mg/day N=3 n (%)	100 mg/day N=9 n (%)	All N=15 n (%)	25 mg/day N=3 n (%)	50 mg/day N=3 n (%)	100 mg/day N=9 n (%)	All N=15 n (%)
Patients with AE(s)	3(100.0)	3(100.0)	9(100.0)	15(100.0)	2(66.7)	1(33.3)	7(77.8)	10(66.7)
Investigations	3(100.0)	3(100.0)	9(100.0)	15(100.0)	2(66.7)	1(33.3)	1(11.1)	4(26.7)
Blood insulin increased	0	1(33.3)	5(55.6)	6(40.0)	0	0	0	0
Eosinophil count increased	3(100.0)	0	3(33.3)	6(40.0)	0	0	0	0
Alanine aminotransferase increased	2(66.7)	1(33.3)	1(11.1)	4(26.7)	2(66.7)	0	0	2(13.3)
Insulin C-peptide increased	0	1(33.3)	3(33.3)	4(26.7)	0	0	0	0
Activated partial thromboplastin time prolonged	0	1(33.3)	2(22.2)	3(20.0)	0	0	0	0
Blood lactate dehydrogenase increased	2(66.7)	1(33.3)	0	3(20.0)	0	0	0	0
Gastrointestinal disorders	2(66.7)	2(66.7)	8(88.9)	12(80.0)	0	0	0	0
Constipation	1(33.3)	0	4(44.4)	5(33.3)	0	0	0	0
Diarrhea	0	1(33.3)	2(22.2)	3(20.0)	0	0	0	0
Stomatitis	0	1(33.3)	2(22.2)	3(20.0)	0	0	0	0
Metabolism and nutrition disorders	0	2(66.7)	8(88.9)	10(66.7)	0	0	3(33.3)	3(20.0)
Decreased appetite	0	0	5(55.6)	5(33.3)	0	0	0	0
Hyperkalemia	0	0	3(33.3)	3(20.0)	0	0	0	0
Hypokalemia	0	1(33.3)	2(22.2)	3(20.0)	0	0	2(22.2)	2(13.3)
Skin and subcutaneous tissue disorders	1(33.3)	2(66.7)	7(77.8)	10(66.7)	0	0	0	0
Rash	0	0	7(77.8)	7(46.7)	0	0	0	0
Pruritus	0	1(33.3)	3(33.3)	4(26.7)	0	0	0	0
Blood and lymphatic system disorders	0	1(33.3)	6(66.7)	7(46.7)	0	0	2(22.2)	2(13.3)
Anemia	0	0	3(33.3)	3(20.0)	0	0	2(22.2)	2(13.3)
General disorders and administration site conditions	0	0	7(77.8)	7(46.7)	0	0	0	0

Fatigue	0	0	5(55.6)	5(33.3)	0	0	0	0
Psychiatric disorders	0	0	6(66.7)	6(40.0)	0	0	1(11.1)	1(6.7)
Mood altered	0	0	3(33.3)	3(20.0)	0	0	0	0
Hepatobiliary disorders	0	0	4(44.4)	4(26.7)	0	0	4(44.4)	4(26.7)
Hepatic function abnormal	0	0	4(44.4)	4(26.7)	0	0	4(44.4)	4(26.7)

Only AEs of which occurrence of all grades in All column in the All grades is greater than or equal to 15% are presented.
Primary SOCs and PTs within primary SOC are sorted in descending order of frequency in the All column in the All grades respectively

Serious Adverse Events and Deaths

Deaths (safety set)

Death	25 mg/day N= 3 n (%)	50 mg/day N= 3 n (%)	100 mg/day N= 9 n (%)
Total	0	0	2 (22.2)
Principal cause of death	0	0	
pneumonitis	0	0	1 (11.1)
hemorrhage/ bleeding-other (left neck region)	0	0	1 (11.1)

Serious Adverse Events and other significant events (safety set)

Adverse event	25 mg/day N= 3 n (%)	50 mg/day N= 3 n (%)	100 mg/day N= 9 n (%)	All N=15 n (%)
Any AE	3 (100.0)	3 (100.0)	9 (100.0)	15 (100.0)
Any AE related to study drug	3 (100.0)	3 (100.0)	9 (100.0)	15 (100.0)
Any SAE	0	0	6 (66.7)	6 (40.0)
Any SAE related to study drug	0	0	5 (55.6)	5 (33.3)
Any AE leading to study drug discontinuation	2 (66.7)	0	3 (33.3)	5 (33.3)
Any AE related to study drug leading to study drug discontinuation	2 (66.7)	0	2 (22.2)	4 (26.7)

Biomarkers

- Glucose metabolism was analyzed in 15 patients on C1D1, C1D8 and C1D28, and the results showed a tendency towards an increase in fasting plasma glucose, C-peptide and insulin with the concentrations of BKM120, reaching the peak at 0.5-1h post-dose at all dose levels. The increases were subtle in most cases, and more pronounced changes were observed with higher exposure to BKM120.
- No clear data supporting direct correlation between clinical activity of BKM120and biomarker changes was obtained.
- Results from ^{18}F-FDG-PET scan showed only stable metabolic disease, since no changes beyond ±25% from baseline in mean of SUVmax were detected except in one patient who showed changes with −46.8% although there is no data to support clinical response in this patient.

Other Relevant Findings

None

Date of Clinical Trial Report

29-Nov-2012

Date Inclusion on Novartis Clinical Trial Results Database

4-Feb-2013

Date of Latest Update