Sponsor

Novartis

Generic Drug Name

Gimatecan

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

None

Study Number

CLBQ707A1101

Title

A phase I dose escalation study of LBQ707 (Gimatecan) administered orally 5 consecutive days to Japanese patients with advanced solid tumor

Phase of Development

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Study Start/End Dates

30 Jun 2006 to 20 Feb 2008

Study Design/Methodology

This was an open-label, dose-escalation study to assess the safety and pharmacokinetics of LBQ707 administered five consecutive days every 28 days orally to adult patients with advanced solid tumors who had progressed despite standard therapy or for whom standard systemic therapy did not exist. For the purpose of estimating a maximum tolerable dose (MTD), the “3+3” design was employed.

Initially, three patients of 1 cohort were treated with LBQ707. After three consecutive patients had completed 4 weeks observation, if no dose limiting toxicity (DLT) was noted in any of these patients, then the study could proceed to the next, higher dose level. If DLT was noted in one of the three patients, the investigational drug was administered to three additional patients. If DLT was noted in one patients among the total of 6 patients, then the study could proceed to the next higher dose level. If DLTs were noted in 2 or more patients in the cohort, the study could not proceed to the next higher dose level and enrolled up to 6 patients at the previous dose level to confirm MTD.

Starting dose was 0.25 mg/day and subsequent dose levels increased to 0.5, 0.75, 1.0 and 1.25 mg/day. If 0.25 mg/day (the starting dose level) was not tolerated, reduced dose level of 0.1 mg/day was examined. If dose of 0.1 mg/day was not tolerated, the study was to be terminated.

This study consisted of four treatment cycles of LBQ707. Thereafter, patients could continue to receive additional cycles of LBQ707 therapy under the extension protocol (LBQ707A1101E1).

Centers

One center in Japan

Publication

None

Objectives

Primary objective(s)

- To estimate the maximum tolerated dose (MTD) of LBQ707 administered orally for 5 consecutive days every 28 days in Japanese patients with advanced solid tumors who had progressed despite standard therapy or for whom no standard therapy existed.

Secondary objective(s)

- To characterize the safety and tolerability profile of single agent LBQ707
- To characterize the single and repeated dose pharmacokinetic profile of LBQ707 including the parent drug and potential metabolite(s) in plasma and urine
- To evaluate preliminary evidence of anti-tumor activity of single agent LBQ707

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

LBQ707 was administered orally for 5 consecutive days every 28 days (day 1-5 drug on/day 6-28 drug off). The study drug had to be taken orally on a fasting condition.

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

None

Criteria for Evaluation

Maximum Tolerated Dose (MTD)/Dose Limiting Toxicity (DLT)

The MTD was defined as the dose level immediately below that at which DLT was observed in at least two out of three to six patients during the initial dosing cycle. DLT was considered unacceptable even in the setting of an incurable solid malignancy and it was evaluated based on the toxicities during the initial 28 days (Cycle 1). An adverse event was determined to be a DLT based on the predefined criteria.

Safety

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of blood test, urine test, regular measurement of vital signs, weight, performance status, physical examination and ECG.

Efficacy

Preliminary antineoplastic activity was evaluated based on the modified RECIST criteria. The responses for tumors were assessed and categorized by the investigator as complete response (CR), partial response (PR), stable disease/no response (SD), progressive disease (PD) or unknown (UNK) at the respective evaluation. Best overall response rates (CR, PR), time to best overall response (CR, PR), duration of stable disease (CR, PR, SD), time to progression and best overall response (CR, PR, SD, PD, UNK) were summarized.

Pharmacokinetics (PK)

PK parameters (including T_{max}, C_{max}, AUC_{0-24h}, $T_{1/2}$) on Days 1 and 5 were determined using a non-compartmental method.

Statistical Methods

Safety population was defined as all patients who have received at least one dose of study medication (LBQ707) and had at least one safety evaluation after administration of study medication. All safety evaluations and analyses were performed in this population. MTD estimating population was defined as all patients who completed the first treatment cycle (Cycle 1) according to protocol or discontinued due to DLT. The first cycle data from this population were used to estimate the MTD in this study. Intent- to-treat (ITT) population was defined as all patients who received at least one dose of the study medication. Efficacy analyses was performed in ITT population and PK analysis was performed in ITT patients who received treatment and who had at least one blood sample available for PK analysis.

Data was presented primarily in a descriptive fashion with respect to demographic and baseline characteristics, efficacy, safety, and pharmacokinetic measurements.

Study Population:

Inclusion criteria

- Patients aged ≥ 20 years, who provided informed consent prior to any screening procedures, with histological or cytological confirmed advanced solid tumors, which had progressed despite standard therapy or for whom no standard therapy existed
- At least one tumor lesion (measurable or non-measurable) as defined by RECIST guideline
- Patients with performance status of 0 or 1 on the ECOG scale, life expectancy of at least 3 months and the ability and agreeable to reminaing in-patient until at least day 8 for first cycle.
- Women of childbearing potential had to have a negative pregnancy test prior to the initiation of study drug. Male and female patients of reproductive potential had to agree to employ an effective method of birth control throughout the study and for up to 3 months following discontinuation of study drug.
- Demonstrate the following hematological /blood chemistry laboratory values within 14 days prior to the first dose of study drug: ANC ≥ 1500/mm3, Hgb ≥ 9.0 g/dL, PLT ≥ 150000/mm3 (non-transfused), Total bilirubin ≤ 1.5 x ULN, AST/ALT/ALP ≤ 2.5 x ULN (Patients with known bone metastases might be eligible with ALP ≤ 5.0 x ULN if ALT and AST were within the normal range and bone metastasis was thought to account for elevated ALP), Serum creatinine ≤ 1.5 x ULN, Serum albumin ≥2.5 g/dL.

Exclusion criteria

- Patients with gastrointestinal dysfunction, such as gastrectomy, that could alter absorption or with malabsorption syndrome, or unable to swallow.
- Patients who had received any investigational compound within the past 28 days. If adverse drug reactions carry over, e.g. in case of sustained-release product, the patient should be excluded
- Severe cardiac insufficiency (NYHA III or IV), with uncontrolled and/or unstable cardiac or coronary artery disease
- Patients with other antineoplastic therapy including chemotherapy, hormone therapy, immunotherapy, radiation therapy within the last 28 days (42 days for Nitrosourea, Mitomycin C and Melphalan). Palliative radiotherapy for local peripheral metastases and OK-432 for pleurodesis were allowed unless within the past 14 days.
- Previous treatment with 4 or more cycles of carboplatin or with 2 or more courses of Nitrosourea or Mitomycin C or Melphalan
- Patients with a history of allergies to the camptothecin family drug.
- Previous radiation therapy greater than or equal to 25% of the hematopoietic reserve
- Patients with CNS and/or leptomeningeal disease metastases were not allowed on study unless asymptomatic and not receiving corticosteroid therapy
- Patients who had not recovered fully from surgery for any cause.
- Patients known to be HIV or hepatitis virus positive, or patients with the presence of active or suspected acute or chronic uncontrolled infection

- Patients with complication of interstitial pneumonia or pulmonary fibrosis proven on a chest X-ray
- Patients with a history of allergies to the camptothecin family drug.
- Patients with a large volume of ascitic and/or pleural fluid which was needed drainage
- A history of noncompliance to medical regimens or inability or unwillingness to return for all scheduled visits
- Concurrent medical conditions that would significantly limit full compliance with the study regimen
- Deemed otherwise unsuitable by the investigator

Number of Subjects

Patient disposition by dose cohort (Enrolled patients)

Disposition Reason	LBQ707 0.25 mg/day N=3	LBQ707 0.5 mg/day N=3	LBQ707 0.75 mg/day N=7	LBQ707 1.0 mg/day N=6	All Patients N=19
Treated	3 (100.0)	3 (100.0)	7 (100.0)	6 (100.0)	19 (100.0)
Discontinued	3 (100.0)	3 (100.0)	6 (85.7)	6 (100.0)	18 (94.7)
Still on treatment 20FEB2008	0	0	1 (14.3)	0	1 (5.3)
Discontinued					
Disease progression	3 (100.0)	3 (100.0)	5 (71.4)	5 (83.3)	16 (84.2)
Adverse event(s)	0	0	1 (14.3)	0	1 (5.3)
Not proceed to extension	0	0	0	1 (6.7)	1 (5.3)

Analysis populations by dose cohort (Enrolled patients)

Analysis populations	LBQ707 0.25 mg/day N=3 n (%)	LBQ707 0.5 mg/day N=3 n (%)	LBQ707 0.75 mg/day N=7 n (%)	LBQ707 1.0 mg/day N=6 n (%)	All Patients N=19 n (%)
All patients	3	3	7	6	19
Safety population	3 (100)	3 (100)	7 (100)	6 (100)	19 (100)
MTD estimation population	3 (100)	3 (100)	6 (85.7)	6 (100)	18 (94.7)
ITT population	3 (100)	3 (100)	7 (100)	6 (100)	19 (100)
PK population	3 (100)	3 (100)	7 (100)	6 (100)	19 (100)

Demographic and Background Characteristics

Demographic summary by dose cohort (Safety population)

Demographic Variable	LBQ707 0.25 mg/day N=3	LBQ707 0.5 mg/day N=3	LBQ707 0.75 mg/day N=7	LBQ707 1.0 mg/day N=6	All Patients N=19
Baseline Age (Year)					
Mean	62.3	60.7	60.3	58.7	60.2
SD	3.79	0.58	7.83	10.23	7.26
Median	64.0	61.0	62.0	62.0	61.0
min	58.0	60.0	44.0	42.0	42.0
max	65.0	61.0	69.0	68.0	69.0
Baseline Age category n(%)					
< 65	2 (66.7)	3 (100.0)	6 (85.7)	4 (66.7)	15 (78.9)
>= 65	1 (33.3)	0	1 (14.3)	2 (33.3)	4 (21.1)
Sex n(%)					
Female	2 (66.7)	2 (66.7)	2 (28.6)	1 (16.7)	7 (36.8)
Male	1 (33.3)	1 (33.3)	5 (71.4)	5(83.3)	12 (63.2)
Height (cm)					
Mean	154.7	159.3	158.4	162.7	159.3
SD	10.07	10.69	6.16	6.06	7.38
Median	156.0	157.0	159.0	162.5	160.0
min	144.0	150.0	149.0	153.0	144.0
max	164.0	171.0	165.0	170.0	171.0
Weight (kg)					
Mean	58.0	53.4	61.3	63.2	60.1
SD	3.86	8.91	4.13	2.97	5.54
Median	58.2	53.9	61.4	62.9	61.4
min	54.0	44.2	54.1	59.8	44.2
max	61.7	62.0	67.5	67.7	67.7
Body surface area (m2)					
Mean	1.6	1.5	1.7	1.7	1.6
SD	0.09	0.17	0.07	0.06	0.10
Median	1.6	1.5	1.7	1.7	1.7
min	1.5	1.4	1.6	1.6	1.4
max	1.7	1.7	1.8	1.8	1.8
ECOG PS n(%)					
0	1 (33.3)	2 (66.7)	2 (28.6)	3 (50.0)	8 (42.1)
1	2 (66.7)	1 (33.3)	5 (71.4)	3 (50.0)	11 (57.9)

Primary Objective Result(s)

DLTs were evaluated in 18 patients for MTD estimation population (3, 3, 6, and 6 patients in the 0.25, 0.5, 0.75, and 1.0 mg/day cohorts, respectively). Four patients of the 18 patients had 5 DLTs during cycle 1 of the LBQ707 treatment.

Incidence of dose limiting toxicity (MTD estimation population)

Dose limiting toxicity (DLT)	LBQ707 0.25 mg/day N=3 n (%)	LBQ707 0.5 mg/day N=3 n (%)	LBQ707 0.75 mg/day N=6 n (%)	LBQ707 1.0 mg/day N=6 n (%)	All Patients N=18 n (%)
Patients with DLT	0	0	1 (14.3)	3 (50.0)	4 (22.2)

DLTs of grade 4 thrombocytopenia and grade 4 neutropenia were observed in one patient at dose level of 0.75 mg/day. At dose level of 1.0 mg/day, three patients had DLTs which are grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 deterioration of cancer related pain, respectively. Dose level of 0.75mg/day was determined as a MTD.

Secondary Objective Result(s)

Safety Results

Number (%) of patients with adverse events regardless of causality by primary system organ class and dose cohort (Safety population)

Primary system organ class	LBQ707 0.25 mg/day N=3 n (%)	LBQ707 0.5 mg/day N=3 n (%)	LBQ707 0.75 mg/day N=7 n (%)	LBQ707 1.0 mg/day N=6 n (%)	All Patients N=19 n (%)
Total no. of patients with AE	3 (100.0)	3 (100.0)	7 (100.0)	6 (100.0)	19 (100.0)
Gastrointestinal disorders	2 (66.7)	3 (100.0)	5 (71.4)	5 (83.3)	15 (78.9)
General disorders and administration site conditions	3 (100.0)	2 (66.7)	3 (42.9)	5 (83.3)	13 (68.4)
Metabolism and nutrition disorders	1 (33.3)	2 (66.7)	3 (42.9)	4 (66.7)	10 (52.6)
Blood and lymphatic system disorders	1 (33.3)	1 (33.3)	2 (28.6)	4 (66.7)	8 (42.1)
Nervous system disorders	2 (66.7)	1 (33.3)	1 (14.3)	3 (50.0)	7 (36.8)
Infections and infestations	1 (33.3)	2 (66.7)	1 (14.3)	2 (33.3)	6 (31.6)
Musculoskeletal and connective tissue disorders	0	1 (33.3)	2 (28.6)	3 (50.0)	6 (31.6)
Neoplasms benign, malignant and unspecified (cysts and polyps)	1 (33.3)	1 (33.3)	1 (14.3)	3 (50.0)	6 (31.6)
Skin and subcutaneous tissue disorders	0	1 (33.3)	2 (28.6)	2 (33.3)	5 (26.3)
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	1 (14.3)	2 (33.3)	4 (21.1)
Cardiac disorders	1 (33.3)	0	1 (14.3)	0	2 (10.5)
Psychiatric disorders	0	0	1 (14.3)	1 (16.7)	2 (10.5)
Hepatobiliary disorders	0	0	0	1 (16.7)	1 (5.3)
Injury, poisoning and proce-	1 (33.3)	0	0	0	1 (5.3)

dural complications					

Primary system organ classes are sorted in descending frequency, as reported in the All patients group.
A patient with multiple AEs within a primary system organ class is counted only once in the system organ class.

Most frequently reported AEs overall by preferred term n (%) with N≥4(Safety population)

Preferred term	**LBQ707 0.25 mg/day N=3 n (%)**	**LBQ707 0.5 mg/day N=3 n (%)**	**LBQ707 0.75 mg/day N=7 n (%)**	**LBQ707 1.0 mg/day N=6 n (%)**	**All Patients N=19 n (%)**
Fatigue	3 (100.0)	2 (66.7)	2 (28.6)	4 (66.7)	11 (57.9)
Anorexia	1 (33.3)	2 (66.7)	3 (42.9)	4 (66.7)	10 (52.6)
Nausea	0	1 (33.3)	3 (42.9)	4 (66.7)	8 (42.1)
Cancer pain	1 (33.3)	1 (33.3)	0	3 (50.0)	5 (26.3)
Constipation	0	2 (66.7)	1 (14.3)	2 (33.3)	5 (26.3)
Lymphopenia	1 (33.3)	1 (33.3)	1 (14.3)	2 (33.3)	5 (26.3)
Alopecia	0	1 (33.3)	2 (28.6)	1 (16.7)	4 (21.1)
Diarrhoea	2 (66.7)	1 (33.3)	0	1 (16.7)	4 (21.1)
Neutropenia	0	0	1 (14.3)	3 (50.0)	4 (21.1)

Number and percentage of patients with adverse event (Safety population)

	LBQ707 0.25 mg/day N=3 n (%)	**LBQ707 0.5 mg/day N=3 n (%)**	**LBQ707 0.75 mg/day N=7 n (%)**	**LBQ707 1.0 mg/day N=6 n (%)**	**All Patients N=19 n (%)**
Any AE	3 (100.0)	3 (100.0)	7 (100.0)	6 (100.0)	19 (100.0)
CTC grade 3	1(33.3)	2 (66.7)	1 (14.3)	3 (50.0)	7 (36.8)
CTC grade 4	0	0	1 (14.3)	2 (33.3)	3 (15.8)
Death	0	0	0	0	0
Serious adverse event	0	0	1 (14.3)	1 (16.7)	2 (10.5)
Discontinuation due to AEs	0	0	1 (14.3)	0	1 (5.3)

Efficacy Results

Best overall response by dose cohort (ITT population)

Best overall response	**LBQ707 0.25 mg/day N=3**	**LBQ707 0.5 mg/day N=3**	**LBQ707 0.75 mg/day N=7**	**LBQ707 1.0 mg/day N=6**	**All Patients N=19**
	n(%)	n(%)	n(%)	n(%)	n(%)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0
Stable Disease(SD)	1 (33.3)	1 (33.3)	2 (28.6)	2 (33.3)	6 (31.6)

Progressive Disease(PD)	2 (66.7)	2 (66.7)	5 (71.4)	4 (66.7)	13 (68.4)
Unknown (UNK)	0	0	0	0	0

Pharmacokinetic Results

Summary of main pharmacokinetic parameters of LBQ707

Parameter	**LBQ707 0.25 mg/day (N=3)**		**LBQ707 0.50 mg/day (N=3)**		**LBQ707 0.75 mg/day (N=7)**		**LBQ707 1.0 mg/day (N=6)**	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5[a]	Day 1	Day 5[b]
T_{max} (hr)	1.00 (0.967, 1.02)	1.00 (0.583, 1.00)	1.00 (0.500, 1.02)	1.00 (1.00, 1.00)	1.00 (1.00, 4.00)	1.00 (0.500, 2.00)	0.508 (0.500, 1.00)	0.50 (0.500, 6.00)
C_{max} (ng/mL)	17.4 ± 4.25	39.0 ± 18.2	31.4 ± 6.33	64.2 ± 23.9	43.6 ± 16.6	112 ± 63.8	80.4 ± 12.8	194 ± 64.1
AUC_{0-24h} (ng·h/mL)	198 ± 115	652 ± 373	369 ± 149	1030 ± 588	512 ± 155	1510 ± 676	926 ± 286	2940 ± 1250
$T_{1/2}$ (hr)	-[c]	92.0 ± 14.7	-[c]	70.1 ± 37.3	-[c]	69.3 ± 18.6	-[c]	72.2 ± 16.4

Each value represents mean ± SD except for T_{max} of median (range)

a: n=6

b: n=5

c: Not derived due to insufficient time period (up to 24 hours after administration)

Safety Results

Discussed under secondary objectives result(s).

Date of Clinical Trial Report

27 Mar 2009

Date Inclusion on Novartis Clinical Trial Results Database

14 Feb 2011

Date of Latest Update