Sponsor

Novartis

Generic Drug Name

Sonidegib

Trial Indication

Locally advanced or metastatic pancreatic adenocarcinoma

CLDE225X2103

Protocol Title

A phase Ib, open-label, multi-center, dose escalation, safety and tolerability study of sonidegib in combination with gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma

Clinical Trial Phase

Ib

Clinical Development Phase

I

Study Start/End Dates

05-Mar-2012 to 02-Jul-2014

Study Design/Methodology

This was a multicenter, open-label, phase Ib study in adults with locally advanced or metastatic pancreatic adenocarcinoma to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of sonidegib in combination with gemcitabine. The study was conducted in 2 phases: dose-escalation and safety-expansion.

A total of 18 patients were enrolled. Nine patients were enrolled in the escalation phase, and the remaining nine patients were enrolled in the dose expansion phase.

Dose Escalation: This study population consisted of adult patients with histologically or cytologically confirmed diagnosis of inoperable locally advanced or metastatic pancreatic adenocarcinoma that had not been previously treated or had progressed despite prior chemotherapy (other than gemcitabine). Patients who had previously received radiation therapy treatment were excluded from participating in the study.

Safety Expansion: This study population consisted of adult patients with histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic

adenocarcinoma who had not been previously treated with cytotoxic therapy including chemotherapy (other than gemcitabine) or radiation.

Centers

5 enrolling centers in 3 countries: United Kingdom (1 center), Spain (1 center), and United States (3 centers)

Publications

None

Objectives:

Primary objectives

The primary objective of this study was to determine the MTD and/or the recommended dose for expansion (RDE) of sonidegib to be administered in combination with standard dose of gemcitabine (1000 mg/m^2).

Secondary objectives

- To characterize the safety and tolerability profile of sonidegib at the MTD when administrated in combination with gemcitabine.
- To characterize the PK of sonidegib when administered in combination with gemcitabine

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

Sonidegib was administered orally on a flat scale of mg/day and not by weight or body surface area. Sonidegib was supplied as 50 mg, 100 mg, and 200 mg hard-gelatin capsules in bottles.

Sonidegib was dispensed at the start of every cycle, as needed.

Sonidegib was administered orally once a day, as part of each 28-day cycle. The investigational site staff informed each patient of their actual daily dose, and this was recorded on the appropriate CRF.

When possible, the individual doses consisted of the minimum number of capsules equaling the total dose given the available capsule sizes.

Gemcitabine was provided as an infusion prepared by a site pharmacist.

Statistical Methods

Full analysis set (FAS) (N=18) comprises all patients who received at least one dose (full or partial) of any study drug component (sonidegib or gemcitabine). Patients were analyzed according to the assigned treatment.

Safety set (N=18) comprises all patients who received at least one (full or partial) dose of any study drug component (sonidegib or gemcitabine). Patients were analyzed according to the treatment they actually received. Treatment actually received was defined as the treatment assigned if it was received at least once or, otherwise, the initial treatment received.

Dose determining set (DDS) (N=9) comprises all patients from the safety set who either met the minimum exposure criterion and had sufficient safety evaluations (as specified below), or experienced a dose limiting toxicity (DLT) within 8 weeks following the first dose. Only patients from the dose escalation were included in the DDS to determine the MTD/RDE.

For patients who did not experience DLTs, the minimum treatment and safety evaluation requirements for dose escalation would have been met if:

- the patient was treated with at least 75% of the planned doses (42 out of 56) of LDE225 and at least 2 out of the 3 planned infusions in each 4-week cycle of gemcitabine have been administered within 8 weeks following the first dose, and the patient was observed for at least 8 weeks following the first dose, and
- the patient completed sufficient safety evaluations, as agreed by the investigators and the sponsor, to determine whether a DLT has occurred or no

The recommendation of the MTD was based on the probability of DLT estimated by a 3-parameter Bayesian Logistic Regression Model guided by the escalation with overdose control (EWOC) principle. The EWOC mandates that any dose with a posterior DLT rate > 25% in the excessive toxicity interval is not considered for the next treatment group. MTD of the study was defined to be the highest dose that has at least 6 evaluable patients and at least 50% posterior probability in the target toxicity interval, among all the doses fulfilling EWOC criterion.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

For **dose escalation** patients:

1. Patients with histologically or cytologically confirmed locally advanced or metastatic pancreatic adenocarcinoma that had not been previously treated or had progressed despite prior chemotherapy (other than gemcitabine, except if administered in an adjuvant session more than 12 months prior to study entry). Patients who had previously received radiation treatment were excluded. Inclusion was irrespective of the stage of the disease or extent of prior therapy.

For **safety expansion** patients:

2. Patients with a histologically or cytologically confirmed locally advanced or metastatic pancreatic adenocarcinoma who had not been previously treated with cytotoxic chemotherapy (other than gemcitabine, except if administered in an adjuvant session more than 12 months prior to study entry) or radiation. Prior adjuvant cytotoxic therapy following potentially curative surgery (eg, a Whipple procedure) was not permitted if within 12 months prior to study entry.

3. At least one measurable lesion (per RECIST 1.0) defined as ≥ 1 lesion that could be accurately measured in ≥ 1 dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. Patients with only non-measurable disease were not eligible for the expansion phase of the study.

For **both** dose escalation and safety expansion patients:

4. Age ≥18 years
5. WHO performance status ≤ 1
6. Patients must have had the following laboratory values:
   - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
   - Hemoglobin (Hgb) ≥ 9 g/dL (5.6 mmol/L)
   - Platelets ≥ 100 x 10^9/L
   - Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal)
   - AST and ALT ≤ 2.5 x ULN if liver metastases are not present or ≤ 5.0 x ULN if liver metastases are present
   - Serum creatinine ≤ 1.5 x ULN or 24-hour creatinine clearance of ≥ 50 mL/minute
   - Blood creatine phosphokinase (CK) level ≤ 1.5 x ULN

Exclusion criteria

For **dose escalation** patients:

1. Patients who have received chemotherapy within a period of time that is less than the cycle length used for that treatment (eg, <6 weeks for nitrosoureas, mitomycin-C) prior to starting study drug or who have not recovered from the side effects of such therapy
2. Patients who have received prior radiotherapy

For **safety expansion** patients:

3. Previously treated with cytotoxic therapy (eg, chemotherapy or radiation) including prior adjuvant cytotoxic therapy within 12 months prior to study entry, except prior gemcitabine if administered in an adjuvant session more than 12 months prior to study entry

For **both** dose escalation and safety expansion patients:

4. Prior treatment with a smoothened antagonist
5. Resectable and/or pancreatic cancer that is potentially curable by surgery

Participant Flow Table

Patient disposition by phase and treatment (FAS)

	Escalation phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9 n(%)	Expansion phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9 n(%)	All patients N=18 n(%)
Patients enrolled			
Treated	9 (100.0)	9 (100.0)	18 (100.0)
Patients treated			
Discontinued	9 (100.0)	9 (100.0)	18 (100.0)
primary reason for treatment discontinuation			
Administrative problems	0	3 (33.3)	3 (16.7)
Adverse event(s)	1 (11.1)	0	1 (5.6)
Disease progression	6 (66.7)	5 (55.6)	11 (61.1)
Patient withdrew consent	2 (22.2)	1 (11.1)	3 (16.7)
Primary reason for study evaluation completion			
Death	4 (44.4)	4 (44.4)	8 (44.4)
Follow up phase completed as per protocol	3 (33.3)	4 (44.4)	7 (38.9)
Patient withdrew consent	2 (22.2)	1 (11.1)	3 (16.7)

Percentage based on N

Demographic and Baseline Characteristics

Demographic and baseline characteristics (FAS)

Demographic variable	Escalation phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9	Expansion phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9	All patients N=18
Age (years)			
Mean (SD)	63.7 (7.37)	67 (8.46)	65.3 (7.88)
Median	64	66	65.5
Min-Max	54 – 74	57 - 86	54 - 86
Age category (years) – n (%)			
<65	5 (55.6)	3 (33.3)	8 (44.4)
≥ 65	4 (44.4)	6 (66.7)	10 (55.6)
Gender – n (%)			
Male	6 (66.7)	3 (33.3)	9 (50.0)
Female	3 (33.3)	6 (66.7)	9 (50.0)

Demographic variable	Escalation phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9	Expansion phase Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=9	All patients N=18
Race – n (%)			
Caucasian	9 (100.0)	9 (100.0)	18 (100.0)
Weight (kg)			
Mean (SD)	69.1 (13.83)	68.6 (23.84)	68.8 (18.91)
Median	71	63	64
Min-Max	52-89.4	49.8-127.6	49.8-127.6
Height (cm)			
Mean (SD)	168.2 (12.27)	159.8 (9.31)	164 (11.41)
Median	168	163	163.1
Min-Max	152-186	146.3-175	146.3-186
Body surface area (m^2)			
Mean (SD)	1.8 (0.22)	1.7 (0.28)	1.8 (0.25)
Median	1.8	1.7	1.7
Min-Max	1.5-2.2	1.4-2.4	1.4-2.4
ECOG performance status – n (%)			
0	3 (33.3)	2 (22.2)	5 (27.8)
1	6 (66.7)	7 (77.8)	13 (72.2)

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation

Primary endpoint

Primary Endpoint Results

Determination of the MTD

Summary of posterior distribution of DLT rates (DDS)

Targeted toxicity interval is [0.16, 0.33]

	Posterior probabilities (%) that Pr(DLT) is in interval:				
	[0, 0.16)	[0.16,0.33)	[0.33-1]	Mean	SD
200 mg sonidegib	0.515	0.432	0.053	0.168	0.088
400 mg sonidegib	0.289	0.571	0.140	0.223	0.096
600 mg sonidegib	0.155	0.553	0.292	0.276	0.114
800 mg sonidegib	0.093	0.464	0.444	0.328	0.138

Summary of posterior distribution of CK elevation DLT rates (DDS)

Targeted toxicity interval [0, 0.16]

	Posterior probabilities (%) that Pr(DLT) is in interval:			
	[0, 0.16)	[0.16, 1.00]	Mean	SD
200 mg sonidegib	0.923	0.077	0.070	0.057
400 mg sonidegib	0.816	0.184	0.105	0.067
600 mg sonidegib	0.615	0.385	0.150	0.086
800 mg sonidegib	0.438	0.562	0.204	0.124

Analysis of pharmacokinetics

Pharmacokinetic results of sonidegib

Summary of PK parameters for sonidegib by treatment for cycle 1 day 1 (PAS)

	Statistics	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 (N=18)	n	15	16	16
	Mean (SD)	1580 (1050)	185 (90.7)	N/A
	CV% mean	66.9	49.0	N/A
	Geo-mean	1360	158	N/A
	CV% geo-mean	57.5	71.7	N/A
	Median	1260	189	3.05
	[Min; Max]	[484; 4950]	[28.9; 356]	[0.920; 7.25]

n - number of patients with non-missing values
CV%= coefficient of variation (%) = sd/mean*100
CV% geo-mean= sqrt (exp (variance for log transformed data)-1)*100

Summary of PK parameters for sonidegib by treatment for cycle 3 day 1 (PAS)

	Statistics	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 (N=18)	n	8	9	9
	Mean (SD)	19500 (15500)	1140 (824)	N/A
	CV% mean	79.7	72.3	N/A
	Geo-mean	14300	903	N/A

	Statistics	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
	CV% geo-mean	106.0	84.3	N/A
	Median	14900	888	2.22
	[Min; Max]	[4330; 43500]	[306; 2810]	[0; 7.50]

n - number of patients with non-missing values
CV%= coefficient of variation (%) = sd/mean*100
CV% geo-mean= sqrt (exp (variance for log transformed data)-1)*100

Summary of Safety

Safety Results

Adverse events (greater than or equal to 15 percent), regardless of study drug relationship, by preferred term, and maximum CTC grade (Safety set)

	Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=18	
	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**
Total	**18 (100.0)**	**14 (77.8)**
Anaemia	10 (55.6)	1 (5.6)
Neutrophil count decreased	9 (50.0)	7 (38.9)
Platelet count decreased	9 (50.0)	0
Pyrexia	9 (50.0)	3 (16.7)
Nausea	7 (38.9)	1 (5.6)
Vomiting	7 (38.9)	1 (5.6)
Abdominal pain	6 (33.3)	1 (5.6)
Alanine aminotransferase increased	5 (27.8)	1 (5.6)
Blood creatine phosphokinase increased	5 (27.8)	2 (11.1)
Diarrhoea	5 (27.8)	2 (11.1)
Fatigue	5 (27.8)	1 (5.6)
Neutropenia	5 (27.8)	4 (22.2)
Thrombocytopenia	5 (27.8)	0
Alopecia	4 (22.2)	0
Aspartate aminotransferase increased	4 (22.2)	3 (16.7)
Asthenia	4 (22.2)	1 (5.6)
Back pain	4 (22.2)	0
Decreased appetite	4 (22.2)	0

Preferred term	Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=18	
	All grades n (%)	Grade 3/4 n (%)
Dizziness	4 (22.2)	0
Urinary tract infection	4 (22.2)	0
Abdominal pain upper	3 (16.7)	0
Constipation	3 (16.7)	0
Musculoskeletal pain	3 (16.7)	0
White blood cell count decreased	3 (16.7)	2 (11.1)

Preferred terms are sorted in descending frequency of "all grades" column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
AEs occurring more than 30 days after the last date of the study treatment are not summarized.

Adverse events, regardless of study drug relationship, by system organ class, and maximum CTC grade (Safety set)

System organ class	Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=18	
	All grades n (%)	Grade 3/4 n (%)
Any system organ class	**18 (100.0)**	**14 (77.8)**
Blood and lymphatic system disorders	12 (66.7)	6 (33.3)
Gastrointestinal disorders	13 (72.2)	4 (22.2)
General disorders and administration site conditions	13 (72.2)	4 (22.2)
Investigations	15 (83.3)	10 (55.6)
Metabolism and nutrition disorders	8 (44.4)	3 (16.7)
Musculoskeletal and connective tissue disorders	8 (44.4)	0
Nervous system disorders	6 (33.3)	1 (5.6)
Skin and subcutaneous tissue disorders	6 (33.3)	0
Vascular disorders -Total	5 (27.8)	0

System organ class	Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=18	
	All grades n (%)	Grade 3/4 n (%)
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. AEs occurring more than 30 days after last date of study treatment are not summarized.		

Deaths, other serious or clinically significant adverse events, or related discontinuations (Safety set)

Category	Sonidegib 400 mg + Gemcitabine 1000 mg/m^2 N=18	
	All grades n (%)	Grade 3/4 n (%)
On-treatment deaths [1]	2 (11.1)	N/A
Pancreatic adenocarcinoma	2 (11.1)	N/A
Adverse events	18 (100.0)	14 (77.8)
Suspected to be drug-related	14 (77.8)	10 (55.6)
Serious adverse events	8 (44.4)	6 (33.3)
Suspected to be drug-related	2 (11.1)	2 (11.1)
AEs leading to discontinuation [2]	1 (5.6)	1 (5.6)

Categories were not mutually exclusive. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
1 - Deaths occurring >30 days after the end of treatment were not included.
2 - The AE leading to discontinuation was an increase in blood creatine phosphokinase

Other Relevant Findings

Not applicable

Conclusion:

The study included 2 phases: dose escalation and safety expansion phase. The objective of the study was to identify the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) for the combination of sonidegib and gemcitabine. Only data from the dose escalation phase were used to determine MTD/RDE.

A total of 18 patients enrolled, 9 of which enrolled in the dose escalation phase and all of them were included in the dose-determining set. Three patients experienced dose limiting toxicities (CK increase, mucositis, and elevated AST). All DLTs were grade 3. Per the

Bayesian Logistic Regression Model, 400 mg sonidegib daily is the highest dose which met the overdose control criterion (EWOC), as confirmed by the two analysis models: the posterior probability of excessive toxicity is 14% and 18.4% respectively, lower than 25%. Therefore, the starting dose was established as both MTD and RDE, the study only had one treatment group.

Both MTD and RDE were declared at 400 mg sonidegib in combination with the standard fixed dose of gemcitabine (1000 mg/m^2).

The pharmacokinetic characteristics of 400 mg once daily sonidegib observed in the current study were similar to what was seen in other clinical studies. Approximately 11.6-fold accumulation was observed from Cycle 3 Day 1 to Cycle 1 Day 1. No pharmacokinetic interactions were observed.

Date of Clinical Trial Report

05-May-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

01-Jul-2015

Date of Latest Update

Not applicable

Reason for Update

Not applicable.