NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

LCL161

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLCL161A1102

Protocol Title

A phase I study of oral LCL161 in Japanese adult patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

19-Nov-2013 to 11-Jun-2015

Reason for Termination (If applicable)

Novartis terminated the study due to change in development strategy of LCL161.

Study Design/Methodology

This was an open-label dose escalation study to estimate the maximum tolerated dose (MTD) / recommended dose (RD) of oral LCL161 when administered as a single agent in Japanese patients with advanced solid tumors for which no further effective standard therapy exists. This study was comprised of two parts. A dose escalation part was designed to estimate the single agent MTD/RD and to gain initial safety data on the combination with weekly paclitaxel. Subsequently a dose expansion part was to be employed to characterize the safety, pharmacokinetic (PK), pharmacodynamics (PD), and preliminary activity of oral LCL161 at

the MTD/RD when administered in combination with weekly paclitaxel. A Bayesian Logistic Regression Model by the escalation with overdose control principle was used to guide the dose escalation and estimate the MTD/RD of LCL161 as a single agent. Paclitaxel could be initiated in addition to LCL161 dosing from Cycle 2 in the dose escalation part as well as the dose expansion part. Each treatment cycle was a 21-day in length.

Centers

2 centers in Japan

Publication

None

Objectives:

Primary objective– dose escalation part:

- Estimate the MTD/RD of oral LCL161 when administered as a single agent in Japanese patients with advanced solid tumors

Co-Primary objective – dose escalation part and dose expansion part:

- Characterize the safety of oral LCL161 when administered in combination with once weekly paclitaxel

Secondary objectives:

- Characterize the safety and tolerability of oral LCL161 when administered as a single agent
- Evaluate the PK of oral LCL161 when administered as a single agent or in combination with once weekly paclitaxel
- Evaluate the PK of paclitaxel when administered in combination with LCL161
- Assess any preliminary anti-tumor activity of LCL161 when administered as a single agent or in combination with once weekly paclitaxel

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

The starting dose of LCL161 in this study was 600 mg p.o. weekly (QW). Doses higher than 1800 mg were not to be explored in this study based on the prior clinical experience of CLCL161A2101 study. Paclitaxel at a fixed dose of 80 mg/m^2 over one hour i.v., was to be administered immediately before oral LCL161 dosing. LCL161 was provided as 300 mg film-coated tablets in bottle. Paclitaxel was provided as 100 mg solution for injection in vial.

Statistical Methods

This study was early terminated due to change in the development strategy of LCL161; Only 9 patients were treated at 2 dose levels in the dose escalation part and no patients were enrolled in the dose expansion part. Study data was analyzed using data with the final database lock after all 9 patients discontinued the study. Some analyses described in the protocol were not performed due to the limited sample size.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Patients with a histologically or cytologically confirmed diagnosis of a solid tumor for which no further effective standard treatment is available.
- Measurable or non-measurable (but evaluable) disease as determined by RECIST version 1.1.
- Male or female patients 18 years or older.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
- Patients must have recovered from all toxicities related to their previous treatment.

Key Exclusion Criteria:

- Patients with primary central nervous system (CNS) tumors or brain metastases.
- Patients with unresolved nausea, vomiting, diarrhea or peripheral neuropathy Common Terminology Criteria for Adverse Events (CTCAE) grade >1.
- History of or current interstitial lung disease.
- History of or current impaired cardiac function or clinically significant cardiac diseases.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception.

Participant Flow Table

Patient disposition (FAS)

	LCL161 600 mg N=5 n (%)	LCL161 1200 mg N=4 n (%)	All patients N=9 n (%)
Patients enrolled			
Treated with LCL161 only [1]	0	2 (50.0)	2 (22.2)
Treated with LCL161 and Paclitaxel [2]	5 (100)	2 (50.0)	7 (77.8)
Patient treated			
Treatment discontinued	5 (100)	4 (100)	9 (100)

	LCL161 600 mg N=5 n (%)	LCL161 1200 mg N=4 n (%)	All patients N=9 n (%)
Primary reason for end of treatment			
Progressive disease	2 (40.0)	4 (100)	6 (66.7)
Adverse event	3 (60.0)	0	3 (33.3)

- [1] Patients received LCL161 monotherapy throughout the study.
- [2] Patients received both LCL161 monotherapy and LCL161+Paclitaxel combination therapy during the study.

Baseline Characteristics

Demographics by treatment (FAS)

	LCL161 600 mg N=5	LCL161 1200 mg N=4	All patients N=9
Age (Years, at screening)			
n	5	4	9
Mean	57.6	55.0	56.4
SD	13.32	7.07	10.45
Median	59.0	52.5	55.0
Min	41	50	41
Max	74	65	74
Age category (Years, at screening) –n (%)			
<65 Years	3 (60.0)	3 (75.0)	6 (66.7)
>=65 Years	2 (40.0)	1 (25.0)	3 (33.3)
Sex -n (%)			
Female	3 (60.0)	2 (50.0)	5 (55.6)
Male	2 (40.0)	2 (50.0)	4 (44.4)
Predominant Race -n (%)			
Asian	5 (100)	4 (100)	9 (100)
Ethnicity -n (%)			
Japanese	5 (100)	4 (100)	9 (100)
Weight (kg, at baseline)			
n	5	4	9
Mean	53.52	56.63	54.90
SD	12.905	5.748	9.916
Median	49.80	57.05	56.60

	LCL161 600 mg N=5	LCL161 1200 mg N=4	All patients N=9
Min	41.9	49.2	41.9
Max	70.4	63.2	70.4
Height (cm, at screening)			
n	5	4	9
Mean	164.22	162.38	163.40
SD	9.130	4.087	6.992
Median	164.60	162.60	164.60
Min	151.8	158.4	151.8
Max	177.2	165.9	177.2
BMI (kg/m^2)			
n	5	4	9
Mean	19.71	21.45	20.48
SD	3.597	1.641	2.885
Median	18.23	21.73	20.89
Min	15.5	19.4	15.5
Max	24.3	23.0	24.3
Body surface area (m^2)			
n	5	4	9
Mean	1.56	1.61	1.58
SD	0.221	0.097	0.169
Median	1.52	1.61	1.59
Min	1.3	1.5	1.3
Max	1.9	1.7	1.9
ECOG performance status -n (%)			
0	3 (60.0)	3 (75.0)	6 (66.7)
1	2 (40.0)	1 (25.0)	3 (33.3)

Primary Outcome Result(s)

Determination of MTD

The MTD of oral LCL161 when administered as a single agent in Japanese patients was not determined in the study because this study was early terminated due to change in development strategy of LCL161. Of the 9 patients, 1 patient had a DLT (rash maculo-papular) at the LCL161 1200 mg QW group during the cycle 1 of LCL161 treatment as a single agent.

Secondary Outcome Result(s)

No patients showed complete response (CR). One patient achieved the best response of partial response (PR) and 4 patients demonstrated the best response of stable disease.

Summary of Safety

Safety Results

All and grade 3/4 adverse events, regardless of study drug relationship, by preferred term and treatment (more than or equal to 2 patients for All grades of All patients) (Safety set)

	LCL161 600 mg N=5		LCL161 1200 mg N=4		All patients N=9	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	5 (100)	4 (80.0)	4 (100)	3 (75.0)	9 (100)	7 (77.8)
Alopecia	5 (100)	0	2 (50.0)	0	7 (77.8)	0
Lymphocyte count decreased	4 (80.0)	3 (60.0)	0	0	4 (44.4)	3 (33.3)
Nausea	2 (40.0)	1 (20.0)	2 (50.0)	0	4 (44.4)	1 (11.1)
Peripheral sensory neuropathy	3 (60.0)	0	1 (25.0)	0	4 (44.4)	0
Vomiting	2 (40.0)	0	2 (50.0)	0	4 (44.4)	0
White blood cell count decreased	3 (60.0)	1 (20.0)	1 (25.0)	1 (25.0)	4 (44.4)	2 (22.2)
Anaemia	2 (40.0)	0	1 (25.0)	0	3 (33.3)	0
Aspartate aminotransferase increased	2 (40.0)	0	1 (25.0)	0	3 (33.3)	0
Decreased appetite	2 (40.0)	1 (20.0)	1 (25.0)	0	3 (33.3)	1 (11.1)
Dysgeusia	2 (40.0)	0	1 (25.0)	0	3 (33.3)	0
Malaise	3 (60.0)	1 (20.0)	0	0	3 (33.3)	1 (11.1)
Neutrophil count decreased	1 (20.0)	0	2 (50.0)	1 (25.0)	3 (33.3)	1 (11.1)
Pruritus	2 (40.0)	0	1 (25.0)	0	3 (33.3)	0
Pyrexia	2 (40.0)	0	1 (25.0)	0	3 (33.3)	0
Alanine aminotransferase increased	1 (20.0)	0	1 (25.0)	0	2 (22.2)	0
Bacteraemia	2 (40.0)	2 (40.0)	0	0	2 (22.2)	2 (22.2)

Preferred term	LCL161 600 mg N=5		LCL161 1200 mg N=4		All patients N=9	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Blood creatinine increased	1 (20.0)	0	1 (25.0)	0	2 (22.2)	0
Diarrhoea	1 (20.0)	1 (20.0)	1 (25.0)	0	2 (22.2)	1 (11.1)
Insomnia	2 (40.0)	0	0	0	2 (22.2)	0
Myalgia	2 (40.0)	0	0	0	2 (22.2)	0
Neutropenia	2 (40.0)	1 (20.0)	0	0	2 (22.2)	1 (11.1)
Oedema peripheral	2 (40.0)	0	0	0	2 (22.2)	0
Rash maculo-papular	0	0	2 (50.0)	1 (25.0)	2 (22.2)	1 (11.1)
Stomatitis	2 (40.0)	0	0	0	2 (22.2)	0

- Preferred terms are sorted in descending frequency of ‘All grades’ column, as reported in the ‘All patients’ column.
- 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 is counted only once in the total row.
- Only AEs occurring during treatment or within 28 days of the last dose of study drug are reported.
- MedDRA version 18.0 and CTCAE version 4.03 have been used for the reporting

Serious Adverse Events and Deaths (Safety set)

	LCL161 600 mg N=5	LCL161 1200 mg N=4	All patients N=9
	n (%)	n (%)	n (%)
Death	1 (20.0)	0	1 (11.1)
SAE(s)	3 (60.0)	1 (25.0)	4 (44.4)
Discontinued due to SAE(s)	2 (40.0)	0	2 (22.2)

Other Relevant Findings

Summary of primary PK parameters for LCL161 (PAS)

Dose	Cmax (ng/mL)	Tmax (h)	AUClast (ng·h/mL)	AUCinf (ng·h/mL)
Cycle1 Day1				
600 mg	1460 ± 691 (47.4)	NA	15200 ± 5280 (34.8)	15200± 5280 (34.8)
n=5	1240 [610; 2210]	3.97 [1; 4.02]	15800 [6720; 21000]	15800 [6720; 21000]
1200 mg	2120± 662 (31.2)	NA	22200 ± 520 (2.3)	22200 ± 551 (2.5)
n=3	2010 [1520; 2830]	1.98 [0.93; 2]	22500 [21600; 22500]	22500 [21600; 22600]
Cycle1 Day8				
600 mg	1590 ± 545 (34.2)	NA	16500 ±5600 (33.9)	16500 ±5600 (33.9)
n=5	1660 [795; 2270]	2 [1; 4.05]	18700 [7810; 21400]	18700 [7810; 21400]
1200 mg	2730 ± 873 (31.9)	NA	24300 ± 3990 (16.4)	24300 ±3990 (16.4)
n=3	3080 [1740; 3380]	2 [1; 4.08]	24900 [20000; 27900]	24900 [20000; 27900]
Cycle2 Day1				
600 mg	1560 ± 593 (37.9)	NA	15000 ± 5670 (37.8)	14500 ± 5120 (35.4)
n=5 *	1560 [930; 2310]	4 [0.95; 6]	13700 [7210; 21100]	14800 [7910; 20400]
1200 mg	3100	NA	25800	27600
n=1	3100 [3100; 3100]	4 [4; 4]	25800 [25800; 25800]	27600 [27600; 27600]

Data represents arithmetic mean± SD (CV%), median [min; max]. Only median [min; max] was shown for Tmax.

* n=4 for AUCinf

Summary of primary PK parameters for paclitaxel (PAS)

Dose	Cmax (ng/mL)	Tmax (h)	AUClast (ng·h/mL)	AUCinf (ng·h/mL)
Cycle2 Day1				
600 mg	3260 ± 761 (23.3)	NA	6280 ± 2230 (35.6)	6400 ± 2190 (34.2)
n=5	2770 [2640; 4290]	1.08 [1.05; 1.18]	5610 [4250; 9940]	5660 [4400; 9980]

Dose	Cmax (ng/mL)	Tmax (h)	AUClast (ng·h/mL)	AUCinf (ng·h/mL)
1200 mg	4000 ± 424 (10.6)	NA	7650 ± 318 (4.2)	7920
n=2 *	4000 [3700; 4300]	1.07 [1.02; 1.12]	7650 [7420; 7870]	7920 [7920; 7920]

Data represents arithmetic mean± SD (CV%), median [min; max]. Only median [min; max] was shown for Tmax.

* n=1 for AUCinf

Conclusion:

The MTD of oral LCL161 when administered as a single agent in Japanese patients was not determined in the study because this study was early terminated due to change in development strategy of LCL161. As the data for the safety profile of LCL161 was limited due to early termination of the study, it was difficult to conclude the tolerability of LCL161 when administered in combination with paclitaxel. No conclusion of efficacy and pharmacokinetic of LCL161 was drawn from the study due to the limited data.

Date of Clinical Trial Report

5 Feb 2016