Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

ceritinib, luminespib

Trial Indication(s)

ALK-rearranged non-small cell lung cancer

Protocol Number

CLDK378X2102

Protocol Title

A Phase Ib, open-label, dose escalation study of LDK378 and AUY922 in patients with ALK-rearranged non-small cell lung cancer

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase III

Study Start/End Dates

10 Jun 2013 to 05 Jan 2016

Reason for Termination

Novartis terminated the study early due to limited efficacy.

Study Design/Methodology

This was a two-part, multi-center, open-label, Phase Ib dose escalation study of ceritinib and luminespib combination in adult patients with ALK rearranged NSCLC, as assessed by fluorescence in-situ hybridization (FISH). The dose escalation part was to be followed by a dose expansion part. Adult patients with locally advanced or metastatic NSCLC that had progressed during or following therapy with an ALK inhibitor were included in the study. The dose escalation part of the study was guided by a Bayesian Logistic Regression Model (BLRM) employing escalation with overdose control (EWOC) principle for determining the MTD and/or identifying the RDE for the combination of ceritinib and luminespib. Dose escalation was initiated at 600 mg once daily for ceritinib and 40 mg/m2 once weekly for luminespib. Patients who received prior treatment with ceritinib were not enrolled at a ceritinib dose level that they were previously not able to tolerate. Per the protocol four dosing regimens were planned to be explored. Due to early recruitment halt patients were treated only under Regimen 1, which included treatment with luminespib on days 1, 8, 15 and 22, and

ceritinib once daily of each 28 day cycle. Various dose pairs of ceritinib and luminespib under Regimen 1 were explored.

On 03-Nov-2014, enrollment into the study was closed early after careful evaluation of trial enrollment and due to limited observed clinical activity observed. This clinical study report (CSR) presents key efficacy and comprehensive safety data collected from all patients treated in Regimen 1 of the dose escalation phase.

Centers

7 centers in 4 participating countries: Italy (1), Singapore (1), Spain (1), United States (4)

Objectives:

Primary objective(s)

- To estimate the MTDs and/or RDE for the combination of ceritinib and luminespib in patients with ALK-rearranged NSCLC

Secondary objective(s)

- To evaluate the safety and tolerability of ceritinib and luminespib across several dosing regimens
- To characterize the pharmacokinetic (PK) profile of ceritinib and luminespib when administered in combination
- To assess the preliminary anti-tumor activity of ceritinib in combination with luminespib in ALK-rearranged NSCLC overall survival

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

Ceritinib was supplied as hard gelatin capsules of dosage strength 150 mg. Patients were to receive either 450 mg or 600 mg in a once daily oral dose.

Luminespib was supplied as sterile solution containing 50 mg/20 mL intravenous infusion and patients were to receive intravenous treatment once weekly.

Statistical Methods

Analysis sets

Full Analysis Set (FAS) included all patients who received at least one dose of either ceritinib or luminespib and was unless otherwise specified the default analysis set used for all analyses.

Safety Set included all patients from the FAS who received at least one dose of ceritinib or luminespib and had at least one valid post-baseline safety assessment.

Dose Determining Analysis Set (DDS) included all patients from the safety set (within the dose-escalation part) who either met the following minimum exposure criterion and had scheduled safety evaluations, or discontinued earlier due to dose limiting toxicity (DLT).

- A patient was considered to have met the minimum exposure criterion if he/she had received at least 75% of planned daily doses of ceritinib (21 out of 28 for Regimen 1) and 75% of planned weekly doses of luminespib (3 out of 4) in the first 28 days of dosing.
- Patients who do not experience DLT during the first cycle were considered to have sufficient safety evaluations if they had observed for $\geq$ 28 days following the first dose, and were considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Pharmacokinetic Analysis Set (PAS) consists of all patients who had at least one blood sample providing evaluable PK data for ceritinib, luminespib, or BJP762 (metabolite of luminespib).

Primary endpoint and analyses: For the dose escalation part of the study, primary variable of the study was the incidence of DLTs in the first cycle of treatment. Estimation of the MTD/RDE of the combination treatment was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. An adaptive BLRM guided by the EWOC principle was used to guide the dose escalation of the combination treatment to its MTD/RDE. All information available about the dose-DLT relationship of single agents, i.e. ceritinib and luminespib, was summarized in prior distributions before the first dose escalation meeting.

Efficacy was the secondary objective. All efficacy assessments including was Overall Response Rate (ORR) duration of response (DOR), time to response (TTR) and progression-free survival (PFS) were to be analyzed. Efficacy results were summarized in terms of the number and proportion of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) for each arm, the observed response assessments followed the RECIST criteria v1.1. Summary of the best overall response (BOR) (based on proportion of responders), including observed ORR, disease control rate (DCR) and their exact 95% confidence intervals were presented.

All new or worsening AEs/SAEs with onset during the treatment period (up to 30 days after end of study treatment) were included in the safety tabulations and listed. Incidences of new or worsening AEs were summarized, by primary system organ class (SOC), preferred term (PT), severity, type of AE, and relationship to the study drug. All laboratory values were converted into SI units and the severity grade calculated using CTCAE grading, as

appropriate. Results of the ophthalmological tests were listed. Notable abnormal vital signs and notable ECG values were summarized per treatment group.

Non-compartmental methods were used to estimate PK parameters for ceritinib, luminespib, and BJP762. Missing values were not imputed. For the purpose of this report, the PK analysis was limited to the following primary parameters for Cycle 2 Day 1:

- Cmax, Tmax and AUC0-24h for ceritinib;
- Cmax, Tmax, T1/2, AUC0-168h, AUClast, AUCinf, Vz/f and CL for luminespib
- Cmax, Tmax, T1/2, AUC0-168h, AUClast and AUCinf for BJP762.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female patients, ≥ 18 years old who provided written informed consent
- locally advanced or metastatic NSCLC that has progressed during or following therapy with an ALK inhibitor
- tumor must carry an ALK rearrangement in 15% or more of tumor cells as measured by FISH
- disease that can be evaluated by RECIST v1.1 and measurable disease

Exclusion Criteria:

- central nervous system (CNS) metastases that are symptomatic or require increasing steroids or CNS-directed therapy to control CNS disease
- history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis
- clinically significant cardiac dysfunction
- inadequate end organ function as defined by specified laboratory values
- use of medications known to be strong inhibitors or inducers of CYP3A4/5 that cannot be discontinued at least 1 week prior to start of treatment
- use of medications that are mainly metabolized by CYP3A4/5 or CYP2C9 that cannot be discontinued at least 1 week prior to start of treatment
- clinically significant, uncontrolled impaired gastrointestinal function or GI disease
- prior treatment with a HSP90 inhibitor
- radiotherapy to lung within 4 weeks prior to the first dose of study treatment or patients who have not recovered from radiotherapy-related toxicities
- pregnant or nursing women
- history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

Participant Flow Table (Full Analysis Set)

	LDK 450mg + AUY 28 mg/m2	LDK 450mg + AUY 40 mg/m2	LDK 450mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	3 (100)	5 (100)	4 (100)	6 (100)	4 (100)	22 (100)
Treatment discontinued	3 (100)	5 (100)	4 (100)	6 (100)	4 (100)	22 (100)
Primary reason for end of treatment						
Adverse event(s)	0	1 (20.0)	0	1 (16.7)	0	2 (9.1)

	LDK 450mg + AUY 28 mg/m2	LDK 450mg + AUY 40 mg/m2	LDK 450mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Administrative problems	0	0	2 (50.0)	0	1 (25.0)	3 (13.6)
Death	0	1 (20.0)	0	1 (16.7)	1 (25.0)	3 (13.6)
Disease progression	3 (100)	3 (60.0)	2 (50.0)	4 (66.7)	2 (50.0)	14 (63.6)
Primary reason for study evaluation completion						
Administrative problems	0	0	2 (50.0)	0	1 (25.0)	3 (13.6)
Death	0	3 (60.0)	1 (25.0)	3 (50.0)	1 (25.0)	8 (36.4)
Disease progression	2 (66.7)	2 (40.0)	1 (25.0)	2 (33.3)	2 (50.0)	9 (40.9)
Follow up phase completed as per protocol	1 (33.3)	0	0	1 (16.7)	0	2 (9.1)

- **Baseline Characteristics**

	LDK 450 mg + AUY 28 mg/m2	LDK 450 mg + AUY 40 mg/m2	LDK 450 mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
Age (years)						
Mean	50.0	49.0	53.5	44.7	59.5	50.7
SD	17.09	11.66	6.56	14.71	6.45	12.03
Median	52.0	49.0	54.5	45.0	57.0	52.0
Minimum	32.0	33.0	45.0	22.0	55.0	22.0
Maximum	66.0	65.0	60.0	67.0	69.0	69.0
Age category - n (%)						
<65 years	2 (66.7)	4 (80.0)	4 (100)	5 (83.3)	3 (75.0)	18 (81.8)
≥ 65 years	1 (33.3)	1 (20.0)	0	1 (16.7)	1 (25.0)	4 (18.2)
Sex – n (%)						
Male	0	2 (40.0)	2 (50.0)	3 (50.0)	3 (75.0)	10 (45.5)
Female	3 (100)	3 (60.0)	2 (50.0)	3 (50.0)	1 (25.0)	12 (54.5)
Predominant race – n (%)						
Caucasian	3 (100)	4 (80.0)	3 (75.0)	3 (50.0)	2 (50.0)	15 (68.2)
Black	0	0	0	1 (16.7)	0	1 (4.5)
Asian	0	1 (20.0)	1 (25.0)	2 (33.3)	2 (50.0)	6 (27.3)
Ethnicity – n (%)						
Hispanic/Latino	0	3 (60.0)	2 (50.0)	2 (33.3)	1 (25.0)	8 (36.4)
Chinese	0	1 (20.0)	1 (25.0)	1 (16.7)	2 (50.0)	5 (22.7)
Indian (Indian subcontinent)	0	0	0	1 (16.7)	0	1 (4.5)
Other	3 (100)	1 (20.0)	1 (25.0)	2 (33.3)	1 (25.0)	8 (36.4)
Weight (kg, at baseline)						
Mean	79.1	71.6	86.8	70.7	68.6	74.6
SD	19.59	21.19	20.02	19.15	11.64	18.18
Median	84.6	79.6	80.0	68.4	70.8	76.5

	LDK 450 mg + AUY 28 mg/m2	LDK 450 mg + AUY 40 mg/m2	LDK 450 mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
Minimum	57.3	41.3	71.0	48.1	53.1	41.3
Maximum	95.3	94.0	116.0	103.0	79.6	116.0
Body surface are (m^2)						
Mean	1.9	1.8	2.0	1.9	1.8	1.9
SD	0.26	0.30	0.21	0.29	0.14	0.24
Median	2.0	1.9	2.0	1.9	1.9	1.9
Minimum	1.6	1.4	1.8	1.5	1.6	1.4
Maximum	2.1	2.2	2.3	2.3	1.9	2.3
Body mass index (kg/m^2)						
Mean	29.4	24.8	30.3	24.5	24.2	26.3
SD	7.44	7.34	8.83	4.89	4.63	6.49
Median	31.1	25.1	27.6	23.4	23.9	24.4
Minimum	21.3	15.2	23.5	19.5	18.8	15.2
Maximum	35.9	34.5	42.6	33.3	30.1	42.6
Baseline WHO performance status - n (%)						
0	2 (66.7)	1 (20.0)	1 (25.0)	1 (16.7)	1 (25.0)	6 (27.3)
1	1 (33.3)	4 (80.0)	3 (75.0)	5 (83.3)	3 (75.0)	16 (72.7)
Smoking status – n (%)						
Never smoked	2 (66.7)	2 (40.0)	1 (25.0)	5 (83.3)	3 (75.0)	13 (59.1)
Current smoker	0	3 (60.0)	1 (25.0)	0	0	4 (18.2)
Ex-smoker	1 (33.3)	0	2 (50.0)	1 (16.7)	1 (25.0)	5 (22.7)

Summary of Efficacy

Refer to safety result section for primary outcome result.

Summary of best overall response as per investigator by treatment group (Full analysis set)

	LDK 450mg + AUY 28 mg/m2	LDK 450mg + AUY 40 mg/m2	LDK 450mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
Best overall response	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Complete Response (CR)	2 (66.7)	0	1 (25.0)	0	0	3 (13.6)
Partial Response (PR)	0	1 (20.0)	0	1 (16.7)	1 (25.0)	3 (13.6)
Stable Disease	0	2 (40.0)	1 (25.0)	4 (66.7)	0	7 (31.8)
Progressive Disease	0	2 (40.0)	2 (50.0)	1 (16.7)	2 (50.0)	7 (31.8)
Unknown	1 (33.3)	0	0	0	1 (25.0)	2 (9.1)
Overall response rate (ORR) (CR or PR)	**2 (66.7)**	**1 (20.0)**	**1 (25.0)**	**1 (16.7)**	**1 (25.0)**	**6 (27.3)**
95% CI	(9.4-99.2)	(0.5-71.6)	(0.6-80.6)	(0.4-64.1)	(0.6-80.6)	(10.7-50.2)
Disease control rate (DCR) (CR or PR or SD)	**2 (66.7)**	**3 (60.0)**	**2 (50.0)**	**5 (83.3)**	**1 (25.0)**	**13 (59.1)**
95% CI	(9.4-99.2)	(14.7-94.7)	(6.8-93.2)	(35.9-99.6)	(0.6-80.6)	(36.4-79.3)

Best overall response is based on Investigator's assessment of disease status using RECIST 1.1
Estimate (95% CI) for ORR and DCR were obtained using the exact (Clopper-Pearson) interval

Summary of Safety

Safety Results

Overview of Adverse Events and Deaths

Category	LDK 450 mg + AUY 28 mg/m2 N=3 n (%)	LDK 450 mg + AUY 40 mg/m2 N=5 n (%)	LDK 450 mg + AUY 55 mg/m2 N=4 n (%)	LDK 600mg + AUY 28 mg/m2 N=6 n (%)	LDK 600mg + AUY 40 mg/m2 N=4 n (%)	All patients N=22 n (%)
Adverse events(AEs)	3 (100)	5 (100)	4 (100)	6 (100)	4 (100)	22 (100)
AEs suspected to be drug-related	3 (100)	5 (100)	4 (100)	5 (83.3)	4 (100)	21 (95.5)
Grade 3-4 AEs	1 (33.3)	3 (60.0)	2 (50.0)	3 (50.0)	3 (75.0)	12 (54.5)
Suspected to be drug-related	1 (33.3)	2 (40.0)	0	1 (16.7)	3 (75.0)	7 (31.8)
Serious adverse events(SAEs)	0	3 (60.0)	0	3 (50.0)	1 (25.0)	7 (31.8)
AEs leading to discontinuation	0	1 (20.0)	0	1 (16.7)	0	2 (9.1)
Grade 3/4 AEs leading to discontinuation	0	1 (20.0)	0	1 (16.7)	0	2 (9.1)
Other significant AEs						
AEs requiring dose adjustment/delay	2 (66.7)	4 (80.0)	1(25.0)	5(83.3)	4 (100)	16 (72.7)
Deaths[1]	0	3	1	3	1	8
On treatment deaths[2]	0	2	0	3	1	6

[1]All deaths are deaths which occurred up to 30 days after the discontinuation of study treatment
[2] Deaths occurring up to 30 days after end of treatment
AEs occurring more than 30 days after the discontinuation of study treatment are not summarized

Adverse Events by System Organ Class

	LDK 450 mg + AUY 28 mg/m2 N=3 n (%)	LDK 450 mg + AUY 40 mg/m2 N=5 n (%)	LDK 450 mg + AUY 55 mg/m2 N=4 n (%)	LDK 600mg + AUY 28 mg/m2 N=6 n (%)	LDK 600mg + AUY 40 mg/m2 N=4 n (%)	All patients N=22 n (%)
Any primary system organ class	**3 (100)**	**5 (100)**	**4 (100)**	**6 (100)**	**4 (100)**	**22 (100)**
Gastrointestinal Disorders	3 (100)	5 (100)	4 (100)	5 (83.3)	4 (100)	21 (95.5)
General Disorders And Administration Site Conditions	2 (66.7)	4 (80.0)	3 (75.0)	3 (50.0)	2 (50.0)	14 (63.6)
Metabolism And Nutrition Disorders	1 (33.3)	3 (60.0)	3 (75.0)	4 (66.7)	1 (25.0)	12 (54.5)
Respiratory, Thoracic And Mediastinal Disorders	1 (33.3)	2 (40.0)	2 (50.0)	5 (83.3)	2 (50.0)	12 (54.5)
Investigations	1 (33.3)	4 (80.0)	0	5 (83.3)	1 (25.0)	11 (50.0)
Nervous System Disorders	3 (100)	1 (20.0)	2 (50.0)	3 (50.0)	2 (50.0)	11 (50.0)
Musculoskeletal And Connective Tissue Disorders	3 (100)	3 (60.0)	1 (25.0)	2 (33.3)	0	9 (40.9)
Eye Disorders	1 (33.3)	2 (40.0)	1 (25.0)	2 (33.3)	2 (50.0)	8 (36.4)
Infections And Infestations	2 (66.7)	1 (20.0)	1 (25.0)	2 (33.3)	1 (25.0)	7 (31.8)
Skin And Subcutaneous Tissue Disorders	3 (100)	0	0	3 (50.0)	0	6 (27.3)
Blood And Lymphatic System Disorders	0	2 (40.0)	0	3 (50.0)	0	5 (22.7)
Renal And Urinary Disorders	1 (33.3)	1 (20.0)	1 (25.0)	0	1 (25.0)	4 (18.2)

	LDK 450 mg + AUY 28 mg/m2	LDK 450 mg + AUY 40 mg/m2	LDK 450 mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vascular Disorders	0	2 (40.0)	1 (25.0)	0	1 (25.0)	4 (18.2)
Cardiac Disorders	1 (33.3)	1 (20.0)	0	1 (16.7)	0	3 (13.6)
Injury, Poisoning And Procedural Complications	1 (33.3)	0	1 (25.0)	1 (16.7)	0	3 (13.6)
Psychiatric Disorders	3 (100)	0	0	0	0	3 (13.6)
Ear And Labyrinth Disorders	1 (33.3)	0	0	1 (16.7)	0	2 (9.1)
Neoplasms Benign, Malignant And Unspecified (Incl. Cysts And Polyps)	0	0	0	1 (16.7)	0	1 (4.5)
Reproductive System And Breast Disorders	0	0	0	1 (16.7)	0	1 (4.5)

Most Frequently Reported AEs Overall by Preferred Term reported for at least 15 percent in all patients n (%)

Preferred term	LDK 450mg + AUY 28 mg/m2	LDK 450mg + AUY 40 mg/m2	LDK 450mg + AUY 55 mg/m2	LDK 600mg + AUY 28 mg/m2	LDK 600mg + AUY 40 mg/m2	All patients
	N=3	N=5	N=4	N=6	N=4	N=22
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	3 (100)	5 (100)	4 (100)	6 (100)	4 (100)	22 (100)
Nausea	2 (66.7)	4 (80.0)	4 (100)	3 (50.0)	2 (50.0)	15 (68.2)
Diarrhoea	2 (66.7)	4 (80.0)	2 (50.0)	3 (50.0)	3 (75.0)	14 (63.6)
Vomiting	2 (66.7)	2 (40.0)	4 (100)	4 (66.7)	0	12 (54.5)
Abdominal Pain	2 (66.7)	2 (40.0)	2 (50.0)	4 (66.7)	0	10 (45.5)
Alanine Aminotransferase Increased	1 (33.3)	2 (40.0)	0	3 (50.0)	1 (25.0)	7 (31.8)
Aspartate Aminotransferase Increased	1 (33.3)	2 (40.0)	0	3 (50.0)	1 (25.0)	7 (31.8)
Cough	1 (33.3)	0	2 (50.0)	3 (50.0)	1 (25.0)	7 (31.8)
Fatigue	2 (66.7)	1 (20.0)	1 (25.0)	1 (16.7)	2 (50.0)	7 (31.8)
Decreased Appetite	1 (33.3)	1 (20.0)	3 (75.0)	1 (16.7)	0	6 (27.3)
Pyrexia	0	1 (20.0)	0	3 (50.0)	2 (50.0)	6 (27.3)
Abdominal Pain Upper	0	1 (20.0)	1 (25.0)	3 (50.0)	0	5 (22.7)
Constipation	1 (33.3)	1 (20.0)	2 (50.0)	1 (16.7)	0	5 (22.7)
Haemoptysis	0	2 (40.0)	1 (25.0)	1 (16.7)	1 (25.0)	5 (22.7)
Headache	2 (66.7)	1 (20.0)	0	2 (33.3)	0	5 (22.7)
Anaemia	0	1 (20.0)	0	3 (50.0)	0	4 (18.2)
Arthralgia	2 (66.7)	1 (20.0)	0	1 (16.7)	0	4 (18.2)
Asthenia	0	2 (40.0)	2 (50.0)	0	0	4 (18.2)
Back Pain	1 (33.3)	1 (20.0)	1 (25.0)	1 (16.7)	0	4 (18.2)
Dizziness	1 (33.3)	0	1 (25.0)	1 (16.7)	1 (25.0)	4 (18.2)
Dyspnoea	0	2 (40.0)	1 (25.0)	1 (16.7)	0	4 (18.2)
Oedema Peripheral	0	3 (60.0)	0	1 (16.7)	0	4 (18.2)

Serious adverse events, regardless of study treatment relationship, by preferred term and treatment (Safety set)

Preferred term	LDK 450 mg + AUY 28 mg/m2 N=3 n (%)	LDK 450 mg + AUY 40 mg/m2 N=5 n (%)	LDK 450 mg + AUY 55 mg/m2 N=4 n (%)	LDK 600mg + AUY 28 mg/m2 N=6 n (%)	LDK 600mg + AUY 40 mg/m2 N=4	All patients N=22
Total	**0**	**3 (60.0)**	**0**	**3 (50.0)**	**1 (25.0)**	**7 (31.8)**
Abdominal Pain	0	1 (20.0)	0	2 (33.3)	0	3 (13.6)
Dyspnoea	0	2 (40.0)	0	1 (16.7)	0	3 (13.6)
Embolism	0	1 (20.0)	0	0	0	1 (4.5)
Myocardial Infarction	0	0	0	1 (16.7)	0	1 (4.5)
Nausea	0	1 (20.0)	0	0	0	1 (4.5)
Phlebitis	0	1 (20.0)	0	0	0	1 (4.5)
Pleural Effusion	0	0	0	1 (16.7)	0	1 (4.5)
Pneumonitis	0	0	0	0	1 (25.0)	1 (4.5)
Respiratory Failure	0	1 (20.0)	0	0	0	1 (4.5)

Other Relevant Findings

None

Conclusion:

- The MTD or RDE of the combination of ceritinib and luminespib was not be determined as the recruitment into study was halted after the enrollment of 22 patients, due to limited clinical activity of the combination.
- The PK of ceritinib was not affected by luminespib and was similar to that of single agent treatment.
- Among the doses tested in the study, all doses seemed to be tolerable with the exception of combination of ceritinib 600 mg once daily and luminespib 40 mg/m2 once weekly which reported two DLTs.
- Limited efficacy was observed among the ceritinib luminespib dose combinations tested with an ORR of 27.3% (three patients with complete response and three patients with partial response) and with DCR of 59.1%.
- In general, the combination of ceritinib and luminespib showed a challenging safety profile and limited efficacy.
- Two DLTs and six treatment related deaths were reported in this study

Date of Clinical Trial Report

Final clinical trial report: 21-Jul-2016