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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib and ceritinib

Trial Indication(s)

ALK-positive Non-Small Cell Lung Cancer (NSCLC)

Protocol Number

CLEE011X2110C

Protocol Title

A phase Ib/II study of the ALK inhibitor ceritinib in combination with the CDK4/6 inhibitor LEE011 in patients with ALK-positive Non-Small Cell Lung Cancer

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: May 2015 (Actual)
Primary Completion Date: September 2018 (Actual)
Study Completion Date: September 2018 (Actual)

Reason for Termination (If applicable)

Phase II part of this study was not initiated and the enrollment in the Phase Ib part was terminated early based on the changes in the treatment landscape for ALK+ NSCLC. The RP2D was later identified based on additional safety data on 19-Apr-2017.

Study Design/Methodology

This was a multi-center, open-label, dose finding, Phase Ib dose escalation study to estimate the maximum tolerated doses (MTD(s)) and/or recommended Phase II doses (RP2D(s)) for the combination of ribociclib and ceritinib, followed by a Phase II to assess the clinical efficacy and to further assess the safety of the combination in patients with ALK-positive NSCLC. Phase II part of this study was not initiated.

Centers

8 centers in 6 countries: United States (1), Spain (1), France (1), Taiwan (2), Italy (2), Korea, Republic of (1)

Objectives:

Primary outcome measures

Phase Ib part:

- To estimate the maximum tolerated doses (MTD(s)) and/or recommended Phase II doses (RP2D(s)) and schedule of ribociclib in combination with ceritinib in ALK-positive NSCLC patients

Phase II part (did not initiate):

- To assess preliminary anti-tumor activity of the ribociclib and ceritinib combination

Secondary outcome measures

- To assess additional preliminary measures of anti-tumor activity of ribociclib and ceritinib combination
- To characterize the safety and tolerability of the ribociclib and ceritinib combination
- To characterize the PK of ribociclib and ceritinib.

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

Study treatments	Pharmaceutical form and route of administration	Strengths available	Dose	Frequency and/or Regimen (28 days cycle)
LEE011 (ribociclib)	Capsule for oral use	50 mg, 200 mg	As assigned during dose escalation or the declared RP2D for the Phase II part	Daily (3 weeks of dosing followed by one week break)
Ceritinib	Capsule for oral use	50 mg, 150 mg	As assigned during dose escalation or the declared RP2D for the Phase II part	Daily (continuous)

Statistical Methods

An adaptive bayesian logistic regression model (BLRM) guided by the escalation with over dose control (EWOC) principle was used to determine maximum tolerated dose(MTD) and/or recommended dose for phase 2 (RP2D). A 5-parameter BLRM for combination treatment was fitted on the Cycle 1 dose-limiting toxicity data (i.e. absence or presence of dose limiting toxicity (DLT)) accumulated throughout the dose escalation to model the dose-toxicity relationship of LEE011 and ceritinib given in combination.

All available information about the dose-DLT relationships of single agents LEE011 and ceritinib during protocol development were summarized in prior distributions. For this study, available clinical data from studies CLEE011X2101 (first-in-human LEE011 oncology study) and CLDK378X2101 (first-in-human ceritinib oncology study) were used to derive informative priors for the BLRM parameters describing the dose-DLT relationships of the 2 agents.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

Patients must be diagnosed with ALK-positive advanced NSCLC. The tumor must be ALK-positive as determined by ALK rearrangement in ≥15% of cells (as measured by FISH using the Vysis break-apart ALK probe) or by using the Ventana ALK IHC test. The analysis may be performed locally.

- Eastern cooperative oncology group (ECOG) performance status ≤ 2.
- Measurable disease as per RECIST v1.1
- Availability of tumor sample:

For ALK inhibitor naïve patients:
A representative tumor sample must be submitted. An archival tumor specimen is acceptable

For patients after progression on an ALK inhibitor:
A new tumor biopsy is required unless a biopsy performed after progression on the patient's most recent ALK inhibitor is available for submission

For all patients a newly obtained tumor specimen must be submitted if no appropriate archival sample is available. In the event that no sample is available and a new biopsy cannot be obtained, enrollment may be considered after discussion with the sponsor.

Exclusion Criteria

For Phase I part:
Patients who have not previously received at least one line of therapy for ALK-positive NSCLC

For Phase II part:
Group A: prior therapy with any ALK inhibitor is not permitted.
Group B: progression following any ALK inhibitor(s) other than ceritinib is required and the last dose of the ALK inhibitor must be no more than 60 days prior to the first dose of study drug. Prior ceritinib is not permitted.
Group C: progression following ceritinib is required and the last dose of ceritinib must be no more than 60 days prior to the first dose of study drug.

Patients who have previously been unable to tolerate ceritinib, in the opinion of the investigator. Exceptions to this exclusion include nausea, vomiting and diarrhea in patients taking ceritinib under fasted conditions.

Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of steroids or local CNS-directed therapy to control their CNS disease

Patients with abnormal laboratory values during screening and on day 1 of pre-dose

Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of ceritinib or LEE011

Patients who are currently receiving treatment (that cannot be discontinued at least 1 week prior to the initiation of the study) with agents that are known to be any of the following: strong inducers or inhibitors of CYP3A4/5; sensitive substrates of CYP3A; substrates of CYP3A4/5 or CYP2C9 with a narrow therapeutic index.

Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

Patient with impaired cardiac function or any clinically significant uncontrolled cardiac disease, and/or, cardiac repolarization abnormality, including any of the following:

Clinically significant heart disease such as CHF requiring treatment (NYH grade ≥ 2), history of angina pectoris, myocardial infarction, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry, documented cardiomyopathy, or left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).

Uncontrolled systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening, Systolic blood pressure (SBP) <90 mmHg

Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by central laboratory
QTcF interval at screening >450 msec (using Fridericia's correction)
Resting heart rate <50 bpm or > 90 bpm
Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
Inability to determine the QTcF interval
Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient disposition by treatment group in Phase Ib (FAS)

Disposition Reason	Ribociclib100 mg + Ceritinib 300 mg N=4 n (%)	Ribociclib 100 mg + Ceritinib 450 mg N=7 n (%)	Ribociclib 200 mg + Ceritinib 300 mg N=4 n (%)	Ribociclib 200 mg + Ceritinib 450 mg N=7 n (%)	Ribociclib 300 mg + Ceritinib 450 mg N=5 n (%)	All patients N=27 n (%)
Patients treated						
End of treatment	4 (100)	7 (100)	4 (100)	7 (100)	5 (100)	27 (100)
Primary reason for end of treatment						
Progressive disease	4 (100)	2 (28.6)	2 (50.0)	3 (42.9)	3 (60.0)	14 (51.9)
Moved to rollover protocol	0	2 (28.6)	1 (25.0)	2 (28.6)	1 (20.0)	6 (22.2)
Adverse event	0	2 (28.6)	0	1 (14.3)	0	3 (11.1)
Protocol deviation	0	1 (14.3)	1 (25.0)	0	0	2 (7.4)
Death	0	0	0	1 (14.3)	0	1 (3.7)
Physician decision	0	0	0	0	1 (20.0)	1 (3.7)

Baseline Characteristics

Demographic Variable	Ribociclib 100 mg + Ceritinib 300 mg N=4	Ribociclib 100 mg + Ceritinib 450 mg N=7	Ribociclib 200 mg + Ceritinib 300 mg N=4	Ribociclib 200 mg + Ceritinib 450 mg N=7	Ribociclib 300 mg + Ceritinib 450 mg N=5	All patients N=27
Mean	52.75	62.43	53.00	47.57	57.00	54.74
SD	8.655	12.501	14.652	12.882	14.000	13.028
Median	54.50	64.00	58.00	49.00	58.00	57.00
Minimum	41.0	43.0	32.0	31.0	38.0	31.0
Maximum	61.0	76.0	64.0	67.0	76.0	76.0
Age category (years) -n (%)						
<40	0	0	1 (25.0)	3 (42.9)	1 (20.0)	5 (18.5)
40-<50	1 (25.0)	2 (28.6)	0	1 (14.3)	0	4 (14.8)
50-<60	2 (50.0)	0	1 (25.0)	2 (28.6)	2 (40.0)	7 (25.9)
60-<70	1 (25.0)	2 (28.6)	2 (50.0)	1 (14.3)	1 (20.0)	7 (25.9)
≥ 70	0	3 (42.9)	0	0	1 (20.0)	4 (14.8)
Sex -n (%)						
Female	1 (25.0)	4 (57.1)	4 (100)	4 (57.1)	3 (60.0)	16 (59.3)
Male	3 (75.0)	3 (42.9)	0	3 (42.9)	2 (40.0)	11 (40.7)
Race -n (%)						
Asian	1 (25.0)	4 (57.1)	1 (25.0)	1 (14.3)	2 (40.0)	9 (33.3)
Other	0	0	0	1 (14.3)	0	1 (3.7)
Unknown	0	0	0	1 (14.3)	0	1 (3.7)
White	3 (75.0)	3 (42.9)	3 (75.0)	4 (57.1)	3 (60.0)	16 (59.3)
Ethnicity -n (%)						
Hispanic Or Latino	0	0	2 (50.0)	2 (28.6)	2 (40.0)	6 (22.2)
Not Hispanic Or Latino	4 (100)	7 (100)	2 (50.0)	4 (57.1)	3 (60.0)	20 (74.1)
Not Reported	0	0	0	1 (14.3)	0	1 (3.7)

Summary of Efficacy

Primary Outcome Result(s)

Incidence rate of dose limiting toxicities (DLTs) during the first cycle of treatment (Phase Ib)

(Time Frame: Day 28)

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	6	4	6	5
Incidence rate of dose limiting toxicities (DLTs) during the first cycle of treatment (Phase Ib) units: Count of Participants					
	0	1	0	0	0

Overall Response Rate (ORR) as per RECIST v1.1 (Phase Ib)

(Time Frame: Up to 24 months)

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	7	4	7	5
Overall Response Rate (ORR) as per RECIST v1.1 (units: participants) Count of Participants					
Complete Response (CR)	1	0	0	0	0
Partial Response (PR)	2	2	2	2	1
Stable Disease (SD)	1	3	1	3	3
Progressive Disease (PD)	0	0	0	0	1
Unknown (UNK)	0	2	1	2	0
Overall Response Rate (ORR: CR+PR)	3	2	2	2	1
Disease Control Rate (DCR: CR+PR+SD)	4	5	3	5	4

Exposure to LEE011 and ceritinib (Phase Ib)

(Time Frame: Up to 36 months)

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use	LEE011 capsule for oral use	LEE011 capsule for oral use	LEE011 capsule for oral use	LEE011 capsule for oral use

	(ribociclib) and Ceritinib for oral use	(ribociclib) and Ceritinib for oral use	(ribociclib) and Ceritinib for oral use	(ribociclib) and Ceritinib for oral use	(ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	7	4	7	5
Exposure to LEE011 and ceritinib (Phase Ib) (units: months) Mean ± Standard Deviation					
	30.90 ± 5.797	13.43 ± 10.769	14.63 ± 12.962	8.49 ± 7.445	7.04 ± 5.356

Secondary Outcome Result(s)

Frequency of dose interruptions and dose reductions (phase Ib & II)

(Time Frame: Up to 24 months)

	Ribociclib 100 mg + Ceritinib 300 mg	**Ribociclib 100 mg + Ceritinib 450 mg**	**Ribociclib 200 mg + Ceritinib 300 mg**	**Ribociclib 200 mg + Ceritinib 450 mg**	**Ribociclib 300 mg + Ceritinib 450 mg**
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	7	4	7	5

Frequency of dose interruptions and dose reductions (phase Ib & II)

(units: participants)
Count of Participants (Not Applicable)

0 dose reductions	3	4	4	5	2
1 dose reduction	1	2	0	1	3
2 dose reductions	0	0	0	1	0
>=3 dose reductions	0	1	0	0	0

Progression free survival (PFS) per RECIST v1.1 - Phase Ib

(Time Frame: median number of day 28 (min-max))

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	7	4	7	5
Progression free survival (PFS) per RECIST v1.1 - Phase Ib & II (units: days) Median (Full Range)					
Progression Free Survival (Days)	845.5 (653 to 1171)	167.0 (1 to 813)	460.5 (1 to 765)	113.0 (1 to 588)	168.0 (48 to 416)

Duration of response (DOR)

(Time Frame: Up to 24 months)

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use
Number of Participants Analyzed [units: participants]	4	7	4	7	5
Duration of response (DOR) (units: median number of days (min-max)) Median (Full Range)					
	706.0 (248 to 868)	84.5 (1 to 763)	413.5 (111 to 716)	254.0 (58 to 460)	113.0 (113 to 113)

Time to response (TTR) - Phase Ib

(Time Frame: Up to 24 months)

	Ribociclib 100 mg + Ceritinib 300 mg	Ribociclib 100 mg + Ceritinib 450 mg	Ribociclib 200 mg + Ceritinib 300 mg	Ribociclib 200 mg + Ceritinib 450 mg	Ribociclib 300 mg + Ceritinib 450 mg
Arm/Group Description	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use	LEE011 capsule for oral use (ribociclib) and Ceritinib for oral use

Number of Participants Analyzed [units: participants]	4	7	4	7	5
Time to response (TTR) - Phase Ib & II (units: median number of days (min-max)) Median (Full Range)					
	62.0 (57 to 924)	53.0 (27 to 56)	53.5 (50 to 57)	52.0 (52 to 335)	56.0 (56 to 56)

Summary of Safety

Safety Results

All-Cause Mortality

Eight patients died during the study; 4 (14.8%) of the deaths were due to study indication. The cause of death was unknown in 2 patients, 1 patient died due to general physical health deterioration and 1 patient died due to suspected myocardial infarction.

On-treatment deaths (i.e., deaths while receiving study medication or up to 30 days after the last dose of study treatment) were reported for 3 patients: 2 of these patients died due to study indication and 1 patient died due to suspected myocardial infarction

Adverse Events

The most frequent preferred terms (with an incidence of ≥ 30%) were diarrhea, vomiting, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, neutrophil count decreased, asthenia, blood creatinine increased, decreased appetite, and nausea.

The most frequently reported AEs (in ≥ 20% of patients) suspected as being study drug-related included diarrhea, vomiting, ALT increased, AST increased, nausea, neutrophil count decreased, blood creatinine increased, neutropenia, decreased appetite.

The most frequently (≥5%) of grade 3/4 AEs suspected to be study treatment related included aspartate aminotransferase increased, neutrophil count decreased, ALT increased, gammaglutamyltransferase (GGT) increased, lipase increased, asthenia, and WBC decreased.

AEs suspected to be study treatment related occurred in 4 patients (100%) at RP2D. One patient had grade 3 GGT increased suspected to be study treatment related at RP2D.

The incidence of specific SAEs was low. The most frequent SAE was dyspnea. No patient treated at the RP2D had SAEs suspected to be study treatment related.

The AEs leading to discontinuation of one or both study drug(s) were ALT increased, AST increased, ECG QT prolonged, lipase increased, myocardial infarction, and neutropenia.

Myelosuppression-neutropenia was the most frequently (in ≥ 30% of patients) occurring AESI safety topic for ribociclib followed by hepatobiliary toxicity, pulmonary toxicity (respiratory disorders).

Adverse events, regardless of study treatment relationship by preferred term, maximum grade and by treatment group in Phase Ib exceeding a frequency of 10% in all patients column (Safety Set)

	Ribociclib 100 mg + Ceritinib 300 mg N=4		Ribociclib 100 mg + Ceritinib 450 mg N=7		Ribociclib 200 mg + Ceritinib 300 mg N=4		Ribociclib 200 mg + Ceritinib 450 mg N=7		Ribociclib 300 mg + Ceritinib 450 mg N=5		All patients N=27	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	4 (100)	2 (50.0)	7 (100)	6 (85.7)	4 (100)	2 (50.0)	7 (100)	5 (71.4)	5 (100)	5 (100)	27 (100)	20 (74.1)
Diarrhoea	4 (100)	0	5 (71.4)	0	4 (100)	0	6 (85.7)	0	4 (80.0)	0	23 (85.2)	0
Vomiting	2 (50.0)	0	5 (71.4)	0	2 (50.0)	0	4 (57.1)	0	4 (80.0)	0	17 (63.0)	0
Alanine aminotransferase increased	1 (25.0)	0	4 (57.1)	3 (42.9)	1 (25.0)	0	3 (42.9)	3 (42.9)	3 (60.0)	2 (40.0)	12 (44.4)	8 (29.6)
Aspartate aminotransferase increased	1 (25.0)	0	4 (57.1)	3 (42.9)	1 (25.0)	0	3 (42.9)	3 (42.9)	3 (60.0)	2 (40.0)	12 (44.4)	8 (29.6)
Neutrophil count decreased	0	0	3 (42.9)	2 (28.6)	0	0	4 (57.1)	2 (28.6)	4 (80.0)	3 (60.0)	11 (40.7)	7 (25.9)
Asthenia	4 (100)	0	0	0	2 (50.0)	0	2 (28.6)	1 (14.3)	1 (20.0)	1 (20.0)	9 (33.3)	2 (7.4)
Blood creatinine increased	1 (25.0)	0	2 (28.6)	0	1 (25.0)	0	3 (42.9)	0	2 (40.0)	0	9 (33.3)	0
Decreased appetite	0	0	3 (42.9)	0	1 (25.0)	0	3 (42.9)	1 (14.3)	2 (40.0)	0	9 (33.3)	1 (3.7)
Nausea	0	0	3 (42.9)	0	3 (75.0)	0	1 (14.3)	0	2 (40.0)	0	9 (33.3)	0
Headache	1 (25.0)	0	1 (14.3)	0	1 (25.0)	0	2 (28.6)	0	2 (40.0)	2 (40.0)	7 (25.9)	2 (7.4)
Neutropenia	2 (50.0)	1 (25.0)	1 (14.3)	0	1 (25.0)	0	3 (42.9)	1 (14.3)	0	0	7 (25.9)	2 (7.4)
Rash	3 (75.0)	0	2 (28.6)	0	1 (25.0)	0	0	0	1 (20.0)	0	7 (25.9)	0
Cough	1 (25.0)	0	2 (28.6)	0	0	0	2 (28.6)	0	1 (20.0)	0	6 (22.2)	0
Non-cardiac chest pain	2 (50.0)	0	1 (14.3)	0	2 (50.0)	0	0	0	1 (20.0)	0	6 (22.2)	0
Abdominal pain	0	0	3 (42.9)	1 (14.3)	1 (25.0)	0	1 (14.3)	0	0	0	5 (18.5)	1 (3.7)

	Ribociclib 100 mg + Ceritinib 300 mg N=4		Ribociclib 100 mg + Ceritinib 450 mg N=7		Ribociclib 200 mg + Ceritinib 300 mg N=4		Ribociclib 200 mg + Ceritinib 450 mg N=7		Ribociclib 300 mg + Ceritinib 450 mg N=5		All patients N=27	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Back pain	2 (50.0)	0	1 (14.3)	0	1 (25.0)	0	0	0	1 (20.0)	0	5 (18.5)	0
Dyspnoea	2 (50.0)	0	1 (14.3)	0	1 (25.0)	1 (25.0)	0	0	1 (20.0)	1 (20.0)	5 (18.5)	2 (7.4)
Gamma-glutamyltransferase increased	0	0	2 (28.6)	1 (14.3)	1 (25.0)	1 (25.0)	2 (28.6)	0	0	0	5 (18.5)	2 (7.4)
Insomnia	1 (25.0)	0	1 (14.3)	0	2 (50.0)	0	1 (14.3)	0	0	0	5 (18.5)	0
Pyrexia	3 (75.0)	0	1 (14.3)	0	1 (25.0)	0	0	0	0	0	5 (18.5)	0
Blood creatine phosphokinase increased	0	0	1 (14.3)	0	0	0	2 (28.6)	1 (14.3)	1 (20.0)	0	4 (14.8)	1 (3.7)
Dizziness	0	0	2 (28.6)	0	0	0	1 (14.3)	0	1 (20.0)	0	4 (14.8)	0
Dyspepsia	1 (25.0)	0	0	0	0	0	1 (14.3)	0	2 (40.0)	0	4 (14.8)	0
Fatigue	0	0	4 (57.1)	0	0	0	0	0	0	0	4 (14.8)	0
Lipase increased	1 (25.0)	1 (25.0)	1 (14.3)	0	1 (25.0)	0	1 (14.3)	1 (14.3)	0	0	4 (14.8)	2 (7.4)
Rhinorrhoea	0	0	1 (14.3)	0	1 (25.0)	0	1 (14.3)	0	1 (20.0)	0	4 (14.8)	0
Stomatitis	1 (25.0)	0	1 (14.3)	0	0	0	2 (28.6)	0	0	0	4 (14.8)	0
Amylase increased	0	0	1 (14.3)	0	0	0	1 (14.3)	0	1 (20.0)	1 (20.0)	3 (11.1)	1 (3.7)
Anaemia	0	0	0	0	1 (25.0)	0	1 (14.3)	0	1 (20.0)	0	3 (11.1)	0
Blood bilirubin increased	0	0	1 (14.3)	0	0	0	2 (28.6)	0	0	0	3 (11.1)	0
Dysphonia	2 (50.0)	0	1 (14.3)	0	0	0	0	0	0	0	3 (11.1)	0
Influenza	2 (50.0)	0	0	0	0	0	0	0	1 (20.0)	1 (20.0)	3 (11.1)	1 (3.7)
Lymphopenia	0	0	0	0	1 (25.0)	0	1 (14.3)	0	1 (20.0)	0	3 (11.1)	0
Oropharyngeal pain	2 (50.0)	0	0	0	0	0	1 (14.3)	0	0	0	3 (11.1)	0
Pruritus	1 (25.0)	0	0	0	0	0	1 (14.3)	0	1 (20.0)	0	3 (11.1)	0
Upper respiratory tract infection	1 (25.0)	0	0	0	1 (25.0)	0	1 (14.3)	0	0	0	3 (11.1)	0

Preferred term	Ribociclib 100 mg + Ceritinib 300 mg N=4		Ribociclib 100 mg + Ceritinib 450 mg N=7		Ribociclib 200 mg + Ceritinib 300 mg N=4		Ribociclib 200 mg + Ceritinib 450 mg N=7		Ribociclib 300 mg + Ceritinib 450 mg N=5		All patients N=27	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Weight decreased	0	0	2 (28.6)	0	0	0	1 (14.3)	0	0	0	3 (11.1)	0
White blood cell count decreased	0	0	1 (14.3)	0	0	0	1 (14.3)	1 (14.3)	1 (20.0)	1 (20.0)	3 (11.1)	2 (7.4)

- Preferred terms are sorted in descending frequency of All Grades column, as reported in the All Patients.
- 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.

Conclusion:

- Ribociclib 200 mg (3 weeks on/1 week off regimen) + ceritinib 300 mg (once daily) was identified as RP2D for the combination treatment in patients with ALK positive NSCLC.

- At the RP2D of ribociclib 200 mg + ceritinib 300 mg dose level, the ORR was 50.0% (2/4 patients) (95% CI: 6.76-93.2) and the DCR was 75% (3/4 patients) (95% CI: 19.41, 99.37).

- Overall safety of the combination treatment was generally consistent with what seen as single agent for ribociclib or ceritinib.

Date of Clinical Trial Report

3 June 2019