NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ceritinib

Trial Indication(s)

ALK-activated non-small cell lung cancer

Protocol Number

CLDK378A2201

Protocol Title

A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib

Clinical Trial Phase

Phase 2

Phase of Drug Development

III

Study Start/End Dates

Study Start Date: November 2012 (Actual)
Primary Completion Date: March 2016 (Actual)
Study Completion Date: March 2016 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

Single-arm, open-label, multicenter, Phase II study with a single stage design to evaluate the efficacy and safety of single-agent ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC (defined as 15% or more positive lung tumor cells as assessed by the FDA-approved FISH test using Vysis break-apart probes). Patients were tested locally without central confirmation of ALK status, although central ALK testing was offered for patients without local documentation of ALK-positive status by the FDA-approved FISH test. Patients were previously treated with cytotoxic chemotherapy (one to three prior lines, of which one must have been a platinum doublet) and then with crizotinib. Prior to enrollment, all the patients had progressed during or within 30 days of the last dose of the most recent treatment with crizotinib. Patients could also have received first-line treatment with crizotinib followed by cytotoxic chemotherapy and, subsequently, a re-challenge treatment with crizotinib. All patients were treated with ceritinib 750 mg administered orally on a once-daily dosing schedule. Assessments of tumor response and progression were performed every eight weeks (every two cycles), starting from the first day of treatment with ceritinib. After all patients completed at least 24 cycles of the treatment or discontinued the treatment earlier, the frequency of tumor assessments was reduced to every 12 weeks. The tumor assessments schedule varied for patients who discontinued treatment with a progressive disease (PD) and without a PD. Patients who discontinued treatment due to PD no longer had tumor assessments, while those who discontinued treatment due to other reasons continued to have tumor assessments until the time of PD.

All patients who discontinued ceritinib were contacted for a safety follow-up 30 days after their last dose of ceritinib. Further, after the final tumor assessment (at the time of PD as assessed by the Investigator) the patient was contacted every three months for a survival follow-up to determine survival status and use of antineoplastic therapies since discontinuation of study treatment.

Centers

62 centers in 13 countries: United States(21), Singapore(1), Spain(4), Canada(3), Hong Kong(2), France(3), Italy(7), Belgium(3), Japan(9), United Kingdom(1), Germany(2), Korea, Republic of(3), Netherlands(3)

Objectives:

Primary Objective

- To demonstrate the antitumor activity of ceritinib, as measured by overall response rate (ORR) by Investigator assessment

Secondary Objectives

Key secondary objectives

- To evaluate response related endpoints:
- Duration of response (DOR), as assessed by both Investigator and Blinded Independent Review Committee (BIRC)
- Disease control rate (DCR), as assessed by both Investigator and BIRC
- Time to response (TTR), as assessed by both Investigator and BIRC
- Overall intracranial response rate (OIRR), as assessed by both Investigator and BIRC
- ORR, as assessed by BIRC

Other secondary objectives

- To evaluate the safety profile of ceritinib
- To evaluate progression-free survival (PFS), as assessed by both Investigator and BIRC
- To evaluate overall survival (OS)

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

Oral hard gelatin capsules of ceritinib (150 mg). Once-daily dose of 5 capsules (750 mg).

Statistical Methods

Analysis sets

Full Analysis Set (FAS) consisted of all patients who received at least one dose of ceritinib. Unless otherwise specified the FAS was the default analysis set used for all analyses, including the primary analysis. The FAS was used for all listings.

The Safety Set consisted of all patients who received at least one dose of ceritinib. All safety data was analyzed using the Safety set. The FAS and Safety set are identical in this study.

The Per-Protocol Set (PPS) consisted of a subset of patients in the FAS who had no protocol deviations leading to exclusion, who had an adequate tumor assessment at baseline and had a follow-up tumor assessment greater than seven weeks after starting treatment (unless PD was observed before that time). The PPS was used only for supportive analysis of the primary efficacy endpoint.

Primary endpoint and analyses

The primary endpoint used to evaluate the anti-tumor activity of ceritinib was the overall response rate (ORR), defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by the Investigator. The best overall response (BOR) was assessed based on reported lesion responses at different evaluation time points. Both CR and PR were confirmed by repeat assessments performed not less than four weeks after the criteria for response were first met. Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or anti-cancer surgery) were considered in the assessment of BOR. If a patient received any further anti-neoplastic therapy while on study, any subsequent assessments were excluded from the BOR determination. Clinical deterioration was not considered as documented disease progression.

The study targeted an ORR of 38%. A response rate of 25% or less was considered as insufficient level of activity for the proposed patient population. At the time of the primary analysis, the hypothesis H0: ORR $\leq$ 25% vs. H1: ORR > 25% was tested using a one-sided test with α=0.025 based on the exact binomial distribution. This was statistically significant at the one-sided 0.025 significant level. No tests of hypothesis were conducted at this final analysis.

ORR, as assessed by the Investigator was estimated and the exact 95% confidence interval (CI) was provided.

Secondary efficacy endpoints and analyses

All key secondary and other secondary efficacy endpoints (associated with the key secondary efficacy objectives and other secondary efficacy objectives described above) were summarized based on the FAS. In addition, a supportive analysis of ORR by BIRC assessment based on the PPS was also performed.

ORR as assessed by the BIRC was estimated and the exact binomial 95% CI was provided following the same methodology as for the primary analysis.

The tumor-related endpoints below were summarized per Investigator and BIRC assessment.

DOR was defined for patients with a confirmed response (PR or CR), as the time from first documented response (PR or CR) to the date of first documented PD or death due to any cause. If a patient did not have an event, DOR was censored at the date of the last adequate tumor assessment. The estimated median (in months), 25th and 75th percentiles along with 95% CIs were reported. Kaplan-Meier estimated probabilities at several time points with corresponding 95% CIs were summarized.

DCR, defined as the proportion of patients with BOR of CR, PR, SD or non-CR/non-PD, was estimated and the exact binomial 95% CI was reported.

TTR, defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients with a confirmed CR or PR, was summarized in 2-month intervals using descriptive statistics.

OIRR was calculated based on response assessments in the brain for patients having brain metastases at baseline. OIRR was defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain per RECIST 1.1 based on target and non-target lesions in the brain. OIRR was estimated and the exact binomial 95% CI was provided.
PFS, defined as the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause, was summarized using Kaplan-Meier methods as described for DOR. If a patient had not progressed or was not known to have died at the date of analysis cut-off or had received any further anticancer therapy, PFS was censored at the date of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever was earlier.

OS was defined as the time from the start date of study drug to the date of death due to any cause. If the patient was alive at the date of the analysis cut-off or lost to follow-up, then OS was censored at the last contact date prior to the data cut-off date. OS was summarized using Kaplan-Meier methods as described for DOR.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion critieria:
- Histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC that carries an ALK rearrangement, as per the FDA-approved FISH assay (Abbott Molecular Inc.).
- Age 18 years or older at the time of informed consent.
- Patients must have NSCLC that has progressed during therapy with crizotinib or within 30 days of the last dose
- Patients must have received 1-3 lines of cytotoxic chemotherapy (of which 1 must have been a platinum doublet) to treat their locally advanced or metastatic NSCLC
- Patients must have a tumor tissue sample available, collected either at the time of diagnosis of NSCLC or any time since.
- Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2, except for patients with grade 2 nausea/vomiting and/or grade 2 diarrhea despite optimal supportive therapy who will not be allowed to participate in the study.

Exclusion criteria:
- Patients with known hypersensitivity to any of the excipients of LDK378.
- Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.
- History of carcinomatous meningitis.
- Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years.
- Clinically significant, uncontrolled heart disease
- Systemic anti-cancer therapy given after the last dose of crizotinib and prior to starting study drug.

Participant Flow Table

Overall Study

	LDK378 750mg
Started	140
Entered post-treatment efficacy f/u	7
Entered survival follow up	98
Discontinued from study	35
Completed	0
Not Completed	140
Rollover patients	16
Adverse Event	12
Progressive disease	69
Physician Decision	14

Subject/guardian decision	20
Lost to Follow-up	1
Death	8

Baseline Characteristics

	LDK378 750mg	Total
Number of Participants [units: participants]	140	140
Age Continuous (units: Years) Mean ± Standard Deviation	51.2±11.62	
Gender, Male/Female (units: Participants)		
Female	70	70
Male	70	70

Summary of Efficacy

Primary Outcome Result(s)

Overall response rate (ORR) to LDK378 per Investigator assessment

	LDK378 750mg
Number of Participants Analyzed [units:	140

participants]	
Overall response rate (ORR) to LDK378 per Investigator assessment (units: Percentage of participants) Number (95% Confidence Interval)	40.7 (32.5 to 49.3)

Secondary Outcome Result(s)

ORR per Blinded Independent Review Committee (BIRC) assessment

	LDK378 750mg
Number of Participants Analyzed [units: participants]	140
ORR per Blinded Independent Review Committee (BIRC) assessment (units: Percentage of participants) Number (95% Confidence Interval)	35.7 (27.8 to 44.2)

Duration of response (DOR) by Investigator

	LDK378 750mg
Number of Participants	57

Analyzed [units: participants]	
Duration of response (DOR) by Investigator (units: Months) Median (95% Confidence Interval)	10.6 (7.4 to 14.7)

Duration of response (DOR) by BIRC

	LDK378 750mg
Number of Participants Analyzed [units: participants]	50
Duration of response (DOR) by BIRC (units: Months) Median (95% Confidence Interval)	12.9 (9.3 to 18.4)

Disease control rate (DCR)

	LDK378 750mg
Number of Participants Analyzed [units: participants]	140
Disease control rate (DCR) (units: Percentage of participants) Number (95% Confidence Interval)	
DCR per Investigator	76.4 (68.5 to 83.2)
DCR per BIRC	80.0 (72.4 to 86.3)

Time to Response (TTR) per Investigator

	LDK378 750mg
Number of Participants Analyzed [units: participants]	57
Time to Response (TTR) per Investigator (units: Months) Mean ± Standard Deviation	3.0 ± 3.54

Time to Response (TTR) per BIRC

	LDK378 750mg
Number of Participants Analyzed [units: participants]	50
Time to Response (TTR) per BIRC (units: Months) Mean ± Standard Deviation	2.2 ± 1.44

Progression-free survival (PFS) per Investigator

	LDK378 750mg
Number of Participants Analyzed [units: participants]	140
Progression-free survival (PFS) per Investigator (units: months)	5.8 (5.4 to 7.6)

Median (95% Confidence Interval)

Progression-free survival (PFS) per BIRC

	LDK378 750mg
Number of Participants Analyzed [units: participants]	140
Progression-free survival (PFS) per BIRC (units: months) Median (95% Confidence Interval)	7.4 (5.6 to 10.9)

Overall intracranial response rate (OIRR) per Investigator

	LDK378 750mg
Number of Participants Analyzed [units: participants]	20
Overall intracranial response rate (OIRR) per Investigator (units: Percentage of participants) Number (95% Confidence Interval)	45.0 (23.1 to 68.5)

Overall intracranial response rate (OIRR) per BIRC

	LDK378 750mg
Number of Participants Analyzed [units:	28

participants]	
Overall intracranial response rate (OIRR) per BIRC (units: Percentage of participants) Number (95% Confidence Interval)	35.7 (18.6 to 55.9)

Overall survival (OS)

	LDK378 750mg
Number of Participants Analyzed [units: participants]	140
Overall survival (OS) (units: Months) Median (95% Confidence Interval)	15.6 (13.6 to 24.2)

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class and Preferred Term

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment

	LDK378 750 mg N = 140
Total participants affected	67 (47.86%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
ANAEMIA	1 (0.71%)
FEBRILE NEUTROPENIA	2 (1.43%)
THROMBOCYTOPENIA	1 (0.71%)
CARDIAC DISORDERS	
CORONARY ARTERY DISEASE	1 (0.71%)
PERICARDIAL EFFUSION	2 (1.43%)
PERICARDITIS	2 (1.43%)
GASTROINTESTINAL DISORDERS	
ABDOMINAL PAIN	3 (2.14%)
ASCITES	1 (0.71%)
CONSTIPATION	1 (0.71%)
DYSPHAGIA	1 (0.71%)
FAECALOMA	1 (0.71%)
GASTROINTESTINAL DISORDER	1 (0.71%)
GASTROINTESTINAL	1 (0.71%)

TOXICITY	
INTESTINAL PERFORATION	1 (0.71%)
NAUSEA	3 (2.14%)
PANCREATITIS	2 (1.43%)
RETROPERITONEAL FIBROSIS	1 (0.71%)
VOMITING	4 (2.86%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
ASTHENIA	3 (2.14%)
DISEASE PROGRESSION	1 (0.71%)
GENERAL PHYSICAL HEALTH DETERIORATION	2 (1.43%)
MALAISE	3 (2.14%)
NON-CARDIAC CHEST PAIN	3 (2.14%)
PAIN	2 (1.43%)
PYREXIA	8 (5.71%)
HEPATOBILIARY DISORDERS	
HEPATIC FUNCTION ABNORMAL	1 (0.71%)
HEPATOCELLULAR INJURY	1 (0.71%)
INFECTIONS AND INFESTATIONS	
EMPYEMA	1 (0.71%)

ENTERITIS INFECTIOUS	1 (0.71%)
LUNG INFECTION	1 (0.71%)
MENINGITIS	1 (0.71%)
PLEURAL INFECTION	1 (0.71%)
PNEUMONIA	6 (4.29%)
RESPIRATORY TRACT INFECTION	1 (0.71%)
SEPTIC SHOCK	1 (0.71%)
URINARY TRACT INFECTION	1 (0.71%)
VIRAL PERICARDITIS	1 (0.71%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
HUMERUS FRACTURE	1 (0.71%)
PUBIS FRACTURE	1 (0.71%)
SPINAL COMPRESSION FRACTURE	1 (0.71%)
INVESTIGATIONS	
ALANINE AMINOTRANSFERASE INCREASED	1 (0.71%)
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.71%)
BLOOD CALCIUM INCREASED	1 (0.71%)
BLOOD CREATINE PHOSPHOKINASE	1 (0.71%)

INCREASED	
BLOOD CREATININE INCREASED	2 (1.43%)
WEIGHT DECREASED	2 (1.43%)
METABOLISM AND NUTRITION DISORDERS	
DECREASED APPETITE	2 (1.43%)
DEHYDRATION	4 (2.86%)
DIABETES MELLITUS	1 (0.71%)
HYPERGLYCAEMIA	1 (0.71%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
BACK PAIN	1 (0.71%)
BONE PAIN	1 (0.71%)
NECK PAIN	1 (0.71%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
COLON CANCER	1 (0.71%)
METASTASES TO LIVER	1 (0.71%)
METASTASES TO LUNG	1 (0.71%)
METASTASES TO MENINGES	2 (1.43%)
NERVOUS SYSTEM DISORDERS	
ALTERED STATE OF	1 (0.71%)

CONSCIOUSNESS	
APHASIA	2 (1.43%)
BRAIN OEDEMA	2 (1.43%)
CEREBROVASCULAR ACCIDENT	1 (0.71%)
DYSARTHRIA	1 (0.71%)
ENCEPHALOPATHY	1 (0.71%)
HEADACHE	1 (0.71%)
HEPATIC ENCEPHALOPATHY	1 (0.71%)
HYPERAESTHESIA	1 (0.71%)
LETHARGY	1 (0.71%)
MOTOR DYSFUNCTION	1 (0.71%)
PARAESTHESIA	1 (0.71%)
PARAPARESIS	1 (0.71%)
SEIZURE	4 (2.86%)
SENSORY LOSS	1 (0.71%)
PSYCHIATRIC DISORDERS	
CONFUSIONAL STATE	2 (1.43%)
RENAL AND URINARY DISORDERS	
HYDRONEPHROSIS	1 (0.71%)
POLLAKIURIA	1 (0.71%)
RENAL FAILURE	1 (0.71%)
RENAL IMPAIRMENT	1 (0.71%)
RESPIRATORY, THORACIC AND	

MEDIASTINAL DISORDERS	
COUGH	1 (0.71%)
DYSPNOEA	7 (5.00%)
LUNG DISORDER	1 (0.71%)
PLEURAL EFFUSION	3 (2.14%)
PLEURISY	2 (1.43%)
PNEUMONITIS	3 (2.14%)
PULMONARY EMBOLISM	2 (1.43%)
PULMONARY HYPERTENSION	1 (0.71%)
RESPIRATORY FAILURE	3 (2.14%)

Other Adverse Events by System Organ Class and Preferred Term

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LDK378 750 mg N = 140
Total participants affected	139 (99.29%)

BLOOD AND LYMPHATIC SYSTEM DISORDERS	
ANAEMIA	25 (17.86%)
GASTROINTESTINAL DISORDERS	
ABDOMINAL PAIN	45 (32.14%)
ABDOMINAL PAIN UPPER	16 (11.43%)
CONSTIPATION	42 (30.00%)
DIARRHOEA	115 (82.14%)
NAUSEA	115 (82.14%)
STOMATITIS	11 (7.86%)
VOMITING	92 (65.71%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
ASTHENIA	25 (17.86%)
FATIGUE	54 (38.57%)
NON-CARDIAC CHEST PAIN	25 (17.86%)
OEDEMA PERIPHERAL	19 (13.57%)
PYREXIA	28 (20.00%)
INFECTIONS AND INFESTATIONS	
NASOPHARYNGITIS	9 (6.43%)
PNEUMONIA	9 (6.43%)
UPPER RESPIRATORY TRACT INFECTION	18 (12.86%)
INVESTIGATIONS	

ALANINE AMINOTRANSFERASE INCREASED	65 (46.43%)
ASPARTATE AMINOTRANSFERASE INCREASED	55 (39.29%)
BLOOD ALKALINE PHOSPHATASE INCREASED	23 (16.43%)
BLOOD CREATININE INCREASED	27 (19.29%)
ELECTROCARDIOGRAM QT PROLONGED	12 (8.57%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	26 (18.57%)
WEIGHT DECREASED	48 (34.29%)
METABOLISM AND NUTRITION DISORDERS	
DECREASED APPETITE	59 (42.14%)
HYPOKALAEMIA	8 (5.71%)
HYPOPHOSPHATAEMIA	9 (6.43%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
ARTHRALGIA	16 (11.43%)
BACK PAIN	28 (20.00%)
MUSCULOSKELETAL CHEST PAIN	9 (6.43%)
MUSCULOSKELETAL PAIN	14 (10.00%)
MYALGIA	10 (7.14%)

NECK PAIN	11 (7.86%)
PAIN IN EXTREMITY	14 (10.00%)
NERVOUS SYSTEM DISORDERS	
DIZZINESS	15 (10.71%)
DYSGEUSIA	12 (8.57%)
HEADACHE	31 (22.14%)
PARAESTHESIA	8 (5.71%)
PSYCHIATRIC DISORDERS	
ANXIETY	11 (7.86%)
INSOMNIA	18 (12.86%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
COUGH	33 (23.57%)
DYSPNOEA	29 (20.71%)
HAEMOPTYSIS	10 (7.14%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
ALOPECIA	9 (6.43%)
DRY SKIN	10 (7.14%)
PRURITUS	8 (5.71%)
RASH	24 (17.14%)

Other Relevant Findings

Not Applicable

Conclusion:

Treatment with ceritinib was associated with rapid and durable responses, and a long progression-free survival in this heavily pretreated population who received 1 - 3 prior lines of chemotherapy and progressed on crizotinib.

The overall safety profile of ceritinib 750 mg under fasting conditions observed in this study is consistent with the known safety profile of ceritinib in this patient population. No new or unexpected safety signals were observed with the longer follow-up, thus allowing for prolonged treatment in patients with ALK-positive NSCLC.

The final analysis of this study confirms the clinical benefit observed in Study X2101 and in the primary analysis of Study A2201. The data from this study combined with the manageable safety profile of ceritinib strongly support a positive benefit-risk balance for ALK-positive NSCLC patients who received 1 - 3 prior lines of chemotherapy and who progressed on crizotinib.

Date of Clinical Trial Report

14-Jun-2016