NOVARTIS

Zykadia®

Protein kinase inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Hard gelatin capsules

150 mg: Size #00 hard gelatin capsule with blue opaque cap with black imprint “LDK 150MG” and white opaque body with black imprint “NVR”, containing white to almost white powder.

Active substance

Ceritinib

Each capsule contains 150 mg ceritinib free base.

Excipients

Capsule content: silica, colloidal anhydrous; hydroxypropylcellulose, low-substituted; magnesium stearate; cellulose, microcrystalline; sodium starch glycolate

Capsule shell: gelatin; indigotine (E132); titanium dioxide (E171)

Printing ink: ammonium hydroxide; iron oxide black (E172); propylene glycol; shellac glaze

Pharmaceutical formulations may vary between countries.

INDICATIONS

Zykadia is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC), with or without metastases to the brain.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

The recommended dose of Zykadia is 450 mg taken orally once daily with food at the same time each day.

The maximum recommended dose is 450 mg taken orally once daily with food.

Continue treatment as long as the patient is deriving clinical benefit from therapy.

Dose adjustments

Temporary dose interruption and/or dose reduction of Zykadia therapy may be required based on individual safety and tolerability. If dose reduction is required due to an adverse drug reaction not listed in Table 1, then the daily dose of Zykadia should be reduced by decrements of 150 mg. Early identification and management of adverse drug reactions with standard supportive care measures should be considered.

Zykadia should be discontinued in patients unable to tolerate 150 mg taken once daily with food.

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Zykadia in the management of selected adverse drug reactions (ADRs).

Table 1 Zykadia dose adjustment and management recommendations for selected adverse drug reactions

Criteria	Zykadia Dosing
Severe or intolerable nausea, vomiting, or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold Zykadia until improved then reinitiate Zykadia by reducing dose by 150 mg.
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with concurrent total bilirubin less than or equal to 2 times ULN	Withhold Zykadia until recovery to baseline ALT/AST levels or to less than or equal to 3 times ULN, then reinitiate Zykadia by reducing dose by 150 mg
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 2 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue Zykadia
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue Zykadia
QTc greater than 500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold Zykadia until recovery to baseline or to a QTc less than 481 msec, then reinitiate Zykadia by reducing dose by 150 mg
QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue Zykadia
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Zykadia at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, reinitiate Zykadia by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue Zykadia if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Zykadia by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b]
Persistent hyperglycaemia greater than 250mg/dL despite optimal anti-hyperglycemic therapy	Withhold Zykadia until hyperglycaemia is adequately controlled, then reinitiate Zykadia by reducing dose by 150 mg If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue Zykadia
Elevated lipase or amylase greater than or equal to grade 3 (greater than 2 times ULN)	Withhold Zykadia until lipase or amylase returns to less than or equal to grade 1 (less than 1.5 times ULN), then reinitiate by reducing dose by 150 mg

[a] Heart rate less than 60 beats per minute (bpm)

[b] Permanently discontinue for recurrence

Strong CYP3A inhibitors

Concurrent use of strong CYP3A inhibitors should be avoided (see section INTERACTIONS). If concomitant use of a strong CYP3A inhibitor is unavoidable, the dose of Zykadia should be reduced by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the Zykadia dose that was taken prior to initiating the strong CYP3A inhibitor.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment as there is no experience with Zykadia in this population (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

For patients with severe hepatic impairment (Child-Pugh C), the dose of Zykadia should be reduced by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. No dose adjustment is necessary in patients with mild ((Child-Pugh) A) or moderate (Child-Pugh B) hepatic impairment (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

The safety and efficacy of Zykadia have not been established in pediatric patients.

Geriatric patients (65 years or above)

The limited data on the safety and efficacy of Zykadia in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section CLINICAL PHARMACOLOGY).

Method of administration

Zykadia should be administered orally once daily with food at the same time every day. Food can range from a snack to a full meal (see section INTERACTIONS and section CLINICAL PHARMACOLOGY). Zykadia should be swallowed whole with water. Zykadia should not be chewed or crushed.

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Cases of hepatotoxicity occurred in 1.1% of patients treated with Zykadia in clinical studies (see section ADVERSE DRUG REACTIONS). Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving Zykadia. Concurrent elevations in ALT/AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of Zykadia.

Liver laboratory tests (including ALT, AST, and total bilirubin) should be performed prior to the start of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

Interstitial lung disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with Zykadia in clinical studies (see section ADVERSE DRUG REACTIONS). Most of these severe/life-threatening cases improved or resolved with interruption of Zykadia.

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded, and Zykadia should be permanently discontinued in patients diagnosed with any grade treatment-related ILD/pneumonitis (see section DOSAGE REGIMEN AND ADMINISTRATION).

QT interval prolongation

QTc prolongation has been observed in clinical studies in patients treated with Zykadia, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death (see section ADVERSE DRUG REACTIONS). A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patient (1.3%), among which six had elevated QTc>450msec at baseline. There were 58 patients (6.3%) with a QTc increase from baseline >60 msec. A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc.

Use of Zykadia should be avoided in patients with congenital long QT syndrome. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g., potassium) is recommended in patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities and in patients who are taking medications that are known to prolong the QT interval. In case of vomiting, diarrhoea, dehydration, or impaired renal function, correct electrolytes as clinically indicated. Zykadia should be permanently discontinued in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Zykadia should be withheld in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then Zykadia should be reinitiated by reducing dose by 150 mg (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

Bradycardia

Asymptomatic cases of bradycardia have been observed in patients treated with Zykadia in clinical studies (see section ADVERSE DRUG REACTIONS).

Use of Zykadia should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure should be monitored regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia if necessary. Zykadia should be permanently discontinued for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, Zykadia should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, Zykadia should be reinitiated by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see section DOSAGE REGIMEN AND ADMINISTRATION).

Gastrointestinal adverse reactions

Diarrhoea, nausea, or vomiting occurred in 76.9% of 108 patients treated with Zykadia at the recommended dose of 450 mg taken with food in a dose optimization study A2112 (ASCEND-8) and were mainly grade 1 events (52.8%) and grade 2 (22.2%) events. Two patients (1.9%) experienced one grade 3 event each (diarrhoea and vomiting). Nine patients (8.3%) required study drug interruption due to diarrhoea or nausea or vomiting. One patient (0.9) required dose adjustment due to vomiting. No patients required discontinuation of Zykadia due to diarrhoea, nausea, or vomiting (see section ADVERSE DRUG REACTIONS).

Patients should be monitored and managed using standards of care, including anti-diarrhoeals, anti-emetics, or fluid replacement, as indicated. Dose interruption and dose reduction may be employed as necessary. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose (see section DOSE REGIMEN AND ADMINISTRATION).

Hyperglycaemia

Events of hyperglycaemia (all grades) have been reported in less than 10% of patients treated with Zykadia in clinical studies; 5.4% of patients reported a grade 3/4 event (see section ADVERSE DRUG REACTIONS). The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Fasting serum glucose should be monitored prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. Anti-hyperglycaemic medications should be initiated or optimized as indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

Lipase and/or amylase elevations

Elevations of lipase and/or amylase have occurred in patients receiving Zykadia in clinical studies (see section ADVERSE DRUG REACTIONS).

Lipase and amylase should be monitored prior to the start of Zykadia treatment and periodically thereafter as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

ADVERSE DRUG REACTIONS

Summary of the safety profile

Adverse drug reactions described below reflect exposure to Zykadia 750 mg once daily fasted in 925 patients with ALK-positive advanced NSCLC across a pool of seven clinical studies, including two randomized, active-controlled, Phase 3 studies (Studies A2301 and A2303).

The median duration of exposure to Zykadia 750 mg fasted was 44.9 weeks (range 0.1 to 200.1 weeks). Dose reductions occurred in 62.2% of patients and dose interruptions in 74.8% of patients. The rate of adverse events (AEs) resulting in permanent discontinuation of Zykadia was 12.1%. The most frequent AEs (>0.5%) leading to discontinuation of Zykadia were pneumonia (0.6%), and respiratory failure (0.6%).

Adverse drug reactions (ADRs) with an incidence of ≥10% in patients treated with Zykadia 750 mg fasted were diarrhoea, nausea, vomiting, liver laboratory test abnormalities, fatigue, abdominal pain, decreased appetite, weight decreased, constipation, blood creatinine increased, rash, anaemia and esophageal disorder.

Grade 3/4 ADRs with an incidence of ≥5% in patients treated with Zykadia 750 mg fasted were liver laboratory test abnormalities, fatigue, vomiting, hyperglycaemia, nausea and diarrhoea.

In the dose optimization study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC, the overall safety profile of Zykadia at the recommended dose of 450 mg with food (N=108) was consistent with Zykadia 750 mg fasted (N=110), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see section CLINICAL PHARMACOLOGY). The incidence and severity of gastrointestinal adverse drug reactions (diarrhoea 59.3%, nausea 42.6%, vomiting 38.0%; 1.9% reported a grade 3/4 event) were reduced for patients treated with Zykadia 450 mg with food compared to 750 mg fasted (diarrhoea 80.0%, nausea 60.0%, vomiting 65.5%; 17.3% reported a grade 3/4 event). In patients treated with Zykadia 450 mg with food, 24.1% of patients had at least one adverse event that required dose reduction and 55.6% of patients had at least one adverse event that required study drug interruption.
Tabulated summary of adverse drug reactions from clinical trials

Table 2 presents the frequency category of ADRs reported for Zykadia in patients treated at a dose of 750 mg fasted (N=925) in 7 clinical studies. The frequency of selected gastrointestinal ADRs (diarrhoea, nausea, and vomiting) are based on patients treated with a dose of 450 mg once daily with food (N=108).

ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 2 Adverse drug reactions in patients (N=925) treated with Zykadia

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood and lymphatic system disorders				
Anaemia	141 (15.2)	Very Common	28 (3.0)	Common
Metabolism and nutrition disorders				
Decreased appetite	365 (39.5)	Very common	20 (2.2)	Common
Hyperglycaemia	87 (9.4)	Common	50 (5.4)	Common
Hypophosphataemia	49 (5.3)	Common	21 (2.3)	Common
Eye disorders				
Vision disorder[m]	65 (7.0)	Common	0	
Cardiac disorders				
Pericarditis[h]	54 (5.8)	Common	24 (2.6)	Common
Bradycardia[e]	21 (2.3)	Common	0	
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[i]	19 (2.1)	Common	11 (1.2)	Common
Gastrointestinal disorders				
Diarrhoea[n]	64 (59.3)	Very common	1 (0.9)	Uncommon
Nausea[n]	46 (42.6)	Very common	0	
Vomiting[n]	41 (38.0)	Very common	1 (0.9)	Uncommon
Abdominal pain[a]	426 (46.1)	Very common	23 (2.5)	Common
Constipation	222 (24.0)	Very common	3 (0.3)	Uncommon
Oesophageal disorder[f]	130 (14.1)	Very common	4 (0.4)	Uncommon
Pancreatitis	5 (0.5)	Uncommon	5 (0.5)	Uncommon
Hepatobiliary disorders				
Abnormal liver function tests[c]	20 (2.2)	Common	9 (1.0)	Common
Hepatotoxicity[d]	10 (1.1)	Common	4 (0.4)	Uncommon
Skin and subcutaneous tissue disorders				
Rash[j]	181 (19.6)	Very common	4 (0.4)	Uncommon
Renal and urinary disorders				
Renal failure[k]	17 (1.8)	Common	2 (0.2)	Uncommon
Renal impairment[l]	9 (1.0)	Common	1 (0.1)	Uncommon
General disorders and administration site conditions				
Fatigue[g]	448 (48.4)	Very common	71 (7.7)	Common
Investigations				
Liver laboratory test abnormalities[b]	560 (60.5)	Very common	347 (37.5)	Very common
Weight decreased	255 (27.6)	Very common	26 (2.8)	Common
Blood creatinine increased	204 (22.1)	Very common	5 (0.5)	Uncommon
Electrocardiogram QT prolonged	90 (9.7)	Common	19 (2.1)	Common
Lipase increased	44 (4.8)	Common	32 (3.5)	Common
Amylase increased	65 (7.0)	Common	29 (3.1)	Common

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
[a] *Abdominal pain includes PTs of Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Epigastric Discomfort* [b] *Liver laboratory test abnormalities includes PTs of Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Gamma-Glutamyltransferase Increased, Blood Bilirubin Increased, Transaminases Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Liver Function Test Increased, Blood Alkaline Phosphatase Increased* [c] *Abnormal liver function tests includes PTs of Hepatic Function Abnormal, Hyperbilirubinaemia* [d] *Hepatotoxicity includes PTs of Drug-Induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury, Hepatotoxicity* [e] *Bradycardia includes PTs of Bradycardia and Sinus Bradycardia* [f] *Esophageal Disorder includes PTs of Dyspepsia, Gastroesophageal Reflux Disease, Dysphagia* [g] *Fatigue includes PTs of Fatigue and Asthenia* [h] *Pericarditis includes PTs of Pericardial Effusion and Pericarditis* [i] *Pneumonitis includes PTs of Interstitial Lung Disease (ILD) and Pneumonitis* [j] *Rash includes PTs of Rash, Dermatitis Acneiform, Rash Maculo-Papular* [k] *Renal Failure includes PTs of Acute Renal Injury and Renal Failure* [l] *Renal Impairment includes PTs of Azotaemia and Renal Impairment* [m] *Vision disorder includes PTs of Visual Impairment, Vision Blurred, Photopsia, Vitreous Floaters, Visual Acuity Reduced, Accommodation Disorder, Presbyopia* [n] *The frequency of these selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) is based on patients treated with the recommended dose of 450 mg with food (N=108) in Study A2112 (ASCEND-8).*				

Special populations

Geriatric population

Across seven clinical studies, 168 of 925 patients (18.2%) treated with Zykadia were aged 65 years and older. The safety profile in patients aged 65 years and older was similar to that in patients less than 65 years of age (see section DOSAGE REGIMEN AND ADMINISTRATION).

INTERACTIONS

Agents that may increase ceritinib plasma concentrations

Strong CYP3A inhibitors

In healthy subjects, co-administration of a single 450 mg fasted ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A/P-gp inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone.

Concurrent use of strong CYP3A inhibitors should be avoided during treatment with Zykadia. If concomitant use of strong CYP3A inhibitors is unavoidable, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone, the dose of Zykadia should be reduced by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, Zykadia should be resumed at the dose that was taken prior to initiating the strong CYP3A inhibitor (see section DOSAGE REGIMEN AND ADMINISTRATION).

P-gp inhibitors

Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If Zykadia is administered with drugs that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and carefully monitor adverse drug reactions.

Agents that may decrease ceritinib plasma concentrations

Strong CYP3A and P-gp inducers

In healthy subjects, co-administration of a single 750 mg fasted ceritinib dose with rifampin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. Co-administration of Zykadia with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort *(Hypericum perforatum)* should be avoided. Caution should be exercised with concomitant use of P-gp inducers.

Agents whose plasma concentration may be altered by ceritinib

CYP3A and CYP2C9 substrates

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed.

Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of Zykadia dosing in patients (750 mg daily fasted) increased the midazolam AUC_{inf} (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone. Co-administration of Zykadia with substrates primarily metabolized by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g., ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus) should be avoided. If unavoidable, dose reduction should be considered for co-administered medicines that are CYP3A substrates with narrow therapeutic indices.

Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of Zykadia dosing in patients (750 mg daily fasted) increased the S-warfarin AUC_{inf} (90% CI) by 54% (36%, 75%) compared to warfarin alone. Co-administration of Zykadia with substrates primarily metabolized by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin) should be avoided. If unavoidable, dose reduction should be considered for co-administered medicines that are CYP2C9 substrates with narrow therapeutic indices. The frequency of international normalized ratio (INR) monitoring should be increased if co-administration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced.

CYP2A6 and CYP2E1 substrates

Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by these enzymes. Caution should be exercised with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions.

Agents that are substrates of transporters

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporters, BCRP, P-gp or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur.

Agents that affect gastric pH

Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. In a drug interaction study in healthy subjects (N=22), co-administration of a single dose of 750 mg of ceritinib fasted and esomeprazole (a proton pump inhibitor) at 40 mg daily for 6 days decreased the ceritinib exposure (AUC_{inf} and Cmax decreased by 76% and 79%, respectively). However, coadministration of a single 750 mg ceritinib dose fasted with proton pump inhibitors for 6 days in a subgroup of patients from Study X2101 suggested less effect on ceritinib exposure than that observed in healthy subjects as AUC (90% CI) decreased by 30% (0%, 52%) and Cmax (90% CI) decreased by 25% (5%, 41%) and no clinically meaningful effect on ceritinib exposure was observed at steady-state after ceritinib once daily dosing.

This is further confirmed by a subgroup analysis based on three clinical studies (N >400) in which patients with and without proton pump inhibitors showed similar steady-state exposure and clinical efficacy and safety.

Drug-food/drink interactions

Zykadia should be taken with food. The bioavailability of ceritinib is increased in the presence of food (see section CLINICAL PHARMACOLOGY).

Patients should be instructed to avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL, INFERTILITY

Pregnancy

Risk summary

There are insufficient data regarding the use of Zykadia in pregnant women. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits. The potential risk in humans is unknown. Zykadia should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Lactation

Risk summary

It is unknown whether ceritinib is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to discontinue breast-feeding or discontinue Zykadia taking into account the importance of Zykadia to the mother.

Females and males of reproductive potential

Contraception

Females

Females of reproductive potential should be advised to use an effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving Zykadia and up to 3 months after discontinuing treatment.

Infertility

Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted. The potential for Zykadia to cause infertility in male and female patients is unknown.

OVERDOSAGE

There is limited reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, ATC Code: L01XE28.

Mechanism of action (MOA)

Ceritinib is an orally highly selective and potent ALK kinase inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*.

ALK translocation determines expression of the resulting fusion protein and consequent aberrant ALK signaling in NSCLC. In the majority of NSCLC cases, EML4 is the translocation partner for ALK; this generates an EML4-ALK fusion protein containing the protein kinase domain of ALK fused to the N-terminal part of EML4. Ceritinib was demonstrated effective against EML4-ALK kinase activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumors in H2228 derived xenografts in mouse and rat.

Pharmacodynamics (PD)

Ceritinib inhibition of ALK kinase activity and ALK-mediated signaling pathways in Karpas 299 (lymphoma cell line) and in H2228 (lung cancer cell line) was demonstrated to be dose-dependent. The inhibitory effect of ceritinib led to inhibition of cancer cell proliferation *in vitro* and tumor regression *in vivo* in mouse and rat xenograft models. Ceritinib is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of the ALK kinase activity (IC50 for inhibition of ALK of 0.15 nanomolar for ceritinib and 3 nanomolar for crizotinib). In a kinase panel of 36 enzymes, ceritinib inhibited only 2 other kinases with approximately 50-fold less potency for ALK inhibition. All other kinases in the panel had greater than 500-fold less potency when compared with ALK, demonstrating a high degree of selectivity. A single-dose pharmacodynamic study and multiple-daily dose efficacy study performed in Karpas 299 lymphoma and H2228 lung cancer tumor models indicated that a 60% to 80% reduction in the ALK signaling pathway may be required to achieve tumor regression.

Pharmacokinetics (PK)

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after a single oral administration in patients. Oral absorption was estimated to be ≥25% based on metabolite percentages in the feces. The absolute bioavailability of ceritinib has not been determined.

Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing.

After a single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by C_{max} and AUC_{last}, increased dose-proportionally over the 50 to 750 mg dose range under fasted conditions. In contrast with single-dose data, pre-dose concentration (C_{min}) after repeated daily dosing appeared to increase in a greater than dose-proportional manner.

Food effect

Systemic exposure of ceritinib was increased when administered with food. Ceritinib AUCinf values were approximately 58% and 73% higher (C_{max} approximately 43% and 41% higher) in healthy subjects when a single 500 mg ceritinib dose (capsule) was administered with a low fat meal (containing approximately 330 calories and 9 grams of fat) and a high fat meal (containing approximately 1000 calories and 58 grams of fat, respectively, as compared with the fasted state.

In a dose optimization study A2112 (ASCEND-8) in patients comparing Zykadia 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) to 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib for the 450 mg with food arm (N=36) compared to the 750 mg fasted arm (N=31), with only small increases in steady-state AUC (90% CI) by 4% (-13%, 24%) and C_{max} (90% CI) by 3% (-14%, 22%). In contrast, the steady-state AUC (90% CI) and C_{max} (90% CI) for the 600 mg with food arm (N=30) increased by 24% (3%, 49%) and 25% (4%, 49%), respectively, compared to the 750 mg fasted arm. The maximum recommended dose of Zykadia is 450 mg taken orally once daily with food (see section DOSAGE REGIMEN AND ADMINISTRATION).

Distribution

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/mL to 10,000 ng/mL. The apparent volume of distribution (Vd/F) is 4230 L in patients after a single 750 mg fasted dose of Zykadia. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

In rats, ceritinib crosses the intact blood brain barrier with a brain-to-blood exposure (AUC_{inf}) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

Biotransformation/metabolism

In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib.

Following a single oral administration of radioactive ceritinib dose at 750 mg fasted, ceritinib was the main circulating component (82%) in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of

≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Elimination

Following single oral doses of ceritinib under fasted conditions, the geometric mean apparent plasma terminal half-life (T1/2) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/hr) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 L/hr) suggesting that ceritinib demonstrates non-linear PK over time.

The primary route of excretion of ceritinib and its metabolites is in the feces. Recovery in the feces accounts for 91% of the administered oral dose (with a mean 68% of an oral dose as unchanged parent compound). Only 1.3% of the administered oral dose is recovered in the urine.

Special populations

Effects of age, gender, and race

Population pharmacokinetics analyses showed that age, gender, and race had no clinically meaningful influence on ceritinib exposure.

Hepatic impairment

The effect of hepatic impairment on the single dose pharmacokinetics of ceritinib (750 mg fasted) was evaluated in subjects with mild (Child-Pugh class A; N = 8), moderate (Child-Pugh class B; N = 7), or severe (Child-Pugh class C; N = 7) hepatic impairment and in 8 healthy subjects with normal hepatic function. The geometric mean systemic exposure (AUCinf) of ceritinib was increased by 18% and 2% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. No dose adjustment is necessary in patients with mild and moderate hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

The geometric mean systemic exposure (AUC_{inf}) of ceritinib was increased by 66% in subjects with severe hepatic impairment compared to subjects with normal hepatic function. For patients with severe hepatic impairment, reduce the dose of Zykadia by approximately one-third rounded to the nearest mutliple of the 150 mg dosage strength (see section DOSAGE REGIMEN AND ADMINISTRATION).

Renal impairment

Ceritinib has not been studied in patients with renal impairment. However, based upon available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

Based on a population pharmacokinetic analysis of 345 patients with mild renal impairment (CLcr 60 to <90 mL/min), 82 patients with moderate renal impairment (CLcr 30 to <60 mL/min) and 546 patients with normal renal function (≥90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment (see section DOSAGE REGIMEN AND ADMINISTRATION). Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trial.

Cardiac electrophysiology

The potential for QT interval prolongation of ceritinib was assessed in 7 clinical studies with Zykadia. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in 925 patients treated with Zykadia 750 mg once daily fasted. A categorical analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%). There were 58 patients (6.3 %) with a QTc increase from baseline >60 msec. A central tendency analysis of the QTc data at average steady-state concentrationsfrom a global phase 3 study (Study A2301) demonstrated that the upper bound of the 2-sided 90% CI for QTc was 15.3 msec at ceritinib 750 mg fasted. A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

Previously untreated ALK-positive locally advanced or metastatic NSCLC - Randomized Phase 3 Study A2301 (ASCEND-4).

The efficacy and safety of Zykadia for the treatment of locally advanced or metastatic ALK-positive NSCLC patients with and without brain metastasis, who have not received previous systemic treatment anti-cancer therapy (including ALK inhibitor) with the exception of neo-adjuvant or adjuvant therapy, was demonstrated in a global multicenter, randomized, open-label Phase 3 Study A2301.

The primary efficacy endpoint was progression-free survival (PFS), as determined by a Blinded Independent Review Committee (BIRC), according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigators and patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression by BIRC.

A total of 376 patients were randomized in a 1:1 ratio (stratified by WHO performance status, prior adjuvant/neoadjuvant chemotherapy and presence/absence of brain metastasis at screening) to receive either ceritinib (750 mg once daily, fasted) or chemotherapy (based on Investigator's choice - pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC 5-6), administered every 21 days). Patients who completed 4 cycles of chemotherapy (induction) without progressive disease subsequently received pemetrexed (500 mg/m^2) as single-agent maintenance therapy every 21 days. One hundred and eighty-nine (189) patients were randomized to ceritinib and one hundred eighty-seven (187) were randomized to chemotherapy.

The overall median age was 54 years (range: 22 to 81 years); 78.5% of patients were younger than 65 years. A total of 57.4% of patients were female. 53.7% of the study population was Caucasians, 42.0% Asians, 1.6% Blacks and 2.6% other races. The majority of patients had adenocarcinoma (96.5%) and had either never smoked or were former smokers (92.0%). The

Eastern Cooperative Oncology Group (ECOG) performance status was 0/1/2 in 37.0%/56.4%/6.4% of patients respectively, and 32.2% had neurologically stable (symptomatic or not) brain metastasis at baseline. Baseline disease characteristics were well-balanced between the two treatment arms. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or had required increasing doses of steroid within the 2 weeks prior to screening to manage CNS symptoms were excluded from the study.

The median duration of follow-up was 19.7 months (from randomization to data cut-off date).

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 45% risk reduction in the ceritinib arm compared to the chemotherapy arm (HR: 0.55 with 95% CI: 0.42, 0.73, p<0.001). The median PFS was 16.6 months (95% CI: 12.6, 27.2) and 8.1 months (95% CI: 5.8, 11.1) for the ceritinib arm and chemotherapy arm, respectively (see Table 3 and Figure 1).

The PFS benefit of ceritinib over chemotherapy was robust and consistent by Investigator assessment and across various subgroups including age, gender, race, smoking class, Eastern Cooperative Oncology Group (ECOG) performance status and disease burden (see Figure 2).

Ceritinib also significantly improved BIRC-assessed ORR as compared to chemotherapy with durable response (see Table 3).

As pre-specified in the protocol, OS was formally tested as the primary efficacy endpoint PFS by BIRC assessment was statistically significant and favoring the ceritinib arm. The overall survival (OS) data was not mature with 107 deaths representing approximately 42.3 % of the required events for the final OS analysis. There were fewer deaths in the ceritinib arm (48 events, 25.4%) than in the chemotherapy arm (59 events, 31.6%), indicating a trend favoring ceritinib (HR: 0.73 with 95% CI: 0.50, 1.08, stratified log-rank test one-sided p=0.056). The median OS was not estimable in the ceritinib arm and was 26.2 months (95% CI: 22.8, NE) in the chemotherapy arm. The estimated OS rate (95% CI) at 24 months was 70.6% (62.2, 77.5) and 58.2% (47.6, 67.5) for ceritinib arm and chemotherapy arm, respectively. Eighty-one patients (43.3%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2301 are summarized in Table 3, and the Kaplan-Meier curves for PFS and OS and Forest plot for PFS by subgroup are shown in Figure 1, Figure 2 and Figure 3.

Table 3 ASCEND-4 (Study A2301) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC

	Ceritinib (N=189)	Chemotherapy (N=187)
Progression-Free Survival (based on BIRC)		
Number of events, n (%)	89 (47.1)	113 (60.4)
Median, months[d] (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
HR (95% CI)[a]	0.55 (0.42, 0.73)	
p-value[b]	<0.001	
Overall Survival[c]		
Number of events, n (%)	48 (25.4)	59 (31.6)
Median, months[d] (95% CI)	NE (29.3, NE)	26.2 (22.8, NE)
OS rate at 24 months[d], % (95% CI)	70.6 (62.2, 77.5)	58.2 (47.6, 67.5)
HR (95% CI)[a]	0.73 (0.50,1.08)	
p-value[b]	0.056	
Tumor Response (based on BIRC)		
Objective response rate (95% CI)	72.5% (65.5, 78.7)	26.7% (20.5, 33.7)
Duration of response (based on BIRC)		
Number of responders	137	50
Median, months[d] (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Event-free rate at 18 months[d], % (95% CI)	59.0 (49.3, 67.4)	30.4 (14.1, 48.6)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable; CR=complete response; PR=partial response

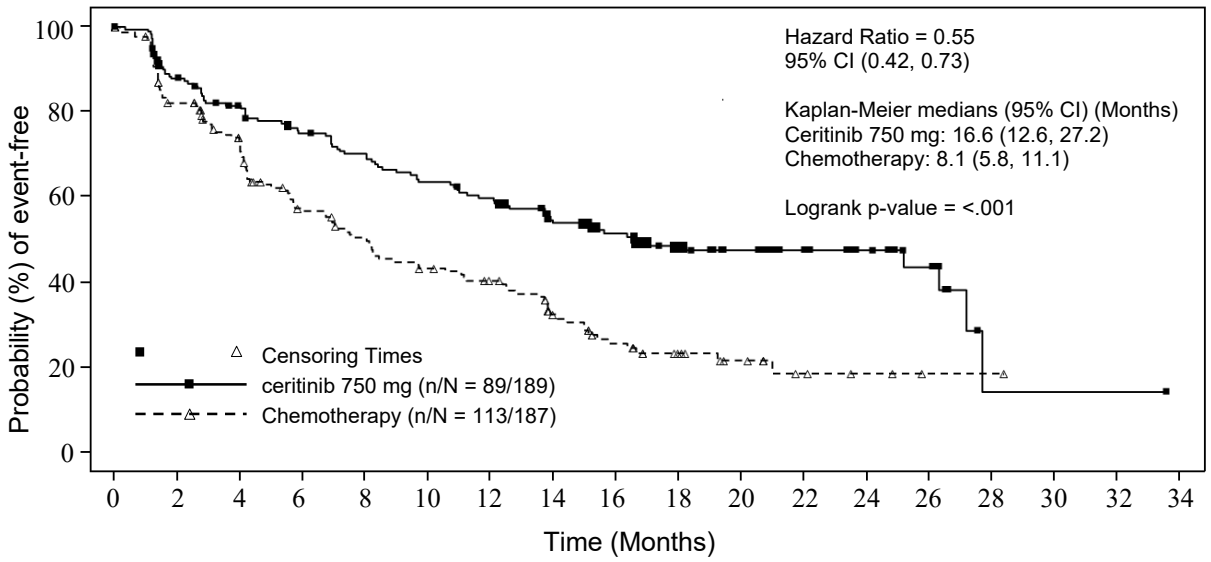
[a] *Based on the Cox proportional hazards stratified analysis.*

[b] *Based on the stratified log-rank test.*

[c] *OS analysis was not adjusted for the effects of cross over.*

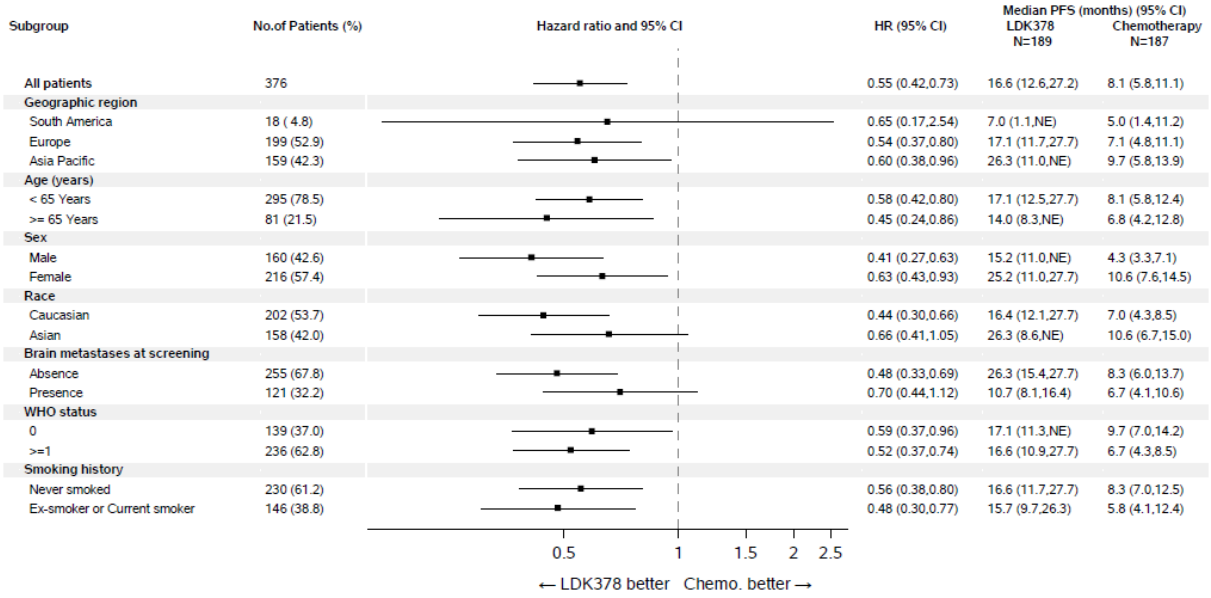
[d] *Estimated using the Kaplan-Meier method.*

Figure 1 ASCEND-4 (Study A2301) - Kaplan-Meier plot of progression-free survival as assessed by BIRC



	No. of patients still at risk																	
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ceritinib 750 mg	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

Figure 2 **ASCEND-4 (Study A2301) - Forest plot for progression-free survival per BIRC assessment by subgroup (FAS)**

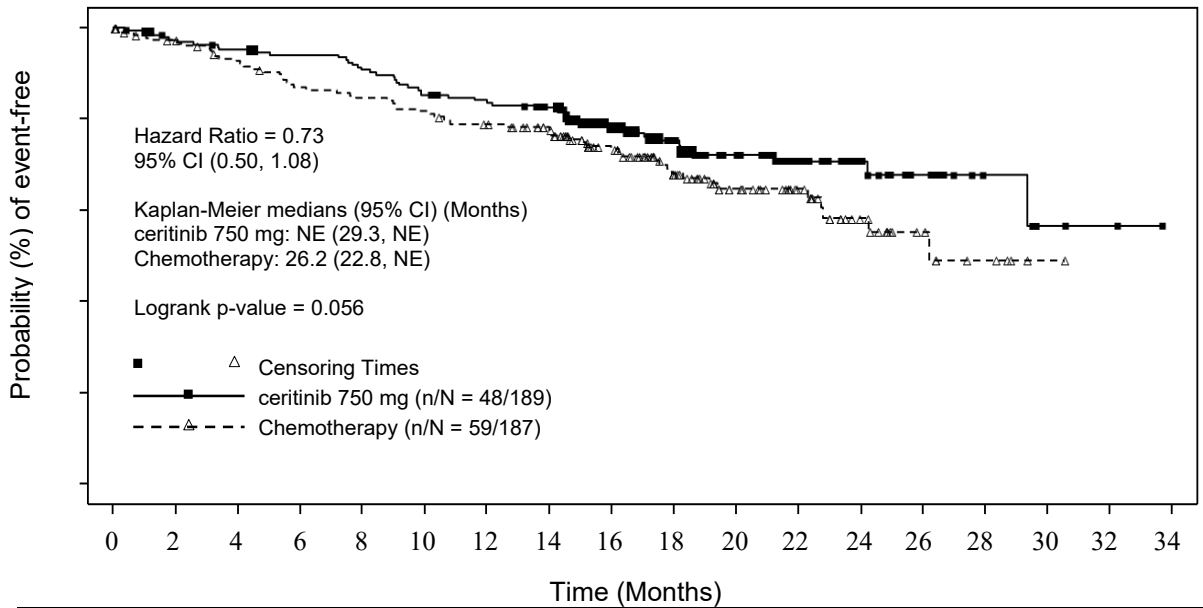


Except for 'WHO status' and 'Brain metastases at screening' the Cox regression model was stratified by presence or absence of brain metastases, prior adjuvant chemotherapy and WHO status.

For 'WHO status', Cox regression model was stratified by presence or absence of brain metastases, prior adjuvant chemotherapy.

For 'Brain metastases at screening', Cox regression model was stratified by WHO status and presence or absence of prior adjuvant chemotherapy.

Figure 3 **ASCEND-4 (Study A2301) - Kaplan-Meier plot of overall survival**



	No. of patients still at risk																	
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ceritinib 750 mg	189	180	175	171	165	155	150	138	103	77	56	39	26	18	6	3	2	0
Chemotherapy	187	172	161	150	146	141	134	124	97	69	49	35	19	10	5	1	0	0

Patient reported outcome questionnaires were completed by 80% or more of patients in the ceritinib and chemotherapy arms for all questionnaires at most of the time points during the course of the study.

Ceritinib significantly prolonged time to deterioration for lung cancer specific symptoms as shown by the composite endpoint of cough, pain and dyspnea in the Lung Cancer Symptom Score (LCSS) (HR = 0.61, 95% CI: 0.41, 0.90) and QLQ-LC13 (HR = 0.48, 95% CI: 0.34, 0.69) instruments compared to chemotherapy. Median time to definitive deterioration for the LC13 composite endpoint (pain, cough, shortness of breath) was 23.6 months (95% CI: 20.7, NE) in the ceritinib arm versus 12.6 months (95% CI: 8.9, 14.9) in the chemotherapy arm.

Patients receiving ceritinib showed significant improvements over chemotherapy in General Quality of Life (LCSS, p <0.001), Global Health Status/QoL (QLQ-C30, p <0.001) as well as in EQ-5D-5L index (p <0.001) and EQ-5D-5L VAS (p < 0.05 from each treatment cycle from 13 until 49). Overall, these results suggest improvements in lung cancer specific symptoms as well as general health status benefits for ALK-positive NSCLC patients treated with ceritinib versus chemotherapy.

In Study A2301, 44 out of 121 patients had active and measurable brain metastasis at baseline and at least one post-baseline brain radiological assessment (22 in the ceritinib arm and 22 patients in the chemotherapy arm). An active brain metastasis is defined as an untreated brain metastasis, new brain metastasis or an existing brain metastasis with documented progression after the end of the brain radiotherapy. These 44 patients were assessed for intracranial response by BIRC neuro-radiologist. The intracranial ORR (OIRR) was higher with ceritinib (72.7%, 95% CI: 49.8, 89.3) as compared to the chemotherapy arm (27.3%, 95% CI: 10.7, 50.2). Among these patients with measurable brain metastasis at baseline and at least one post-baseline, 59.1% (13/22) in the ceritinib arm and 81.8% (18/22) in the chemotherapy arm did not receive prior radiotherapy to the brain.

The median PFS by BIRC and Investigator using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases (based on the extent of cancer CRF, see Table 4).

Table 4 ASCEND-4 (Study A2301) – PFS with and without brain metastases

	BIRC		Investigator	
	Ceritinib	**Chemotherapy**	**Ceritinib**	**Chemotherapy**
With Brain Metastases	**N=59**	**N=62**	**N=59**	**N=62**
Progression Free Survival				
Median, months (95% CI)	10.7 (8.1, 16.4)	6.7 (4.1, 10.6)	13.5 (9.0, 16.7)	6.7 (4.2, 10.6)
HR (95% CI)	0.70 (0.44, 1.12)		0.58 (0.36, 0.92)	
Without Brain Metastases	**N=130**	**N=125**	**N=130**	**N=125**
Progression Free Survival				
Median, months (95% CI)	26.3 (15.4, 27.7)	8.3 (6.0, 13.7)	25.2 (13.9, NE)	8.3 (5.8, 11.1)
HR (95% CI)	0.48 (0.33, 0.69)		0.44 (0.31, 0.63)	

Previously treated ALK-positive locally advanced or metastatic NSCLC - Randomized Phase 3 Study A2303 (ASCEND-5).

The efficacy and safety of Zykadia for the treatment of locally advanced or metastatic ALK-positive NSCLC patients with and without brain metastasis, who have received previous treatment with crizotinib, was demonstrated in a global multicenter, randomized, open-label Phase 3 Study A2303.

The primary efficacy endpoint was PFS, as determined by BIRC, according to RECIST 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigator, PFS by Investigator and patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression confirmed by BIRC.

A total of 231 patients with advanced ALK positive NSCLC who have received prior treatment with crizotinib and chemotherapy (one or two regimen including a platinum-based doublet) were included in the analysis. 115 patients were randomized to ceritinib and 116 were randomized to chemotherapy (either pemetrexed or docetaxel). 73 patients received docetaxel and 40 received pemetrexed. In the ceritinib arm, 115 patients were treated with 750 mg once daily fasted.

Baseline disease characteristics were well-balanced between the two treatment arms. The median age was 54.0 years (range: 28 to 84 years); 77.1% of patients were younger than 65 years. A total of 55.8% of patients were female. 64.5% of the study population were Caucasians, 29.4% Asians, 0.4% Blacks and 2.6% other races. The majority of patients had adenocarcinoma (97.0%) and had either never smoked or were former smokers (96.1%). The ECOG performance status was 0/1/2 in 46.3%/47.6%/6.1% of patients respectively, and 58.0% had brain metastasis at baseline. All patients were treated with prior crizotinib. 198 patients (81.8%) received crizotinib as last treatment (81.7% in the ceritinib arm, 81.9% in the chemotherapy arm). All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ceritinib arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimen for advanced disease.

The median duration of follow-up was 16.5 months (from randomization to data cut-off date).

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 51% risk reduction in the ceritinib arm compared to chemotherapy arm (HR: 0.49 with 95% CI: 0.36, 0.67). The median PFS was 5.4 months (95% CI: 4.1, 6.9) and 1.6 months (95% CI: 1.4, 2.8) for the ceritinib arm and chemotherapy arm, respectively (see Table 5 and Figure 4).

The PFS benefit of ceritinib over chemotherapy was robust and consistent by Investigator assessment and across various subgroups including age, gender, race, smoking class, ECOG performance status, and presence of brain metastases or prior response to crizotinib (see Figure 5).

The benefit was further supported analysis of ORR and disease control rate (DCR). Ceritinib also significantly improved BIRC-assessed ORR as compared to chemotherapy with durable response (see Table 5).

As pre-specified in the protocol, OS was formally tested as the primary efficacy endpoint PFS by BIRC assessment was statistically significant and favoring the ceritinib arm. OS data was not mature with 48 (41.7%) events in the ceritinib arm and 50 (43.1%) events in the chemotherapy arm, corresponding to approximately 50% of the required events for final OS.

In addition, 81 patients (69.8%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2303 are summarized in Table 5, and the Kaplan-Meier curves for PFS and OS and Forest plot for PFS by subgroup are shown in Figure 4, Figure 5 and Figure 6.

Table 5 ASCEND-5 (Study A2303) – Efficacy result in patients with previously treated ALK-positive locally advanced or metastatic NSCLC

	Ceritinib (N=115)	Chemotherapy (N=116)
Progression-free survival (based on BIRC)		
Number of events, n (%)	83 (72.2%)	89 (76.7%)
Median, months (95% CI)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
HR (95% CI)[a]	0.49 (0.36, 0.67)	
p-value[b]	<0.001	
Overall survival[c]		
Number of events, n (%)	48 (41.7%)	50 (43.1%)
Median, months (95% CI)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)
HR (95% CI)[a]	1.00 (0.67,1.49)	
p-value[b]	0.496	
Tumor response (based on BIRC)		
Objective response rate (95% CI)	39.1% (30.2, 48.7)	6.9% (3.0, 13.1)
Duration of response		
Number of responders	45	8
Median, months[d] (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months[d] (95% CI)	31.5% (16.7%, 47.3%)	45.7% (6.9%, 79.5%)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable;

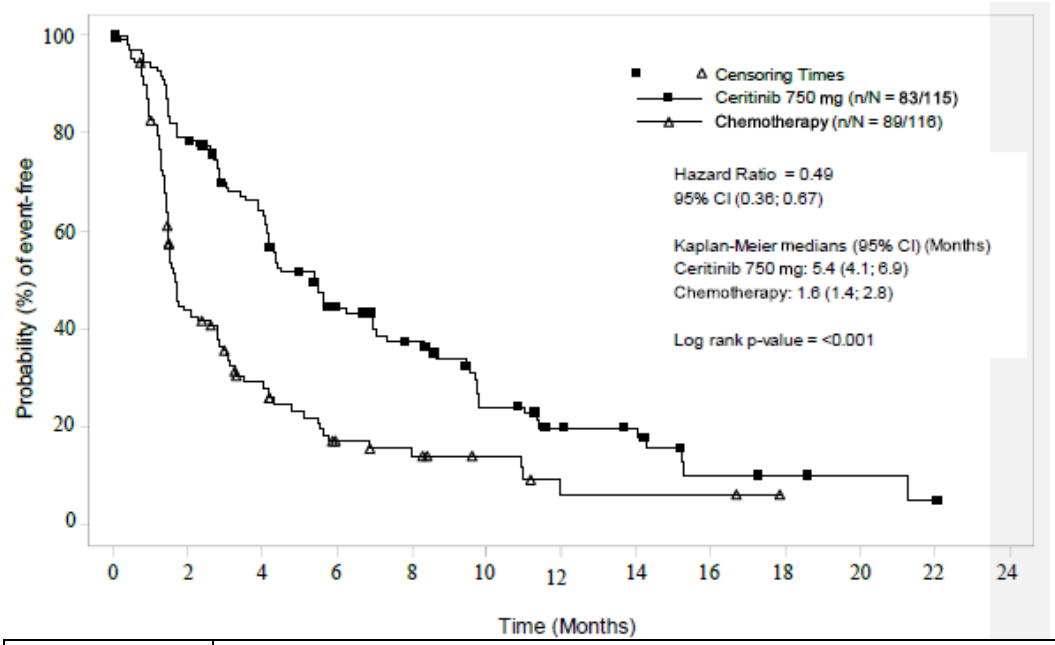
[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] OS analysis was not adjusted for the effects of cross over.

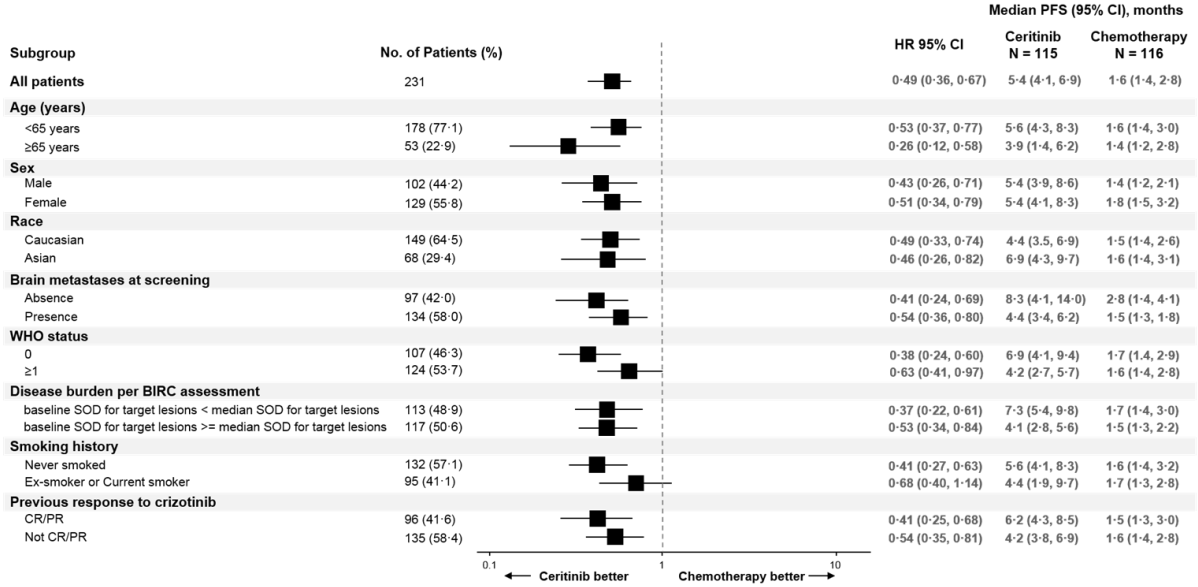
[d] Estimated using the Kaplan-Meier method.

Figure 4 **ASCEND-5 (Study A2303)- Kaplan-Meier plot of progression-free survival as assessed by BIRC**



	No. of patients still at risk												
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
Ceritinib 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

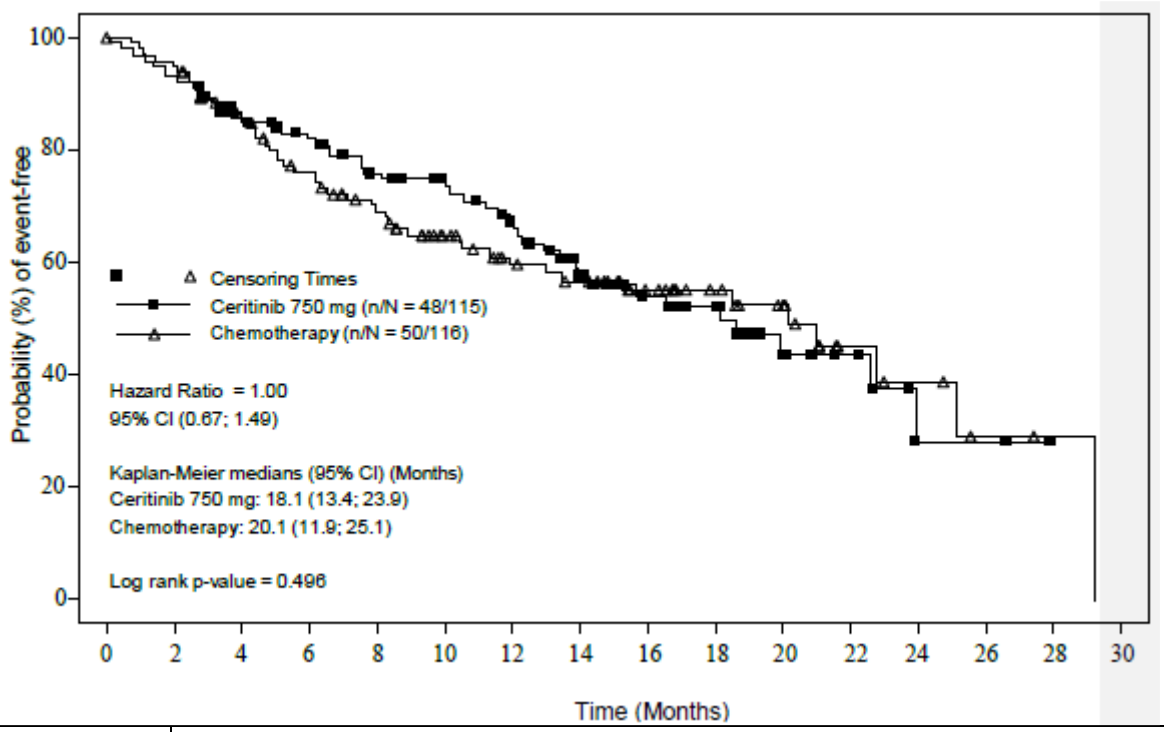
Figure 5 ASCEND-5 (Study A2303) - Forest plot for progression-free survival per BIRC assessment by subgroup (FAS)



BIRC=blinded independent review committee. CI=confidence interval. RECIST=Response Evaluation Criteria in Solid Tumours. WHO=World Health Organization. CR=complete response. PR=partial response. SOD=sum of diameters.

Except for 'WHO status' and 'Brain metastases at screening', hazard ratios are based on Cox regression model stratified by presence or absence of brain metastases and WHO status as per IRT at randomization.
Brain metastases at screening is as per CRF data at baseline
For 'Brain metastases at screening' Cox regression model was stratified by WHO status as per randomization (IRT).
For 'WHO status', Cox regression model was stratified by presence or absence of brain metastases as per randomization (IRT).
The subgroup of ex-smokers or current smokers includes five patients who were current smokers.

Figure 6 ASCEND-5 (Study A2303) - Kaplan-Meier plot of overall survival



	No. of patients still at risk															
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Ceritinib 750 mg	115	107	92	83	71	61	52	37	28	23	13	8	2	2	0	0
Chemotherapy	116	109	91	78	66	53	43	39	29	22	17	7	5	2	1	0

Patient reported outcome questionnaires were completed by 75% or more of patients in the ceritinib and chemotherapy arms for all questionnaires at most of the time points during the course of the study.

Significant improvements were reported for the majority of lung cancer specific symptoms for Zykadia versus chemotherapy (LCSS and QLQ-LC13 scores). Time to deterioration for cough, pain and dyspnea was significantly prolonged for the individual scales (p-value<0.05) or when combined into a composite score (p-value <0.001) in the LCSS and LC13 instruments. Median time to definitive deterioration for the LCSS composite endpoint (pain, cough, shortness of breath) was 18 months (95% CI: 13.4, NE) in the ceritinib arm versus 4.4 months (95% CI: 1.6, 8.6) in the chemotherapy arm. Median time to definitive deterioration for the same endpoint in the LC13 instrument was 11.1 months (95% CI 7.1, 14.2) in the ceritinib arm versus 2.1 months (95% CI: 1.0, 5.6) in the chemotherapy arm.

The EQ-5D questionnaire showed a significant overall health status improvement for Zykadia in comparison to the chemotherapy.

In Study A2303, 133 patients with baseline brain metastasis (66 patients in the ceritinib arm and 67 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist. The intracranial ORR (OIRR) in patients with measurable disease in the brain at baseline and at least one post-baseline assessment was higher with ceritinib (35.3%, 95% CI: 14.2, 61.7) compared to chemotherapy (5.0%, 95% CI: 0.1, 24.9).

The median PFS by BIRC and Investigator using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases (based on the extent of cancer CRF, see Table 6).

Table 6 ASCEND-5 (Study A2303) – PFS with and without brain metastases

	BIRC		Investigator	
	Ceritinib	**Chemotherapy**	**Ceritinib**	**Chemotherapy**
With Brain Metastases	**N=65**	**N=69**	**N=65**	**N=69**
Progression Free Survival				
Median, months (95% CI)	4.4 (3.4, 6.2)	1.5 (1.3, 1.8)	5.4 (3.9, 7.0)	1.5 (1.3, 2.1)
HR (95% CI)	0.54 (0.36, 0.80)		0.45 (0.31, 0.66)	
Without Brain Metastases	**N=50**	**N=47**	**N=50**	**N=47**
Progression Free Survival				
Median, months (95% CI)	8.3 (4.1, 14.0)	2.8 (1.4, 4.1)	8.3 (5.6, 13.4)	2.6 (1.4, 4.2)
HR (95% CI)	0.41 (0.24, 0.69)		0.32 (0.19, 0.54)	

Dose optimization Study A2112 (ASCEND-8)

The efficacy of Zykadia 450 mg with food was evaluated in a multicenter, open-label dose optimization Study A2112 (ASCEND-8). A total of 147 previously untreated patients with ALK-positive locally advanced or metastatic NSCLC were randomized to receive Zykadia 450 mg once daily with food (N=73) or Zykadia 750 mg once daily under fasted conditions (N=74). ALK-positivity was identified by VENTANA IHC. A key secondary efficacy endpoint was overall response rate (ORR) according to RECIST 1.1 as evaluated by a Blinded Independent Review Committee (BIRC).

The population characteristics of treatment-naive patients with ALK-positive locally advanced or metastatic NSCLC in the 450mg with food arm and the 750 mg fasted arm are summarized in Table 7 below.

Table 7 ASCEND-8 (Study A2112) – Demographic summary of treatment-naïve patients with ALK-positive locally advanced or metastatic NSCLC in 450 mg with food arm and 750 mg fasted arm

Demographic variable	**Zykadia 450 mg with food (N=73)**	**Zykadia 750 mg fasted (N=74)**
Mean age (years)	54.3	51.3
Age <65 years (%)	78.1	83.8
Female (%)	56.2	47.3
Caucasian (%)	49.3	54.1
Asian (%)	39.7	35.1
Never smoked or former smoker (%)	90.4	95.9
WHO performance status 0 or 1 (%)	91.7	91.9
Adenocarcinoma histology (%)	98.6	93.2
Brain metastases (%)	32.9	28.4

Efficacy results from ASCEND-8 are summarized in Table 8 below.

Table 8 ASCEND-8 (Study A2112) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC by BIRC

Efficacy Parameter	Zykadia 450 mg with food (N=73)	Zykadia 750 mg fasted (N=74)
Overall Response Rate (ORR: CR+PR), n (%) (95% CI)[a]	57 (78.1) (66.9, 86.9)	56 (75.7) (64.3, 84.9)

BIRC: *Blinded Independent Review Committee;* ***CI:*** *Confidence Interval*

CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

Overall response rate determined based on BIRC assessment per RECIST 1.1

[a]*Exact binomial 95% confidence interval*

Single-arm studies X2101, A2203 and A2201

The use of Zykadia in the treatment of ALK-positive NSCLC patients was investigated in 3 global, multicenter, open-label, single-arm studies (Study X2101, Study A2203 and Study A2201).

The primary efficacy endpoint for these studies was overall response rate (ORR) by Investigator for patients who were treated with a Zykadia dose of 750 mgfasted, defined as the proportion of patients with best response of complete response (CR) or partial response (PR) confirmed by repeat assessments performed not less than 4 weeks after the criteria for response was first met. Additional evaluations included duration of response (DOR) and progression-free survival (PFS) by Investigator assessment, and overall survival (OS). Tumor evaluations were performed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 in Study X2101 and RECIST 1.1 in Studies A2203 and A2201.

Study X2101 was a global, multicenter, open-label, phase 1 study which included a dose-escalation phase and an expansion phase, at a dose of 750 mg fasted. All patients enrolled in the study had locally advanced or metastatic malignancy that had progressed despite standard therapy and all patients were previously tested for ALK rearrangement. Patients with controlled or asymptomatic brain metastases were eligible for the study. Prior ALK inhibitor therapy was permitted. Two-hundred and ninety of the 304 patients enrolled in the study were ALK-positive NSCLC patients. A total of 246 ALK-positive NSCLC patients were enrolled who were treated at a Zykadia dose of 750 mg fasted: 163 who had received prior treatment with an ALK inhibitor and 83 who were ALK inhibitor naïve.

Across the 246 ALK-positive NSCLC patients treated at a dose of 750 mg fasted in the study, the median age was 53 years (range: 22 to 80 years); 84.1% of patients were younger than 65 years. A total of 53.7% of patients were female. Caucasians comprised 63.4% of the study population, Asians 33.3%, Blacks 1.6%, and other races 1.6%. The vast majority of patients had adenocarcinoma (92.7%) and were either never or former smokers (97.6%). More than two-thirds (67.5%) of the patients were treated with 2 or more regimens prior to enrollment into the study, 26.0% with 1 prior regimen, and 6.5% with 0 prior regimens.

Both **Study A2203 and Study A2201** were global, multicenter, open-label, single-arm, phase 2 studies designed to evaluate the efficacy and safety of 750 mg ceritinib fasted in patients with locally advanced or metastatic ALK-positive NSCLC. Study A2203 enrolled 124 crizotinib-naïve patients who were either chemotherapy-naïve or who had been previously treated with up to 3 lines of cytotoxic chemotherapy. Study A2201 enrolled 140 patients who had been previously treated with 1 to 3 prior lines of cytotoxic chemotherapy followed by treatment with crizotinib, and then progressed on crizotinib.

In Study A2203, 124 patients were treated at a dose of 750 mg fasted. The median age was 56 years (range: 27 to 82 years); 75.8% of patients were younger than 65 years. A total of 59.7%

of patients were female. Asians comprised 59.7% of the study population, Caucasians 38.7%, Blacks 0.8%, and other races 0.8%. The vast majority of patients had adenocarcinoma (96.8%). All patients, except 2 who were naïve to anti-cancer treatment, were treated with prior chemotherapy. 54 (43.5%) patients were treated with 1 regimen and 68 (54.8%) were treated with 2 or more regimens prior to enrollment into this study. All patients were ALK inhibitor naïve.

In Study A2201, 140 patients were treated at a dose of 750 mg fasted. The median age was 51 years (range: 29 to 80 years); 87.1% of patients were younger than 65 years. A total of 50.0% of patients were female. Caucasians comprised 60.0% of the study population, Asians 37.9% and other races 2.1%. The vast majority of patients had adenocarcinoma (92.1%). All patients were treated with 2 or more regimens prior to enrollment into the study. All patients had received prior treatment with an ALK inhibitor.

Main efficacy results from Studies X2101, A2203 and A2201

In Study X2101 with a median follow-up time of 11.1 months, out of the 246 ALK-positive NSCLC patients in the 750 mg dose group (ALK inhibitor naïve or with prior ALK inhibitor treatment), the ORR by Investigator assessment was 61.8% (95% CI: 55.4, 67.9). The median DOR in patients who responded was 9.7 months (95% CI: 8.3, 11.4). The median time to the first objective tumor response that was subsequently confirmed was 6.1 weeks (3.0 to 42.1). The median PFS was 9.0 months (95% CI: 6.9, 11.0).

The main efficacy data for all 3 studies are summarized in Table 9 for ALK-positive NSCLC patients who are ALK inhibitor naïve and in Table 10 for ALK-positive NSCLC patients with prior ALK inhibitor treatment. Patients responded to Zykadia regardless of whether they received a prior ALK inhibitor as shown in Tables 9 and 10. With longer follow-up (median duration > two years), patients continued to demonstrate a clinical response to Zykadia.

Table 9 Overview of efficacy data in ALK-positive NSCLC patients who are ALK inhibitor naïve per Investigator assessment

	Study X2101 ceritinib 750 mg N=83		Study A2203 ceritinib 750 mg N=124	
Duration of follow-up				
Median (months) (min – max)	12.5* (0.4 – 22.2)	39.8** (33.1 – 52.5)	9.3** (5.6 – 17.2)	25.9** (22.2 – 33.8)
Overall response rate (CR + PR), n (%)	60 (72.3)	61 (73.5)	79 (63.7)	84 (67.7)
(95% CI)	(61.4, 81.6)	(62.7, 82.6)	(54.6, 72.2)	(58.8, 75.9)
Duration of response* **				
Median (months) (95% CI)	17.0 (11.3, NE)	14.2 (11.3, 22.1)	9.3 (9.1, NE)	22.1 (14.8, NE)
% Event-free probability estimate (95% CI) at 18 months	37.6 (9.7, 66.3)	42.8 (29.9, 55.1)	NE	55.7 (44.2, 65.7)
Progression-free survival				
Median (months) (95% CI)	18.4 (11.1, NE)	15.2 (12.1, 19.5)	11.1 (9.3, NE)	16.6 (11.0, 22.1)
% Event-free probability estimate (95% CI) at 18 months	50.6 (36.1, 63.5)	44.2 (32.8, 55.1)	NE	49.1 (39.7, 57.9)
Overall survival				
Median (months) (95% CI)	NE (19.6, NE)	39.1 (32.9, NE)	NE (NE, NE)	NE (NE, NE)
% Event-free probability estimate (95% CI) at 18 months	79.6 (66.5, 88.0)	75.2 (63.8, 83.5)	NE	73.4 (64.6, 80.4)
Data cut-off date	14-Apr-2014	3-May-2016	27-Jun-2014	15-Nov-2015

NE = not estimable
Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0
Study A2203: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
**From start date of study treatment to date of death or censoring*
***From start date of study treatment to cut-off date*
****Includes only patients with confirmed CR, PR*

Table 10 Overview of efficacy data in ALK-positive NSCLC patients with prior ALK inhibitor treatment per Investigator assessment

	Study X2101 ceritinib 750 mg N=163		Study A2201 ceritinib 750 mg N=140	
Duration of follow-up				
Median (months) (min – max)	10.2* (0.1 – 24.1)	40.0** (33.1 – 52.7)	8.3** (5.6 – 14.8)	33.4** (30.6 – 39.8)
Overall response rate (CR + PR), n (%)	92 (56.4)	92 (56.4)	52 (37.1)	57 (40.7)
(95% CI)	(48.5, 64.2)	(48.5, 64.2)	(29.1, 45.7)	(32.5, 49.3)
Duration of response* **				
Median (months) (95% CI)	8.3 (6.8, 9.7)	8.3 (6.8, 9.7)	9.2 (5.6, NE)#	10.6 (7.4, 14.7)
Progression-free survival				
Median (months) (95% CI)	6.9 (5.6, 8.7)	6.9 (5.6, 8.5)	5.7 (5.3, 7.4)	5.8 (5.4, 7.6)
Overall survival				
Median (months) (95% CI)	16.7 (14.8, NE)##	20.3 (15.2, 24.3)	14.0 (10.3, 14.0)	15.6 (13.6, 24.2)
Data cut-off date	14-Apr-2014	3-May-2016	26-Feb-2014	29-Mar-2016

NE = not estimable
Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0
Study A2201: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

**From start date of study treatment to date of death or censoring*

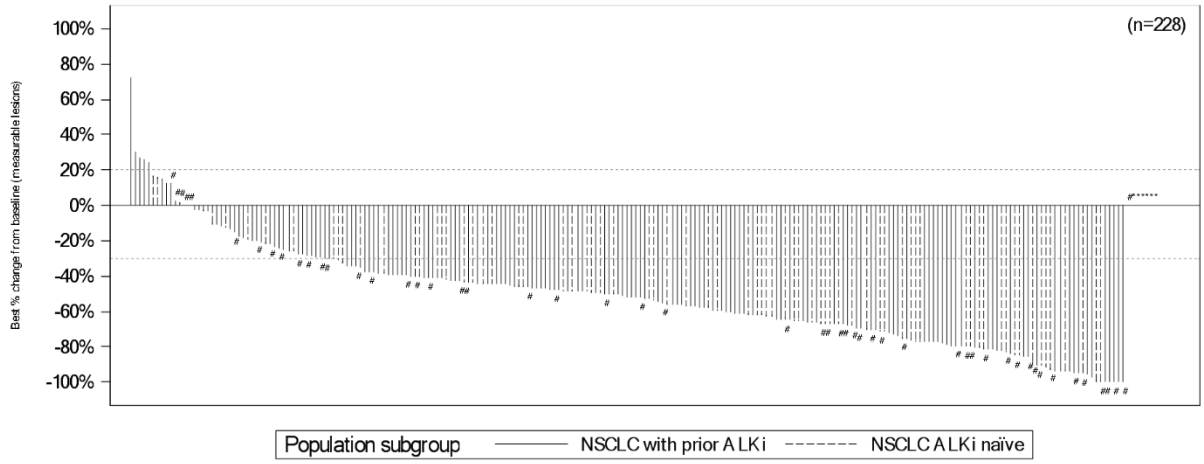
***From start date of study treatment to cut-off date*
****Includes only patients with confirmed CR, PR*

 # DOR rate at 8 months is 51.3% (32.7, 67.1)

OS rate at 18 months is 47.5% (36.4, 57.8)

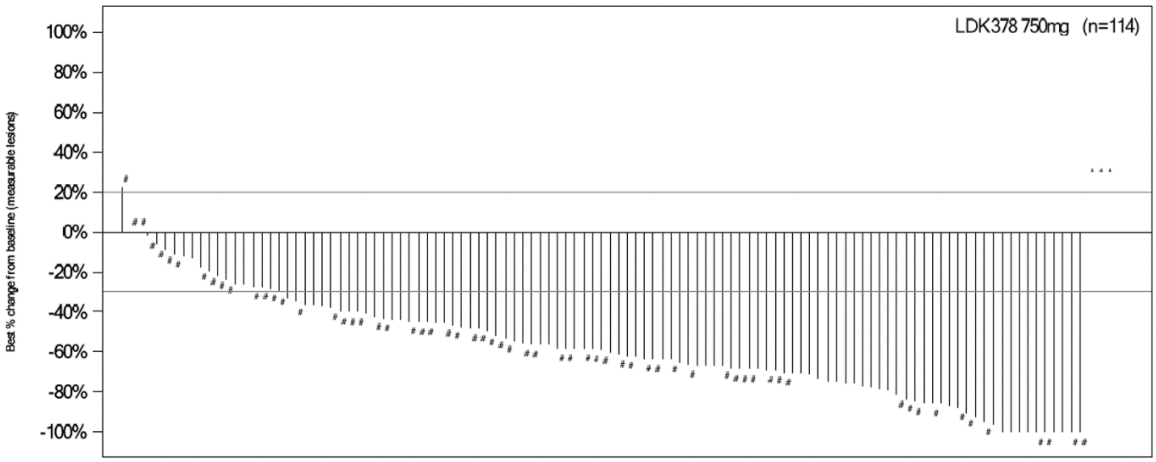
Based on Investigator assessment, the majority of patients treated with Zykadia had a reduction in tumor burden. Waterfall plots illustrating the maximum decrease from baseline in the sum of the longest tumor diameters for all 3 studies with long-term follow-up (>two years) are shown in Figure 7, Figure 8 and Figure 9.

Figure 7 **Waterfall plot of best percentage change from baseline in sum of diameters by Investigator assessment in Study X2101 (ALK inhibitor naïve patients and patients with prior ALK inhibitor treatment) - Data cut-off 3-May-2016**



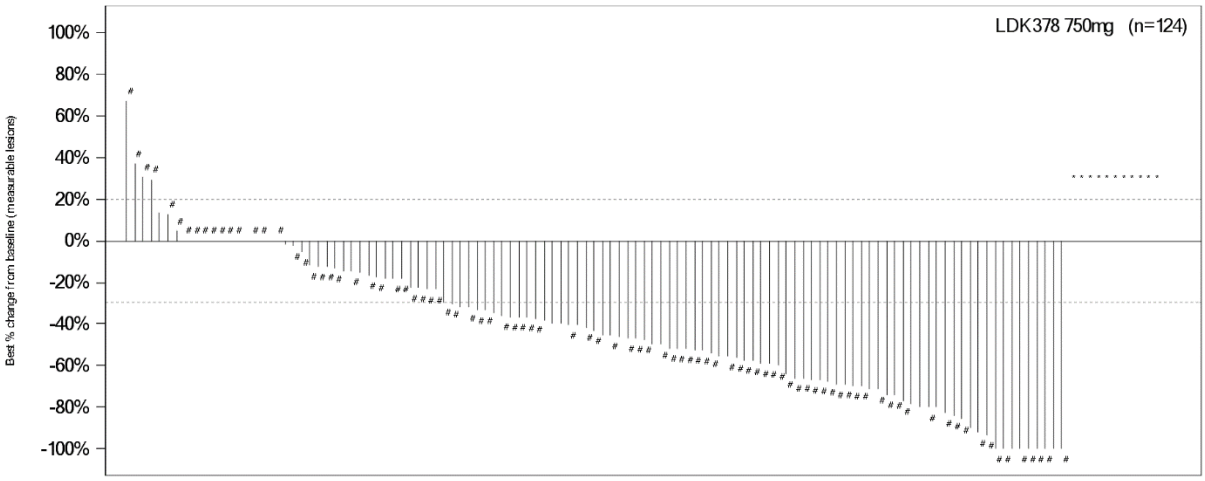
Best percentage change from baseline <0 207 (90.79%)
Best percentage change from baseline >0 12 (5.26%)
Best percentage change from baseline =0 2 (0.88%)
**% change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 7 (3.07%)*
n (number of patients with measurable disease at baseline and at least one valid post-baseline assessment) is used for calculation of percentages.
A post-baseline assessment with unknown response for target lesion or unknown overall lesion response is considered invalid.
 # PFS event.
ALKi: ALK inhibitor

Figure 8 **Waterfall plot of best percentage change from baseline in sum of diameters by Investigator assessment in Study A2203 (ALK inhibitor naïve patients) - Data cut-off 15-Nov-2015**



Best percentage change from baseline <0 108 (94.74%)
Best percentage change from baseline >0 1 (0.88%)
Best percentage change from baseline =0 2 (1.75%)
** % change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 3 (2.63%)*
n (number of patients with measurable disease at baseline and at least one valid post-baseline assessment) is used for calculation of percentages.
A post-baseline assessment with unknown response for target lesion or unknown overall lesion response is considered invalid.
 # PFS event.

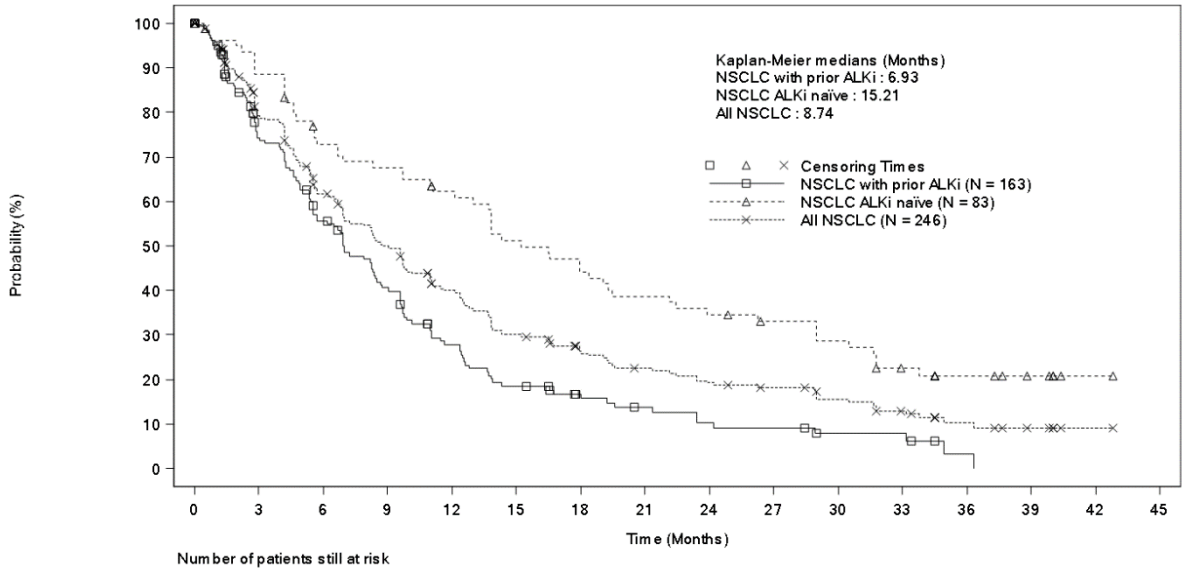
Figure 9 **Waterfall plot of best percentage change from baseline in sum of diameters by Investigator assessment in Study A2201 (patients with prior ALK inhibitor treatment) - Data cut-off 29-Mar-2016**



Best percentage change from baseline <0 94 (75.81%)
Best percentage change from baseline >0 7 (5.65%)
Best percentage change from baseline =0 12 (9.68%)
**% change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 11 (8.87%)*
n (number of patients with measurable disease at baseline and at least one valid post-baseline assessment) is used for calculation of percentages.
A post-baseline assessment with unknown response for target lesion or unknown overall lesion response is considered invalid.
 # PFS event.

Kaplan-Meier curves of PFS per Investigator assessment for all 3 studies are shown in Figure 10, Figure 11 and Figure 12.

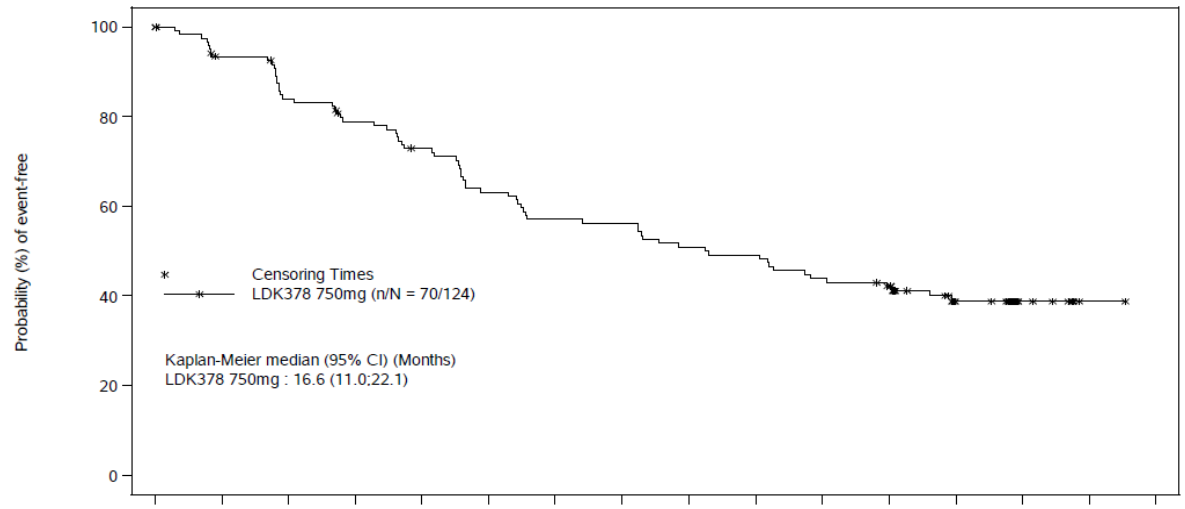
Figure 10 **Kaplan-Meier plot of PFS based on Investigator assessment in Study X2101 (ALK inhibitor naïve patients and patients with prior ALK inhibitor treatment) - Data cut-off 3-May-2016**



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
NSCLC with prior ALKi	163	108	79	56	36	24	16	12	9	8	5	5	1	0	0	0
NSCLC ALKi naïve	83	69	55	51	45	37	32	28	25	22	19	13	8	5	1	0
All NSCLC	246	177	134	107	81	61	48	40	34	30	24	18	9	5	1	0

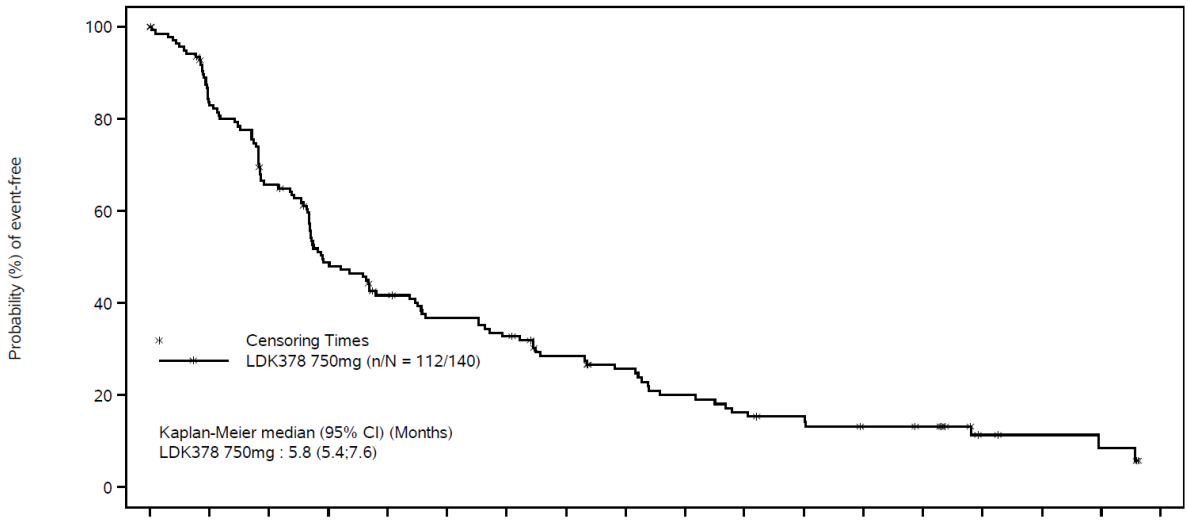
Figure 11 **Kaplan-Meier plot of PFS based on Investigator assessment in Study A2203 (ALK inhibitor naïve patients) - Data cut-off 15-Nov-2015**



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
LDK378 750mg	124	111	99	91	83	72	65	64	58	56	50	46	27	9	1	0

Figure 12 **Kaplan-Meier plot of PFS based on Investigator assessment in Study A2201 (patients with prior ALK inhibitor treatment) - Data cut-off 29-Mar-2016**

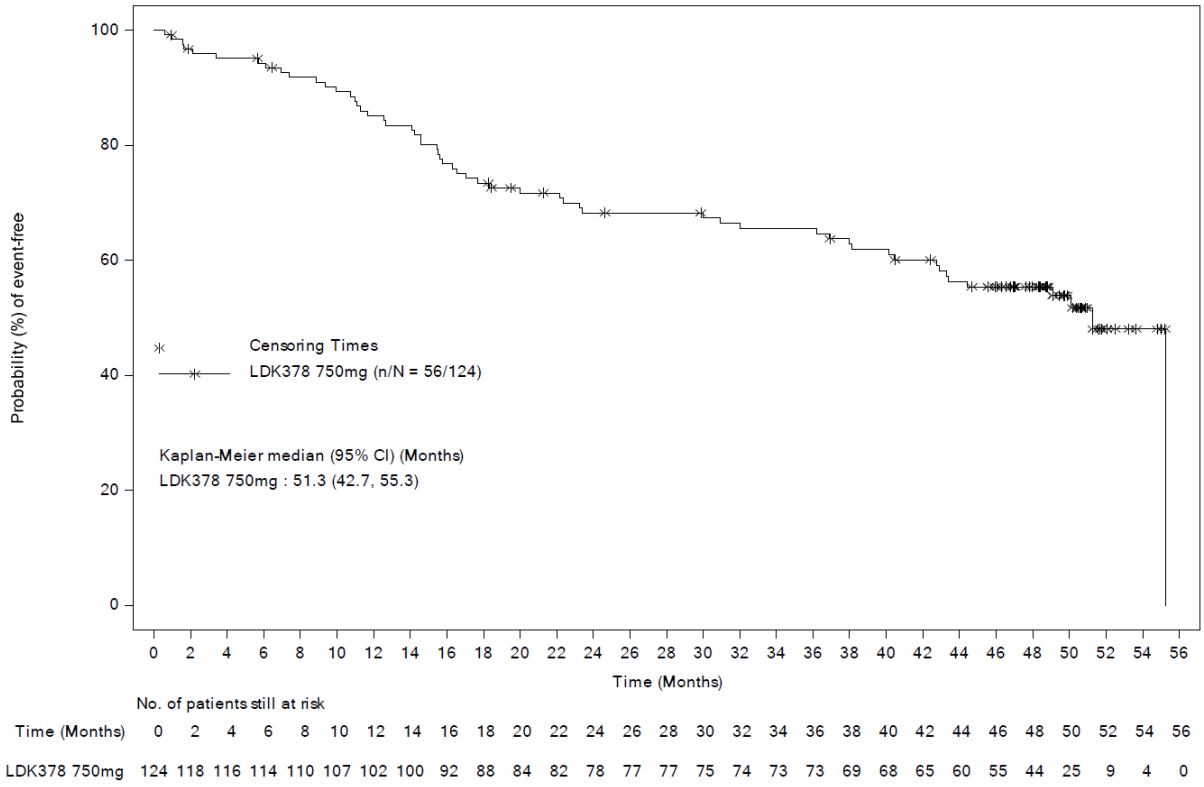


No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
LDK378 750mg	140	112	87	63	52	45	40	32	27	21	17	15	12	11	5	4	3	0

A Kaplan-Meier curve of OS for Study A2203 (data cut-off date: 22-Jan-2018) is shown in Figure 13.

Figure 13 Kaplan-Meier plot of OS in Study A2203 (ALK inhibitor naïve patients) – Data cut-off 22-Jan-2018



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
LDK378 750mg	124	118	116	114	110	107	102	100	92	88	84	82	78	77	77	75	74	73	73	69	68	65	60	55	44	25	9	4	0

Patients with brain metastases

In the analysis of Studies X2101, A2203 and A2201 at an early cut-off date, brain metastases were seen in 50.0%, 40.3%, and 71.4% of patients, respectively.

The main efficacy data for patients with brain metastases at baseline for all 3 studies are summarized in Table 11.

Table 11 Overview of efficacy data in ALK-positive NSCLC patients with brain metastases at baseline

	Patients who are ALK inhibitor naïve		Patients with prior ALK inhibitor treatment	
	Study X2101 ceritinib 750 mg	Study A2203 ceritinib 750 mg	Study X2101 ceritinib 750 mg	Study A2201 ceritinib 750 mg
	N=26	N=50	N=98	N=100
Overall response rate (CR + PR), n (%)	19 (73.1)	29 (58.0)	50 (51.0)	33 (33.0)
(95% CI)	(52.2, 88.4)	(43.2, 71.8)	(40.7, 61.3)	(23.9, 43.1)
Duration of response*				
Median (months) (95% CI)	12.6 (5.5, NE)	9.1 (7.5, NE)	6.9 (5.4, 8.3)	6.1 (5.4, NE)
Progression-free survival				
Median (months) (95% CI)	9.7 (4.6, NE)	10.8 (7.3, NE)	6.9 (4.9, 8.4)	5.4 (4.7, 6.4)
Data cut-off date	14-Apr-2014	27-Jun-2014	14-Apr-2014	26-Feb-2014

NE = not estimable
Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0
Studies A2203 and A2201: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
**Includes only patients with confirmed CR, PR*

Intracranial response

In Study X2101, there were 14 ALK-positive NSCLC patients with investigator-assessed measurable brain metastases at baseline in the 750 mg dose group. The overall intracranial response rate (OIRR) at the cut-off date 14-Apr-2014 as assessed by the Investigator was 50.0% (95% CI: 23.0, 77.0), including 2 patients having a CR in the brain and 5 patients with a confirmed PR in the brain; in addition, 3 patients had stable disease (SD).

In Study A2203, 10 out of the 124 patients with ALK-positive NSCLC had brain metastases at baseline considered to be target lesions by the Investigator. In these patients, the OIRR at the cut-off date 27-Jun-2014 based on Investigator assessment was 20.0% (95% CI: 2.5, 55.6), including 2 patients with a confirmed PR in the brain.

In Study A2201, 20 out of the 140 patients with ALK-positive NSCLC had brain metastases at baseline considered to be target lesions by the Investigator. In these patients, the OIRR at the cut-off date 26-Feb-2014 based on Investigator assessment was 35.0% (95% CI: 15.4, 59.2), including 2 patients with a confirmed CR in the brain and 5 patients with a confirmed PR in the brain.

Intracranial response without prior irradiation

In addition, for ALK-positive NSCLC patients with measurable brain lesions at baseline that had not been irradiated, Zykadia induced responses in the brain that matched or exceeded the systemic tumor responses in the majority of ALK-positive NSCLC patients previously treated with an ALK inhibitor and in ALK inhibitor naïve patients.

In Study X2101, 41 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated (30 previously treated with an ALK inhibitor and 11 ALK inhibitor naïve), 4 of whom had measurable brain lesions at baseline (3 previously treated with an ALK inhibitor and 1 ALK inhibitor naïve). At the cut-off date 14-Apr-2014, all 4 of the patients (100%) with measurable brain lesions at baseline that had not been irradiated had responses in the brain that matched or exceeded the systemic tumor responses including 2 complete brain metastases responses (1 for a patient previously treated with an ALK inhibitor and 1 for an ALK inhibitor naïve patient). In addition to the 2 CRs, there was 1 PR and 1 SD.

In Study A2203, 23 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated, 6 of whom had measurable brain lesions at baseline. At the cut-off date 27-Jun-2014, all 6 of the patients (100%) had responses in the brain that matched the systemic tumor responses. There were 2 PRs, 3 SDs, and 1 "Unknown".

In Study A2201, 28 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated, 6 of whom had measurable brain lesions at baseline. 4 of the 6 patients (66.7%) had responses in the brain that matched or exceeded the systemic tumor responses including 2 complete brain metastases responses. In addition to the 2 CRs, there were 2 PRs and 2 SDs.

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC_{50} for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar at 33°C to 35°C (near body temperature). An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

The principal toxicity related to ceritinib administration in rats and monkeys was inflammation of the extra-hepatic bile ducts accompanied by increased neutrophil counts in the peripheral blood. Mixed cell/neutrophilic inflammation of the extra-hepatic ducts extended to the pancreas and/or duodenum at higher doses. GI toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhoea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and submucosa. Liver was also affected in both species, but only at the highest dose levels studied, and included minimal increases in liver transaminases in a few animals, and vacuolation of the intra-hepatic bile duct epithelium. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Target organ effects showed partial to complete recovery.

Carcinogenicity and mutagenicity

Carcinogenicity studies have not been performed with ceritinib.

The Ames assay for ceritinib indicated it was not a potential mutagen, and the chromosomal aberration assay in cultured human peripheral blood lymphocytes did not indicate the potential to cause structural chromosomal aberrations. The micronucleus test using cultured human peripheral blood lymphocytes was negative. An *in vivo* rat micronucleus test revealed no adverse chromosomal effects on the bone marrow at any dose level after oral dosing in the rat.

Fertility and reproductive toxicityFor information on fertility and reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

PHARMACEUTICAL INFORMATION

Incompatibilities

Not applicable.

Special precautions for storage

See folding box.

Zykadia should not be used after the date marked “EXP” on the pack.

Zykadia must be kept out of the reach and sight of children.

Store at or below 30°C.

Instructions for use and handling

There are no special requirements for use or handling of this product.

Pack Size:

Multipacks containing 150 (3 packs of 50) and 50 hard capsules.

Not all presentations may be available locally.

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