Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ceritinib

Proprietary Product Name: Zykadia

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of first round report: 3 August 2015

Date of second round report: 1 February 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>

Contents

List of abbreviations

Abbreviations	Meaning
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	adverse drug reaction
AE	Adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{tau}	Area under the plasma concentration-time curve for each dosing interval (from time 0 to 24 h sample) determined using the linear trapezoidal rule
AUC_{inf}	The area under the blood or plasma concentration-time curve from time zero extrapolated to infinity when feasible.
AUC_{last}	The area under the blood or plasma concentration-time curve from time zero to last sampling time
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BOR	Best overall response
bpm	Beats per minute
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval

Abbreviations	Meaning
CL/F	Total body clearance divided by the oral bioavailability
C_{max}	The maximum (peak) blood or plasma concentration after single dose administration
C_{trough}	Trough concentration
$C_{trough,ss}$	Steady state trough concentration
CEAS	Central Efficacy Analysis Set
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CSF	Clinical Service Formulation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
DSC	Differential Scanning Calorimeter
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECOG	Eastern cooperative oncology group
EDTA	Ethylene diamine tetra acetic acid
EGFR	Epidermal growth factor receptor
EU	European Union
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviations	Meaning
FISH	Fluorescence in situ hybridisation
FMI	Final Market Image
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ILD	Interstitial Lung Disease
Lambda_z	Terminal elimination rate constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDK378	Ceritinib
LLOQ	Lower limit of quantification
LMWH	Low molecular weight heparin
LSC	Liquid scintillation counting
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Not estimable
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetics

Abbreviations	Meaning
pKa	Dissociation constant
PPS	Per-Protocol Set
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PXR	Pregnane X receptor
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Frederica formula
Racc	Accumulation ratio
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	standard deviation
SOC	System organ classes
SOD	Sum of diameters
SPC	Summary of Product Characteristic
SS	Steady state
$T_{1/2}$	Elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve
TKI	Tyrosine Kinase Inhibitor
T_{last}	Last sampling time T
T_{max}	The time to reach maximum blood or plasma concentration following drug administration
TTR	Time to response
ULN	Upper limit of normal
US	United States

Abbreviations	Meaning
Vz/F	Volume of distribution divided by the oral bioavailability
WHO	World Health Organization

1. Introduction

This is a full submission to register a new chemical entity ceritinib as Zykadia.

1.1. Drug class and therapeutic indication

Ceritinib is an orally active, small molecule, adenosine triphosphate (ATP)-competitive inhibitor of anaplastic lymphoma kinase (ALK). It inhibits autophosphorylation of ALK, ALK mediated phosphorylation of downstream signalling proteins and proliferation of ALK dependent cancer cells.

The proposed indication is '*Zykadia is indicated for the treatment of adult patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with an ALK-inhibitor*'.

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths: 150 mg hard capsules

1.3. Dosage and administration

The dosage and administration as set out in the proposed Product Information (PI) are:

'*The recommended dose of Zykadia is 750 mg taken orally once daily at the same time each day. Continue treatment as long as the patient is deriving clinical benefit from therapy.*

The maximum recommended dose is 750 mg daily.'

1.4. Other proposed changes to the PI

Not applicable.

2. Clinical rationale

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Further, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2011, lung cancer was the most common cause of cancer death for men and women (8114 deaths overall: 4959 in men; 3155 in woman), accounting for 18.8% of all cancer deaths here in Australia (Australian Cancer Incidence and Mortality Books).

The two most prevalent sub-types of lung cancer are small cell lung cancer and NSCLC. Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer in the United States (US), and is also the most frequently occurring in non-smokers (American Cancer Society 2013).

NSCLC is associated with high mortality rates as > 70% of the patients are diagnosed with locally advanced or metastatic disease (Molina et al 2008) [stages III and IV according to the American Joint Committee on Cancer Staging (AJCC)]. Historically, patients with locally advanced or

metastatic NSCLC have been treated with standard chemotherapy and/or radiation, and while these treatments may provide modest survival benefits, they are rarely curative.

Systemic chemotherapy is a cornerstone in the management of locally advanced or metastatic NSCLC. Standard first-line treatment typically consists of a platinum-based doublet (cisplatin or carboplatin in combination with other chemotherapy agents), unless a patient has a known mutation, candidate for targeted therapy (NCCN Guidelines v7.2015, Vansteenkiste et al 2013). The outcomes with this type of chemotherapy remain poor, with response rates of 15 to 35% and median progression-free survival (PFS) and overall survival (OS) of 4 to 7 months and 10 to 16 months, respectively (Scagliotti et al 2008, Ciuleanu et al 2009, Ettinger et al 2010, Paz-Ares et al 2012). Pemetrexed/cisplatin (or carboplatin) combination therapy and carboplatin/paclitaxel with (or without) bevacizumab represent a therapeutic option in patients with advanced non-squamous NSCLC. These regimens are commonly used based on Phase III randomised trials (NCCN Fuiswlinwa v7.2015). However neither pemetrexed nor bevacizumab is reimbursed here in Australia for first line setting. The outcomes with second-line chemotherapy are dismal, with response rates of less than 10%, median PFS of 2 to 3 months, and median OS of 5 to 8 months (Shepherd et al 2000, Fossella et al 2000, and Hanna et al 2004).

Although chemotherapy is appropriate for many patients with lung cancer, there is a sense that the use of traditional chemotherapeutic agents has reached a therapeutic plateau. Increased understanding of cancer biology has revealed numerous potential therapeutic strategies targeting oncogenic signal transduction pathways. Where NSCLC was previously considered to be a single disease treated with standard cytotoxic chemotherapy, it is now becoming more appropriate to consider NSCLC as a collection of disease subtypes according to the driving oncogenic aberration, and to select treatment accordingly (Bang 2011).

Personalised targeted therapy for advanced NSCLC relies primarily on the concept of 'oncogene addiction', in which cancers that contain multiple genetic abnormalities rely on only one or several genes for the maintenance of the malignant phenotype and their survival (Ma 2012). Several molecular aberrations have been identified in NSCLC, with subsequent development of drugs that target these aberrations. Gefitinib, erlotinib and afatinib for the treatment of NSCLC harbouring epidermal growth factor receptor (EGFR) mutations or overexpression, and crizotinib for the treatment of NSCLC with the ALK fusion translocation oncogenes are examples of this rational targeted approach to treating cancer (Ma 2012, Yang et al 2012).

Multiple large randomised clinical trials have demonstrated that patients harbouring activating EGFR mutations benefit more from treatment with EGFR tyrosine kinase inhibitors (TKIs) than with standard chemotherapy in terms of response rate (62 to 85%), PFS, toxicity profile and quality of life (reviewed in NCCN Guidelines v7.2015, Gettinger et al 2011). The success of EGFR TKIs highlights the importance of identifying specific NSCLC molecular drivers to appropriately develop targeted agents for treating specific patient populations.

ALK, a receptor tyrosine kinase, was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic large cell lymphoma (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal transduction activity, and oncogenic function. ALK has since been linked with many different fusion partners in different tumour types (Soda et al 2007).

The frequency of ALK gene rearrangements in patients with NSCLC (referred to as ALK-positive NSCLC from here onwards) is relatively low; it is present in approximately 2 to 7% of tumours tested. However, considering the high incidence of lung cancer, this small percentage translates into about 60,000 patients annually worldwide. With an annual incidence of 10,296 lung cancer diagnosis in 2010, up to 720 patients annually could be diagnosed with ALK-positive cancer in Australia.

Patients with ALK-positive NSCLC are associated with specific demographic and clinical features, including never or light smoking history, younger age, and adenocarcinoma histology (Shaw et al 2009, Wong et al 2009, and Rodig et al 2009). In addition, several reports have associated ALK positivity with a more advanced stage at diagnosis and worse prognosis (Shaw et al 2009, Yang et

al 2012). Further, ALK gene rearrangements are largely mutually exclusive with EGFR or KRAS mutations (Gainor et al 2013), consistent with the notion that ALK gene rearrangements defines a unique molecular subset of NSCLC. In these patients, ALK gene rearrangements serve as a key and strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, a non-specific small molecule ALK inhibitor is the only targeted agent currently approved for the treatment of locally advanced or metastatic ALK-positive NSCLC. Early single-arm trials of crizotinib in patients with ALK-positive NSCLC demonstrated impressive activity and with response rates of 50 to 61% and duration of response of 6 to 10 months (Ou 2011). Crizotinib (Xalkori) is registered by TGA for the treatment of patients with ALK-positive advanced non-small cell lung cancer and received PBS reimbursement in Australia as of 1 July 2015 under the Managed Entry Scheme for the treatment of adults with Stage IIIB or IV non-squamous type of NSCLC harbouring an ALK gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.

The clinical benefit of crizotinib treatment in patients with locally advanced or metastatic ALK-positive NSCLC in the second-line setting following treatment with at least one prior chemotherapy regimen has been confirmed in a Phase III trial (PROFILE 1007). Crizotinib prolonged PFS to a median of 7.7 months compared to 3.0 months in patients who received single-agent chemotherapy (Hazard ratio (HR) =0.49; 95% confidence interval (CI): 0.37–0.64; p<0.001). In addition, crizotinib significantly increased overall response rate over chemotherapy (65% versus. 20%, p<0.001), and improved symptom control and quality of life. The analysis of the OS rate was not sufficiently mature to draw conclusions, and was confounded by the cross-over of patients from chemotherapy to crizotinib (Shaw et al 2013).

While crizotinib is effective in patients with ALK-positive NSCLC, disease progression invariably occurs, typically within one year, due to the development of acquired drug resistance. Crizotinib resistant ALK-positive NSCLC frequently conserves the ALK gene rearrangements, but may result from the development of resistant ALK mutations, ALK amplification, and/or activation of alternate aberrant signalling pathways (Katayama et al 2012, Doebele et al 2012). Furthermore, not all patients respond to or tolerate crizotinib treatment. These patients have no available effective therapy options. Additionally, brain metastases pose a clinical challenge in NSCLC due to the high overall incidence, and because brain metastases are often the initial site of progression, in particular after crizotinib treatment (Yang et al 2012, Camidge and Doebele 2012, Camidge et al 2012). Therefore an unmet medical need exists for more potent ALK inhibitors that are highly active in crizotinib-resistant ALK-positive NSCLC.

Comment: Patients with metastatic ALK-positive NSCLC do progress after crizotinib therapy and current standard of care is conventional chemotherapy. While I agree that there is an unmet need for use of more potent ALK inhibitors that are highly active in ALK-positive NSCLC, it is possibly more important to determine fully the mechanism of crizotinib resistance and see how that influences ceritinib efficacy in that setting.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a full clinical development programme of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

- 4 clinical pharmacology studies, including four (A2101, A2104, A2105, A2106) that provided pharmacokinetic (PK) data and no specific studies that provided pharmacodynamic data.
- 1 population PK analyses (based on X2101, X1101, A2201, A2203).

- Pivotal efficacy/safety studies (X2101, X1101, A2201, A2203) of which X2101 and X1101 also provide PK and pharmacodynamics data
- 2 dose-finding studies (X2101, X1101).

3.2. Paediatric data

The submission did not include paediatric data. Other regulatory bodies found this to be acceptable. The EMA confirmed that ceritinib in the proposed indication falls under the scope of the class waiver on 12 April 2013. Similarly, in the US, ceritinib has an orphan drug designation, and is therefore exempt from the requirements of the Pediatric Research Equity Act.

Comment: Given ALK- positive lung cancer occurs in adult population, I think it is reasonable not to include paediatric data.

3.3. Good clinical practice

All the clinical studies in the submission are complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose (750 mg)	A2105	Human ADME
	- Multi-dose	No studies	
	Bioequivalence† - Single dose	No studies	
	- Multi-dose	No studies	
	Food effect – 2 x single doses (500 mg)	A2101*	Food effect
PK in special populations	Target population § - Single dose	X2101*	PK parameters and exposure-response relationships
		X1101*	PK in Japanese patients
		X2101	PK parameters
	- Multi-dose	X1101	
		A2201	
		A2203	
	Hepatic impairment	No studies	A2110 ongoing
	Renal impairment	No studies	
	Neonates/infants/children/ adolescents	No studies	
	Elderly	No studies	
Genetic/gender-	Males versus females	No specific studies	

PK topic	Subtopic	Study ID	Primary aim
related PK			
PK interactions	Ketoconazole (2 x single doses; 450 mg)	A2104	DDI (ketoconazole)
	Rifampin (2x single doses; 750 mg)	A2106	DDI (rifampin)
Population PK analyses	Healthy subjects	No studies	
	Target population	X2101	
		X1101	
		A2201	
		A2203	

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ADME = absorption, distribution, metabolism and excretion. DDI = drug-drug interaction. None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

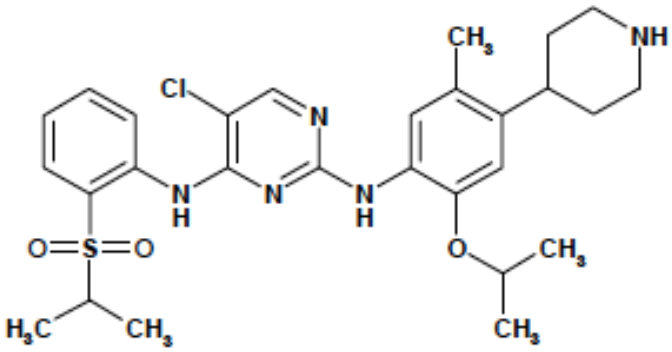
The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries.

Ceritinib is available as strongly crystalline, high melting, finely divided particles (up to 400µm diameter in suspension). The structure of ceritinib is shown in Figure 1. Relative molecular mass of ceritinib is 558.14 and the salt/base ratio on anhydrous basis is 1 (no salt). The Molecular formula is $C_{28}H_{36}N_5O_3C1S$.

Figure 1: Chemical structure of ceritinib



The chemical structure for ceritinib does not possess a chiral centre and it does not display tautomerism.

Ceritinib solubility in aqueous media is pH-dependent. It has good solubility at low pH values (pH=1) and poor solubility at neutral pH values (pH=6.8).

The melting point is 174°C, determined by Differential Scanning Calorimeter (DSC).

Ceritinib is a weak base exhibiting two dissociation constants (pKa) with respective values of 9.7 and 4.1.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanisms of absorption

Ceritinib was slowly absorbed: plasma concentrations peaked at approximately 6 to 8 h in healthy subjects. The terminal half-life ranged from 36 to 48 h across doses of 450 to 750 mg in healthy subjects.

Following administration of single oral dose of 750 mg ceritinib, median maximum plasma concentrations were reached after 8 h with mean C_{max} of 228 ng/mL and AUC_{inf} of 11300 (ng*h/mL)/mg (A2105). The slow absorption of ceritinib was further confirmed in drug-interaction Studies A2104 and A2106.

All the PK studies performed in healthy subjects involved single dose administration only; therefore absorption following multiple doses is unknown in healthy subjects. Multi-dose PK was performed in target population (patients that are ALK-positive) in Studies X2101, X1101, A2201 and A2203.

4.2.2.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of ceritinib after oral administration has not been investigated. The drug is formulated as an oral tablet.

Bioavailability relative to an oral solution or micronised suspension

This has not been investigated in human.

Bioequivalence of clinical trial and market formulations

The Clinical Service Formulation (CSF), which is formulated in hard gelatin capsule (25mg, 50 mg and 150 mg) for oral administration utilising common compendia excipients has been used in all completed and ongoing clinical studies of ceritinib. Only the 150 mg capsule formulation is being further developed to obtain marketing authorisation. The final market image (FMI) intended for the market is identical to the 150 mg CSF capsule.

Bioequivalence of different dosage forms and strengths

Only the 150 mg formulation will be marketed.

Influence of food

Results from the food effect Study A2101 in healthy subjects showed that the bioavailability of ceritinib was increased when given with a meal (Table 2). Compared to the fasted state, a low-fat meal increased C_{max} and AUC_{inf} of a single oral dose of ceritinib 500 mg by 43% and 58%, respectively, whereas a high-fat meal increased C_{max} and AUC_{inf} by 41% and 73%, respectively. No food should be eaten for at least 2 h before, and for 2 h after the dose of ceritinib is taken. This was reflected in the Australian PI.

Table 2: Summary statistics of ceritinib pharmacokinetic parameters under fasted or fed conditions (Study A2101-PAS)

Parameter[a]	Ceritinib (500 mg), fasted (Treatment A) N=27	Ceritinib (500 mg), low-fat (Treatment B) N=14	Ceritinib (500 mg), high-fat (Treatment C) N=14	Comparison	Geo-mean Ratio (90%CI)
Tmax (h)	8.00 (6.00-12.0)	7.00 (3.00-12.1)	10.0 (6.00-12.0)	B-A	-2.00 (-6.00-6.10)
	n=27	n=14	n=14	C-A	0 (-4.00-6.00)
Cmax (ng/mL)	159 (43.5)	220 (19.7)	235 (29.4)	B/A	1.43 (1.21-1.71)
	n=27	n=14	n=14	C/A	1.41 (1.18-1.68)
AUCinf (ng*h/mL)	6910 (41.8)	10300 (22.6)	12700 (31.7)	B/A	1.58 (1.34-1.86)
	n=27	n=14	n=14	C/A	1.73 (1.46-2.05)
AUClast (ng*h/mL)	6630 (42.2)	9910 (22.6)	12200 (31.9)	B/A	1.59 (1.35-1.87)
	n=27	n=14	n=14	C/A	1.72 (1.45-2.03)
T1/2 (h)	36.2 (23.9)	34.6 (11.9)	34.2 (15.2)		
	n=27	n=14	n=14		
CL/F (L/h)	72.3 (41.8)	48.4 (22.6)	39.3 (31.7)		
	n=27	n=14	n=14		
Vz/F (L)	3770 (55.1)	2410 (28.0)	1940 (35.2)		
	n=27	n=14	n=14		

n: number of subjects with non-missing values

[a] Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

Dose proportionality

In Study A2105, only ceritinib 750 mg as a single dose was administered in healthy subjects. Therefore, the evaluator could not find any dose proportionality data in healthy volunteers.

Bioavailability during multiple-dosing

No multiple-dosing studies were performed in healthy volunteers. This was studied in the target population (ALK-positive patients) in Studies X2101, X1101, A2201 and A2203 in the ceritinib development programme.

Effect of administration timing

This was not studied.

4.2.2.3. Distribution

Volume of distribution

The geometric median apparent volume of distribution (Vz/F) was 4670 L (range: 2280 to 9100 L) in healthy volunteers receiving a single dose of ceritinib 750 mg, suggesting that ceritinib is extensively distributed.

Plasma protein binding

No human studies (healthy subjects nor target population) could be found dealing with plasma protein binding. The fraction of ceritinib bound to human plasma proteins in vitro is approximately 97% and is independent of concentration from 50ng/mL to 10,000 ng/mL (Study R0900777).

Erythrocyte distribution

In Study A2105, the mean blood and plasma concentration ratio for total radioactivity, averaged over a range of post-dose time points (3 to 24 h) was 1.56. This value was similar to the mean in vitro distribution of [^{14}C]-LDK378 with C_{blood}/C_{plasma} value of 1.35 determined in humans, suggesting that ceritinib has a slight preferential distribution to blood cells (Study R0900777).

Tissue distribution

No human studies (healthy subjects nor target population) could be found dealing with tissue distribution.

4.2.2.4. Metabolism

Interconversion between enantiomers

Even though the chemical structure for ceritinib does not possess a chiral centre, no data have been submitted regarding the interconversion between parent and metabolites.

Sites of metabolism and mechanisms / enzyme systems involved

The geometric mean apparent terminal half-life ranged from 36 to 48 h across the 450 to 750 mg dose groups in healthy subjects.

Hepatic microsomal oxidative metabolism of ceritinib is primarily mediated by CYP3A, based on vitro drug metabolism studies. In humans, the primary biotransformation pathways of ceritinib included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation, dehydrogenation and the addition of a thiol group.

Metabolites identified in humans

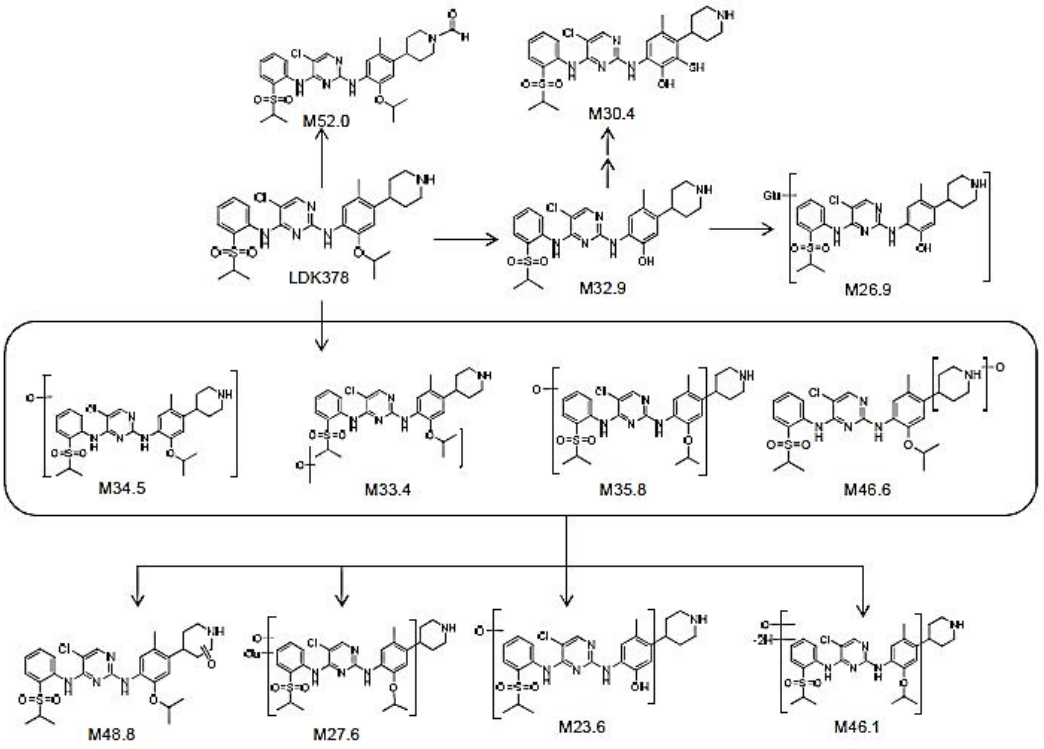
Active metabolites

Unchanged ceritinib was the most abundant drug-related chemical species found in both the plasma and excreta. On average, 82% of the circulating radioactivity in plasma was attributable to ceritinib. A total of eleven metabolites were found circulating in plasma at low levels (mean contribution to the radioactivity AUC ≤ 2.3% for each metabolite). Additionally, no single metabolite contributed > 5.8% to the plasma radioactivity AUC of any individual subject in the study.

Other metabolites

A proposed biotransformation scheme for ceritinib in humans is displayed in Figure 2.

Figure 2: Biotransformation scheme for ceritinib in humans



Pharmacokinetics of metabolites

No data was provided in regard to the PK of metabolites. This is reasonable given the majority of metabolites found in plasma and excreta were unchanged ceritinib.

Consequences of genetic polymorphism

This has not been investigated in the ceritinib development programme so far.

4.2.2.5. Excretion

Routes and mechanisms of excretion

Consistent with preclinical studies in rats (Study R0900773a) and monkeys (Study R1200422), the majority of the radioactivity dose in humans was eliminated in the faeces (mean: 91.0%) with only a minor amount eliminated in the urine (mean: 1.3%) following a single oral dose of 750 mg of ceritinib to healthy male subjects (Study A2105). The mean percentage of the dose eliminated in the faeces as unchanged ceritinib was 68.0% while all the metabolites were present at low levels, with no individual metabolite contributing greater than 2.3% to the radioactivity AUC. Hepatic metabolism and potentially biliary excretion and gastrointestinal secretion all contribute to ceritinib elimination in humans.

Mass balance studies

Mass balance determination in urine and faeces following oral administration of radiolabelled [^{14}C]-LDK378 was performed in the Study A2105 as above to determine the rates and routes of excretion of ceritinib and its metabolites. The overall recovery radioactivity in the excreta was ≥ 90.1% in all six subjects indicating that good mass balance was achieved.

Renal clearance

Kidney appears to play a negligible role in the elimination of ceritinib (mean 1.3%).

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

Moderate to high inter-subject variability in ceritinib PK parameters has been observed in healthy subjects under fasting condition (also in target population). Following single oral doses of 450 to

750 mg in healthy subjects when ceritinib was given alone, the inter-subject variability (geometric mean coefficient of variation; CV% range) was 42 to 74% and 35 to 94% for AUC_{last} and C_{max}, respectively.

4.2.3. Pharmacokinetics in the target population

No apparent differences in the PK of ceritinib were observed between healthy volunteers and patients. Observations made in healthy volunteers receiving ceritinib monotherapy are therefore considered to be transferrable to the target population.

The following sections look at certain aspects of PK in the target population, which were either not assessed in healthy subjects, or serve as comparison to PKs in healthy individuals.

4.2.3.1. Absorption

Ceritinib was slowly absorbed in target population also. The plasma concentrations peaked at approximately 4 to 6 h in patients (approximate 6 to 8 h in healthy subjects).

4.2.3.2. Bioavailability

C_{max} and AUC_{last} increased dose-proportionally across the 50 to 750 mg dose range following a single oral dose; however, pre-dose C_{trough} appeared to increase with dose in a greater than-proportional manner following multiple daily doses at steady-state.

Ceritinib demonstrated non-linear PK in patients over time with lower apparent clearance at steady state after daily oral dosing at maximum tolerated dose (MTD) of 750 mg than after a single oral dose. Highest dose investigated in the dose-escalation study was 750 mg; thus PK above this dose is not known.

Following dosing at the recommended dose (RD) of 750 mg daily, steady-state conditions were achieved by approximately 15 days, with geometric mean accumulation (assessed by AUC_{tau}) of 4.7-fold after 1 week and 6.2-fold after 3 weeks: exposure stayed relatively stable over the 12 week treatment period. Ceritinib demonstrated non-linear PK over time, as indicated by the observed difference in apparent clearance (CL/F) between single-dose administration (88.5 L/h at 750 mg) and at steady-state (33.2 L/h at 750 mg).

4.2.3.3. Distribution

The geometric mean apparent volume of distribution (Vz/F) ranged from 1990 to 6230 L across the 400 to 750 mg dose group (Study X2101), suggesting that ceritinib is extensively distributed. The volume of distribution of ceritinib is similar in healthy subjects.

4.2.3.4. Metabolism

The terminal half-life was similar in target population (ranged of 31 to 41 h across doses of 400 to 750 mg in patients) and healthy subjects (36 to 48 h across doses of 450 mg to 750 mg).

4.2.3.5. Intra- and inter-individual variability of pharmacokinetics

Overall, the inter-patient variability in exposure parameter estimates was high in target population also, with coefficients of variation of 93% and 87% for AUC_{last} and C_{max}, respectively, based on a model developed for dose proportionality analysis.

The assessment of intra-patient variability demonstrated moderate variability (CV%: 24 to 50%) in steady state C_{trough} as observed in Study X2101 (at 750 mg dose level), A2201 and A2203. Assessment of inter-patient variability demonstrated moderate variability also (CV%: 28 to 46%) in steady state C_{trough} as observed in Study A2201 and A2203. It is 48% (geometric mean CV%) in Study X2101 based on C_{min} at Cycle 2 Day 1 for patients at 750 mg dose level.

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

As ceritinib is eliminated primarily by the liver, hepatic impairment is likely to increase the systemic exposure of ceritinib. However, the extent of increase is not anticipated to be substantial,

as ceritinib is not extensively metabolised based on results from human ADME study, in which unchanged ceritinib was the major circulating species in plasma and the dominant form eliminated in faeces following a single oral dose of 750 mg ceritinib in healthy subjects.

Based on a population PK analysis using data from Study X2101, baseline alanine aminotransferase (ALT) and total bilirubin had no significant influence on the oral clearance (CL/F) of ceritinib. However, it is important to note that the analysis is limited by the fact that no patients with moderate or severe hepatic impairment were enrolled in the study. A study in subjects with varying degrees of hepatic impairment (mild, moderate, severe, based on Child-Pugh classification) and matched subjects with normal hepatic function is ongoing (Study A2110) and no data has been provided in the clinical dossier.

Comments: Given the current lack of specific data in patients with moderately to severely impaired hepatic function, CHMP has mandated the following wording on their Summary of Product Characteristic (SmPC): 'Ceritinib is not recommended in patients with moderate to severe hepatic impairment'. However, the evaluator notes that the US Prescribing Information simply stated that a recommended dose has not been determined for patients with moderate to severe hepatic impairment. Similarly the Canadian Product Monograph stated 'caution should be used in patients with hepatic impairment'. The Australian PI is in line with the US and Canada where it states 'caution should be used in patients with moderate to severe hepatic impairment'. The evaluator thinks it is to the patients' best interest to be more conservative in the wording of this issue until hepatic impairment data (Study A2110) becomes available, particularly given that hepatotoxicity was observed in the efficacy-safety study for the target population.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

As ceritinib is minimally eliminated by the kidney (1.3% of a single oral administered dose) no studies have been carried out in impairment renal patients. However, taking into account both, the population PK analysis and the mass balance study, it seems that no dose reductions are necessary in moderate renal impairment patients. Regarding the severe renal impairment patients, even though no data have been submitted, these patients were excluded from clinical studies and therefore no data have been collected. Based on the population PK analysis, the steady-state AUC_{tau} in moderate renal impairment patients was 19% higher than normal subjects, so it seems reasonable to expect higher levels for severe renal impairment, despite the low excretion by the renal route.

Comments: Therefore the evaluator thinks the inclusion of a general warning in the Australian PI under the section of 'Dosage Adjustment' is reasonable.

4.2.4.3. Pharmacokinetics according to age

A dedicated study in elderly individuals has not been performed. No formal studies were conducted to examine the effect of age on the PK of ceritinib. No significant difference in the predicted steady-state exposure of ceritinib was observed between patients aged ≥ 65 years and aged < 65 years. Hence, no dose adjustment is required on the basis of age. However, PK data in patients > 75 years is lacking.

Comments: This is unlikely to be a clinically significant problem in the population of ALK-positive NSCLC, given it tends to affect patients of younger age.

4.2.4.4. Pharmacokinetics related to genetic factors

No formal studies were conducted to examine the effects of gender or race on the PK of ceritinib. In the population PK model, gender had no statistically significant effect on the systemic exposures of ceritinib. The population PK model predicted that the steady-state AUC_{tau} in females (32351 ng*h/mL) was 14% higher than that in males (28425 ng*h/mL). This magnitude of increase is probably not clinically meaningful.

In the population PK model, race had no statistically significant effect on CL/F of ceritinib. The final population PK model predicted that Asian patients had approximately 10% higher steady-state exposures (AUC_{tau}, C_{max} and C_{min}) than non-Asian patients.

Among the patients included in the population PK analysis, 207 patients were non-Asians (Caucasian, Black, and other) and 95 patients were Asians. The race effect on CL/F was excluded in the analysis as the slightly higher exposure estimated in Asian patients was likely explained by the lower body weight observed in Asians (mean ± SD: 61.3 ± 10.4 kg) than non-Asians (mean ± SD: 72.3 ± 16.4 kg). The current analysis would thus suggest the use of the same dosing regimen (750 mg daily) in Asian and non-Asian patients.

4.2.4.5. Pharmacokinetics related to weight

No formal studies were conducted to examine the effects of weight on the PK of ceritinib. In the population PK analysis, effects of body weight were examined simultaneously with race and other covariates of interest. Weight was found to have a significant effect on the PK of ceritinib. Exposure of ceritinib decreased with increasing body weight. Relative to the group of patients of 60 to 80 kg, the AUCτ,ss predicted by the Population PK model increased by 20% for a patient below 60 kg, and decreased by 18% for a patient over 80 to kg.

According to Novartis, no dose adjustment from the recommended 750 mg daily dosing is required on the basis of body weight.

Comments: The evaluator has concerns regarding expected AE rates in patients with weight significantly less than 60kg, given the established relationship between AE and ceritinib exposure. The evaluator cannot see any specific data addressing this. It is reasonable for Novartis to comment on this.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

In vivo and in vitro data have shown that the concomitant use of CYP3A/P-gp inhibitors can increase the ceritinib plasma concentrations. In fact, results from the ketoconazole study (CYP3A inhibitor) show that the estimated geometric mean ratios for AUC_{inf} and C_{max} were increased almost 3 fold and 1 fold respectively. Results from the DDI study with rifampin (a CYP3A inducer) clearly indicate that strong CYP3A inducer decreases the ceritinib concentrations, leading to a reduction of both the C_{max} and AUC_{inf} (44% and 70%, respectively).

No information is available regarding the interaction with pH-elevating agents, such as H2-blockers or proton pump inhibitors. From the in vitro data, it is shown that ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases. Therefore pH-elevating agents may alter ceritinib bioavailability. Thus the SPC has included the following: 'Gastric acid-reducing agents (for example, 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*. A dedicated study to evaluate the effect of gastric acid-reducing agents on the bioavailability of ceritinib has not been conducted'

Comments: The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, the evaluator thinks it would be reasonable to include this in the PI.

4.2.5.2. Clinical implications of in vitro findings

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. The steady-state C_{max} value of ceritinib at the recommended clinical dose of 750 mg daily may exceed the Ki values for the inhibition of CYP3A and CYP2C9 suggesting that ceritinib could inhibit the clearance of other medication metabolised by these enzymes at clinically relevant concentrations. Dose reduction may be needed for co-administered medication that are predominantly metabolised by CYP3A and CYP2C9.

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 metabolised by these enzymes.

On the other hand, 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.

Ceritinib might induce CYPs regulated by Pregnane X receptor (PXR), as indicated in vitro by one marker enzyme for PXR induction, CYP3A4. As there is also time-dependent inhibition of CYP3A4, it is agreed that the net effect is likely inhibition for CYP3A4 itself. However, for other PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if for example, UGTs are induced. Presently, it is unknown whether ceritinib may be a teratogen. Nevertheless, highly effective contraception is recommended at treatment with ceritinib. The evaluator notes that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.

4.3. Evaluator's overall conclusions on pharmacokinetics

The clinical pharmacology documentation of ceritinib seems to be satisfactory. However, there are a few ambiguities in the documentation that should be discussed further by the sponsor.

Ceritinib PK has not been investigated in patients with mild, moderate and severe hepatic impairment. A study in non-cancer patients with varying degrees of impaired hepatic function is currently ongoing (A2110 – protocol attached for review in Clinical Dossier). Among the patients included in the population PK analysis, 48 had mild pre-existing hepatic impairment. The steady-state AUC_{tau} of ceritinib in these patients was estimated to be similar to that in patients with normal liver function, but the analysis is limited since none of the patients included in the population analysis had pre-existing moderate or severe hepatic impairment, as they were excluded from participating in the trials.

In vivo and in vitro data have shown that the concomitant use of CYP3A/P-gp inhibitors can increase the ceritinib plasma concentrations. In fact, results from the ketoconazole study, show that the estimated geometric mean ratios for AUC_{inf} and C_{max} were increased almost 3 fold and 1 fold respectively. Results from a DDI study with rifampin clearly indicate that strong CYP3A inducer decreases the ceritinib concentrations, leading to reduce both the C_{max} and AUC_{inf} (44% and 70%, respectively). This was addressed appropriately in the PI under 'Interactions with other Medicine'.

Based on in vitro data, ceritinib competitively inhibits the metabolism of CYP3A and CYP2C9 substrates but no clinical studies have been submitted for review. I understand that an interaction with midazolam (CYP3A4 substrate) as well as with warfarin (CYP2C9) is being performed post-approval (ClinicalTrials.gov Identifier: NCT02422589). Furthermore ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations in the in vitro experiments. The evaluator thinks this has been adequately addressed in the Australian PI, but clinical studies have not been performed. In addition, according to the EU Guideline on Interactions, all important CYPs (as listed in the guideline) should be evaluated for time-dependent inhibition. Such data seems to be lacking for CYP1A2, CYP2C8, CYP2C19, and CYP2D6.
The proposed PI is generally an adequate and accurate summary of the PK presented in the submission. However the following points need further consideration based on the above discussion:

- Given the current lack of specific data in patients with moderately to severely impaired hepatic function, the evaluator thinks it is to the patients best interest to be more conservative in the wording of this issue until hepatic impairment data (Study A2110) becomes available,

particularly given that hepatotoxicity was observed in the efficacy-safety study for the target population (Section 8.5). Consideration should be made to change the phrasing to 'Ceritinib is not recommended in patients with moderate to severe hepatic impairment'.

- Ceritinib might induce CYPs regulated by PXR. For some PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if UGTs are induced. The evaluator notes that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced with concomitant use of ceritinib was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.
- The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, the evaluator thinks it would be reasonable to include this in the PI.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table Table 3 shows the studies relating to each pharmacodynamic topic and the location of each study summary. No specific clinical pharmacodynamics studies have been conducted. Studies below contained report of some pharmacodynamics data for review as a result.

Table 3: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on efficacy (ORR)	X2101
		A2201
		A2203
	Effect on safety (hepatotoxicity, hyperglycaemia, QT prolongation, GI related AEs	X2101
		A2201
		A2203

5.2. Summary of pharmacodynamics

Data on clinical pharmacodynamics have not been submitted. All other data available concerning mechanism of action are from preclinical studies. Some pharmacodynamic effects were presented based on clinical studies using ceritinib as treatment in patients with ALK-positive tumours.

5.2.1. Mechanism of action

As mention above, the available data concerning mechanism of action are from preclinical studies. Therefore, knowledge is lacking concerning the drug exposure and degree of target inhibition in patients with response as compared to those without a response.

Although there is a clear biological rational that ceritinib would have anti-tumour effect in ALK-positive NSCLC patients, and impressive response rates have been observed, there may still be a potential for further refining the target population, given some eligible patients did not derive a response from ceritinib. Therefore, molecular profiling defining the most sensitive population is needed. Twenty-eight of the patients enrolled in Study A2101 appearing with no response neither on crizotinib nor ceritinib (non- responders on ALK-TKIs), could be false positives by the FISH testing or other mechanism of resistance was at play. The applicant should discuss the lack of response in eligible patients and what characterise responders versus non-responders at a molecular level.

Based on pre-clinical studies, ceritinib appears to have both a higher potency and to be more specific than crizotinib and has been shown to have significant activity in crizotinib-resistant

patients. In a recent paper, it is observed that ceritinib may suppress resistance mutations promoted by crizotinib in vivo, and that rarer mutations may be selected by treatment with ceritinib (Friboulet et al., 2014). More knowledge about the resistance mechanisms for ceritinib seems important for making treatment decisions.

In all clinical efficacy studies (X2101, X1101, A2201, A2203), one of the exploratory objectives included identification of predictive biomarkers for ceritinib and potential mechanism of resistance, both de novo and secondary. It appears that Novartis has an active biomarker plan, which is detailed in the document of Response to D180 List of Outstanding Issues on Clinical Aspects. While this will be helpful in refining the target population and therefore, potentially increase the response rate, spare patients who are unlikely to respond, at this point, the impressive response rate demonstrated by ceritinib in the setting of crizotinib-resistant disease justify consideration for TGA registration.

The FISH cut-off for 15% was based on initial crizotinib studies, and therefore the appropriateness of using 15% as a cut-off for ceritinib use was questioned. The sponsor provided further data in the document of Response to D180 List of Outstanding Issues on Clinical Aspects. The analysis of patients in Study A2203 showed that responses to ceritinib were observed for patients with percent of positive cells as low as 15% (Table 4). Therefore it confirms that FISH is a qualitative assay and the percent positive tumour cells by FISH, over the cut-off for positivity of 15%, are not a determinant of response.

Table 4: Summary statistics for percent positive cells by FISH (Study A2203)

		Investigator Assessment		BIRC Assessment	
	All patients	Responders	Non-responders	Responders	Non-responders
FISH positive					
N	124	79	45	73	51
Mean (SD)	58.6 (19.94)	61.9 (19.01)	52.9 (20.44)	60.6 (18.21)	55.7 (22.06)
Median	56.0	60.0	54.0	58.0	54.0
Min-Max	15.0 – 100.0	19.0 – 100.0	15.0 – 88.0	15.0 – 100.0	15.0 – 96.0
IHC Positive					
N	87	56	31	50	37
Mean (SD)	62.1 (18.72)	64.6 (19.01)	57.6 (17.60)	63.7 (18.31)	60.0 (19.32)
Median	58.0	67.0	56.0	66.0	57.0
Min-Max	19.0 – 100.0	22.0 – 100.0	19.0 – 88.0	25.0 – 100.0	19.0 – 96.0

FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; SD = standard deviation
Responders are patients with confirmed PR or CR per RECIST 1.1.

5.2.2. Pharmacodynamic effects

Dose investigations presented for ceritinib were limited by few patients and therefore results from dose-efficacy analyses were not submitted. Preliminary statistical exposure-response analyses suggest only a trend regarding a relationship between higher steady-state exposure of ceritinib and higher objective response rate (ORR). However, a rather clear relationship is indicated between exposure of ceritinib and increases in more serious adverse events (elevation of transaminases, hyperglycemia, QT/QTc- prolongation). At present, it is therefore unclear how a lower, and perhaps more acceptable, dose would affect the efficacy of ceritinib. Further exploration of the dose-exposure-response relationship of ceritinib in population PK analysis may provide further data.

In the overall safety population, QTc-prolongation was observed in about 6% of the patients in the overall safety population, including 3.3% suspected to be treatment-related. A clear trend towards increasing changes in QTc-interval with increasing doses was observed in a linear mixed effects model. The influence on heart rate and QTc interval of ceritinib has only been investigated by ECG measurements in a Phase I, first-in-man study (X2101). The fact that symptoms of possible heart failure (QT prolongation (5.95), syncope 1.6%, cardio-respiratory arrest (0,4%) were seen with increasing doses of ceritinib, focuses the lack of a proper QT/QTc study. In addition, preclinical studies showed increases in QT/QTc in one of four monkeys exposed with ceritinib concentrations twice the C_{max} of patients, and indirectly, probable influence on the QT-interval was demonstrated

by in vitro blocking of hERG ion channels.

Comments: Novartis does not plan to conduct a Thorough QT/QTc (TQT) study. Study X2101 included the collection of ECGs along with time-matched ceritinib plasma concentrations, and given the wide ranges of doses studied in this trial (50 to 750 mg), these data enable a robust characterisation of the ceritinib concentration-QTc relationship. Further data will come from the two Phase II studies (A2201 and A2203) and ongoing Phase III studies (A2303 and A2301), where triplicate ECGSs along with time-matched ceritinib plasma concentrations at pre-dose and at various post-dose time-points will be obtained and analysed. The evaluator thinks the sponsor's justification is acceptable.

5.3. Evaluator's overall conclusions on pharmacodynamics

The submitted dossier does not contain proper clinical PD studies. In addition, dose investigations presented for ceritinib were limited by few patients. While this is a major limitation, the proposed mechanism of ALK inhibition based on pre-clinical studies and the impressive response of ceritinib in the clinical studies, would justify the use of ceritinib in the proposed indication.

However, further refinement of the target population and understanding the de novo and secondary resistance to ceritinib would benefit the clinical management of ALK-positive NSCLC. The Novartis biomarker programme will hopefully elucidate this clinical [information redacted]. The lack of molecular characterisation in the current application is not a significant problem that would prevent approval of use in the crizotinib-resistant setting in NSCLC patients.

6. Dosage selection for the pivotal studies

Determination of MTD has been conducted as part of registration Study X2101. This study was originally designed as a Phase I dose escalation trial for the determination of the MTD. It was a first-in-human, open-label, Phase I study that comprised a dose-escalation phase (to determine the MTD and RD), and an expansion phase to characterise the efficacy, safety and pharmacokinetics (PK) of ceritinib.

The dose-escalation phase included a 3 day single dose PK run-in and the 750 mg daily dose was selected for further testing into the following period of daily dosing in continuous 21 day treatment cycles. Patients could continue treatment until disease progression or non-assumable toxicity. Patients treated at the RD during the dose-escalation phase and who met the criteria for one of the four expansion arms were considered to be included in the appropriate expansion arm.

The MTD/RD was determined based on the BLRM model assessing the probability of DLTs in Cycle 1 and the clinical assessment of safety and efficacy data.

In the dose-escalation phase, 59 patients were treated in 15 cohorts across nine different dose levels (50 mg to 750 mg), and 54 patients were included in the Dose Determining Set (DDS). At the time that the MTD was determined, eight DLTs had occurred during the first cycle of treatment in six patients.

- At 400 mg: Grade 3 hypophosphatemia in one patient, and Grade 3 transaminase increased evolving from grade 2 ALT increased in one patient.
- At 600 mg: Grade 3 diarrhoea and Grade 3 dehydration in one patient each.
- At 750 mg: Grade 3 diarrhoea with Grade 3 vomiting in one patient and intolerable grade 2 diarrhoea in one patient.

Additional support to establish MTD/RD at 750 mg came from the experience of the first 10 patients in the expansion phase (no DLTs were observed) and the preliminary data on tumour activity, which had shown tumour response with doses > 400 mg.

7. Clinical efficacy

7.1. ALK-positive NSCLC previously treated with ALK inhibitor

7.1.1. Pivotal efficacy studies

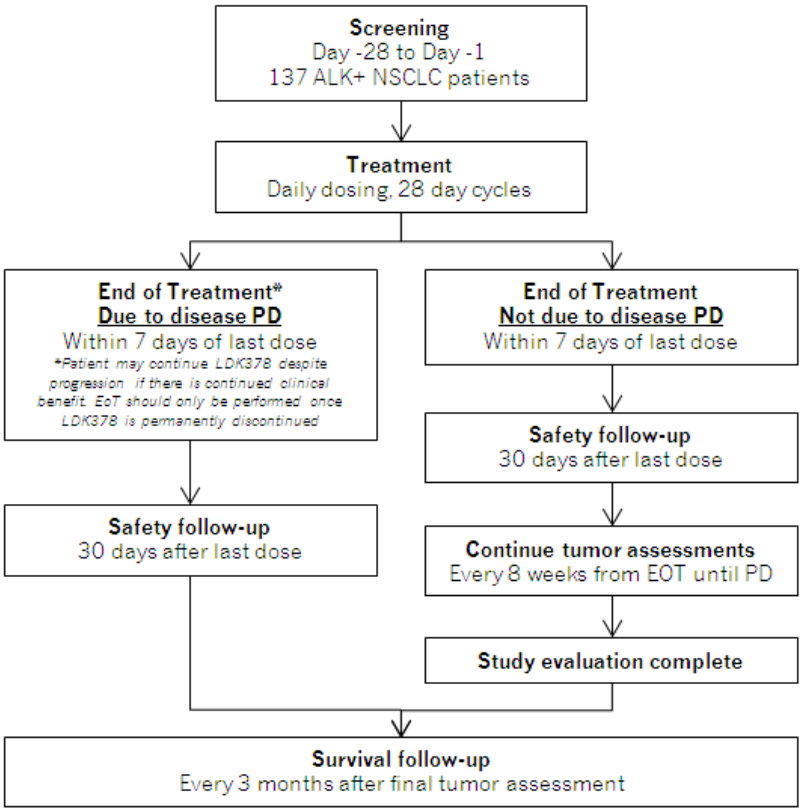
7.1.1.1. Study A2201

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

Study design, objectives, locations and dates

Study A2201 was a single-arm, open-label, Phase II study with a single stage design. It assessed the efficacy and safety of single agent ceritinib 750 mg orally on a once-daily dosing schedule in patients with locally advanced or metastatic ALK-positive NSCLC previously treated with cytotoxic chemotherapy, and which has progressed during the most recent crizotinib therapy prior to enrolment in the study. Figure 3 illustrates the A2201 study design.

Figure 3: A2201 study design



Primary objective:

To demonstrate the anti-tumour activity of ceritinib, as measured by overall response rate (ORR) by investigator assessment

Secondary Objectives:

- To evaluate response related endpoints including duration of response (DOR), disease control rate (DCR), time to response (TTR), overall intracranial response rate and ORR as assessed by blinded independent review committee (BIRC)
- To evaluate the safety profile of ceritinib
- To evaluate progression-free survival (PFS)

- To evaluate overall survival (OS)

The study was multi-centre and was conducted in Canada, France, Germany, Hong Kong, Italy, Japan, South Korea, Netherlands, Singapore, Spain, United Kingdom and United States. No Australian sites were included.

The study [information redacted] primary analysis data cut-off date was 26 Feb 2014 when all patients have either completed at least six treatment cycles (24 weeks) or discontinued study drug earlier. The study is ongoing.

Inclusion and exclusion criteria

Inclusion

- Patients ≥ 18 ears with histologically or cytologically confirmed diagnosis of Stage IIIB or IV NSCLC carrying an ALK rearrangement defined as 15% or more positive tumour cells as assessed by the FDA-approved Vysis ALK break-apart FISH test (Abbott Molecular Inc.) using Vysis break-apart probes
- NSCLC should have progressed during therapy with crizotinib or within 30 days of the last dose, regardless of whether the patient had previously shown tumour regression or not.
- Previously treated with cytotoxic chemotherapy (one to three prior lines, of which one must have been a platinum doublet) and had to have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2 (CTCAE v 4.03) except for nausea, vomiting and diarrhoea)
- WHO performance status 0 to 2
- Life expectancy of ≥ 12 weeks at study entry
- Presence of at least one measurable lesion as defined by RECIST 1.1

Exclusion

- Patients with known hypersensitivity to any of the excipients of ceritinib
- Symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within two weeks prior to study start to control their CNS disease;
- History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (that is,, affecting activities of daily living or requiring therapeutic intervention)
- Prior or current history of a second malignancy, impaired GI function (that significantly altered the absorption of ceritinib), history of carcinomatous meningitis, or clinically significant cardiac disease
- Patients with thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who had not recovered from radiotherapy-related toxicities
- Major surgery (for example, intra-thoracic, intra-abdominal or intra-pelvic) within four weeks prior (two weeks for resection of brain metastases) to starting study drug or who had not recovered from side effects of such procedures
- Patients treated with medications that were known to be strong inhibitors or inducers of CYP3A4/5, medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 and medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes

Study treatments

All patients were treated with ceritinib, supplied as 150 mg hard gelatin capsules and were administered orally, once daily at a dose of 750 mg on a continuous dosing schedule (5 x 150 mg capsules). Ceritinib was continued until the patient experienced unacceptable toxicity that

precluded further treatment, discontinued treatment at the discretion of the patient or investigator, started a new anti-cancer therapy or died.

Efficacy variables and outcomes

The primary efficacy outcome was ORR as measured by investigator assessment.

Contrast-enhanced CT or MRI of chest and upper abdomen for tumor evaluation was performed at baseline within 6 weeks prior to enrollment and then every eight weeks after Day 1 of Cycle 1 for response determination. For post-baseline tumor assessments, all lesions that were present at baseline were to be accounted for using the same technique as used at baseline so that the comparison was consistent. Partial Response (PR) and Complete Response (CR) were to be confirmed by a subsequent imaging assessment at least four weeks after the criteria for response were first met.

Other efficacy outcomes included:

- Duration of response (DOR), as assessed by both investigator and 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, as assessed by both investigator and BIRC
- ORR, as assessed by BIRC
- PFS, as assessed by both investigator and BIRC
- OS

Randomisation and blinding methods

This was a single–arm, open-label study. Therefore no randomisation or blinding was required.

Analysis populations

The **Full Analysis Set** (FAS) consisted of all patients who received at least one dose of ceritinib (n=140). FAS was the default analysis set used for all analyses including the primary analysis.

The **Safety Set** consisted of all patients who received at least one dose of ceritinib. All safety data was analysed using the Safety Set. This was identical to FAS (n=140).

The **Per-Protocol Set** (PPS) consists of a subset of patients in the FAS who had no major protocol deviations, who had an adequate tumour assessment at baseline and had a follow-up tumour assessment greater than seven weeks after starting treatment (unless progressive disease [PD] was observed before that time). This was used only for supportive analysis of the primary efficacy endpoint (n=128 for ORR by investigator assessment and n=104 for ORR by BIRC).

Sample size

The primary endpoint used to evaluate the anti-tumour activity of ceritinib was the ORR by the local investigator. The primary efficacy analysis was performed on the FAS. 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. Therefore, H0: ORR ≤ 25% was tested versus. H1: ORR > 25%using a one-sided test with α=0.025 based on the exact binomial distribution.

The null hypothesis was to be rejected and the study declared positive based on the probability of obtaining the observed ORR under a binomial distribution with underlying parameter p0=0.25. Based on 137 patients required to test the null hypothesis, if 45 or more responses were observed (observed ORR of 32.8%), H0 was to be rejected at a one-sided α= 0.025.

Statistical methods

ORR, as assessed by the Investigator per RECIST 1.1, was estimated and the exact 95% confidence interval (CI) was provided. Confirmed PR or CR reported prior to any additional anticancer therapy was considered as responses in the calculation of the ORR irrespective of the number of missed

assessments before response. Patients with a best overall response (BOR) of 'Unknown' per RECIST 1.1 were considered as non-responders when estimating ORR. Patients who had disease progression and continued to receive study drug after progression qualified for PD at the time of progression and were counted as PD in the derivation of ORR and any other efficacy endpoints.

The following supportive analyses were also carried out:

Per protocol analysis: If the primary analysis on ORR by Investigator assessment is statistically significant, the primary analysis was to be repeated on the PPS.

Waterfall plots: Waterfall plots representing the best percentage change from baseline in the sum of the tumor measured diameters for target lesions were produced.

Subgroup analysis: If the primary analysis on ORR by Investigator assessment is statistically significant, ORR by Investigator assessment was also summarised by the subgroups based on Investigator assessment:

- Geographic region (North America, Europe, Asia Pacific)
- Age group (< 65 years, ≥ 65 years)
- Gender (male, female)
- Race (Caucasian, Black, Asian, other)
- Brain metastases at screening (presence, absence)
- WHO status (0, 1, ≥ 2)
- Number of prior regimens (1, 2, 3, > 3)
- Disease burden per Investigator assessment (baseline sum of diameters (SOD) for target lesions < median SOD for target lesions, baseline SOD for target lesions ≥ median SOD for target lesions)
- Disease burden per BIRC assessment (baseline SOD for target lesions < median SOD for target lesions, baseline SOD for target lesions ≥ median SOD for target lesions)
- Number of target lesions at baseline per Investigator assessment: (1, 2, 3, 4, 5); (1, ≥ 2)
- Number of target lesions at baseline per BIRC assessment (0, 1, 2, 3, 4, 5); (≤ 1, ≥ 2)

The secondary outcomes were analysed based on FAS. The ones mentioned in the draft PI included:

- DOR by investigator assessment and BIRC. This was defined 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 tumour assessment. This was described using Kaplan-Meier methods. The estimated median (in months), along with 95% CIs, as well as 25th and 75th percentiles were reported.
- PFS by investigator assessment and by BIRC. PFS was 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. PFS was described using Kaplan-Meier methods.
- 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 described using Kaplan-Meier methods.

Participant flow

Of the 140 ALK-positive NSCLC patients treated with ceritinib, treatment was ongoing for 75 patients (53.6%) at the time of the data cut-off date. A total of 65 patients discontinued from the treatment phase, including six patients (4.3%) who entered the post-treatment efficacy follow-up, 47 patients (33.6%) who entered the post-treatment survival follow-up, and 12 patients (8.6%) who discontinued from the study.

The primary reason for treatment discontinuation was disease progression in 37 patients (26.4%) and AEs in 10 patients (7.1%). Death was the primary reason for treatment discontinuation for five patients (3.6%), four deaths due to study indication and one death due to respiratory failure.

In addition to the patients described above, seven additional patients discontinued from the study without entering into any of the follow-up phases due to the patient/guardian's decision (three patients), AEs (two patients), PD (one patient), and lost to follow-up (one patient).

Of the six patients who entered the post-treatment efficacy follow-up, one patient was still ongoing in the efficacy follow-up phase at the time of the data cut-off date. The primary reason for discontinuation from the post-treatment efficacy follow-up phase was death in four patients and disease progression in one patient. All the four patients who discontinued due to 'death' as the primary reason died due to study indication (progressive disease).

Major protocol violations/deviations

At least one protocol deviation was reported in 89 patients (63.6%). Majority of these were considered not to impact efficacy evaluations such as key procedures (ECG, patient reported outcome [PRO] assessment) not performed as per protocol and deviation in treatments.

Major protocol deviations leading to exclusion from the PPS were observed in three patients. These patients were identified retrospectively not to have local documentation of ALK-positive status using the FDA-approved FISH test. Although central testing was attempted in all three, one patient was unable to submit a tumour sample for testing, one patient's sample would not be tested due to technical reason and one was tested and reported as ALK-negative.

Comments: This is unlikely to have altered the overall primary endpoint (using FAS). If anything, it would underestimate the ORR, given ceritinib is unlikely to exert an anti-tumour effect in ALK-negative patients.

Baseline data

Overall, the evaluator thinks the demographic characteristics of the patients in this study are representative of the patients with metastatic ALK-positive NSCLC previously treated with multiple lines of therapy and would be representative of the patients who will receive the drug if the submission is approved.

Table 5 details the demographics and baseline characteristics, while Table 6 shows the disease characteristics. Table 7 demonstrates prior antineoplastic therapy. All are based on FAS.

Table 5: Study A2201 demographics and baseline characteristics

Demographic Variables	Ceritinib 750 mg (n=140)
Age (years)	
N	140
Mean (SD)	51.2 (11.62)
Median	51.0
Minimum - Maximum	29.0 – 80.0
Sex – n (%)	
Female	70 (50.0)
Male	70 (50.0)
Race – n (%)	
Caucasian	84 (60.0)
Asian	53 (37.9)

Demographic Variables	Ceritinib 750 mg (n=140)
Other	3 (2.1)
Ethnicity – n (%)	
Hispanic or Latino	13 (9.3)
East Asia	43 (30.7)
Southeast Asian	6 (4.3)
South Asian	2 (1.4)
West Asian	2 (1.4)
Other	48 (34.3)
Unknown	10 (7.1)
Nor reported	16 (11.4)
Body mass index (kg/m^2)	
N	140
Mean (SD)	23.7 (4.79)
Median	23.4
Minimum - maximum	13.4 – 47.2
ECOG PS – n (%)	
0	42 (30.0)
1	78 (55.7)
2	20 (14.3)

Table 6: Study A2201 disease characteristics

	Ceritinib 750 mg (n=140)
Primary site of cancer – n (%)	
Lung	140 (100)
Histology/Cytology	
Adenocarcinoma	129 (92.1)
Adenosquamous cell carcinoma	1 (0.7)
Bronchoalveolar carcinoma	1 (0.7)
Mucinous adenocarcinoma	2 (1.4)
Papillary serous	1 (0.7)
Squamous cell carcinoma	3 (2.1)
Undifferentiated carcinoma	1 (0.7)
Other	2 (1.4)
Histological grade – n (%)	
Well differentiated	9 (6.4)
Moderately differentiated	25 (17.9)
Poorly differentiated	31 (22.1)

	Ceritinib 750 mg (n=140)
Undifferentiated	4 (2.9)
Unknown	70 (50.0)
Missing	1 (0.7)
Metastatic site of cancer – n (%)	
Adrenal	14 (10.0)
Bone	81 (57.9)
Brain	100 (71.4)
Kidney	9 (6.4)
Liver	52 (37.1)
Lung	47 (33.6)
Pleura	52 (37.4)
Soft tissue	3 (2.1)
Lymph nodes	73 (52.1)
Metastatic	18 (12.9)
Axillary lymph nodes	7 (5.0)
Cervical lymph nodes	4 (2.9)
Inguinal lymph nodes	2 (1.4)
Mesenteric lymph nodes	2 (1.4)
Pelvic nodes	2 (1.4)
Retroperitoneal lymph nodes	4 (2.9)
Local	48 (34.3)
Bronchopulmonary lymph nodes	6 (4.3)
Mediastinum lymph nodes	39 (27.9)
Sub clavicular lymph nodes	4 (2.9)
Supraclavicular lymph nodes	5 (3.6)
Other lymph nodes	28 (20.0)
other	37 (26.4)
Thoracic involvement of cancer, n (%)	
Lung or pleura/pleural effusion or thoracic lymph nodes	129 (92.1)
Lung	115 (82.1)
Pleura/pleural effusion	60 (42.9)
Thoracic lymph nodes	59 (42.1)
Stage at time of study entry – n (%)	
IV	133 (95%)
IVA	1 (0.7)
IVB	6 (4.3)
Type of lesions at baseline (investigator assessment) – n (%)	

	Ceritinib 750 mg (n=140)
Both target and non-target	136 (97.1)
Target only	4 (2.9)
Disease burden (SOD at baseline for target lesions based on investigator assessment) (cm)	
N	140
Mean (SD)	6.7 (6.21)
Median	4.3
Minimum – maximum	1.0 – 38.0
Disease burden (SOD at baseline for target lesions based on BIRC assessment (cm)	
N	138
Mean (SD)	4.9 (4.70)
Median	3.7
Minimum – maximum	0.0 – 23.6
Number of target lesions at baseline based on investigator assessment	
1	60 (42.9)
2	38 (27.1)
3	18 (12.9)
4	13 (9.3)
5	11 (7.9)
Number of target lesions at baseline based on BIRC assessment	
0	24 (17.1)
1	38 (27.1)
2	43 (30.7)
3	20 (14.3)
4	9 (6.4)
5	4 (2.9)
Missing *	2 (1.4)
Time since initial diagnosis of primary site (months)	
N	140
Mean (SD)	33.8 (27.98)
Median	26.2
Minimum – maximum	5.6 – 181.4
Time from initial diagnosis to first recurrence/progression (months)	
N	140
Mean (SD)	11.4 (16.19)
Median	7.7
Minimum – maximum	0.5 – 166.5
Time since most recent relapse/progression (months)	

	Ceritinib 750 mg (n=140)
N	140
Mean (SD)	20 (2.55)
Median	1.2
Minimum – maximum	0.2 – 15.9

SOD = sum of diameters. Metastatic sites as collected in CRF page of diagnosis and extent of cancer. Thoracic involvement is based on the investigator reported lesion location for the baseline RECIST evaluation and was complemented by the metastatic site of cancer at baseline as reported in the 'Diagnosis and Extent of Cancer' eCRF when no thoracic lesion was identified from the RECIST evaluation. *No baseline assessment per BIRC. One patient had no identifiable disease at baseline, while for another patient the scans could not be send to BIRC therefore no read was possible.

Table 7: Study A2201 Prior antineoplastic therapy

	Ceritinib 750 mg (n=140) N (%)
Any prior antineoplastic therapy [1]	
Yes	140 (100)
Surgery	
No	103 (73.6)
Yes [2]	37 (26.4)
Radiotherapy	
No	41 (29.3)
Yes	99 (70.7)
Medication: chemotherapy setting [3]	
Adjuvant	12 (8.6)
Neoadjuvant	5 (3.6)
Prevention	10 (7.1)
Palliative	114 (81.4)
Therapeutic	6 (4.3)
Other	16 (11.4)
Medication: other therapy setting [3]	
Adjuvant	2 (1.4)
Prevention	7 (5.0)
Palliative	114 (81.4)
Therapeutic	6 (4.3)
Other	16 (11.4)
Number of prior regimens	
2	61 (43.6)
3	50 (35.7)
4	17 (12.1)

	Ceritinib 750 mg (n=140) N (%)
5	10 (7.1)
6	1 (0.7)
7	1 (0.7)
Prior anti-cancer medications	
Crizotinib	140 (100)
Afatinib	1 (0.7)
Bevacizumab	34 (24.3)
Carboplatin	80 (57.1)
Chemotherapeutics, other	1 (0.7)
Cisplatin	89 (63.6)
Cixutumumab	1 (0.7)
Dacomitinib	2 (1.4)
Docetaxel	23 (16.4)
Erlotinib	19 (13.6)
Etoposide	5 (3.6)
Gefitinib	6 (4.3)
Gemcitabine	32 (22.9)
Irinotecan	2 (1.4)
Paclitaxel	37 (26.4)
Pemetrexed	114 (81.4)
Tegafur	1 (0.7)
TS 1	1 (0.7)
Vinorelbine	10 (7.1)
Investigational drug	6 (4.3)

(1) Any prior antineoplastic therapy includes patients who have had medication, radiotherapy or surgery. (2) Prior surgery = YES excludes diagnostic biopsies. (3) A patient may have multiple settings.

Results for the primary efficacy outcome

The median duration of follow-up from the start of study drug to last contact date on or prior to the data cut-off date for the 140 patients in the FAS was 7.39 months (range: 0.1 to 14.0 months).

The study met its primary objective. Based on local investigator assessment, three patients had a BOR of CR and 49 patients had a BOR of PR, resulting in an ORR of 37.1% (95% CI: 29.1, 45.7). This was statistically significant with a one-sided p-value of < 0.001 (Table 8).

Table 8: Best overall response by investigator assessment (FAS)

	Ceritinib 750 mg N=140		
	n (%)	95% CI [1]	p-value [2]
Best overall response			
Complete response (CR)	3 (2.1)		
Partial response (PR)	49 (35%)		
Stable disease (SD)	56 (40.0)		
Progressive disease (PD)	19 (13.6)		
Unknown (UNK)	13 (9.3)		
Overall response rate (ORR: CR + PR)	52 (37.1)	29.1, 45.7	< 0.001*
Disease control rate (DCR: CR + PR + SD)	108 (77.1)	69.3, 83.8	

N: the total number of patients in FAS. It is the denominator for percentage calculation. n: number of patients who are in the corresponding category. [1] exact binomial 95% confidence interval. [2] p-value associated with exact test of H_0: ORR ≤ 25% versus. H_1: ORR > 25% based on exact binomial distribution. * indicates statistical significance (one-sided) at the 0.025 level.

Results for other efficacy outcomes

Per protocol analysis

Since ORR was statistically significant based on FAS, it is also evaluated based on PPS (n=128) as a supportive analysis. Further, the ORR was also assessed by BIRC using FAS and PPS.

In the FAS, 48 patients were determined to have either CR or PR by BIRC assessment, resulting in a 34.3% ORR (95% CI: 26.5, 42.8) (Table 9).

In the PPS, the ORR based on investigator assessment was 40.6% (95% CI: 32.0, 49.7). Similarly the ORR based on BIRC assessment was 46.2% (95% CI: 36.3, 56.2) (Table 9).

Table 9: Summary efficacy results (ORR, DOR and PFS) by investigator and BIRC assessment

Efficacy Parameter	By investigator assessment	By BIRC assessment
In Full Analysis Set (FAS)	**N=140**	**N=140**
Overall response rate (CR+PR) [1], n (%) [95% CI]	52 (37.1) [29.1, 45.7]	48 (34.3) [26.5, 42.8]
Duration of response (median [95% CI]), months	9.2 [5.6, NE]	9.2 [5.5, NE]
Progression-free survival (median [95% CI]), months	5.7 [5.3, 7.4]	6.1 [5.4, 7.4]
In Per Protocol Set (PPS)	**N=128**	**N=104**
Overall response rate (CR+PR) [1], n (%) [95% CI]	52 (40.6) [32.0, 49.7]	48 (46.2) [36.3, 56.2]

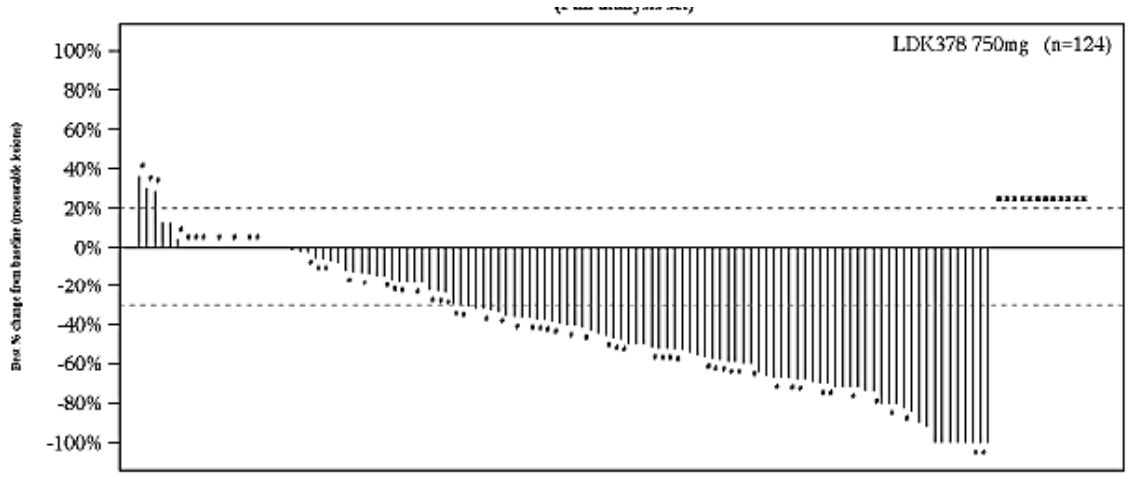
[1] CR, PR confirmed. NE = not estimable

Best percentage change from baseline in sum of measured diameters

Based on investigator assessment, 92 patients (74.3%) had a tumour reduction (best percentage

change from baseline < 0%). Only six patients (4.8%) had tumour growth (best percentage change from baseline > 0%) (Figure 4).

Figure 4: Waterfall plot for best percentage change from baseline in sum of diameters per investigator assessment (FAS)



Best percentage change from baseline>0 6 (4.84%)
Best percentage change from baseline<0 92 (74.19%)
Best percentage change from baseline=0 14 (11.29%)
* %change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 12 (9.68%)
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.
/report/pgm_eff/f_wfall_esr.sas@@/main/1 24JUN14:02:39

Subgroup analyses

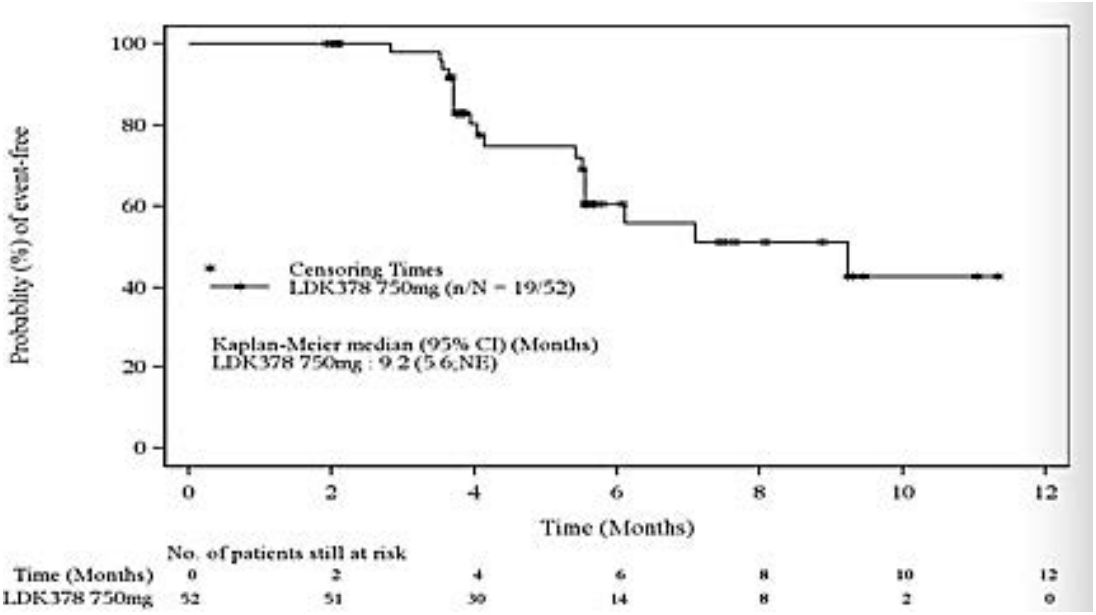
The subgroup analyses of ORR based on investigator assessment did not reveal any meaningful differences in ORR (that is, all differences in point estimate were ≤ 15% with overlapping 95% CIs) within most of the subgroups with the exception of ECOG status at baseline and target lesions at baseline.

- Patients with ECOG PS 0 (33.3%) and ECOG PS 1 (42.3%) compared to ECOG PS ≥ 2 (25%)
- Patients with ≤ 1 target lesion at baseline (26.7%) compared with patients with ≥ 2 target lesions (45%)

Duration of response (DOR) as a key secondary outcome

Based on investigator assessment, the estimated median DOR was 9.2 months (95% CI: 5.6, NE) for the 52 patients with a confirmed CR and PR (Figure 5). The results based on BIRC assessment were similar with the estimated median DOR of 9.2 months (95% CI: 5.5, NE) for the 48 patients with a confirmed CR or PR (Table 9).

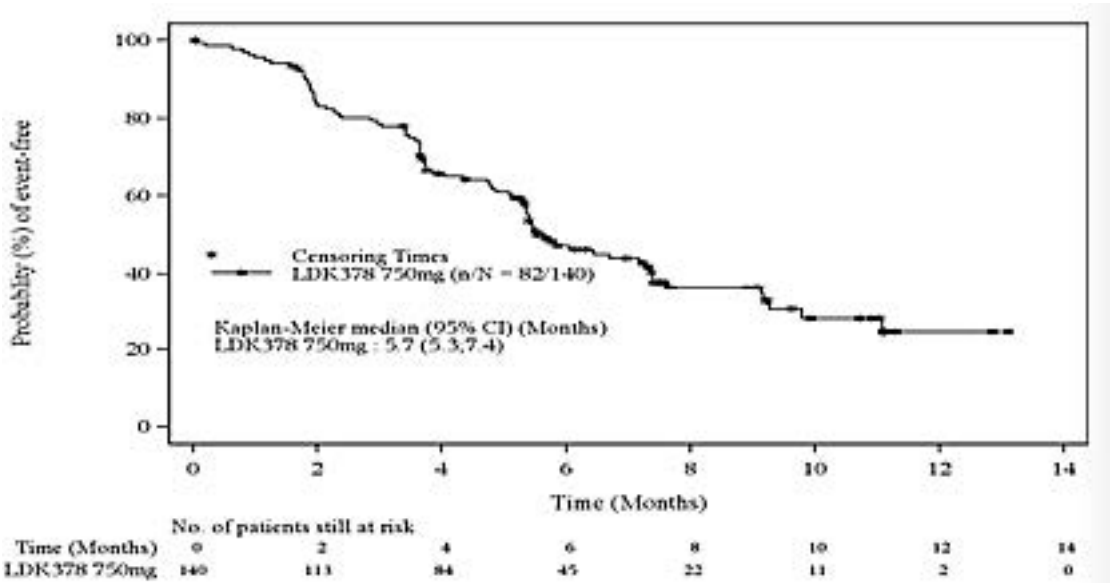
Figure 5: Kaplan-Meier plot of duration of response per investigator assessment (FAS – patients with confirmed CR or PR)



Progression-free survival as a key secondary outcome

Based on investigator assessment, 82 PFS events were observed and median PFS was 5.7 months (95% CI: 5.3, 7.4) (Figure 6). Similar results were observed based on BIRC assessment with 77 PFS events and a median PFS of 6.1 months (95% CI: 5.4, 7.4) (Table 9).

Figure 6: Kaplan-Meier plot of PFS per investigator assessment (FAS)



Overall survival as a key secondary outcome

As of the data cut-off date 39 deaths had been reported. The median OS was 14 months (95% CI: 10.3, 14.0). A total of 101 patients (72.1%) were censored for survival including 100 patients who were alive and one patient who was lost to follow-up as of the data cut-off date. Given the majority of patients are alive the OS data is immature and should be interpreted with caution (Figure 7).

Figure 7: Kaplan-Meier plot of overall survival (FAS)

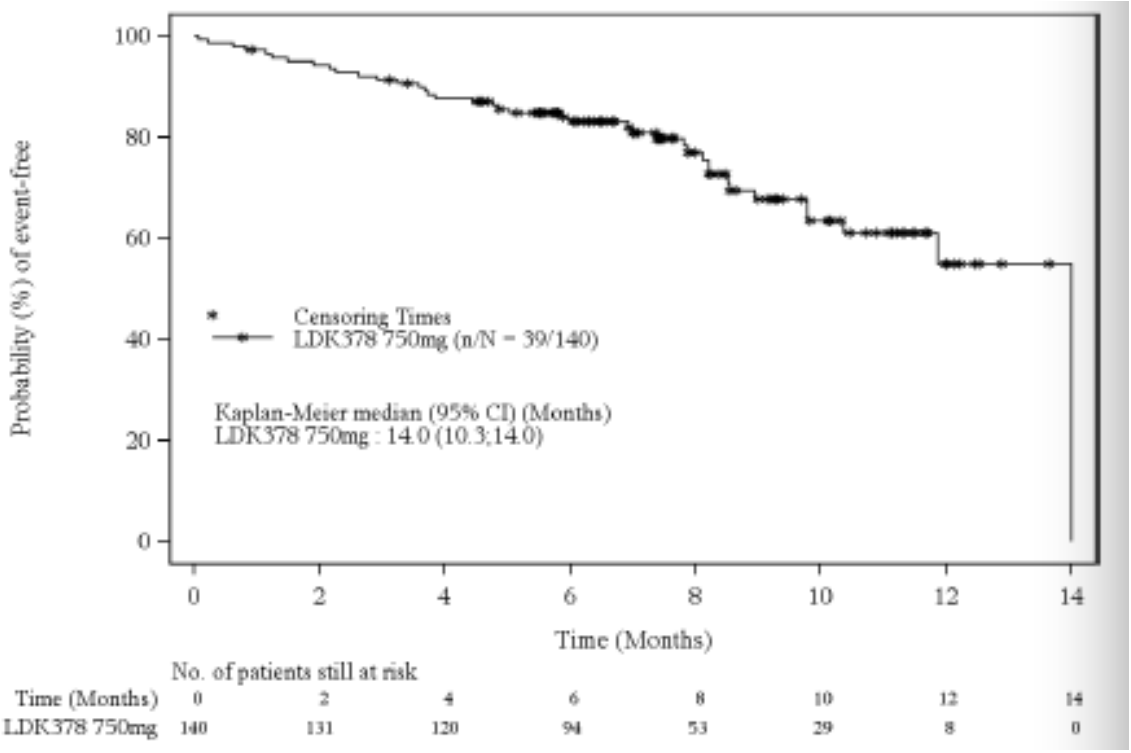


Table 9 summaries the key efficacy results assessed both by investigator and BIRC.

Comments: While investigator determined best overall response is subjective to bias and therefore questionable whether this should be chosen as the primary endpoint, the supportive analyses suggest that overall efficacy results were similar between investigator's versus BIRC assessments.

Patients with brain metastases

This group of patients are separately discussed here due to the high proportion of patients with brain metastases included in this study (71.4%). This is due to the ALK-positive patients having predilection to having brain metastases. This was also discussed in the proposed Australian PI.

For the 100 ALK inhibitor treated patients with brain metastases, the ORR was 33.0% (95% CI: 23.9, 43.1.). Furthermore in the FAS, 20 out of the 140 patients had brain metastases at baseline considered to be target lesions by the Investigator per the RECIST 1.1 criteria. In these patients, the overall intracranial response rate (OIRR) based on Investigator assessment was 35% (95% CI: 15.4, 59.2). The intracranial DCR based on Investigator assessment was 80% (95% CI: 56.3, 94.3).

Comments: The evaluator notes that the ORR and OIRR rates in the Australian PI are discrepant to the information provided in the A2201 Full Clinical Study Report.

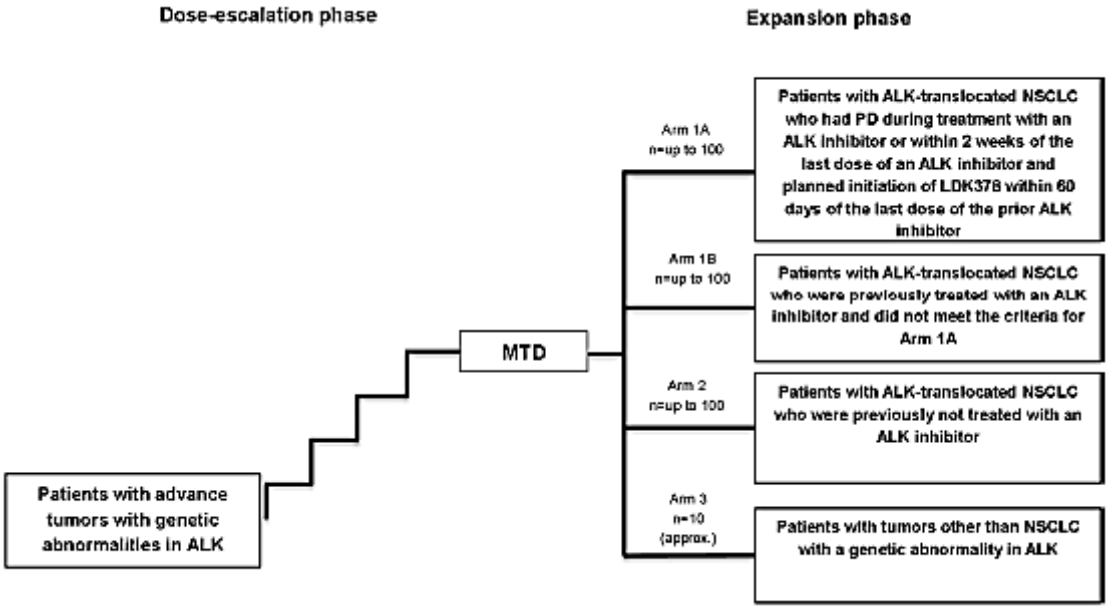
7.1.1.2. Study X2101

A Phase I, multicentre, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumours characterised by genetic abnormalities in anaplastic lymphoma kinase (ALK

Study design, objectives, locations and dates

This is a first-in-human, Phase I, open label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumour activity of oral, once-daily, continuous dosing of ceritinib in adult patients with advanced tumours confirmed to have genetic abnormalities in ALK.

Figure 8: Study Design of X2101



Primary objective was to determine the MTD of ceritinib as a single agent when administered orally to adult patients with tumour characterised by genetic abnormalities in ALK.

Secondary objectives:

- To characterise the safety and tolerability of ceritinib, including both acute and chronic toxicities.
- To characterise single and multiple-dose PK of ceritinib.
- To assess anti-tumour activity of ceritinib as a single agent when administered orally to adult patients with tumours characterised by genetic abnormalities in ALK at RD by CT/MRI.

Exploratory Objectives:

- To identify mutations in the ALK gene or other molecular abnormalities associated with clinical progression after treatment with an ALK inhibitor in tumour samples collected during the pre-screening period in cases where ALK testing was performed centrally
- To assess OS in patients treated with ceritinib.

This study was conducted in Australia, Belgium, Germany, Italy, Netherlands, Spain, UK, Canada, Singapore, Korea and US.

The trial enrolled its first patient on 24 January 2011 and was closed to enrolment on 31 July 2013. The primary analysis data cut-off date was 2 August 2013. This study is currently ongoing.

Inclusion and exclusion criteria

Inclusion

- Diagnosis of a locally advanced or metastatic malignancy that has progressed despite standard therapy or for which no effective standard therapy exists
- Patients with tumour characterised by genetic abnormalities in ALK. For NSCLC, an ALK translocation must be detected by FISH in ≥ 15% of tumour cells. In patients with diseases other than NSCLC, ALK translocation is not required and overexpression of ALK protein may be considered indicative of a genetic abnormality in ALK
- Patients with measurable or non-measurable disease as determined by modified RECIST version 1.0 in dose-escalation phase and patients with at least one measurable lesion as determined by RECIST 1.0 in expansion phase

- Patients ≥ 18 years
- ECOG performance status of ≤ 2
- Life expectancy of ≥ 12 weeks

Exclusion

- Patients with symptomatic CNS metastases who were neurologically unstable or required increasing doses of steroids to control their CNS disease. (Patients with controlled CNS metastases, or asymptomatic CNS metastases that did not require local antineoplastic therapy, such as radiotherapy or surgery were allowed).
- History of a second malignancy, impaired GI function (that significantly altered the absorption of ceritinib), history of pancreatitis or increased amylase or lipase, known diagnosis of HIV, and clinically significant cardiac disease.
- Patients treated with chemotherapy or biologic therapy or other investigational agents < 2 weeks prior to starting study drug or compounds with a half-life ≤ 3 days, and < 4 weeks prior to starting study drug for compounds with a prolonged half-life.
- Patients treated with medications that were known to be a strong inhibitors or inducers of CYP3A4/5 that could not be discontinued at least a week prior to start of treatment with ceritinib and for the duration of the study.

Study treatments

Ceritinib was the study drug. This came in 3 formulations: ceritinib 25 mg, ceritinib 50 mg and ceritinib 150 mg. Once the MTD/RD was established in the dose-escalation phase, all patients enrolled in the expansion phase of the study were treated at that dose (750 mg). Ceritinib was administered continuously, orally every day and it was taken with a glass of water and consumed over a short period of time. Each daily dose of ceritinib was taken at least 2 h after the last meal and patients could not eat for at least 2 h after ceritinib was taken.

In both dose escalation and expansion phases, patients were treated until objective evidence of disease progression or until the patient experienced unacceptable toxicity. Patients could also continue treatment with ceritinib after disease progression if in the opinion of the investigator the patients were still experiencing clinical benefit. During the treatment period, patients were regularly monitored to assess the safety and anti-tumour activity of ceritinib.

Dose adjustments were permitted for patients who experienced a DLT with ceritinib, if it was considered in the best interest of the patient to continue therapy. If a patient experienced a DLT, the investigators were generally advised to interrupt treatment with ceritinib until the event resolved to Grade 1or the patient's baseline, and if continued treatment was considered to be in the best interest of the patient, to resume ceritinib at one dose-level lower.

Efficacy variables and outcomes

The main efficacy variables were ORR assessed by CT/MRI according to RECIST version 1.0 based on investigators' assessment. After protocol amendment 4, BIRC assessment was performed.

The primary efficacy outcome was ORR and DOR.

These measures were summarised for patients with ALK-positive NSCLC only:

- By treatment dose group (each of the ceritinib dose groups from 50 mg to 750 mg);
- For the ceritinib 750 mg treatment dose group, by population subgroup as per the Amendment 5 of the study protocol:
- Prior ALK inhibitor therapy (Arms 1A + 1B),
- Disease progression (PD) during treatment with (or within 2 weeks of last dose) last prior ALK inhibitor therapy (subset of Arms 1A + 1B),

- No PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy (subset of Arms 1A + 1B),
- ALK inhibitor therapy naïve (Arm 2),
- All NSCLC (Arms 1A + 1B + 2).

Additional efficacy endpoints included PFS and OS.

Randomisation and blinding methods

No randomisation and blinding were required in the study.

Analysis populations

The **Full Analysis Set (FAS)** consists of all patients (including NSCLC and non-NSCLC) who received at least one dose of ceritinib. Patients were classified according to the intended treatment dose group.

The subset of FAS including only ALK-positive NSCLC patients across all doses (FAS-NSCLC) was used for the supportive analysis of tumour response data, ORR, DOR and PFS based on investigator assessments and for analysis of OS.

The **Efficacy Analysis Set (EAS)** is a subset of the FAS-NSCLC and consists of ALK-positive NSCLC across all doses who received the first dose of ceritinib at least 18 weeks prior to analysis cut-off date. The EAS was the primary data set used for the analysis of tumour response data (ORR, DOR and PFS based on investigator assessment) and for the analysis of OS.

The **Central Efficacy Analysis Set (CEAS)** is a subset of the EAS and consists of ALK-positive NSCLC patients across all doses:

- Who received the first dose of ceritinib at least 18 weeks prior to the analysis cut-off date, and
- For whom EITHER the baseline scan and at least one post-baseline scan were sent to and could be read by the BIRC OR no post-baseline scan was performed in the study due to early death or discontinuation.

This was used for the analysis of tumour response data based on independent central review assessment.

The **Safety Set** consists of all patients (including NSCLC and non-NSCLC) who received at least one dose of ceritinib. This was used for all safety analyses with the exception of the analyses based on DLTs, which used the dose-determining set.

Sample size

Dose-escalation phase

No formal statistical power calculations to determine sample size were performed for this study. It was estimated that 40 patients would be enrolled in the dose-escalation phase including at least 6 patients treated at the MTD level. The actual number of patients would depend on the number of dose levels/cohorts tested. Based on the simulation study to evaluate operating characteristics of the Bayesian logistic regression model (BLRM), at least 21 patients were expected to be treated in the dose-escalation phase for the model to have reasonable operating characteristics relating to its MTD recommendation.

Expansion phase

During the expansion phase, up to 310 patients could be enrolled (including all patients treated at the RD during the dose-escalation phase who were eligible for the safety set) with at least 25 and up to 100 patients in each of NSCLC arms (Arms 1A, 1B and 2), and approximately 10 patients in Arm 3.

Statistical methods

The primary endpoints used to evaluate the anti-tumour activity of ceritinib were ORR and DOR as assessed by the investigator per RECIST 1.0. ORR and DOR were both defined similarly to the A2201 study. The ORR was estimated and 95% CIs based on the exact binomial distribution were presented. The DOR was described using Kaplan-Meier methods.

Waterfall graphs were used to depict the anti-tumour activity. These plots display the best percentage change from baseline in the sum of the longest diameter of all target lesions for each patient and were presented for patients with ALK-positive NSCLC in the 750 mg dose group by population subgroups.

Additional efficacy endpoints were PFS per RECIST 1.0 and OS. The definition of PFS and OS was the same as the A2201 study and were described using Kaplan-Meier method.

Table 10 summarises the statistical methods used for the efficacy outcomes including primary analyses, supportive analyses and secondary analyses.

Table 10: Analyses of anti-tumour activity of ceritinib and OS for each treatment dose group, patient population and analysis set for ALK-positive NSCLC

Endpoint	Treatment dose group	Population (subgroup)	Analysis Set
Primary analyses			
ORR (confirmed PR or CR) by Investigator Assessment DOR by Investigator Assessment	750 mg	–NSCLC with prior ALK inhibitor –NSCLC with PD during treatment with last prior ALK inhibitor therapy (or within 2 weeks of the last dose) –NSCLC without PD during treatment with (or within 2 weeks of the last dose of) last prior ALK inhibitor therapy – NSCLC ALK inhibitor naïve –All NSCLC	EAS
Supportive analyses			
ORR (confirmed PR or CR) by BIRC Assessment DOR by BIRC Assessment	750 mg	As for primary analyses	CEAS
Key secondary analyses			
PFS by Investigator Assessment OS	750 mg	As for primary analyses	EAS
Other secondary analyses			
ORR (confirmed PR or CR) by Investigator Assessment	750 mg	Each of Arm 1A, Arm 1B, and NSCLC with prior crizotinib therapy	EAS
	Each of 50 mg to 750 mg doses	All NSCLC patients	EAS
DOR by Investigator Assessment PFS by Investigator Assessment OS	Same treatment dose groups and patient populations as for ORR other secondary analyses		EAS
ORR (confirmed PR or CR) by BIRC Assessment DOR by BIRC Assessment PFS by BIRC Assessment	Same treatment dose groups and patient populations as for ORR other secondary analyses		CEAS
ORR (confirmed PR or CR) by Investigator Assessment DOR by Investigator Assessment PFS by Investigator Assessment OS	Same treatment dose groups and patient populations as for ORR primary and other secondary analyses		FAS - NSCLC
Dose-escalation and expansion phases combined for the 750 mg dose group. Arms 1A+1B = NSCLC patients previously treated with an ALK inhibitor			

Participant flow

A total of 304 patients with locally advanced or metastatic, ALK-positive tumours were enrolled in Study X2101 (59 in the dose-escalation and 245 in the expansion phases). Among them, 290 were

patients with ALK-positive NSCLC; of these 246 patients were treated at the RD of ceritinib (750 mg).

The participant flow is illustrated for both the dose-escalation phase and expansion phase in Figure 9 and Figure 10.

Figure 9: Patient flow in the dose-escalation phase

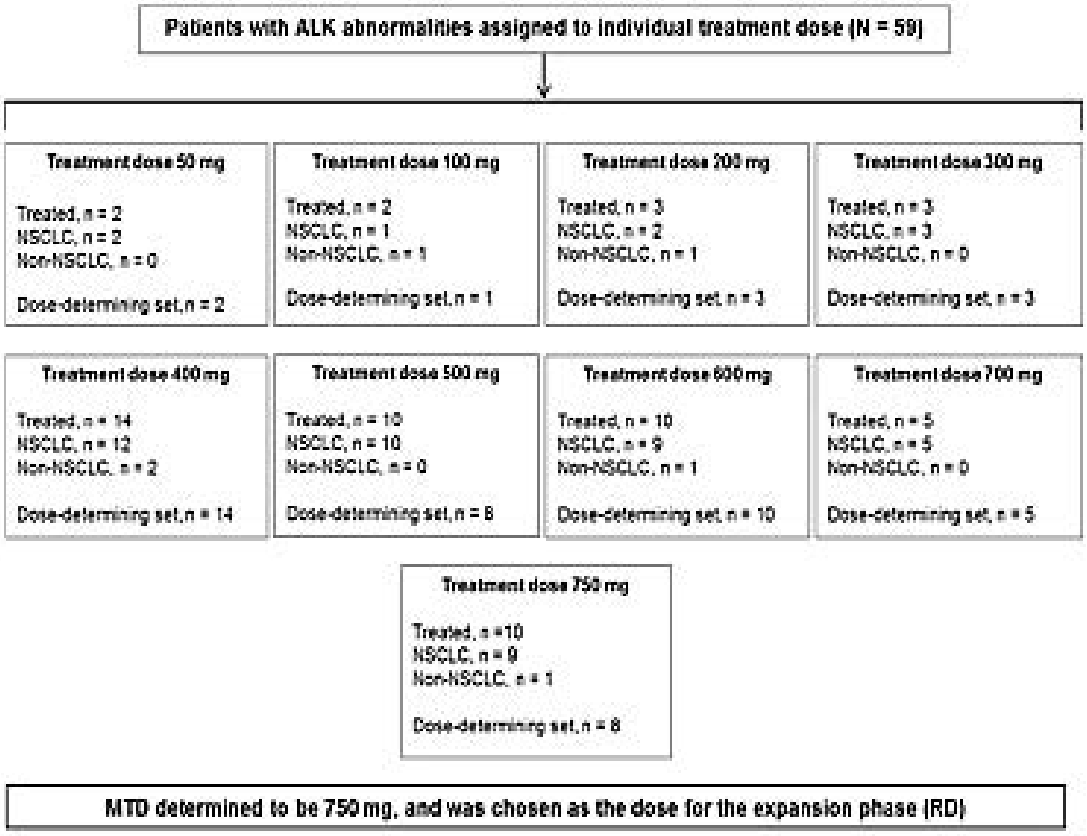
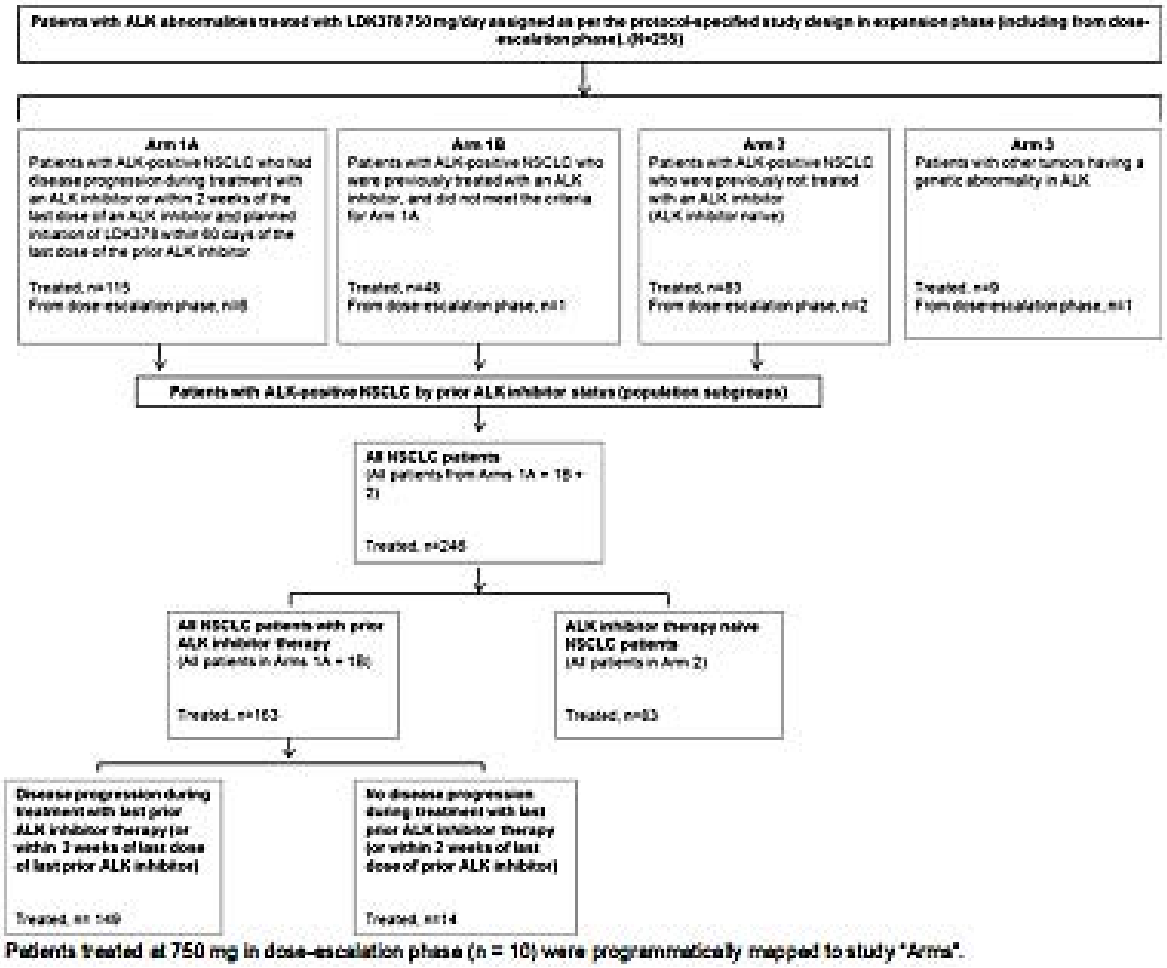


Figure 10: Patient flow for the 750 mg treatment dose group



Major protocol violations/deviations

Frequency counts and percentages of patients in the FAS with any protocol deviations (inclusion/exclusion criteria not met, key procedures not performed as per protocol, study drug deviation, non-compliance with assessments use of prohibited concomitant medication) were tabulated by the deviation category.

All patients (NSCLC and non-NSCLC) – by treatment dose group

At least one protocol deviation was reported in 24% of the 304 patients treated with at least one dose of ceritinib. The deviation categories reported were: deviations in treatment where patients did not take ceritinib dosing as per protocol (9.2%, 28 patients), use of prohibited concomitant medications (8.2%, 25 patients), deviations in inclusion/exclusion criteria (3.6%, 11 patients), key procedures not performed as per protocol (3.3%, 10 patients) and subject not withdrawn as per the protocol (0.3%, 1 patient). None of the patients with protocol deviations were excluded from the analyses.

NSCLC patients at 750 mg – by prior ALK inhibitor status

Protocol deviations were reported in 23.2% of the 246 ALK-positive NSCLC patients at 750 mg. The deviation categories reported were: use of prohibited concomitant medications (8.9%, 22 patients), deviations in treatment where patients did not take ceritinib dosing as per protocol (8.1%, 20 patients), deviations in selection criteria (3.3%, 8 patients – for 2 patients ALK expression/translocation was detected by a method other than FISH and 1 patient did not have a tumor with evidence of ALK expression), key procedures not performed as per protocol (2.8%, 7 patients) and subject not withdrawn as per the protocol (0.4%, 1 patient). None of the patients with deviations were excluded from the analyses. No imbalances were evident across the

population subgroups.

Comments: The evaluator did not consider any of those protocol deviations to be major, with the exception of inclusion of patients without protocol defined ALK positivity. This is unlikely to have a major impact on the overall efficacy results.

Baseline data

The evaluator will present the data for the NSCLC patients who were treated with 750 mg of ceritinib using the FAS dataset (n=246), as this is the most relevant for the efficacy outcome for the indication sought by the sponsor.

Following tables summarises the demographic (Table 11) and disease (Table 12) characteristics and prior anti-cancer therapy details (Table 13).

Table 11: Demographic characteristics in NSCLC patients at 750 mg, by prior ALK inhibitor status (FAS – NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			**NSCLC ALK inhibitor naïve patients N=83**	**All NSCLC patients[4] N=246**
	All patients with prior ALK inhibitor[1] N=163	Patients with PD during last prior ALK inhibitor[2] N=149	Patients without PD during last prior ALK inhibitor[3] N=14		
Age (years)					
N	163	149	14	83	246
Mean (SD)	51.5 (11.63)	51.6 (11.6)	51.2 (12.42)	53.9 (12.03)	52.3 (11.80)
Median	52	51	54	55	53
Min-max	24-80	24-80	29-66	22-80	22-80
Sex – n (%)					
Male	75 (46.0)	71 (47.7)	4 (28.6)	39 (47.0)	114 (46.3)
Female	88 (54.0)	78 (52.3)	10 (71.4)	44 (53.0)	132 (53.7)
Predominant race – n (%)					
Caucasian	108 (66.3)	100 (67.1)	8 (57.1)	48 (57.8)	156 (63.4)
Black	4 (2.5)	3 (2.0)	1 (7.1)	0	4 (1.6)
Asian	47 (28.8)	42 (28.2)	5 (35.7)	35 (42.2)	82 (33.3)
Native American	1 (0.6)	1 (0.7)	0	0	1 (0.4)
Other	3 (1.8)	3 (2.0)	0	0	3 (1.2)
Ethnicity – n (%)					
Hispanic/Latino	16 (9.8)	14 (9.4)	2 (14.3)	10 (12.0)	26 (10.6)
Chinese	12 (7.4)	12 (8.1)	0	5 (6.0)	17 (6.9)
Indian (Indian subcontinent)	3 (1.8)	2 (1.3)	1 (7.1)	3 (3.6)	6 (2.4)
Mixed ethnicity	1 (0.6)	1 (0.7)	0	0	1
Other	131 (80.4)	120 (80.5)	11 (78.6)	65 (78.3)	196 (79.7)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients N=83	All NSCLC patients[4] N=246
	All patients with prior ALK inhibitor[1] N=163	Patients with PD during last prior ALK inhibitor[2] N=149	Patients without PD during last prior ALK inhibitor[3] N=14		
BMI (kg/m²)					
N	162	148	14	83	245
Mean (SD)	25.1 (4.58)	25.1 (4.63)	24.8 (4.24)	23.6 (3.90)	24.6 (4.41)
Median	24.6	24.7	24.3	23.0	24.3
Min-max	16.6 – 42.5	16.6 – 42.5	19.7 – 37.4	16.7 – 41.8	16.6 – 42.5
ECOG performance status – n (%)					
0	38 (23.3)	34 (22.8)	4 (28.6)	25 (30.1)	63 (25.6)
1	104 (63.8)	96 (64.4)	8 (57.1)	51 (61.4)	155 (63.0)
2	20 (12.3)	19 (12.8)	1 (7.1)	7 (8.4)	27 (11.0)
> 2	1 (0.6)	0	1 (7.1)	0	1 (0.4)
Smoking history – n (%)					
Never smoked	109 (66.9)	100 (67.1)	9 (64.3)	44 (53.0)	153 (62.2)
Ex-smoker	49 (30.1)	44 (29.5)	5 (35.7)	38 (45.8)	87 (35.4)
Current smoker	5 (3.1)	5 (3.4)	0	1 (1.2)	6 (2.4)

This table presents data for NSCLC patients at 750 mg (750 mg treatment dose group from FAS-NSCLC, a subset of FAS). [1] All patients with prior ALK inhibitor were treated with crizotinib; in addition 5 patients received CH5424802 as their last prior ALK inhibitor [2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [4]All patients include all ALK-positive NSCLC patients at ceritinib 750 mg.

Table 12: Disease characteristics in NSCLC patients from the 750 mg/day treatment dose group, by prior ALK inhibitor status (FAS – NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients N=83	All NSCLC patients [4] N=246
	All patients with prior ALK inhibitor [1] N=163	Patients with PD during last prior ALK inhibitor [2] N=149	Patients without PD during last prior ALK inhibitor [3] N=14		
Details of tumour histology/cytology – n (%)					
Adenocarcinoma	152 (93.3)	139 (93.3)	13 (92.9)	76 (91.6)	228 (92.7)
Squamous cell carcinoma	3 (1.8)	3 (2.0)	0	0	3 (1.2)
Adenosquamous cell carcinoma	2 (1.2)	2 (1.3)	0	1 (1.2)	3 (1.2)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients N=83	All NSCLC patients [4] N=246
	All patients with prior ALK inhibitor [1] N=163	Patients with PD during last prior ALK inhibitor [2] N=149	Patients without PD during last prior ALK inhibitor [3] N=14		
Large cell carcinoma	2 (1.2)	1 (0.7)	1 (7.1)	0	2 (0.8)
Spindle cell	0	0	0	1 (1.2)	1 (0.4)
Other	2 (1.2)	2 (1.3)	0	5 (6.0)	7 (2.8)
Missing	2 (1.2)	2 (1.3)	0	0	2 (0.8)
Histological grade – n (%)					
Well differentiated	7 (4.3)	7 (4.7)	0	3 (3.6)	10 (4.1)
Moderately differentiated	15 (9.2)	15 (10.1)	0	9 (10.8)	24 (9.8)
Poorly differentiated	56 (34.4)	53 (35.6)	3 (21.4)	24 (28.9)	80 (32.5)
Undifferentiated	3 (1.8)	3 (2.0)	0	1 (1.2)	4 (1.6)
Unknown	82 (50.3)	71 (47.7)	11 (78.6)	46 (55.4)	128 (52.0)
Disease burden based on investigator assessment [5]					
N	163	149	14	83	246
Mean (SD)	8.98 (6.53)	9.01 (6.59)	8.68 (6.03)	8.62 (6.07)	8.86 (6.36)
Median	7.9	8.0	7.2	6.6	7.5
Min-max	1.0 – 42.4	1.0 – 42.4	1.4 – 25.1	1.0 – 42.4	
Disease burden based on BIRC assessment [5]					
N	140	128	12	75	215
Mean (SD)	9.85 (7.52)	10.09 (7.69)	7.27 (5.00)	10.66 (7.81)	10.13 (7.62)
Median	8.1	8.3	5.8	8.3	8.2
Min-max	1.04 – 34.3	1.4 – 34.3	1.7 – 15.2	1.5 – 34.2	1.4 – 34.3
Site of metastases (≥ 10% in all patients) – n (%)					
Lung	111 (68.11)	103 (69.1)	8 (57.1)	62 (74.7)	173 (70.3)
Thoracic lymph node	89 (54.6)	83 (55.7)	6 (42.9)	43 (51.8)	132 (53.7)
Brain	97 (59.5)	88 (59.1)	9 (64.3)	26 (31.3)	123 (50.0)
Liver	68 (41.7)	63 (42.3)	5 (35.7)	30 (36.1)	98 (39.8)
Bone	69	62	7 (50.0)	26	95

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor or naïve patients N=83	All NSCLC patients [4] N=246
	All patients with prior ALK inhibitor [1] N=163	Patients with PD during last prior ALK inhibitor [2] N=149	Patients without PD during last prior ALK inhibitor [3] N=14		
	(42.3)	(41.6)		(31.3)	(38.6)
Pleura	41 (25.2)	38 (25.5)	3 (21.4)	24 (28.9)	65 (26.4)
Pleural effusion (malignant)	26 (16.0)	23 (15.4)	3 (21.4)	15 (18.1)	41 (16.7)
Para-aortic abdominal lymph nodes	20 (12.3)	20 (13.4)	0	17 (20.5)	37 (15.0)
Cervical lymph nodes	23 (14.1)	23 (15.4)	0	4 (4.8)	27 (11.0)
Adrenal	15 (9.2)	12 (8.1)	3 (21.4)	10 (12.0)	25 (10.2)
other	31 (19.0)	30 (20.1)	1 (7.1)	19 (22.9)	50 (20.3)
Time from initial diagnosis to first dose of study drug (months) – n (%)					
N	163	149	14	83	246
Mean (SD)	28.59 (24.94)	29.00 (25.45)	24.26 (18.72)	15.52 (20.34)	24.18 (24.25)
Median	21.2	22.2	18.6	8.1	18.0
Min-max	2.4 – 174.2	2.4 – 174.2	7.3 – 66.9	1.0 – 109.3	1.0 – 174.2
Time from most recent relapse to first dose of study drug (months) – n (%)					
N	159	145	14	80	239
Mean (SD)	1.41 (1.95)	1.43 (2.01)	1.15 (1.06)	1.96 (3.41)	1.59 (2.54)
Median	1.0	1.0	0.7	1.1	1.0
Min-max	0.1 – 17.2	0.1 – 17.2	0.1 – 4.1	0.1 – 19.3	0.1 – 19.3

This table presents data for NSCLC patients at 750 mg (750 mg treatment dose group from FAS-NSCLC, a subset of FAS). [1] All patients with prior ALK inhibitor were treated with crizotinib; in addition 5 patients received CH5424802 as their last prior ALK inhibitor. [2] Includes patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [3] Patients who did not have PD during treatment with (or within 2 weeks of last dose) last prior ALK inhibitor therapy. [4] Patients include all ALK-positive NSCLC patients at 750 mg. [5] Disease burden = Sum of longest diameter at baseline for target lesions.

Table 13: Prior anti-cancer medications in NSCLC patients from the 750 mg treatment dose group, by prior ALK inhibitor status (FAS – NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients N=83 n (%)	All NSCLC patients [4] N=246 n (%)
	All patients with prior ALK inhibitor [1] N=163 n (%)	Patients with PD during last prior ALK inhibitor [2] N=149 n (%)	Patients without PD during last prior ALK inhibitor [3] N=14 n (%)		
Prior antineoplastic medications					
No	0	0	0	16 (19.3)	16 (6.5)
Yes	163 (100.0)	149 (100.0)	14 (100.0)	67 (80.7)	230 (93.5)
Setting at last medication					
Adjuvant	2 (1.2)	2 (1.3)	0	2 (2.4)	4 (1.6)
Prevention	0	0	0	1 (1.2)	1 (0.4)
Therapeutic	161 (98.8)	147 (98.7)	14 (100.0)	64 (77.1)	225 (91.5)
Number of prior regimens					
0	0	0	0	16 (19.3)	16 (6.5)
1	26 (16.0)	23 (15.4)	3 (21.4)	38 (45.8)	64 (26.0)
2	45 (27.6)	43 (28.9)	2 (14.3)	16 (19.3)	61 (24.8)
3	35 (21.5)	32 (21.5)	3 (21.4)	7 (8.4)	42 (17.1)
> 3	57 (35.0)	51 (34.2)	6 (42.9)	6 (7.2)	63 (25.6)
Prior ALK inhibitor					
Yes	163 (100.0)	149 (100.0)	14 (100.0)	0	163 (66.3)
No	0	0	0	83 (100.0)	83 (33.7)
Reason for discontinuation of last prior ALK inhibitor [5]					
Adverse event	4 (2.5)	0	4 (28.6)	-	4 (2.5)
Disease progression	150 (92.0)	144 (96.6)	6 (42.9)*	-	150 (92.0)
Completed prescribed regimen	1 (0.6)	1 (0.7)	0	-	1 (0.6)
Other	8 (4.9)	4 (2.7)	4 (28.6)	-	8 (4.9)
Prior anti-cancer medications					

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients N=83 n (%)	All NSCLC patients [4] N=246 n (%)
	All patients with prior ALK inhibitor [1] N=163 n (%)	Patients with PD during last prior ALK inhibitor [2] N=149 n (%)	Patients without PD during last prior ALK inhibitor [3] N=14 n (%)		
Crizotinib	163 (100.0)	149 (100.0)	14 (100.0)	0	163 (66.3)
Bevacizumab	39 (23.9)	36 (24.2)	3 (21.4)	5 (6.0)	44 (17.9)
Docetaxel	39 (23.9)	38 (25.5)	1 (7.1)	14 (16.9)	53 (21.5)
Erlotinib	32 (19.6)	31 (20.8)	1 (7.1)	7 (8.4)	39 (15.9)
Gefitinib	6 (3.7)	6 (4.0)	0	4 (4.8)	10 (4.1)
Gemcitabine	38 (23.3)	35 (23.5)	3 (21.4)	17 (20.5)	55 (22.4)
Paclitaxel	33 (20.2)	27 (18.1)	6 (42.9)	13 (15.7)	46 (18.7)
Pemetrexed	119 (73.0)	110 (73.8)	9 (64.3)	46 (55.4)	165 (67.1)
Vinorelbine	22 (13.5)	20 (13.4)	2 (14.3)	7 (8.4)	29 (11.8)
Any platinum compounds (total)	133 (81.6)	122 (81.9)	11 (78.6)	65 (78.3)	198 (80.5)
Carboplatin	78 (47.9)	71 (47.7)	7 (50.0)	21 (25.3)	99 (40.2)
Cisplatin	82 (50.3)	74 (49.7)	8 (57.1)	49 (59.0)	131 (53.3)

This table presents data for NSCLC patients at 750 mg (750 mg treatment dose group from FAS-NSCLC, a subset of FAS). *6 patients progressed from 16 to 48 days after discontinuation of the last prior ALK inhibitor, with a reason for discontinuation being PD. In 4 cases the complete date of discontinuation is known and confirmed by the investigator; in 2 cases the complete date is not known and the date of PD was imputed using a predefined algorithm. [1] All patients with prior ALK inhibitor were treated with crizotinib; in addition 5 patients received CH5424802 as their last prior ALK inhibitor. [2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [4] All patients include all ALK-positive NSCLC patients at ceritinib 750 mg. [5] The percentage calculation is based on the patients with prior ALK inhibitor.

Results for the primary efficacy outcome

The subjects recruited in this trial consisted of a heavily pre-treated population with 163 patients previously exposed to an ALK inhibitor. Of them 121 subjects received the first dose of ceritinib at least 18 weeks prior to the cut-off date, being the target population of this application. Table 14 details the number of patients analysed for efficacy.

Table 14: Analysis sets in NSCLC patients at 750 mg, by prior ALK inhibitor status (Study X2101-FAS-NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naive patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor [2]	Patients without PD during last prior ALK inhibitor [3]		
	N=163	N=149	N=14	N=83	N=246
	n (%)	n (%)	n (%)	n (%)	n (%)
Full analysis set (FAS-NSCLC 750mg)	163 (100)	149 (100)	14 (100)	83 (100)	246 (100)
Efficacy analysis set (EAS-NSCLC 750 mg)	121 (74.2)	110 (73.8)	11 (78.6)	59 (71.1)	180 (73.2)
Central efficacy analysis set (CEAS-NSCLC 750 mg)	118 (72.4)	108 (72.5)	10 (71.4)	59 (71.1)	177 (72.0)
Safety set (Safety set-NSCLC 750 mg)	163 (100)	149 (100)	14 (100)	83 (100)	246 (100)
Pharmacokinetic analysis set (PAS-NSCLC 750 mg)	160 (98.2)	146 (98.0)	14 (100.0)	83 (100.0)	243 (98.8)

This table presents data for patients with NSCLC treated with LDK378 750 mg/day (750 mg/day treatment dose group from FAS-NSCLC, a subset of FAS).
[1] All patients with prior ALK inhibitor were treated with crizotinib, in addition 5 patients received CH5424802 as their last prior ALK inhibitor.
[2] Includes patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy
[3] Includes patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[4] All patients include all ALK-positive NSCLC patients treated with LDK378 750 mg/day.

Of the 246 ALK-positive NSCLC patients at 750 mg, 180 patients (73.2%) were included in the EAS-NSCLC 750 mg treatment dose group. The remaining 66 patients were not included in the EAS because they started treatment with ceritinib less than 18 weeks prior to the analysis cut-off date. The median duration of follow-up for the 180 patients in the EAS-NSCLC 750 mg treatment dose group was 6.0 months (range: 0.1 to 16.5).

ORR by Investigator assessment in NSCLC patients at 750 mg – by prior ALK inhibitor status

The ORR for all patients with prior ALK inhibitor assessed by the investigator was 55.4%. Table 15 shows the detail of the BOR.

Table 15: Summary of best overall response based on investigator assessment in NSCLC patients at 750 mg, by prior ALK inhibitor status (EAS-NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor[2]	Patients without PD during last prior ALK inhibitor[3]		
	N=121	N=110	N=11	N=59	N=180
	n (%)	n (%)	n (%)	n (%)	n (%)
Best overall response					
Complete response (CR)	2 (1.7)	2 (1.8)	0	1 (1.7)	3 (1.7)
Partial response (PR)	65 (53.7)	61 (55.5)	4 (36.4)	40 (67.8)	105 (58.3)
Stable disease (SD)	23 (19.0)	22 (20.0)	1 (9.1)	13 (22.0)	36 (20.0)
Progressive disease (PD)	13 (10.7)	12 (10.9)	1 (9.1)	0	13 (7.2)
Unknown	18 (14.9)	13 (11.8)	5 (45.5)	5 (8.5)	23 (12.8)
Overall response rate (ORR) (CR or PR),	67 (55.4)	63 (57.3)	4 (36.4)	41 (69.5)	108 (60.0)
95% CI	[46.1, 64.4]	[47.5, 66.7]	[10.9, 69.2]	[56.1, 80.8]	[52.4, 67.2]

This table presents data for ALK-positive NSCLC patients at 750 mg treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, **EAS-NSCLC 750 mg group.**
[1] All patients with prior ALK inhibitor were treated with crizotinib, in addition 5 patients received CH5424802 as their last prior ALK inhibitor.
[2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[4] All patients include all ALK-positive NSCLC patients treated with LDK378 750 mg/day
Best overall response is based on Investigator's assessment of disease status using RECIST 1.0 criteria
CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.
Exact binomial 95% Confidence Interval

DOR by Investigator assessment in NSCLC patients at 750 mg – by prior ALK inhibitor status

Based on investigator assessment, the estimated median DOR was 9.69 months (95% CI: 6.93, 11.40) for the 108 ALK-positive NSCLC patients with a confirmed CR or PR (60%, 108/180). For the population relevant to the indication proposed here, that is, 67 patients treated with prior ALK inhibitor with a confirmed PR or CR, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12). Table 16 summarises the DOR based on investigator assessment.

Table 16: Analyses of duration of response based on investigator assessment in NSCLC patients at 750 mg, by prior ALK inhibitor status (EAS-NSCLC 750 mg, confirmed PR or CR)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor [2]	Patients without PD during last prior ALK inhibitor [3]		
	N=67	N=63	N=4	N=41	N=108
No. of events, n (%)	29 (43.3)	28 (44.4)	1 (25.0)	8 (19.5)	37 (34.3)
Progression	29 (43.3)	28 (44.4)	1 (25.0)	8 (19.5)	37 (34.3)
Death	0	0	0	0	0
No. of patients censored	38 (56.7)	35 (55.6)	3 (75.0)	33 (80.5)	71 (65.7)
Kaplan-Meier estimates (%) **DOR rate [95% CI]** at:					
3 months	94.7 [84.4, 98.3]	94.3 [83.3, 98.1]	100 [100, 100]	94.2 [78.7, 98.5]	94.5 [87.3, 97.7]
6 months	58.5 [43.5, 70.8]	56.1 [40.7, 68.9]	100 [100, 100]	71.1 [49.8, 84.6]	63.2 [51.2, 72.9]
12 months	9.0 [0.7, 31.7]	0.0 [NE, NE]	50.0 [0.6, 91.0]	71.1 [49.8, 84.6]	21.2 [4.9, 45.0]
25th percentile (month) [95%CI]	4.17 [3.45, 5.42]	4.17 [3.35, 5.42]	7.85 [7.85, NE]	5.55 [3.25, NE]	4.50 [4.14, 5.52]
Median (month) [95%CI]	7.39 [5.42,10.12]	7.29 [5.09, 10.12]	NE [7.85, NE]	NE [5.55, NE]	9.69 [6.93,11.40]
75th percentile (month) [95%CI]	11.04 [9.69, NE]	10.12 [9.69, 11.40]	NE [7.85, NE]	NE [NE, NE]	11.40 [10.12, NE]

This table presents data for NSCLC patients at 750 mg (who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, **EAS-NSCLC 750 mg group**.)
[1] All patients with prior ALK inhibitor were treated with crizotinib.
[2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[4] All patients include all ALK-positive NSCLC patients treated with LDK378 750 mg/day
% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
N : Total number of patients included in the analysis.

Results for other efficacy outcomes

ORR by BIRC assessment as supportive analysis

At the time of data cut-off, 177 out of the 180 patients (98.3%) in the EAS-NSCLC 750 mg group were included in the CEAS-NSCLC 750 mg group. The assessment of response by the BIRC was supportive of the results obtained by Investigator assessment. Based on the BIRC assessments, amongst the 177 patients in the CEAS, 1 patient achieved a best overall response of CR and 89 patients achieved a best overall response of PR resulting in an ORR of 50.8% (95% CI: 43.2, 58.4). More relevant to this application, in the 118 patients treated with prior ALK inhibitor the ORR was 44.1% (95% CI: 34.9%, 53.5%). Of note, most of these patients (n=108) had PD during treatment with the last prior ALK inhibitor and the ORR in these patients was 46.3% (95% CI: 36.7, 56.2).

DOR by BIRC assessment as supportive analysis

Based on BIRC assessment, the estimated median DOR was 9.69 months (95% CI: 5.98, NE) for the 90 ALK-positive NSCLC patients with a confirmed CR or PR. In addition, in the 52 patients treated with a prior ALK inhibitor with a confirmed PR or CR, the estimated median DOR was 7.06 months (95% CI: 4.80, NE). All these patients had received prior treatment with crizotinib. Of note, most of these patients (n=50) had PD during treatment with the last prior ALK inhibitor and the median DOR in these patients was: 7.06 months (95% CI: 5.52, NE).

PFS as key secondary efficacy outcome

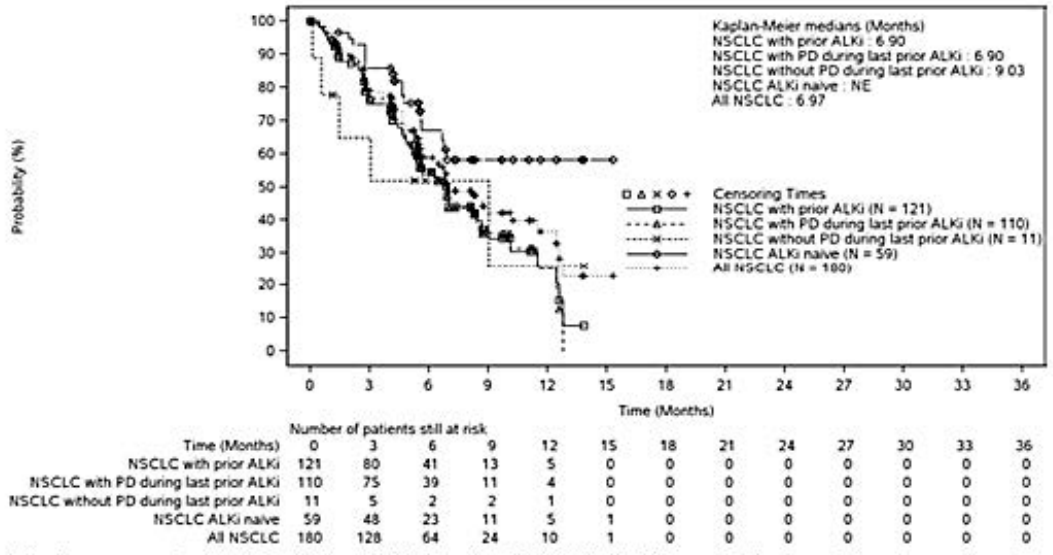
In the 180 patients with ALK-positive NSCLC at 750 mg, at the time of the data cut-off date, based

on the Investigator assessments, 82 PFS events (71 progressions and 11 deaths) were observed, and the median PFS was 6.97 months (95% CI: 6.21, 10.12) with 54.4% patients censored (Figure 11). Further, the estimated PFS rate was 58.7% at 6 months and 36.6% at 12 months.

The primary reason for censoring patients in the PFS analyses based on Investigator assessment was that the patients did not have a PFS event at the time of the analysis data cutoff (in 77.6% of the patients). The other reasons for censoring patients were initiation of new anticancer therapy (7.1%), withdrew consent (6.1%) and adequate assessment no longer available (6.1%), and event documented after two or more missing tumor assessment (3.1%).

The estimated median PFS was 6.90 months (95% CI: 5.39, 8.67) in patients previously treated with an ALK inhibitor, while the median PFS was not reached in the ALK inhibitor naïve patients (95% CI: 6.67, NE).

Figure 11: Kaplan-Meier plot of PFS based on investigator assessment in NSCLC patients at 750 mg, by prior ALK inhibitor status (EAS-NSCLC 750 mg)

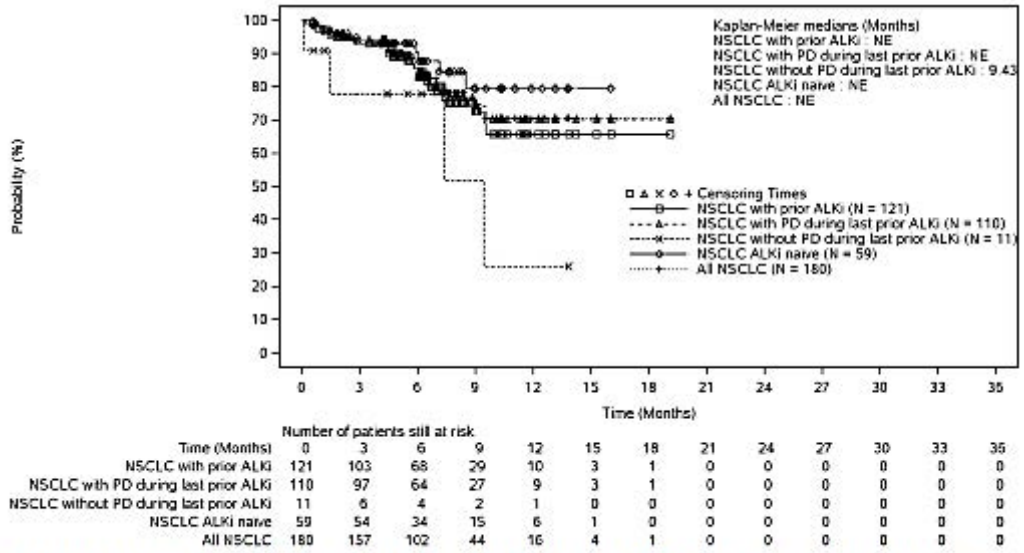


This figure presents data for patients with ALK-positive NSCLC in the 750 mg/day treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, **EAS-NSCLC 750 mg group**.

OS as key secondary efficacy outcome

At the time of the analysis data cut-off date, 33 deaths were reported in the 180 ALK-positive NSCLC patients at 750 mg. The median OS was not reached as the majority (81.7%, 147) of the patients were censored including 117 who were alive and 30 who had been lost to follow-up at the time of analysis cut-off date (Figure 12). The probability of being alive was 86.3% at 6 months and 70.6% at 12 months. The probability of being alive at 12 months was 65.7% in patients treated with a prior ALK inhibitor. No conclusion could be drawn due to the immature nature of the OS data.

Figure 12: Kaplan-Meier plot of OS in NSCLC patients at 750 mg, by prior ALK inhibitor status (EAS-NSCLC 750 mg)



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36
NSCLC with prior ALKi	121	103	68	29	10	3	1	0	0	0	0	0	0
NSCLC with PD during last prior ALKi	110	97	64	27	9	3	1	0	0	0	0	0	0
NSCLC without PD during last prior ALKi	11	6	4	2	1	0	0	0	0	0	0	0	0
NSCLC ALKi naive	59	54	34	15	6	1	0	0	0	0	0	0	0
All NSCLC	180	157	102	44	16	4	1	0	0	0	0	0	0

This figure presents data for patients with ALK-positive NSCLC in the 750 mg/day treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, **EAS-NSCLC 750 mg group.**

Subgroup analyses

Analyses of ORR were performed in subgroups of patients based on demographic characteristics and prognostic factors, (Table 17), by brain metastases at baseline (Table 18) and by prior ALK inhibitor history (Table 19). The submitted efficacy seems consistent across all patients' subgroups although some of the analyses appear immature.

Table 17: ORR, DOR and PFS by investigator in NSCLC patients at 750 mg by demographic characteristics and prognostic factors (EAS-NSCLC 750 mg)

Subgroups	n	ORR (95% CI) n (%)	n[#]	Median DOR months (95% CI)	n	Median PFS months (95% CI)
Region						
North America	81	55.6 (44.1, 66.6)	45	7.39 (4.50, 11.04)	81	6.90 (5.32, 9.03)
Europe	48	56.3 (41.2, 70.5)	27	11.40 (4.21, NE)	48	6.67 (4.63, NE)
Asia Pacific	51	70.6 (56.2, 82.5)	36	10.12 (7.29, NE)	51	11.50 (6.77, NE)
Age						
< 65 years	151	61.6 (53.3, 69.4)	93	7.85 (6.93, 11.40)	151	6.97 (5.68, 10.12)
≥ 65 years	29	51.7 (32.5, 70.6)	15	10.12 (4.14, NE)	29	11.50 (4.63, NE)
Gender						
Male	79	63.3 (51.7, 73.9)	50	9.69 (7.29, 11.04)	79	8.67 (6.21, 12.45)
Female	101	57.4 (47.2, 67.2)	58	7.85 (5.09, NE)	101	6.77 (5.32, NE)
Race*						
Caucasian	118	56.8 (47.3, 65.9)	67	6.93 (4.50, 11.40)	118	6.67 (5.32, 8.41)
Asian	55	69.1 (55.2, 80.9)	38	10.12 (7.29, NE)	55	11.50 (6.90, NE)
ECOG status						
0	49	73.5 (58.9, 85.1)	36	NE (9.69, NE)	49	12.45 (6.97, NE)
≥ 1	131	55.0 (46.0, 63.7)	72	7.29 (5.42, 11.04)	131	6.21 (5.32, 8.41)
Disease burden						
Baseline SLD for target lesion < median	90	62.2 (51.4, 72.2)	56	NE (7.29, NE)	90	12.45 (6.90, NE)
Baseline SLD for target lesion ≥ median	90	57.8 (46.9, 68.1)	52	6.93 (5.09, 11.04)	90	6.47 (4.73, 7.00)
ALK positive by FISH, using Vysis probe and positivity definition ≥ 15%						
Met the criteria	129	58.9 (49.9, 67.5)	76	9.69 (6.93, 11.40)	129	6.97 (6.21, 10.12)
Did not meet the criteria	50	64.0 (49.2, 77.1)	32	NE (4.17, NE)	50	8.67 (4.73, NE)

*The number of patients in the "Black" (n=4) and "Other" (n=3) ethnicities was too low to enable meaningful comparisons.
[#]EAS - NSCLC 750 mg patients with confirmed CR or PR

Table 18: ORR, DOR and PFS in NSCLC patients at 750 mg, by brain metastases at baseline (EAS-NSCLC 750 mg)

Efficacy parameters	Brain metastases at baseline		No brain metastases at baseline	
	n	Parameter (95% CI)	n	Parameter (95% CI)
ORR, n (%)				
By investigator assessment	95	54.7 (44.2, 65.0)	85	65.9 (54.8, 75.8)
By BIRC assessment	93	45.2 (34.8, 55.8)	84	57.1 (45.9, 67.9)
Median DOR, months				
By investigator assessment	52	7.39 (5.45, 11.04)	56	10.12 (5.52, NE)
By BIRC assessment	42	9.69 (5.62, NE)	48	8.31 (5.91, NE)
Median PFS, months				
By investigator assessment	95	6.90 (5.39, 9.03)	85	11.50 (5.62, NE)
By BIRC assessment	93	8.21 (5.55, 11.07)	84	9.69 (6.97, NE)

The ORR, DOR and PFS is based on systemic response (all tumor lesions including brain) per RECIST

Table 19: ORR, DOR and PFS by investigator in NSCLC patients at 750 mg, by prior ALK inhibitor history (EAS-NSCLC 750 mg)

Subgroups	n	ORR (95% CI)	n*	Median DOR months (95% CI)	n	Median PFS months (95% CI)
Prior response to ALK inhibitors						
Yes	68	61.8% (49.2, 73.3)	42	7.29 (4.21, 11.04)	68	6.80 (5.32, 8.41)
No	53	47.2% (33.3, 61.4)	25	10.12 (4.50, 11.40)	53	6.90 (4.63, 12.78)
Time from last dose of last prior ALK inhibitor to first dose of LDK378						
≤ 2 months	92	57.6% (46.9, 67.9)	53	7.29 (5.09, 10.12)	92	6.97 (5.32, 10.12)
> 2 months and ≤ 4 months	15	40.0% (16.3, 67.7)	6	NE (4.01, NE)	15	5.39 (1.45, NE)
> 4 months	14	57.1% (28.9, 82.3)	8	7.85 (3.15, 7.85)	14	6.21 (4.17, 9.03)

* EAS - NSCLC 750 mg patients with confirmed CR or PR

Overall intracranial response rate (OIRR)

For all patients in the trial an OIRR of 45.5% (95% CI: 16.7, 76.6) was demonstrated. This is considered to be of significant clinical importance, but as only a small number of patients (11 out of 180) had brain metastases at baseline considered as target lesions, this needs to be interpreted with caution.

Comments: Again the data for patients with brain metastases in the PI differ to the information presented in Full Clinical Study Report of X2101.

7.1.2. Other efficacy studies

7.1.2.1. A2203

This is a Phase II, multicentre, single-arm study of oral ceritinib in crizotinib-naïve adult patients with ALK-activated NSCLC. This study [information redacted] primary analysis data cut-off date was [information redacted] June 2014. This study is currently ongoing. Patients were eligible if they have received prior treatment with cytotoxic chemotherapy (up to 3 lines) and following the release of Amendment 2 dated 27 August 2013, chemotherapy naïve patients were also enrolled into the study. All patients were then treated with ceritinib 750 mg orally on a once-daily dosing schedule. The primary objective of this study was the same as the Study A2201, which was to demonstrate the anti-tumour activity of ceritinib, as measured by ORR by investigator assessment.

While approximately 105 patients were planned to be enrolled, a total of 124 patients (FAS) were enrolled and treated with ceritinib from 41 centres across 16 countries (including Australia). All patients were ALK inhibitor naïve with metastatic disease and 122 patients were previously treated with at least one platinum-based regimen. The median duration of follow-up from the start of study drug to last contact date on or prior to the data cut-off date was 8.31 months. For FAS, the median age was 56 years and 96.8% had adenocarcinoma of the lung. The percentage of patients with brain metastases (40.3%) was higher than the average observed in patients with NSCLC. Most patients (92.7%) had been treated with 1 to 3 prior antineoplastic regimen and 5.6% of the patients were treated with > 3 prior regimens.

The study met its primary objective. In the FAS, there were 79 patients with a best overall response of CR or PR based on investigator assessment resulting in an ORR of 63.7% (90% CI: 57.6%, 68.7%). This was statistically significant at the one-sided 0.05 critical alpha level (one sided p <0.001, based on Simon's optimal two-stage design). The ORR was 58.9% based on BIRC assessment in the FAS. The estimated median DOR was 9.3 months (95% CI: 9.1, NE) in the 79 patients with a PR based on investigator assessment. Furthermore, the median PFS was 11.1 months (95% CI: 9.3 – NE) based on investigator assessment and median OS was not reached as most of the patients were censored.

Although not a primary endpoint, the brain metastases outcome were of interest in this study given the higher than average incidence, which probably reflects the biology of ALK-positive disease. In the FAS, 10 out of the 124 patients had brain metastases at baseline considered as target lesions by the investigator per RECIST v. 1.1 criteria. In these patients, the OIRR based on investigator assessment was 20% (95% CI: 2.5%, 55.6%).

Comments: The evaluator did not consider this trial to be pivotal given the study population differs to those sought for the indication by the sponsor. However, the treatment with ceritinib in this heavily pre-treated population (but ALK inhibitor naïve) was associated with a high rate of response, which further supports the molecularly targeted approach with ceritinib in ALK-positive NSCLC population.

7.1.2.2. X1101

This is a Phase I, multicentre, open-label dose escalation study of ceritinib, administered orally in Japanese patients with tumours characterised by genetic alterations in ALK. This study [information redacted] primary analysis data cut-off was 2 August 2013. The study is ongoing. It investigated the safety, PK, and preliminary anti-tumour activity. At least 3 but not more than 6 patients were to be enrolled per dose cohort, with at least 6 patients at the MTD/RD. Dose-escalation was guided by an adaptive BLRM employing the escalation with overdose control principle.

This study enrolled 19 patients and it is ongoing. As of the analysis cut-off date, a total of 19 patients enrolled in the dose-escalation phase received at least one dose of ceritinib: 300 mg/day (n=3), 450 mg/day (n=6), 600 mg/day (n=4), and 750 mg/day (n=6). All 19 patients had advanced or metastatic disease. Eighteen patients (94.7%) had NSCLC with ALK translocation and 1 patient (5.3%) had another tumour with an ALK alteration (inflammatory myofibroblastic tumour; IMT). Fifteen patients including the patient with IMT were treated with a prior ALK inhibitor (including crizotinib, CH5424802 or ASP3026) and 4 patients were ALK inhibitor naïve.

The efficacy analysis set (EAS) consisted of NSCLC patients who had received the first dose of ceritinib at least 18 weeks prior to the analysis cut-off date. Based on investigator assessment across all dose groups, ORR was documented at 100%, 50%, 50% and 40% at doses of 300, 450, 600 and 750 mg per day, respectively in all ALK-positive NSCLC patients. Of particular interest, 8 out of 14 patients with ALK-positive NSCLC previously treated with an ALK inhibitor had a confirmed PR. Responses were observed regardless of the type of prior ALK inhibitor.

Comments: The evaluator considered this study as a supportive study rather than pivotal, due to its small number of patients enrolled. However, the magnitude of benefit appears similar to the two previously described pivotal efficacy studies.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled analyses or meta-analyses were submitted for review.

7.1.4. Evaluator's conclusions on clinical efficacy for the indication 'ALK-positive NSCLC previously treated with ALK inhibitor

Overall, 515 ALK-positive NSCLC patients have been treated with ceritinib 750 mg (83 ALK inhibitor naïve and 163 ALK inhibitor pretreated patients in Study X2101; 140 ALK inhibitor pretreated patients in Study A2201 and 124 ALK inhibitor naïve patients in Study A2203; 6 additional patients have been treated at the proposed dose of 750g in study X1101). With regards

to patient disposition, a significant proportion of patients are still ongoing in the 3 studies (99 of 246 in Study X2101, 75 of 140 in A2201 and 91 of 124 in A2203). This means that for both Phase II studies, although the primary objective has been met, full OS data is not available.

Of the 246 NSCLC patients in the Study X2101, 180 patients (73.2%) who received the first dose of ceritinib at least 18 weeks prior to the data cut-off date were included in the EAS-NSCLC 750 mg group. The 18 week period was prospectively selected so that patients would have sufficient follow-up for assessment and confirmation of response. The primary efficacy endpoints are ORR and DOR, as assessed by the Investigator per RECIST 1.0. Taking into consideration that ORR is a measure of anti-tumour activity and does not provide direct evidence on patient's benefit, PFS/OS (included as secondary endpoints in this pivotal efficacy study) should have been considered. However, given ceritinib has a clear mechanism of action where it targets ALK, the evaluator thinks the ORR will likely translate into clinical benefit such as PFS and patient reported outcomes (PRO). This was the case for crizotinib (an ALK-inhibitor that is registered in Australia) where the Phase III trials confirmed the clinical benefit that was hinted by impressive ORR in earlier phase trials. Therefore the evaluator thinks the endpoint of ORR is reasonable at this point. Study A2303 is a Phase III, multi-centre, randomised open-label study of ceritinib versus. Standard second-line chemotherapy (pemetrexed or docetaxel) in patients previously treated with chemotherapy and crizotinib, and is currently enrolling patients.

Overall, the profile of the patient population in Study X2101 and A2201 largely resembles the population included in the pivotal studies that supported the approval of crizotinib.

It is interesting to note that the primary endpoint of ORR per investigator showed less magnitude of effect in the Phase II study of A2201 (37.1%) than in the Phase I study of X2101 (55.4%) in the ALK inhibitor-treated NSCLC patients. Supportive PFS endpoint also showed the same trend. However, patients in both studies appeared to have a similar clinical benefit. The DCR was similarly high in both studies (77.1% in Study A2201 and 74.2% in Study X2101). The differences in the ORR in the two studies may be explained by several factors, including a higher rate of baseline brain metastases (71.4% in A2201 versus. 60.1% in X2101) and more advanced disease in Study A2201 than in Study X2101 (median time from diagnosis to first dose of ceritinib of 26.2 months in Study A2201 versus. 21.2 months in Study X2101). In addition, different RECIST criteria were used to evaluate ORR in the two studies (RECIST 1.0 in Study X2101 versus. RECIST 1.1 in Study A2201), making direct comparison inaccurate.

While investigator determined BOR is subject to bias and therefore questionable as the primary endpoint, the supportive analyses in Study A2201 suggested that overall efficacy results were similar between investigator versus BIRC assessments, including ORR, DOR and PFS.

In conclusion, the overall efficacy of ceritinib in the treatment of ALK-positive NSCLC is based on the results of three uncontrolled, open label studies (the extension phase of one phase I and two Phase II clinical trials). The efficacy of ceritinib in the treatment of ALK-positive NSCLC patients who have had a prior ALK inhibitor (TGA-indication sought) is based on a subgroup of the phase I trial as well as the A2201 phase 2 study. The absence of direct comparative data with other agents such as, chemotherapy in the crizotinib-treated patients is an important limitation. The lack of controlled studies leaves the comparative size of the benefit on PFS, the real effect on patient reported outcomes (PROs) and OS as unknown. However, despite these limitations, the results represent a clinically meaningful value for patients with prior ALK inhibitor treatment for whom there exists an unmet medical need. The efficacy result in the generally heavily pre-treated patients included in the trial is better than would have been expected if treated with conventional chemotherapy only. For example, the estimated ORR for second line chemotherapy was only 20% and a median PFS of 3.0months in the Phase III crizotinib trial (Shaw AT et al, 2013). Therefore there is a favourable benefit risk balance for the proposed indication where patients were previously treated with an ALK inhibitor.

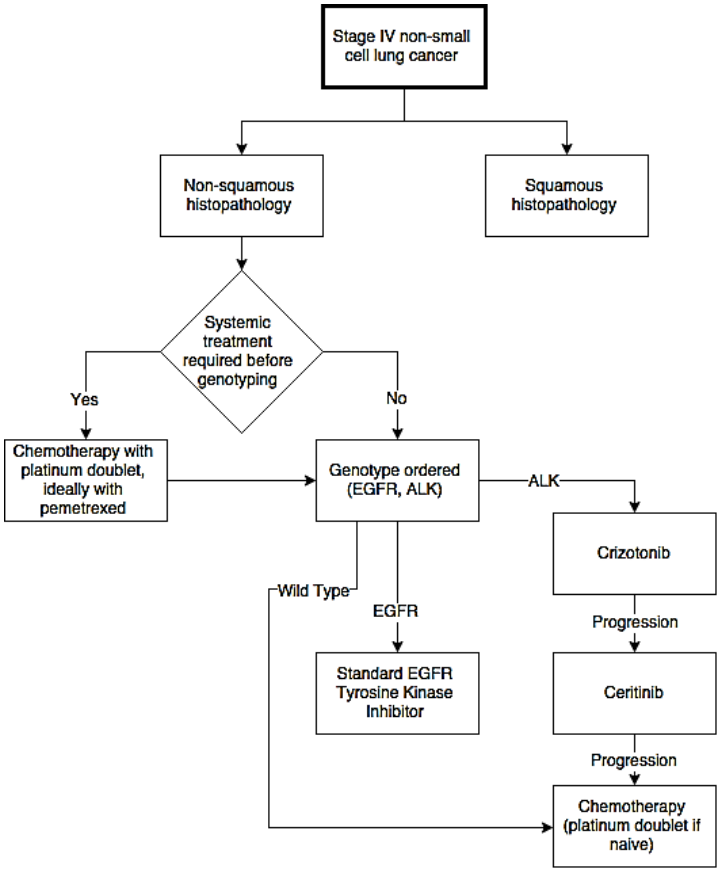
In contrast, ALK inhibitor naïve patients have no unmet medical need given crizotinib is registered and reimbursed here in Australia. Consequently, the appropriateness of using a single arm study (with ORR as primary endpoint) to assess efficacy in ALK inhibitor naïve patients is not

appropriate, in view of the absence of controlled studies with robust endpoints. Moreover, alectinib, another novel ALK inhibitor is being compared with crizotinib in ALK inhibitor naïve patients in a Phase III trial (ALEX study; NCT02075840) and the lack of direct comparison between ceritinib and crizotinib is a deficit in the application. In addition, it is worth mentioning the results from crizotinib Phase III trial where patients were ALK inhibitor naïve but chemotherapy pre-treated (Shaw AT et al, 2013). In the trial, 65% of the patients had a PR with approximately 8 months of DOR and 7.7 months of median PFS. While direct cross-trial comparison should not be made, there is no convincing signal that ceritinib in the ALK-inhibitor naïve patients is superior.

Currently there is insufficient evidence to support a first line indication.

Figure 13 illustrates a suggested Australian algorithm for treatment for ALK-positive NSCLC in 2015, if ceritinib becomes available for use. This obviously may change depending on the outcome of the Phase III randomised trials of alectinib versus crizotinib and ceritinib versus chemotherapy in the first line setting. Understanding in the mechanism of resistance for ALK inhibitors may also assist in the sequential use of different ALK inhibitors.

Figure 13: A suggested Australian algorithm for treatment of ALK-positive NSCLC in 2015 if ceritinib is registered for use



8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: X2101, X1101, A2201 and A2203.

8.1.1. Pivotal efficacy studies

In the pivotal efficacy study of X2101, the following safety data were collected:

- General adverse events (AEs) were assessed by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 for Study X2101. Assessments were usually performed at baseline/screening, pre-dose on PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in the expansion phase, and varying frequencies in every treatment cycle and at the end of treatment.
- AEs of particular interest, including hepatotoxicity, interstitial lung disease/pneumonitis and QT prolongation, Bradycardia, Hyperglycaemia and GI toxicity (diarrhoea, nausea, vomiting).
- Laboratory tests, including haematology, basic metabolic blood chemistry, liver function tests (AST, ALT, total bilirubin, and alkaline phosphatase), serum amylase, and lipase, were performed at:
- Baseline/screening
  - PK run-in Day 1 (prior to first dose in escalation phase)
  - Cycle 1 Day 1 (within 3 days prior to the administration of ceritinib)
  - Cycle 1 Day 8
  - Cycle 1 Day 15
  - Day 1 and Day 15 of Cycle 2 to Cycle 6 (± 3 days)
  - Day 1 of Cycle 7 and subsequent cycles thereafter (± 3 days)
  - End of treatment
- Urinalysis, routine monitoring of vital signs (respiratory rate, sitting pulse, sitting blood pressure, and body temperature), weight, ECOG performance status and physical examination: assessments were usually performed at baseline/screening, pre-dose on PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in the expansion phase, and varying frequencies in every treatment cycle and at the end of treatment.
- Chest CT scan performed every second cycle
- Cardiac assessments with standard 12 lead ECG at the following time points:
  - Baseline/screening, single ECG within 14 days prior to first dose of ceritinib
  - PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in expansion phase, three serial ECGs at least 5 to 10 minutes apart prior to the first dose of ceritinib and single ECGs 4, 8 and 24 h post-dose
  - Cycle 1 Day 8 in the dose-escalation phase, single ECG pre-dose and 4 h post-dose
  - Day 1 of Cycle 2 to Cycle 6, single ECG pre-dose
  - After Cycle 6, ECGs should only be performed if clinically indicated
  - End of treatment, single ECG

The same safety data were collected at similar intervals in Study A2201.

8.1.2. Pivotal studies that assessed safety as a primary outcome

All safety data is derived from the above mentioned efficacy studies but there was no single pivotal study that assessed safety as a primary outcome. The study design has been described in detail above.

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable.

8.1.4. Other studies evaluable for safety only

Not applicable.

8.1.4.1. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2. Patient exposure

The safety dataset includes 525 patients exposed to ceritinib in the clinical studies (Studies X2101, A2201, A2203 and X1101) and treated at the proposed dose of 750 mg, as well as 62 patients treated with lower doses (from Studies X2101 and X1101). Information on deaths and SAE reported to the Novartis safety database has also been provided. The median duration of exposure was 33 weeks (range: 0.3 to 106.1 weeks): 71.6% of patients had been exposed for at least 24 weeks and 25.7% of patients had been exposed for at least 48 weeks. The duration of exposure in the pooled dataset is summarised in the Table 20.

Table 20: Duration of exposure to study drug in the pooled dataset (Safety set)

	X2101	A2201	A2203	X1101	All patients pool
	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg
	N=255	N=140	N=124	N=6	N=525
Exposure category, weeks – n (%)					
<1	2 (0.8)	3 (2.1)	1 (0.8)	0	6 (1.1)
1 - <12	48 (18.8)	22 (15.7)	11 (8.9)	2 (33.3)	83 (15.8)
12 - <24	34 (13.3)	16 (11.4)	10 (8.1)	0	60 (11.4)
24 - <36	32 (12.5)	58 (41.4)	41 (33.1)	2 (33.3)	133 (25.3)
36 -<48	38 (14.9)	22 (15.7)	46 (37.1)	2 (33.3)	108 (20.6)
48 - <60	37 (14.5)	18 (12.9)	12 (9.7)	0	67 (12.8)
≥ 60	64 (25.1)	1 (0.7)	3 (2.4)	0	68 (13.0)
Duration of exposure (weeks)					
Mean (SD)	40.1 (26.63)	28.5 (15.17)	33.7 (14.01)	25.7 (17.57)	35.3 (21.89)
Median	38.7	28.1	34.9	34.6	33.0
Min-Max	0.4-106.1	0.3-60.1	0.4-70.3	3.0-39.7	0.3-106.1

A patient is counted in only one duration range.
Duration of exposure (weeks) = (Last dosing date – First dosing date + 1)/7.
Data cut-off dates for the individual studies: X2101: 14-Apr-2014, A2201: 26-Feb-2014, A2203: 27-Jun-2014, X1101: 02-Aug-2013.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

In the main safety set (Study X2101), almost all of the patients (253/255 patients, 99.2%) at the proposed dose of 750 mg reported at least one AE during the study. The most common AEs were gastrointestinal disorders (249 patients; 97.6%), general disorders and administrative site conditions (164 patients; 64.3%), and investigations (155 patients; 60.8%). Grade 3-4 AEs were reported in 168 patients (66%). Majority of adverse events, were assessed as treatment-related by the investigators.

All the AE data (> 10% of patients for all grades, or > 3% for Grade 3 to 4) is shown in Table 21.

Table 21: Frequent adverse events (all patients pool, > 10% of patients for all grades, or > 3% of patients for Grade 3-4) (Safety Set)

	X2101 Ceritinib 750 mg N=255		A2201 Ceritinib 750 mg N=140		A2203 Ceritinib 750 mg N=124		X1101 Ceritinib 750 mg N=6		All patients Ceritinib 750 mg N=525	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	255 (100)	208 (80.8)	140 (100)	94 (67.1)	123 (99.2)	80 (64.5)	6 (100)	4 (66.7)	524 (99.8)	384 (73.1)
Diarrhoea	221 (86.7)	15 (5.9)	112 (80.0)	9 (6.4)	102 (82.3)	4 (3.2)	5 (83.3)	0	440 (83.8)	28 (5.3)
Nausea	211 (82.7)	15 (5.9)	111 (79.3)	9 (6.4)	92 (74.2)	4 (3.2)	5 (83.3)	0	419 (79.8)	28 (5.3)
Vomiting	157 (61.6)	12 (4.7)	87 (62.1)	6 (4.3)	83 (66.9)	6 (4.8)	3 (50.0)	0	330 (62.9)	24 (4.6)
Alanine Aminotransferase Increased	112 (43.9)	76 (29.8)	56 (40.0)	19 (13.6)	50 (40.3)	19 (15.3)	1 (16.7)	1 (16.7)	219 (41.7)	115 (21.9)
Decreased Appetite	95 (37.3)	4 (1.6)	56 (40.0)	5 (3.6)	61 (49.2)	2 (1.6)	4 (66.7)	0	216 (41.1)	11 (2.1)
Fatigue	110 (43.1)	13 (5.1)	46 (32.9)	9 (6.4)	40 (32.3)	7 (5.6)	3 (50.0)	0	199 (37.9)	29 (5.5)
Abdominal Pain	98 (38.4)	3 (1.2)	43 (30.7)	2 (1.4)	41 (33.1)	0	2 (33.3)	0	184 (35.0)	5 (1.0)
Aspartate Aminotransferase Increased	83 (32.5)	25 (9.8)	42 (30.0)	7 (5.0)	38 (30.6)	9 (7.3)	1 (16.7)	0	164 (31.2)	41 (7.8)
Constipation	79 (31.0)	0	33 (23.6)	3 (2.1)	19 (15.3)	0	1 (16.7)	0	132 (25.1)	3 (0.6)
Weight Decreased	46 (18.0)	5 (2.0)	45 (32.1)	6 (4.3)	36 (29.0)	1 (0.8)	0	0	127 (24.2)	12 (2.3)
Cough	74 (29.0)	0	26 (18.6)	0	21 (16.9)	0	0	0	121 (23.0)	0
Dyspnoea	63 (24.7)	11 (4.3)	25 (17.9)	7 (5.0)	17 (13.7)	1 (0.8)	0	0	105 (20.0)	19 (3.6)
Blood Creatinine Increased	43 (16.9)	0	20 (14.3)	0	26 (21.0)	0	4 (66.7)	0	93 (17.7)	0
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)	21 (15.0)	4 (2.9)	25 (20.2)	8 (6.5)	1 (16.7)	0	92 (17.5)	25 (4.8)
Asthenia	50 (19.6)	2 (0.8)	22 (15.7)	6 (4.3)	18 (14.5)	2 (1.6)	0	0	90 (17.1)	10 (1.9)
Abdominal Pain Upper	60 (23.5)	2 (0.8)	16 (11.4)	1 (0.7)	11 (8.9)	0	1 (16.7)	0	88 (16.8)	3 (0.6)
Back Pain	50 (19.6)	1 (0.4)	18 (12.9)	1 (0.7)	19 (15.3)	1 (0.8)	0	0	87 (16.6)	3 (0.6)
Pyrexia	42 (16.5)	0	29 (20.7)	4 (2.9)	13 (10.5)	1 (0.8)	2 (33.3)	0	86 (16.4)	5 (1.0)
Headache	51 (20.0)	4 (1.6)	20 (14.3)	0	11 (8.9)	1 (0.8)	0	0	82 (15.6)	5 (1.0)
Rash	34 (13.3)	0	20 (14.3)	0	19 (15.3)	1 (0.8)	1 (16.7)	0	74 (14.1)	1 (0.2)
Gamma-Glutamyltransferase Increased	14 (5.5)	7 (2.7)	25 (17.9)	17 (12.1)	33 (26.6)	23 (18.5)	0	0	72 (13.7)	47 (9.0)
Non-Cardiac Chest Pain	26 (10.2)	2 (0.8)	23 (16.4)	2 (1.4)	16 (12.9)	1 (0.8)	0	0	65 (12.4)	5 (1.0)
Anaemia	31 (12.2)	13 (5.1)	20 (14.3)	3 (2.1)	8 (6.5)	1 (0.8)	1 (16.7)	0	60 (11.4)	17 (3.2)
Insomnia	39 (15.3)	0	12 (8.6)	0	7 (5.6)	0	0	0	58 (11.0)	0
Musculoskeletal Pain	37 (14.5)	0	8 (5.7)	0	9 (7.3)	0	0	0	54 (10.3)	0
Hypokalaemia	29 (11.4)	11 (4.3)	8 (5.7)	4 (2.9)	11 (8.9)	5 (4.0)	0	0	48 (9.1)	20 (3.8)
Pneumonia	25 (9.8)	12 (4.7)	9 (6.4)	5 (3.6)	8 (6.5)	4 (3.2)	0	0	42 (8.0)	21 (4.0)
Hyperglycaemia	21 (8.2)	15 (5.9)	6 (4.3)	3 (2.1)	13 (10.5)	7 (5.6)	1 (16.7)	1 (16.7)	41 (7.8)	26 (5.0)
Lipase Increased	24 (9.4)	16 (6.3)	0	0	0	0	0	0	24 (4.6)	16 (3.0)

The most frequently observed primary system organ class (SOCs) were: gastrointestinal disorders (97.9%), investigations (73.5%), general disorders and administrative site conditions (68.0%), metabolism and nutrition disorders (59.6%) and respiratory, thoracic and mediastinal disorders (50.3%).

Findings across the different dose ranges (50 to 750 mg) in the safety set followed the same trend observed for the 750 mg group (Table 22). In addition, safety data available from the rest of on-going studies suggest similar trends.

In terms of duration, these events were persistent (median duration of 62.0 days, 53.0 days, 19.0 days and 81 days, for diarrhoea AEs, nausea AEs, vomiting AEs and their combination, respectively) and recurrent, with the majority of patients in the integrated summary (77%) experienced > 10 AEs, with a median of 17 AEs (ranging from 1 to 171).

Table 22: Adverse events regardless of study drug relationship, by primary system organs class (all SOCs) in all patients (NSCLC and non-NSCLC), by dose group (Study X2101 – Safety set)

Primary system organ class	LDK378 50-300 mg N=10 n (%)	LDK378 400-700 mg N=39 n (%)	LDK378 750 mg N=255 n (%)	All patients[1] N=304 n (%)
Any SOC	**10 (100.0)**	**39 (100.0)**	**253 (99.2)**	**302 (99.3)**
Gastrointestinal disorders	7 (70.0)	39 (100.0)	249 (97.6)	295 (97.0)
General disorders and administration site conditions	6 (60.0)	29 (74.4)	164 (64.3)	199 (65.5)
Investigations	5 (50.0)	27 (69.2)	155 (60.8)	187 (61.5)
Metabolism and nutrition disorders	3 (30.0)	19 (48.7)	129 (50.6)	151 (49.7)
Respiratory, thoracic and mediastinal disorders	7 (70.0)	19 (48.7)	120 (47.1)	146 (48.0)
Musculoskeletal and connective tissue disorders	6 (60.0)	22 (56.4)	112 (43.9)	140 (46.1)
Infections and infestations	4 (40.0)	13 (33.3)	99 (38.8)	116 (38.2)
Nervous system disorders	3 (30.0)	17 (43.6)	96 (37.6)	116 (38.2)
Skin and subcutaneous tissue disorders	1 (10.0)	15 (38.5)	81 (31.8)	97 (31.9)
Psychiatric disorders	2 (20.0)	8 (20.5)	56 (22.0)	66 (21.7)
Blood and lymphatic system disorders	1 (10.0)	7 (17.9)	34 (13.3)	42 (13.8)
Cardiac disorders	1 (10.0)	5 (12.8)	36 (14.1)	42 (13.8)
Eye disorders	1 (10.0)	5 (12.8)	32 (12.5)	38 (12.5)
Renal and urinary disorders	0	2 (5.1)	34 (13.3)	36 (11.8)
Vascular disorders	2 (20.0)	4 (10.3)	25 (9.8)	31 (10.2)
Injury, poisoning and procedural complications	1 (10.0)	3 (7.7)	23 (9.0)	27 (8.9)
Ear And Labyrinth Disorders	0	2 (5.1)	13 (5.1)	15 (4.9)
Reproductive System And Breast Disorders	1 (10.0)	1 (2.6)	9 (3.5)	11 (3.6)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (10.0)	1 (2.6)	8 (3.1)	10 (3.3)
Immune system disorders	0	1 (2.6)	7 (2.7)	8 (2.6)
Hepatobiliary disorders	0	0	2 (0.8)	2 (0.7)
Congenital, familial and genetic disorders	0	1 (2.6)	0	1 (0.3)
Endocrine disorders	0	0	1 (0.4)	1 (0.3)

This table presents data for all patients (NSCLC and non-NSCLC) treated with at least one dose of LDK378 (Safety set). [1] All patients include 14 non-NSCLC patients (50-300 mg: 2 patients, 400-700 mg: 3 patients, and 750 mg: 9 patients). Primary system organ classes are sorted in descending frequency, as reported in the all patients column; A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple adverse events within a primary system organ class is counted only once in the total row. Only AEs occurring during treatment or within 28 days of the last dose of study drug are reported.

8.3.2. Treatment-related adverse events (adverse drug reactions)

The AEs suspected to be study drug related (all grades) reported in ≥ 25% of the patients in the Study X2101were: diarrhoea (78.6%), nausea (74%), vomiting (53.3%), ALT increased (31.3%), abdominal pain (26.3%) and fatigue (25.3%). Most of the patients experienced mild-moderate AEs. Grade 3-4 AEs were reported in 168 patients (66%), the most common being elevated ALT (in 21.2% of patients), followed by elevated AST (in 7.5% of patients). Majority of adverse events (95.7%) in patients treated with the proposed dose of 750 mg were assessed as treatment-related by the investigators.

ADRs were screened and identified based on a number of factors such as investigator's causality (for example, related AEs/SAEs), frequency and consistency of reporting, biological plausibility, class effects, and dechallenge and rechallenge information. Once the ADRs were selected, their frequency calculation was made from the totality of the events reported for each AE. The ADRs and respective frequencies are summarised in the Table 23.

Table 23: Integrated summary of adverse drug reactions in the ceritinib 750 mg dose group (Safety set)

Primary System Organ Class Preferred Term	Ceritinib 750 mg, N=525			
	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood and lymphatic system disorders				
Anemia	60 (11.4)	Very common	17 (3.2)	Common
Metabolism and nutrition disorders				
Decreased appetite	216 (41.1)	Very common	11 (2.1)	Common
Hyperglycemia	41 (7.8)	Common	26 (5.0)	Common
Hypophosphatemia	28 (5.3)	Common	11 (2.1)	Common
Eye disorders				
Vision disorder[m]	39 (7.4)	Common	0	
Cardiac disorders				
Pericarditis[h]	31 (5.9)	Common	16 (3.0)	Common
Bradycardia[e]	10 (1.9)	Common	0	
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[i]	17 (3.2)	Common	10 (1.9)	Common
Gastrointestinal disorders				
Diarrhea	440 (83.8)	Very common	28 (5.3)	Common
Nausea	419 (79.8)	Very common	28 (5.3)	Common
Vomiting	330 (62.9)	Very common	24 (4.6)	Common
Abdominal pain[a]	253 (48.2)	Very common	8 (1.5)	Common
Constipation	132 (25.1)	Very common	3 (0.6)	Uncommon
Esophageal disorder[f]	79 (15.0)	Very common	2 (0.4)	Uncommon
Hepatobiliary disorders				
Abnormal liver function tests[c]	11 (2.1)	Common	8 (1.5)	Common
Hepatotoxicity[d]	3 (0.6)	Uncommon	3 (0.6)	Uncommon
Skin and subcutaneous tissue disorders				
Rash[j]	100 (19.0)	Very common	2 (0.4)	Uncommon
Renal and urinary disorders				
Renal failure[k]	11 (2.1)	Common	1 (0.2)	Uncommon
Renal impairment[l]	7 (1.3)	Common	1 (0.2)	Uncommon
General disorders and administration site conditions				
Fatigue[g]	265 (50.5)	Very common	39 (7.4)	Common
Investigations				
Liver laboratory test abnormalities[b]	265 (50.5)	Very common	153 (29.1)	Very common

Primary System Organ Class Preferred Term	Ceritinib 750 mg, N=525			
	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood creatinine increased	93 (17.7)	Very common	0	
Electrocardiogram QT prolonged	34 (6.5)	Common	4 (0.8)	Uncommon
Lipase increased	24 (4.6)	Common	16 (3.0)	Common

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
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, Gastrooesophageal 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 Renal Failure Acute 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

8.3.3. Deaths and other serious adverse events

In the pooled dataset (n=525), 201 (38.3%) patients reported SAEs. The most frequent SAEs

(irrespective of causality) reported in ≥ 2% of all patients were: pneumonia (4.2%), dyspnea (2.9%), convulsion (2.5%), pneumonitis (2.3%), and pyrexia (2.1%). Ceritinib related SAEs were reported in 13.1% of patients. Ceritinib-related SAEs were each reported in <1% of patients, with the exception of pneumonitis (1.9%), pericarditis (1.5%), nausea (1.1%) and pneumonia (1.0%).

With regards to deaths, a total of 68 on-treatment deaths (13.0%) were reported in the safety set (all patients; n=525). All deaths, with the exception of 3 deaths, were not suspected to be related to study drug. These included:

- One death due to ILD (Study X2101)
- One death due to multi-organ failure that occurred in the context of infection and ischaemic hepatitis (Study X2101)
- One death due to pneumonia (Study A2201).

Overview of deaths and serious adverse events is presented in Table 24.

Table 24: Overview of deaths and other serious or clinically relevant adverse events in the pooled dataset (Safety Set)

	X2101 N=255	A2201 N=140	A2203 N=124	X1101 N=6	All patients N=525
All deaths [a]	83 (32.5)	39 (27.9)	13 (10.5)	0	135 (25.7)
On-treatment deaths [b]	41 (16.1)	17 (12.1)	10 (8.1)	0	68 (13.0)
Study indication	26 (10.2)	15 (10.7)	8 (6.5)	0	49 (9.3)
Other	15 (5.9)	2 (1.4)	2 (1.6)	0	19 (3.6)
Serious adverse events	121 (47.5)	51 (36.4)	27 (21.8)	2 (33.3)	201 (38.3)
Suspected to be drug related	32 (12.5)	25 (17.9)	10 (8.1)	2 (33.3)	69 (13.1)
AEs leading to discontinuation	26 (10.2)	10 (7.1)	9 (7.3)	1 (16.7)	46 (8.8)
AEs requiring dose adjustment or interruption	197 (77.3)	101 (72.1)	90 (72.6)	5 (83.3)	393 (74.9)
AEs requiring additional therapy	254 (99.6)	130 (92.9)	117 (94.4)	6 (100.0)	507 (96.6)
AEs of special interest					
Hepatotoxicity	126 (49.4)	73 (52.1)	75 (60.5)	5 (83.3)	279 (53.1)
ILD/pneumonitis	12 (4.7)	3 (2.1)	2 (1.6)	1 (16.7)	18 (3.4)
QT prolongation	16 (6.3)	9 (6.4)	15 (12.1)	0	40 (7.6)
Hyperglycemia	32 (12.5)	11 (7.9)	15 (12.1)	2 (33.3)	60 (11.4)
Bradycardia	21 (8.2)	10 (7.1)	17 (13.7)	0	48 (9.1)
GI toxicity [c]	246 (96.5)	134 (95.7)	118 (95.2)	6 (100)	504 (96.0)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[a] All deaths, including those > 30 days after last dose of study drug.
[b] Deaths occurring >30 days after last dose of study drug are not included.
[c] GI toxicity: nausea, diarrhoea, vomiting
Only AEs occurring during treatment or within 30 days of the last dose of study drug are reported.

8.3.4. Discontinuation due to adverse events

The AEs leading to discontinuation of the study drug in the 750 mg dose group occurred in 8.8% of patients, with the most frequent AEs being pneumonia (0.8%), pneumonitis (0.8%) and nausea (0.6%). This is summarised in Table 25.

Table 25: Summary of adverse events leading to study drug discontinuation for ceritinib 750 mg group (n ≥ 2 in all grades) by preferred term in pooled dataset (n=525), including Study X2101, X1101, A2201 and A2203.

Preferred Term	All patients N=525	
	All grades N (%)	Grade 3/4 N (%)
- Total	46 (8.8%)	37 (7.0%)
Pneumonitis	4 (0.8%)	3 (0.6%)
Interstitial lung disease	2 (0.4%)	1 (0.2%)
Pneumonia aspiration	2 (0.4%)	2 (0.4%)
Respiratory failure	2 (0.4%)	2 (0.4%)
Infection/infestations	7 (1.3%)	7 (1.3%)
Pneumonia	4 (0.8%)	4 (0.8%)
Nausea	3 (0.6%)	1 (0.2%)
Fatigue	2 (0.4%)	2 (0.4%)
General physical health deterioration	2 (0.4%)	2 (0.4%)
Increased AST	2 (0.4%)	1 (0.2%)
Cardiac tamponade	2 (0.4%)	2 (0.4%)
Decreased appetite	2 (0.4%)	1 (0.2%)

The AEs requiring dose adjustments or interruptions was reported for a larger proportion of patients (74.9%) in the pooled dataset; 49.5% of patients had a Grade 3-4 AE leading to dose adjustment or interruption. The most frequent (any grade, ≥ 5% of patients) AEs requiring dose adjustment or interruption were increased transaminases (ALT 29.0%, AST 15.6%), GI toxicity (nausea 18.7%, vomiting 18.7%, diarrhoea 16.0%), fatigue (6.9%), abdominal pain (6.1%) and decreased appetite (5.3%).

The most frequent (≥ 3% of patients) Grade 3-4 AEs requiring dose adjustment or interruption were increased transaminases (ALT 20.6%, AST 6.5%), GI toxicity (diarrhoea 4.4%, nausea 3.8%, vomiting 3.6%), and fatigue (3.0%).

Comments: The rates of dose reductions and interruptions in the pooled dataset are very high (74.9%) but the discontinuation rate due to ceritinib AEs is relatively low at (8.8%). This suggests to the evaluator that ceritinib is not a well-tolerated drug but the side effects seem to be managed with supportive measures and/or dose reduction. Majority of patients continued ceritinib despite the AEs. While this is reassuring that a significant proportion of patients in the clinical trials ended up receiving 600 mg of ceritinib or less and still deriving the efficacy, the evaluator wonders if starting at 600 mg would be justified, particularly given that there is little relationship between ceritinib exposure and clinical efficacy in PK studies.

8.4. Laboratory tests

8.4.1. Liver function

Hepatotoxicity is considered an adverse event of special interest (AESI). Hepatotoxicity AEs (primarily increased ALT and AST) were frequently reported in the pooled analysis (n=525) of all 4

studies (in 53.1% of patients with the proposed dose of 750 mg), with Grade 3-4 AEs reported in 31.0% of patients. These events were managed with dose reductions or temporary interruptions in 34.9% of patients and led to discontinuation in 0.8% of patients. The events were serious in 2.3% of patients. There were no deaths due to a hepatotoxicity AE.

Of the 12 patients (2.3%) with the hepatotoxicity SAEs reported in the pooled dataset, 9 patients had an event that was considered related to study drug. No cases of Hy's law or deaths due to hepatic failure have been reported in the ceritinib programme, up to the data cut-off date (Table 26)

Hepatotoxicity is a common AE associated with ALK inhibitors. Given the intended second line place in therapeutics, after prior treatment with other ALK inhibitor, the sponsor should discuss whether a higher incidence or seriousness of hepatotoxicity might be expected in those patients.

Table 26: Hepatotoxicity events in the pooled dataset (Safety set)

Hepatotoxicity AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	126 (49.4)	73 (52.1)	75 (60.5)	5 (83.3)	279 (53.1)
Alanine Aminotransferase Increased	112 (43.9)	56 (40.0)	50 (40.3)	1 (16.7)	219 (41.7)
Aspartate Aminotransferase Increased	83 (32.5)	42 (30.0)	38 (30.6)	1 (16.7)	164 (31.2)
Gamma-Glutamyltransferase Increased	14 (5.5)	25 (17.9)	33 (26.6)	0	72 (13.7)
Blood Bilirubin Increased	9 (3.5)	0	5 (4.0)	0	14 (2.7)
Transaminases Increased	9 (3.5)	0	2 (1.6)	0	11 (2.1)
Hepatic Function Abnormal	0	4 (2.9)	4 (3.2)	2 (33.3)	10 (1.9)
Hepatic Enzyme Increased	0	3 (2.1)	4 (3.2)	1 (16.7)	8 (1.5)
Liver Function Test Abnormal	1 (0.4)	2 (1.4)	3 (2.4)	0	6 (1.1)
Bilirubin Conjugated Increased	3 (1.2)	0	0	0	3 (0.6)
Ascites	2 (0.8)	0	0	0	2 (0.4)
Drug-Induced Liver Injury	1 (0.4)	0	0	1 (16.7)	2 (0.4)
Hepatitis	0	0	2 (1.6)	0	2 (0.4)
Ammonia Increased	0	0	1 (0.8)	0	1 (0.2)
Asterixis	0	1 (0.7)	0	0	1 (0.2)
Hepatic Encephalopathy	0	1 (0.7)	0	0	1 (0.2)
Hepatitis Cholestatic	1 (0.4)	0	0	0	1 (0.2)
Hepatocellular Injury	0	1 (0.7)	0	0	1 (0.2)
Hepatotoxicity	0	1 (0.7)	0	0	1 (0.2)
Hyperbilirubinaemia	1 (0.4)	0	0	0	1 (0.2)
Ischaemic Hepatitis	1 (0.4)	0	0	0	1 (0.2)
Jaundice	1 (0.4)	0	0	0	1 (0.2)
CTC grade 3/4 AEs	82 (32.2)	35 (25.0)	43 (34.7)	3 (50.0)	163 (31.0)
AEs suspected to be drug related	117 (45.9)	68 (48.6)	66 (53.2)	5 (83.3)	256 (48.8)
SAEs	5 (2.0)	4 (2.9)	1 (0.8)	2 (33.3)	12 (2.3)
Alanine Aminotransferase Increased	4 (1.6)	1 (0.7)	0	0	5 (1.0)
Aspartate Aminotransferase Increased	2 (0.8)	1 (0.7)	0	0	3 (0.6)
Drug-Induced Liver Injury	1 (0.4)	0	0	1 (16.7)	2 (0.4)
Hepatic Function Abnormal	0	1 (0.7)	0	1 (16.7)	2 (0.4)
Hepatic Encephalopathy	0	1 (0.7)	0	0	1 (0.2)
Hepatitis	0	0	1 (0.8)	0	1 (0.2)
Hepatitis Cholestatic	1 (0.4)	0	0	0	1 (0.2)
Hepatocellular Injury	0	1 (0.7)	0	0	1 (0.2)
AEs leading to discontinuation	1 (0.4)	1 (0.7)	1 (0.8)	1 (16.7)	4 (0.8)
AEs requiring dose adjustment/interruption	85 (33.3)	45 (32.1)	50 (40.3)	3 (50.0)	183 (34.9)
Deaths	0	0	0	0	0

8.4.2. Kidney function

Increases in creatinine values (primarily Grade 1-2) were seen in 63% of patients in the pooled dataset (Grade 1: 19.0%, Grade 2: 42.3%, Grade 3: 1.5% of patients; none were Grade 4). The increases in creatinine seen in the laboratory evaluations were generally without clinical consequences. In the pooled dataset, 22.5% of patients had an AE related to 'acute renal failure': the most frequent AE was blood creatinine increased (17.7% of patients). Other AEs reported in ≥ 1 % of patients were creatinine renal clearance decreased (2.1%), renal failure acute (1.3%),

proteinuria (1.1%) and renal failure (1.0%). Most of the AEs were grade 1-2 (Grade 3-4 AEs were reported 1.1% of patients). The events were serious in 1.1% of patients, required study drug adjustment/interruption in 4.8% of patients, and led to discontinuation in 0.2% of patients (a single patient discontinued due to acute renal failure).

8.4.3. Other clinical chemistry

G1-2 abnormalities in clinical chemistry were commonly observed in the pooled dataset. The most frequently observed new or worsened Grade 3 and Grade 4 clinical chemistry abnormalities in the pooled dataset (n=5250 were increases in ALT (23.1% and 1.9%), AST (10.6% and 1.7%), ALP (10.3% and 0%) and glucose (11.1% and 1.0%).

The hepatic changes have already been discussed above. AEs associated with increased glucose values will be discussed below as this is also considered an AESI.

Furthermore, increased lipase and amylase were observed in the ceritinib clinical development programme. Increased lipase was reported in 7.2% of patients (4.0% Grade 3-4) in the pooled dataset. These AEs were primarily isolated biochemical elevations of lipase (or amylase) without accompanying clinical symptoms, and only 2 cases (both not suspected to be related to ceritinib by investigator) of pancreatitis were reported in any of the studies. Five cases were characterised by lipase/amylase Grade 3 increases and concurrent abdominal pain. None were considered likely cases of pancreatitis based on the unclear association between lipase/amylase increases and abdominal pain in these patients, the absence of overall clinical suspicion by the investigators (that is, not reported as pancreatic AEs) and the resolution of events without hospitalisation. However, this could potentially be associated with treatments given the evidence from the nonclinical studies where the pancreas was identified as a target organ in the rat at high doses in 2 to 4 week studies. Ceritinib treatment led to acinar cell atrophy and inflammation, which were mostly mild and reversible.

8.4.4. Haematology

G1-2 abnormalities in haematology were again, commonly observed in the pooled dataset. The most frequently observed new or worsened Grade 3 and 4 haematological abnormalities were decreased lymphocytes (18.2% and 3.1%, respectively). For the other parameters such as decreased white blood cells, neutrophils, haemoglobin and platelets, new or worsened Grade 3-4 values were seen in <5% of patients. Very few haematological abnormalities required dose modifications (0.2% due to lymphopaenia; 2.3% due to leukopenia; 1.1% due to anaemia; and 0.2% due to thrombocytopenia) and none led to discontinuation of study drug. Haematological toxicity does not appear to be of any clinical consequences in the use of ceritinib.

8.4.5. Hyperglycaemia

Hyperglycaemia AEs (primarily hyperglycaemia and diabetes mellitus as preferred terms) were reported in 11.4% of patients with Grade 3-4 AEs reported in 6.1% in the pooled dataset. The event required dose adjustment or interruption in 2.1% of patients and led to discontinuation in 0.2% (2 patients). The event was serious in 2.3% of patients. There were no deaths due to a hyperglycaemia AE.

Of the 32 patients with Grad 3-4 AEs, 22 patients did not require any dose interruptions or reduction of ceritinib, 9 patients required interruption or dose reduction of ceritinib and one patient with hyperglycaemia (Grade 4) required ceritinib discontinuation.

The occurrence of hyperglycaemia SAEs was confounded by either the use of steroid or underlying diabetes mellitus, with the exception of 1 patient where grade 4 occurred on Day 77 at 750 mg dose. This resolved after discontinuation of ceritinib.

8.4.6. Electrocardiograph

QT prolongation and bradycardia were considered AESIs.

In the pooled dataset, QT prolongation AEs were reported in 7.6% of patients, with Grade 3-4 AEs reported in 1.5% of patients. The event required dose adjustment or interruption in 1.0% of

patients and led to discontinuation in 0.2% of patients. The event was serious in 0.4% of patients (not suspected to be related to ceritinib) and there were no deaths due to a QT prolongation AE (Table 27), and there were no cases of Torsades de Pointes.

Table 27: QT prolongation events in the pooled dataset (Safety set)

QT prolongation AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	16 (6.3)	9 (6.4)	15 (12.1)	0	40 (7.6)
Electrocardiogram QT Prolonged	10 (3.9)	9 (6.4)	15 (12.1)	0	34 (6.5)
Syncope	4 (1.6)	0	0	0	4 (0.8)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
Loss Of Consciousness	1 (0.4)	0	0	0	1 (0.2)
Ventricular Arrhythmia	0	0	1 (0.8)	0	1 (0.2)
CTC grade 3/4 AEs	7 (2.7)	0	1 (0.8)	0	8 (1.5)
Electrocardiogram QT Prolonged	3 (1.2)	0	1 (0.8)	0	4 (0.8)
Syncope	3 (1.2)	0	0	0	3 (0.6)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
AEs suspected to be drug related	9 (3.5)	8 (5.7)	15 (12.1)	0	32 (6.1)
Electrocardiogram QT Prolonged	9 (3.5)	8 (5.7)	15 (12.1)	0	32 (6.1)
Ventricular Arrhythmia	0	0	1 (0.8)	0	1 (0.2)
SAEs	2 (0.8)	0	0	0	2 (0.4)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
Loss Of Consciousness	1 (0.4)	0	0	0	1 (0.2)
AEs leading to discontinuation	0	0	1 (0.8)	0	1 (0.2)
Electrocardiogram QT Prolonged	0	0	1 (0.8)	0	1 (0.2)
AEs requiring dose adjustment/interruption	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Electrocardiogram QT Prolonged	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Deaths	0	0	0	0	0

In addition, QT prolongation SAEs were retrieved for 3 patients in the Novartis global pharmacovigilance safety database. Two patients had ceritinib-related ECG QT prolongation. One patient's ceritinib was reduced to 600 mg and another discontinued his ceritinib; both recovered from the event.

Extensive ECG monitoring with time-matched ceritinib plasma concentration measurements was performed in the Study X2101 in a subset of patients. Analysis of data from Study X2101 showed that increased exposure of ceritinib is associated with increased QTcP with an estimated 13.6 ms QTcP increase from baseline at steady-state C_{max} (1080 ng/mL at Cycle 2 Day 1). These data indicate a modest QT prolongation effect of ceritinib.

Another AESI is bradycardia in the ceritinib clinical development programme. Bradycardia AEs were reported in 48 patients (9.1%) of patients, with Grade 3 to 4 AEs reported in 1.3% of patients. The preferred terms 'bradycardia' and 'sinus bradycardia' were reported in 1.0% of patients each (all Grade 1), with 1.9% of patients having either a bradycardia and/or a sinus bradycardia AE. Bradycardia AEs required dose adjustment or interruption in 1.0% of patients and led to discontinuation in 0.2% of patients. In 38 patients, the bradycardia AEs were suspected to be study drug related. There were no bradycardia SAEs, and there were no deaths due to a bradycardia AE.

8.4.7. Vital signs

No clinically relevant changes in pulse, respiratory rate, or temperature were noted. Weight loss was reported as an AE in 24.2% of patients in the pooled dataset, which is not unexpected in this heavily treated patient population of metastatic NSCLC. Weight decrease was considered related to study drug in 16.4% of patients, and required dose reduction or interruption in 1.3% of patients. The event was serious in 0.6% of patients and led to discontinuation of study drug in 0.2% of patients.

8.4.8. Interstitial lung disease/Pneumonitis

This was considered an AESI. In the pooled dataset, interstitial lung disease (ILD)/pneumonitis events were reported in 3.4% of patients, with Grade 3 to 4 AEs reported in 1.9% of patients; in 3.0% of patients, events were suspected to be related to study drug (Table 28). The event required dose adjustment or interruption in 2.1% of patients and led to discontinuation in 1.1% of patients. The event was serious in 2.9% of patients.

Fifteen patients had an ILD/pneumonitis SAE, one of them with an outcome of death (due to treatment-related ILD). ILD occurred on Day 23 with 750 mg dose. Despite antibiotics and steroids, patient continued to deteriorate and died 19 days later.

Additionally, one SAE of ILD/pneumonitis was reported for one ceritinib-treated patient in the Novartis Global Pharmacovigilance safety data. This case which occurred in Study X2102 (ceritinib + AUY922 combination study), had an outcome of death, and was assessed as related to study drug.

Table 28: ILD/pneumonitis events in the pooled dataset (Safety set)

ILD/pneumonitis AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	12 (4.7)	3 (2.1)	2 (1.6)	1 (16.7)	18 (3.4)
Pneumonitis	9 (3.5)	3 (2.1)	1 (0.8)	1 (16.7)	14 (2.7)
ILD	2 (0.8)	0	1 (0.8)	0	3 (0.6)
Lung Infiltration	1 (0.4)	0	0	0	1 (0.2)
CTC grade 3/4 AEs	9 (3.5)	1 (0.7)	0	0	10 (1.9)
AEs suspected to be drug related	11 (4.3)	2 (1.4)	2 (1.6)	1 (16.7)	16 (3.0)
SAEs	12 (4.7)	3 (2.1)	0	0	15 (2.9)
Pneumonitis	9 (3.5)	3 (2.1)	0	0	12 (2.3)
Interstitial Lung Disease	2 (0.8)	0	0	0	2 (0.4)
Lung Infiltration	1 (0.4)	0	0	0	1 (0.2)
AEs leading to discontinuation	3 (1.2)	2 (1.4)	1 (0.8)	0	6 (1.1)
AEs requiring dose adjustment/interruption	8 (3.1)	1 (0.7)	1 (0.8)	1 (16.7)	11 (2.1)
Deaths	1 (0.4)	0	0	0	1 (0.2)

8.4.9. GI toxicity

GI toxicity was considered an AESI. GI AEs included diarrhoea, nausea and vomiting. This was reported in 96.0% of patients and was suspected to be related to study drug by the investigator in 94.9%. Most of the AEs were Grade 1 to 2, while Grade 3 to4 were reported in 12.2% of patients. The event required dose adjustment or interruption in 33.0% of patients.

A total of 3.6% of patients had GI SAEs and the GI AEs led to discontinuation in only 0.6% of patients. GI AEs were managed mainly with supportive medications (reported in 84.8% of patients) and/or with dose adjustment or interruption of ceritinib (33.0%). There were no deaths due to GI AE.

In addition, GI SAEs were reported in 9 patients in the Novartis global pharmacovigilance safety database. Of these, 7 patients had SAEs that were suspected to be related to ceritinib. All SAEs were managed with supportive treatment including anti-emetic/anti-diarrhoeal medications and hydration and/or dose interruption/dose reduction of ceritinib. There were no life-threatening or fatal cases of GI AEs associated with the use of ceritinib.

8.5. Post-marketing experience

Up to [information redacted] June 2014, there were a total of 20 cases identified and retrieved from the Novartis global pharmacovigilance safety database. Fifteen (15) cases were solicited reports from post-marketing studies [all assessed as related] including 3 serious and 12 non-serious. Five (5) cases of spontaneous reports were identified including 3 serious and 2 non-serious. The majority of the cases had events that either were considered as expected for Zykadia (for example,

diarrhoea, nausea, vomiting or abdominal pain) or required more information to allow a meaningful assessment.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

This has been discussed above. There are currently no cases of Hy's law or death due to hepatic failure, although hepatotoxicity AEs were common. A continuing Pharmacovigilance plan is important, particularly given the lack of data in ceritinib use in patients with moderate and severe hepatic impairment.

8.6.2. Cardiovascular safety

Cardiac issues including QT prolongation and bradycardia are discussed above. There is good clinical evidence of ceritinib prolonging QT interval, but there were no deaths or Torsade de Pointes. Warning and recommendation regarding monitoring and dose adjustment is well documented in the draft PI. A Pharmacovigilance plan is in place to monitor this on an ongoing basis.

8.6.3. Interstitial lung disease/Pneumonitis

This is potentially an issue for major regulatory impact. One death was observed attributed to this AE due to ceritinib in the clinical trials and a further patient was captured in the Novartis Global Pharmacovigilance safety database. Recommendation is made regarding monitoring patients for pulmonary symptoms indicative of pneumonitis is made in the draft PI. Ongoing surveillance of this TKI-class effect is required.

8.6.4. Haematological toxicity

Please refer to discussion above. Haematological toxicity does not appear to be a major issue.

8.6.5. Serious skin reactions

AEs in 'Skin and subcutaneous tissue disorder' as a system organ class was documented in 189 patients (36%) with very low incidence of Grade 3 to 4 reactions (0.8%). Pruritus and dry skin occurred in 6.7% and 6.5% of patients respectively, with 0.2% and 0% Grade 3 to 4 severities, respectively. Ceritinib does not appear to have significant skin toxicity that would have major regulatory impact.

8.7. Other safety issues

8.7.1. Safety in special population Use in Pregnancy and Lactation

There are no data regarding the use of ceritinib in pregnant women. Reproductive toxicology studies in pregnant rats and rabbits indicated fetal toxicity or teratogenicity after dosing with ceritinib during organogenesis, with the maternal plasma exposure less than that observed at the recommended dose of ceritinib 750 mg in clinical trials.

It is unknown whether ceritinib is excreted in human milk.

The potential for ceritinib to cause infertility in humans is also unknown.

8.7.2. Safety related to drug-drug interactions and other interactions (food/drink)

Drug-drug interaction has been discussed in the Pharmacokinetic interactions section above.

The bioavailability of ceritinib is increased in the presence of food (see above). Ceritinib should be taken on an empty stomach (No food for at least two h before and two h after the dose of ceritinib). Patients should avoid any naranjin containing products, such as grapefruit or grapefruit juice, pomelos and Seville orange products, as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

8.7.3. Withdrawal and rebound

No studies have been conducted to assess withdrawal and rebound effects of ceritinib.

8.7.4. Effects on ability to drive or operate machinery or impairment of mental ability

No studies have been performed on the effects of ceritinib on the ability to drive or operate machinery. Patients do experience fatigue as a result of ceritinib (in addition to disease symptom burden) and therefore this may affect patient's ability to drive or operate machinery.

8.8. Evaluator's overall conclusions on clinical safety

The median duration of exposure to ceritinib 750 mg up to the data cut-off date is the following: 38.7 weeks (range 0.4-106.1) in Study X2101; 28.1 weeks (range 0.3-60.1) in Study A2201; 34.9 weeks (range 0.4-70.3) in Study A2203; and 33.0 weeks (range 0.3-106.1) in the pooled dataset.

AEs occurred commonly in patients treated with ceritinib at a daily dose of 750 mg in the clinical development programme. Almost all patients (99.8%) experienced an AE, with 73.1% of AEs being graded as 3 to 4. In addition over half of the AEs were suspected to be drug-related. The most common AEs observed across studies were GI disorders, followed by general disorders and administrative site conditions, and investigations. The most frequently reported Grade 3-4 AEs were increased ALT, increased GGT, increased AST, fatigue, diarrhoea, nausea and hyperglycaemia. The AEs experienced by patients also tended to be these events were persistent and recurrent, and the AEs requiring dose adjustments or interruptions was also reported for a large proportion of patients (74.9%). Furthermore significant proportion of patients (84.8%) required supportive medications for management of their GI AEs. Despite this, treatment discontinuation was not frequent (8.8%). It is however important to bear in mind that the target population in these studies included heavily pre-treated NSCLC, where symptom burden is typically high.

There were no clinically meaningful differences in the safety findings of ceritinib in patients previously treated with ALK inhibitor and ALK inhibitor naïve patients.

Although hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions, very few patients had to discontinue ceritinib due to hepatic AEs (0.8%). Importantly, no cases of Hy's law or deaths due to hepatic failure have been reported in the ceritinib programme, up to the data cut-off date.

Ceritinib has been associated with ILD/pneumonitis, a class-effect in some TKIs. A total of 18 cases were detected in all studies (n=525), including one case of pneumonitis with fatal outcome. There was another case with ceritinib-related ILD/pneumonitis leading to an outcome of death in the Novartis Global Pharmacovigilance safety data.

Cardiac disorders including bradycardia and ECG abnormalities have also been observed during the ceritinib development programme. Taking into consideration that QTc prolongation is a pharmacological class effect and an important safety concern for TKIs (including crizotinib), a QTc effect was documented in the studies. QT prolongation AEs were reported in 7.6% of patients (Grade 3-4 in 1.5%), but there were no deaths or cases of Torsades de Pointes. It is interesting to note that Study X2101 showed that increased exposure of ceritinib was associated with increased QTcP, indicating a modest QT prolongation effect of ceritinib. This needs clear documentation in the PI and warning regarding drug interaction and monitoring is required.

Other safety concerns identified were: hyperglycemia, increased lipase, visual disorders, bradycardia, neuropathy, increase creatinine levels/renal failure, and oedema.

In conclusion, the available safety findings suggest that, although the AEs seem to be manageable, ceritinib is not particularly well tolerated. This is further supported by the persistent and recurrent nature of the most frequent AEs and the need for dose reduction in majority of patients.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Zykadia in the proposed usage (in ALK-positive locally advanced or metastatic NSCLC previously treated with an ALK-inhibitor) are:

- Zykadia has an ORR of 37.1% in A2201 and 55.4% in X2101 in patients who were heavily pre-treated, with more than half of the patients having received at least 3 prior regimens including crizotinib. Similarly, the duration of response was similarly long in both studies (median 9.2 months and 7.39 months, respectively).
- Furthermore, the PFS seen in these patients ranged from a median of 5.7 months in Study A2201 to 6.9 months in Study X2101, while preliminary median OS ranged from a median of 14 months in Study A2201 to 'not reached' in Study X2101. These secondary efficacy measures were immature to draw definitive conclusions.
- While these results came from uncontrolled, open-label clinical trials and the primary endpoint was ORR based on investigator assessment, these ORR rates exceed what is expected with chemotherapy in this setting (ORR of 20% and PFS of 3 months in chemotherapy arm of the Phase III crizotinib trial) and indicates that patients who have progressed on a prior ALK inhibitor would have a high likelihood of responding to ceritinib and therefore derive a clinical benefit.
- Phase III comparative study in ALK-positive NSCLC previously treated with platinum doublet and crizotinib (ceritinib versus. chemotherapy) is ongoing (ClinicalTrials.gov Identifier: NCT01828112).
- Consideration should be made to include a warning for decreasing effectiveness of oral contraceptives with concomitant use of Zykadia and the potential effect of gastric acid-reducing agents on Zykadia (subject of an ongoing clinical trial) as discussed in the Pharmacokinetics section.

9.2. First round assessment of risks

The risks of Zykadia in the proposed usage are:

- The most common adverse events observed across studies (comprising 525 patients exposed to ceritinib 750 mg, with a median duration of treatment of 33 weeks) were GI disorders (nausea, diarrhoea, vomiting and constipation), followed by general disorders and administrative site conditions, and investigations. The most frequently reported Grade 3-4 adverse events were increased ALT, increased GGT, increased AST, fatigue, diarrhoea, nausea and hyperglycaemia.
- Hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions and discontinuation (only 0.8% of patients). There were no AEs leading to death or cases of Hy's law.
- Interstitial lung disease/pneumonitis has been associated with Zykadia, a class-effect known for some TKIs. A total of 18 cases were detected in the trials presented in the dossier, with one outcome of death.
- Cardiac disorders including QT prolongation and bradycardia were observed. No deaths or Torsades de Pointes were observed. It appears that increased exposure of ceritinib was associated with increased QTc.
- While Zykadia associated AEs appears manageable, Zykadia is not well tolerated. This is supported by the persistent and recurrent nature of the frequent AEs.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Zykadia, given the proposed usage, is favourable.

Although the true clinical benefit of Zykadia is unknown due to the limitations of immature PFS and OS data and the uncontrolled nature of the clinical trials, the impressive effect of Zykadia on tumour burden in previously heavily pre-treated patients is clinically meaningful in a population with limited options of treatment. From the literature, it is known that this degree of ORR is not usually observed in solid tumours including ALK-positive NSCLC after several lines of chemotherapy. In the Phase III crizotinib trial (Shaw AT et al, 2013), patients treated with chemotherapy in second line have shown an ORR of 20% only and a median PFS of 3.0 months.

Previous experience of crizotinib showed a clear initial response rate translating into true clinical benefit in ALK-positive lung cancer patients in Phase III trials, the evaluator thinks the currently available data could support approval of Zykadia given the similar mechanism of action, provided confirmatory data of the benefit of Zykadia could be provided through the ongoing Phase III clinical trial.

While ceritinib did not seem to be well tolerated based on the data, it was manageable. The high AE rates may also be related to the inherent nature of the target population in the studies, that is, heavily pre-treated patients. In view of the likely clinical benefit in an area of unmet needs, the profile of AEs presented is acceptable. In addition the Risk Management Plan is satisfactory in ongoing monitoring of the safety profile of Zykadia.

10. First round recommendation regarding authorisation

Based on the clinical data submitted the evaluator recommends that the application for Zykadia be approved.

11. Clinical questions

The evaluator has raised a number of questions through this report:

- Ceritinib is conditionally approved overseas only. Given that TGA does not have conditional approval, the evaluator thinks communication regarding the limitations of the data in the PI should be stated clearly.
- Given the current lack of specific data in patients with moderately to severely impaired hepatic function, CHMP has mandated the following wording on their Summary of Product Characteristic (SmPC): '*Ceritinib is not recommended in patients with moderate to severe hepatic impairment*'. However, the evaluator notes that the US Prescribing Information simply stated that a recommended dose has not been determined for patients with moderate to severe hepatic impairment. Similarly the Canadian Product Monograph stated 'caution should be used in patients with hepatic impairment'. Our PI is in line with the US and Canada where it states 'caution should be used in patients with moderate to severe hepatic impairment'. The evaluator thinks it is to the patient's best interest to be more conservative in the wording of this issue until hepatic impairment data (Study A2110) becomes available, particularly given that hepatotoxicity was observed in the efficacy-safety study for the target population. Consideration should be made to change the phrasing to '*Ceritinib is not recommended in patients with moderate to severe hepatic impairment*'. In addition, is there an update in the study in non-cancer patients with varying degrees of impaired hepatic function (A2110)?
- The evaluator has concerns regarding expected AE rates in patients with weight significantly less than 60kg, given the established relationship between AE and ceritinib exposure. The evaluator cannot see any specific data addressing this and a comment from sponsor is necessary.

- The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, the evaluator thinks it would be reasonable to include this in the PI. The evaluator would also like to ask the sponsor whether such studies are underway. If such studies are not being planned, the sponsor should justify the reasons for it. Submission for evaluation should be condition of registration.
- Ceritinib might induce CYPs regulated by PXR. For some PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if UGTs are induced. The evaluator notes that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced with concomitant use of ceritinib was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.
- According to the EU Guideline on Interactions, all important CYPs (as listed in the guideline) should be evaluated for time-dependent inhibition. Such data seems to be lacking for CYP1A2, CYP2C8, CYP2C19, and CYP2D6. Are there plans to examine this?
- The evaluator notes some discrepancy in the efficacy results in the Study X2101 and A2201 from the Full Clinical Study Report and the Clinical Overview Report. The evaluator has based this review on data from Module 5 and the evaluator assumes the difference was due to an update undertaken to produce the Clinical Overview Report? This accounted for some discrepant results of ORR and OIRR in my report versus that of the draft Australian PI (which is based on the Clinical Overview Report). Having said that, the differences are trivial and do not change the evaluator's overall assessment.
- The safety dataset only included 525 patients, which is a comparatively small number of patients for a new drug entity, especially in the absence of randomised controlled trial. Therefore accurate safety issues can still be difficult to identify. The evaluator thinks this very important limitation should be clearly stated in the PI, with appropriate boxed warning for the AESI.
- The rates of dose reductions and interruptions in the pooled dataset are very high (74.9%) but the discontinuation rate due to ceritinib AEs is relatively low at (8.8%). This suggests to the evaluator that ceritinib is not a well-tolerated drug but the side effects seem to be managed with supportive measures and/or dose reduction. Majority of patients continued ceritinib despite the AEs. While this is reassuring that a significant proportion of patients in the clinical trials ended up receiving 600 mg of ceritinib or less and still deriving the efficacy, the evaluator wonders if starting at 600 mg would be justified, particularly given that there is little relationship between ceritinib exposure and clinical efficacy in PK studies. The evaluator would like the sponsor to comment on whether 600 mg should be the starting dose.
- In Hepatotoxicity under Precautions in the PI, it is stated that cases of hepatotoxicity occurred in less than 1% of patients treated with Zykadia in clinical studies'. This is slightly misleading in that it only refers to adverse drug reactions and not all adverse events. Furthermore, 'hepatotoxicity' was defined using Preferred Term of Drug-induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury and Hepatotoxicity, and does not include 'Abnormal liver function tests'. This should be corrected
- Hepatotoxicity is a common AE associated with ALK inhibitors. Given the intended second line place in therapeutics, after prior treatment with other ALK inhibitor, the sponsor should discuss whether a higher incidence or seriousness of hepatotoxicity might be expected in those patients.
- While the increased lipase and amylase observed in the clinical trial were generally mild, there were instances where it was associated with abdominal pain. In a single arm study, the causation is often difficult to determine, therefore, the evaluator thinks it is reasonable to include this as a warning in the Australian PI, as it is in the Canadian Product Monograph. Please comment.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Responses to clinical questions

12.1.1. Draft PI Comment 1:

In Hepatotoxicity under Precautions, it is stated that cases of hepatotoxicity occurred in less than 1% of patients treated with Zykadia in clinical studies'. This is slightly misleading in that it only refers to adverse drug reactions and not all adverse events. Furthermore, 'hepatotoxicity' was defined using Preferred Term of Drug-induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury and Hepatotoxicity, and does not include 'Abnormal liver function tests'.

12.1.1.1. Sponsor's Answer:

Sponsor has clarified the use of the ADR terms for hepatotoxicity and Abnormal liver function test and made appropriate changes to the Australian PI.

12.1.1.2. Evaluator's response and acceptability

The evaluator is satisfied with the responses and the changes made to the Australian PI.

12.1.2. Draft PI Comment 2:

In Table 2, the column of Study D was included. This was the X1101 study which is only inconspicuously stated at the end of the table which is 2 pages away. The evaluator thinks an asterisk marking the presence of the legend would be idea.

12.1.2.1. Sponsor's Answer:

The sponsor has made the change suggested in Table 2.

12.1.2.2. Evaluator's response and acceptability:

There are no further issues in regard to Table 2.

12.1.3. Draft PI Comment 3

In Table 4, conversion of the glucose unit commonly used in Australia would be useful.

12.1.3.1. Sponsor's Answer:

The sponsor has changed the glucose unit to mmol/L.

12.1.3.2. Evaluator's response and acceptability:

The evaluator thinks this will be helpful to the Australian physicians.

12.1.4. Draft PI Comment 4:

In Dosage Adjustment Section, a reduction by 1/3 with concomitant use of a strong CYP3A inhibitor is recommended. The evaluator does not think this clinically verified and if so, it should be stated in the PI and the need for careful monitoring for safety even with the dose reduction

12.1.4.1. Sponsor's Answer:

Since no study of multiple-dose drug-drug interaction has been conducted in ALK-positive NSCLC patients, the sponsor has adopted an approach using the mechanistic physiologically-based pharmacokinetic model. This approach was deemed acceptable by the FDA and EMA.

12.1.4.2. Evaluator's response and acceptability:

The evaluator accepts the sponsor's explanation and no changes to the Australian PI are required.

12.1.5. Draft PI Comment 5:

In Section of Patients with hepatic impairment under Dosage Adjustment Section, the draft PI only stated 'Caution should be used in patients with moderate to severe hepatic impairment'. Given the current lack of specific data in patients with moderately to severely impaired hepatic function and the ongoing study in patients with hepatic impairment (Study A2110), the evaluator wondered if a more explicit wording such as not recommended should be used (see Pharmacokinetics). Consideration should be made to change the phrasing to 'Ceritinib is not recommended in patients with moderate to severe hepatic impairment'.

12.1.5.1. Sponsor's Answer

The sponsor accepted the suggestion and agreed to make the relevant changes to the Australian PI sections Dosage and Administration, Precautions and Pharmacodynamics.

12.1.5.2. Evaluator's response and acceptability

The evaluator has no further comments to the changes that are made.

12.1.6. Draft PI Comment 6

Ceritinib might induce CYPs regulated by PXR. For some PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if UGTs are induced. I note that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced with concomitant use of ceritinib was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.

12.1.6.1. Sponsor's Answer

The sponsor acknowledged the uncertainty regarding the potential interaction with the CYO and PXR enzymes, but has added the additional sentence regarding the potential interaction between oral contraceptives and ceritinib in the Australian PI.

12.1.6.2. Evaluator's response and acceptability

The evaluator is happy with the changes in the Australian PI.

12.1.7. Draft PI Comment 7

The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, the evaluator thinks it would be reasonable to include this in the PI.

12.1.7.1. Sponsor's Answer

Sponsor agreed to include this in the Interactions section of the PI.

12.1.7.2. Evaluator's response and acceptability

The evaluator is satisfied with the response.

12.1.8. Draft PI Comment 8

The sponsor should clarify the reasons for the discrepant efficacy results presented in the draft PI to the Full Clinical Study Report, in particularly the results presented for patients with brain metastases seemed quite different to the data presented in the X2101 and A22201 Full Clinical Study Reports.

12.1.8.1. Sponsor's Answer

The sponsor has explained the different data cut-off dates for the discrepancy for the results. The evaluator also noted the amendment made in the Australian PI.

12.1.8.2. Evaluator's response and acceptability

The evaluator has no further comments in relation to the response.

12.1.9. Draft PI Comment 9

On Page 14, in addition to grapefruit or grapefruit juice, any naranjin containing products such as pomelos, Seville orange products should also be included here.

12.1.9.1. Sponsor's Answer

Based on the University of Washington's Drug Interaction Database and FDA/EMA DDI guidance, pomelos and Seville orange products are not considered potent or moderate CYP3A inhibitors. Therefore it is argued that no change is required for the Australian PI.

12.1.9.2. Evaluator's response and acceptability

The evaluator accepts the sponsor's comments with no changes made in the Australian PI.

12.1.10. Draft PI Comment 10

Ceritinib is conditionally approved overseas only. Given that TGA does not have conditional approval, the evaluator thinks communication regarding the limitations of the data (small number of patients included in the non-randomised setting) in the PI should be stated clearly.

12.1.10.1. Sponsor's Answer

The sponsor has acknowledged the recommendation

12.1.10.2. Evaluator's response and acceptability

The Australian PI has been appropriately revised to the evaluator's satisfaction.

12.1.11. Draft PI Comment 11:

While the increased lipase and amylase observed in the clinical trial were generally mild, there were instances where it was associated with abdominal pain. In a single arm study, the causation is often difficult to determine, therefore, the evaluator thinks it is reasonable to include this as a warning in the Australian PI, as it is in the Canadian Product Monograph.

12.1.11.1. Sponsor's Answer

This has been acknowledged and sponsor accepted the recommendation.

12.1.11.2. Evaluator's response and acceptability

The evaluator thinks this has been revised satisfactorily.

12.1.12. Draft PI Comment 12

The safety dataset only included 525 patients, which is a comparatively small number of patients for a new drug entity, especially in the absence of randomised controlled trial. Therefore accurate safety issues can still be difficult to identify. The evaluator thinks this very important limitation should be clearly stated in the PI, with appropriate boxed warning for the AESI, such as hepatotoxicity, Prolonged QT interval and interstitial lung disease/pneumonitis included in the Australian PI.

12.1.12.1. Sponsor's Answer

The sponsor has included the safety limitations under the Adverse Effects section of the PI now.

12.1.12.2. Evaluator's response and acceptability

The evaluator has reviewed the revised version and found them acceptable.

12.1.13. Draft CI Comment 13

In regard to Use in Pregnancy, the evaluator agrees with the appraisal in the text as well as the animal data presented. Does this constitute Category X according to the Australian guideline given the severity and number of species affected?

12.1.13.1. Sponsor's Answer

The nonclinical data does not indicate a 'high risk of causing permanent damage'. However the sponsor will take on board the outcome of the first round nonclinical assessment.

12.1.13.2. Evaluator's response and acceptability

The evaluator thinks sponsor's comments are reasonable. Given that there is no clinical data, the evaluator will be guided by the outcome of the first round nonclinical assessment. If the nonclinical assessor is of the view that ceritinib does not have a high risk of causing permanent damage in the animal model, then category D designation would be reasonable.

12.1.14. Question 1

Ceritinib is conditionally approved overseas only. Given that TGA does not have conditional approval, the evaluator thinks communication regarding the limitations of the data in the PI should be stated clearly.

12.1.14.1. Sponsor's Answer

This has been addressed in Draft PI Comment 10.

12.1.14.2. Evaluator's response and acceptability

As per Draft PI Comment 10.

12.1.15. Question 2

Given the current lack of specific data in patients with moderately to severely impaired hepatic function, CHMP has mandated the following wording on their Summary of Product Characteristic (SmPC): '*Ceritinib is not recommended in patients with moderate to severe hepatic impairment'*. However, the evaluator notes that the US Prescribing Information simply stated that a recommended dose has not been determined for patients with moderate to severe hepatic impairment. Similarly the Canadian Product Monograph stated, '*Caution should be used in patients with hepatic impairment'*. Our PI is in line with the US and Canada where it states 'caution should be used in patients with moderate to severe hepatic impairment'. The evaluator thinks it is to the patient's best interest to be more conservative in the wording of this issue until hepatic impairment data (Study A2110) becomes available, particularly given that hepatotoxicity was observed in the efficacy-safety study for the target population. Consideration should be made to change the phrasing to '*Ceritinib is not recommended in patients with moderate to severe hepatic impairment*'. In addition, is there an update in the study in non-cancer patients with varying degrees of impaired hepatic function (A2110)?

12.1.15.1. Sponsor's Answer

As per Draft PI Comment 5.

12.1.15.2. Evaluator's response and acceptability

As per Draft PI Comment 5.

12.1.16. Question 3

The evaluator has concerns regarding expected AE rates in patients with weight significantly less than 60 g, given the established relationship between AE and ceritinib exposure. The evaluator cannot see any specific data addressing this and a comment from sponsor is necessary.

12.1.16.1. Sponsor's Answer

The effect of body weight on Ceritinib exposure was estimated using model-based simulation. The simulation estimated that the AUCss in patients with lower body weight (<60kg) was 1.15-fold higher than the reference body weight group (60-80 kg). Despite this, it appears that the incidence of the exposure-dependent safety endpoints such as ALT/AST elevation, hyperglycaemia and QTc prolongation was comparable across the different weight groups.

12.1.16.2. Evaluator's response and acceptability

The evidence presented by the sponsor would suggest that the predicted higher exposure in the lower body weight range is unlikely to result in a safety concern. The evaluator is happy that no adjustment is recommended based on patient's body weight.

12.1.17. Question 4

The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, I think it would be reasonable to include this in the PI. The evaluator would also like to ask the sponsor whether such studies are underway. If such studies are not being planned, the sponsor should justify the reasons for it. Submission for evaluation should be condition of registration.

12.1.17.1. Sponsor's Answer

As per Draft PI Comment 7.

12.1.17.2. Evaluator's response and acceptability

As per Draft PI Comment 7.

12.1.18. Question 5

Ceritinib might induce CYPs regulated by PXR. For some PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if UGTs are induced. The evaluator notes that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced with concomitant use of ceritinib was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.

12.1.18.1. Sponsor's Answer

As per Draft PI Comment 6.

12.1.18.2. Evaluator's response and acceptability

As per Draft PI Comment 6.

12.1.19. Question 6

According to the EU Guideline on Interactions, all important CYPs (as listed in the guideline) should be evaluated for time-dependent inhibition. Such data seems to be lacking for CYP1A2, CYP2C8, CYP2C19, and CYP2D6. Are there plans to examine this?

12.1.19.1. Sponsor's Answer

CYP2B6, CYP2C8 and CYP2C19 have been evaluated for time-dependent inhibition in a follow-up study now and it showed no apparent time-dependent inhibition of those enzymes at concentrations of up to 50 μM.

12.1.19.2. Evaluator's response and acceptability

The evaluator is satisfied with the sponsor's response.

12.1.20. Question 7

The evaluator notes some discrepancy in the efficacy results in the Study X2101 and A2201 from the Full Clinical Study Report and the Clinical Overview Report. The evaluator has based this review on data from module 5 and assumes the difference was due to an update undertaken to produce the Clinical Overview Report? This accounted for some discrepant results of ORR and OIRR in my report versus that of the draft Australian PI (which is based on the Clinical Overview Report). Having said that, the differences are trivial and do not change the overall assessment.

12.1.20.1. Sponsor's Answer

As per Draft PI Comment 8.

12.1.20.2. Evaluator's response and acceptability

As per Draft PI Comment 8.

12.1.21. Question 8

The safety dataset only included 525 patients, which is a comparatively small number of patients for a new drug entity, especially in the absence of randomised controlled trial. Therefore accurate safety issues can still be difficult to identify. The evaluator thinks this very important limitation should be clearly stated in the PI, with appropriate boxed warning for the AESI.

12.1.21.1. Sponsor's Answer

As per Draft PI Comment 12.

12.1.21.2. Evaluator's response and acceptability

As per Draft PI Comment 12.

12.1.22. Question 9

The rates of dose reductions and interruptions in the pooled dataset are very high (74.9%), but the discontinuation rate due to ceritinib AEs is relatively low at (8.8%). This suggests that ceritinib is not a well-tolerated drug but the side effects seem to be managed with supportive measures and/or dose reduction. Majority of patients continued ceritinib despite the AEs. While this is reassuring that a significant proportion of patients in the clinical trials ended up receiving 600 mg of ceritinib or less and still deriving the efficacy, the evaluator wonders if starting at 600 mg would be justified, particularly given that there is little relationship between ceritinib exposure and clinical efficacy in PK studies. The evaluator would like the sponsor to comment on whether 600 mg should be the starting dose.

12.1.22.1. Sponsor's Answer

Nonclinical data demonstrate that the highest possible dose of ceritinib provides maximum anti-tumour activity and lead to a higher likelihood of efficacy in the setting of initial and more importantly, acquired crizotinib resistance which is the indication being sought here.

In the clinical data from Study X2101, the median relative dose intensity at the 750 mg daily dose was 82.8% of the planned dose. Dose reductions occurred throughout the treatment period and were not limited to the initial 2 cycles and the median duration of dose interruption was 1 week. Therefore a significant proportion of the study patients remained on the 750 mg dose, in which the median time to response for patients with a confirmed PR or CR was 6.1 weeks.

Furthermore, a randomised food effect study is being conducted to assess the steady-state PK and safety of reduced doses (450 mg and 600 mg) of ceritinib taken with a low-fat meal, as compared with 750 mg ceritinib taken in the fasted state in patients with metastatic ALK-positive NSCLC.

12.1.22.2. Evaluator's response and acceptability

The evaluator thinks the sponsor's response is acceptable and starting dose of 750 mg daily is reasonable currently given the following rationale:

- The pre-clinical data of superior anti-tumour effect with highest dose of ceritinib
- Relatively high dose intensity at 750 mg daily dose in Study X2101
- Manageable AE profile
- Sponsor efforts in exploring potential lower starting dose with food interaction study (Study Protocol CLDK378A2112). The results of this study is important given it is known that systemic exposure of ceritinib was increased when administered with a meal.

12.1.23. Question 10

In Hepatotoxicity under Precautions in the PI, it is stated that cases of hepatotoxicity occurred in less than 1% of patients treated with Zykadia in clinical studies'. This is slightly misleading in that it only refers to adverse drug reactions and not all adverse events. Furthermore, 'hepatotoxicity' was defined using Preferred Term of Drug-induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury and Hepatotoxicity, and does not include 'Abnormal liver function tests'. This should be corrected.

12.1.23.1. Sponsor's Answer

As per Draft PI Comment 1.

12.1.23.2. Evaluator's response and acceptability

As per Draft PI Comment 1.

12.1.24. Question 11

Hepatotoxicity is a common AE associated with ALK inhibitors. Given the intended second line place in therapeutics, after prior treatment with other ALK inhibitor, the sponsor should discuss whether a higher incidence or seriousness of hepatotoxicity might be expected in those patients.

12.1.24.1. Sponsor's Answer

The hepatotoxicity events were similar across the 3 studies (Study X2101, A2201 and A2203), and similar for ALK inhibitor-treated and ALK inhibitor-naïve patients. It appears that the hepatoxicity events were similar in incidence and seriousness, regardless of when patients received ceritinib.

12.1.24.2. Evaluator's response and acceptability

Based on the data presented, the evaluator agrees with sponsor's response.

12.1.25. Question 12

While the increased lipase and amylase observed in the clinical trial were generally mild, there were instances where it was associated with abdominal pain. In a single arm study, the causation is often difficult to determine, therefore, the evaluator thinks it is reasonable to include this as a warning in the Australian PI, as it is in the Canadian Product Monograph. Please comment.

12.1.25.1. Sponsor's Answer

As per Draft PI Comment 11.

12.1.25.2. Evaluator's response and acceptability

As per Draft PI Comment 11.

12.1.26. Additional Comment 1

Based on the population PK analysis, the steady-state AUC_{tau} in moderate renal impairment patients was 19% higher than normal subjects, so it seems reasonable to expect higher levels for severe renal impairment, despite the low excretion by the renal route. Therefore the evaluator thinks the inclusion of a general warning in the Australian PI under the section of 'Dosage Adjustment' is reasonable.

12.1.26.1. Sponsor's Answer

The population PK analysis revealed only a mild increasing trend for exposure in patients with mild or moderate impaired renal function and is not considered clinically relevant. Furthermore, the human mass balance study in healthy subjects reported that only 1.3% of radioactive administered dose was excreted in urine following a single oral dose of 750 mg of [^{14}C]-ceritinib.

12.1.26.2. Evaluator's response and acceptability

Based on the renal excretion data of ceritinib, it does appear that the kidney plays a negligible role in ceritinib elimination in human. The evaluator accepts the sponsor's response based on the data presented.

12.1.27. Additional Comment 2

Twenty-eight of the patients enrolled in Study A2101 appearing with no response neither on crizotinib nor ceritinib (non- responders on ALK-TKIs), could be false positives by the FISH testing or other mechanism of resistance was at play. The applicant should discuss the lack of response in eligible patients and what characterise responders versus non-responders at a molecular level.

12.1.27.1. Sponsor's Answer

Twenty patients had both SD or PD with initial crizotinib and subsequent ceritinib therapy in the Study X2101. All had positive ALK FISH test. There were no meaningful differences in efficacy by demographic and disease characteristics of these patients, such as region, age, gender, race and disease burden at baseline.

12.1.27.2. Evaluator's response and acceptability

The evaluator appreciates the complexity of the ALK-inhibitor resistance mechanisms and the sponsor's continuing efforts in exploring the potential biomarkers of response and resistance. [information redacted].The evaluator has no further comments in this regard.

12.1.28. Additional Comment 3

Microdose of ceritinib as a solution to IV formulation (the evaluator could not find anything in the clinical dossier addressing this issue and therefore absolute bioavailability cannot be ascertained).

12.1.28.1. Sponsor's Answer

Sponsor clarified that a robust estimate of the absolute bioavailability has already been provided using existing preclinical and clinical data.

12.1.28.2. Evaluator's response and acceptability:

The evaluator accepts the sponsor's explanations and that no further investigations into the absolute bioavailability of ceritinib are warranted.

Sponsor comments on the first round evaluation report

The sponsor has not made any other additional comments in regard to the first round evaluation report besides the response to the questions and comments raised in the first round report.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The responses to the Clinical questions have not altered the initial assessment of benefits.

The benefits of Zykadia in the proposed usage (in ALK-positive locally advanced or metastatic NSCLC previously treated with an ALK-inhibitor) are:

- Zykadia has an ORR of 37.1% in A2201 and 55.4% in X2101 in patients who were heavily pre-treated, with more than half of the patients having received at least 3 prior regimens including crizotinib. Similarly, the duration of response was long in both studies (median 9.2 months and 7.39 months, respectively).
- Furthermore, the PFS seen in these patients ranged from a median of 5.7 months in Study A2201 to 6.9 months in Study X2101, while preliminary median OS ranged from a median of 14

months in Study A2201 to not reached in Study X2101. These secondary efficacy measures were immature to draw definitive conclusions.

- While these results came from uncontrolled, open-label clinical trials and the primary endpoint was ORR based on investigator assessment, these ORR rates exceed what is expected with chemotherapy in this setting (ORR of 20% and PFS of 3 months in chemotherapy arm of the Phase III crizotinib trial) and indicates that patients who have progressed on a prior ALK inhibitor would have a high likelihood of responding to ceritinib and therefore derive a clinical benefit.
- Phase III comparative study in ALK-positive NSCLC previously treated with platinum doublet and crizotinib (ceritinib versus. chemotherapy) is ongoing (ClinicalTrials.gov Identifier: NCT01828112).

13.2. Second round assessment of risks

The responses to the Clinical questions have not altered the initial assessment of risks.

The risks of Zykadia in the proposed usage are:

- The most common adverse events observed across studies (comprising 525 patients exposed to ceritinib 750 mg, with a median duration of treatment of 33 weeks) were GI disorders (nausea, diarrhoea, vomiting and constipation), followed by general disorders and administrative site conditions, and investigations. The most frequently reported Grade 3-4 adverse events were increased ALT, increased GGT, increased AST, fatigue, diarrhoea, nausea and hyperglycaemia.
- Hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions and discontinuation (only 0.8% of patients). There were no AEs leading to death or cases of Hy's law.
- Interstitial lung disease/pneumonitis has been associated with Zykadia, a class-effect known for some TKIs. A total of 18 cases were detected in the trials presented in the dossier, with one outcome of death.
- Cardiac disorders including QT prolongation and bradycardia were observed. No deaths or Torsades de Pointes were observed. It appears that increased exposure of ceritinib was associated with increased QTc.
- While Zykadia-associated AEs appears manageable, Zykadia is not well tolerated. This is supported by the persistent and recurrent nature of the frequent AEs.

13.3. Second round assessment of benefit-risk balance

The responses to the Clinical questions have not altered the initial assessment of benefit-risk balance. The evaluator continues to believe that the benefit-risk balance of Zykadia, given the proposed usage, is favourable.

Although the true clinical benefit of Zykadia is unknown due to the limitations of immature PFS and OS data and the uncontrolled nature of the reported clinical trials, the impressive anti-tumour effect of Zykadia in previously heavily pre-treated patients is clinically meaningful in a population with limited options of treatment. From the literature, it is known that this degree of ORR is not usually observed in solid tumours including ALK-positive NSCLC after several lines of chemotherapy. In the Phase III crizotinib trial (Shaw AT et al, 2013), patients treated with chemotherapy in second line have shown an ORR of 20% only and a median PFS of 3.0 months.

Previous experience of crizotinib showed a clear initial response rate translating into true clinical benefit in ALK-positive lung cancer patients in Phase III trials; the evaluator thinks the currently available data could support approval of Zykadia given the similar mechanism of action, if

confirmatory data of the benefit of Zykadia could be provided through the ongoing Phase III clinical trial.

While ceritinib did not seem to be well tolerated based on the data, it was manageable. The high AE rates may also be related to the inherent nature of the target population in the studies, that is, heavily pre-treated patients. In view of the likely clinical benefit in an area of unmet needs, the profile of AEs presented is acceptable.

The evaluator believes the revised changes made to the Australian PI clearly communicate the potential risks and drug interactions to the prescribers. In addition the Risk Management Plan is satisfactory in ongoing monitoring of the safety profile of Zykadia.

14. Second round recommendation regarding authorisation

Based on the clinical data originally submitted, as well as the responses to the Clinical questions, the evaluator recommends that the application for Zykadia be approved.

15. References

American Cancer Society. Cancer Facts & Figures 2013.

Australian Cancer Incidence and Mortality (ACIM) Books – Lung Cancer for Australia (ICD10 C33-C34). http://www.aihw.gov.au/acim-books (accessed July 2015)

Bang YJ. The potential for crizotinib in non-small cell lung cancer: a perspective review. Ther Adv Med Oncol 2011;3:279-91.

Camidge DR et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a Phase I study. Lancet 2012;13:1011-9.

Camidge DR and Doebele RC. Treating ALK-positive lung cancer – early successes and future challenges. Nature 2012;9:268-77.

Ciuleanu T et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, Phase III study. Lancet 2009: 374:1432-40.

Doebele RC et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-82.

Ettinger DS et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2010;8:740-801.

Friboulet L et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov 2014;4:662-73.

Fossella FV. Randomzied Phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-62.

Gainor JF et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res 2013;19:4273-81.

Gettinger S. A decade of advances in treatment for advanced non-small cell lung cancer. Clin Chest Med 2011;32:839-51.

Hanna N et al. Randomized Phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.

Katayama R et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 2012;4:120ra17.

Ma PC. Personalized targeted therapy in advanced non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:eS56-60.

Molina JR et al. Non-small cell lung cancer; epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.

NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer Version .2015

Ou SH. Crizotinib: a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. Drug Des Devel Ther 2011;5:471-85.

Rodig SJ et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-23.

Scagliotti GV et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.

Shaw AT et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.

Shaw AT et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.

Shepherd FA. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.

Soda M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.

Paz-Ares L. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, Phase III, randomised controlled trial. Lancet Oncol 2012;13:247-55.

Vansteenkiste J et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;Suppl 6:vi89-98.

Wong DW et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-33.

Yang P et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. J Thorac Oncol 2012;7:90-7

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au