18 May 2017
EMA/386332/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Zykadia

International non-proprietary name: ceritinib

Procedure No. EMEA/H/C/003819/II/0012

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AEMPS | Agencia Española de Medicamentos y Productos Sanitarios |
| AESI | Adverse events of special interest |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUCinf | Area under the plasma concentration-time curve extrapolated to infinity |
| AUCtau | Area under the curve (exposure) to the end of the dosing period |
| BM | Brain Metastases |
| BIRC | Blinded Independent Review Committee |
| CDS | Core Data Sheet |
| CI | Confidence interval |
| CLcr | Creatinine clearance |
| Cmax | Peak concentration |
| CNS | Central nervous system |
| CR | Complete response |
| CRF | Case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough | Trough concentration |
| DCR | Disease control rate |
| DMC | Data Monitoring Committee |
| DOR | Duration of response |
| DOIR | Duration of intracranial response |
| ECG | Electrocardiogram |
| EORTC-QLQC30 | The European Organization for Research and Treatment of Cancer's core quality of life questionnaire |
| EU | European Union |
| EQ-5D | The EuroQOL five dimensions index |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FPFV | First patient first visit |
| GGT | Gamma-glutamyltransferase |
| GI | Gastrointestinal |
| HR | Hazard ratio |
| ICBR | Intracranial clinical benefit rate |
| IDCR | Intracranial disease control rate |
| IHC | Immunohistochemistry |
| ILD | Interstitial lung disease |
| IRT | Interactive response technology |
| iv | Intravenous |
| LC13 | Lung cancer specific questionnaire |
| LCSS | Lung cancer symptom scale |
| LPLV | Last patient last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPA | Medical Products Agency |
| NCCN | National Comprehensive Cancer Network |

| | |
|---|---|
| NCI-ODWG | National Cancer Institute Organ Dysfunction Working Group |
| NSCLC | Non-small cell lung cancer |
| NE | Not-estimable |
| OIRR | Overall intracranial response rate |
| ORR | Overall response rates |
| OS | Overall survival |
| PD | Disease progression/progressive disease |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PPIs | Proton pump inhibitors |
| PPS | Per-Protocol Set |
| PR | Partial response |
| PRO | Patient reported outcome |
| PS | Performance status |
| PSUR | Periodic Safety Update Report |
| PT | Preferred term |
| QoL | Quality of life |
| RDI | Relative dose intensity |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RPSFT | Rank-preserving structural failure time |
| SAE | Serious adverse event |
| SCP | Summary of clinical pharmacology |
| SCE | Summary of clinical efficacy |
| SCS | Summary of clinical safety |
| SD | Stable disease |
| SmPC | Summary of Product Characteristics |
| SOC | System organ class |
| TBILI | Total bilirubin |
| TTR | Time to response |
| TKI | Tyrosine kinase inhibitor |
| ULN | Upper limit of normal |
| US | United States |
| USPI | US Prescribing Information |
| VAS | Visual analogue score |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 5 December 2016 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of Indication to include new indication/population for Zykadia as first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC); as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated to update the information based primarily on the supporting study, CLDK378A2301 (ASCEND-4). The Package Leaflet is updated in accordance. An updated Risk Management Plan (Version 6) is also included in the application.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

## *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Scientific advice*

The applicant did not seek Scientific Advice at the CHMP.

### 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Bjorg Bolstad

| Timetable | Actual dates |
|---|---|
| Submission date | 5 December 2016 |
| Start of procedure: | 24 December 2016 |
| CHMP Rapporteur Assessment Report | 1 March 2017 |
| CHMP Co-Rapporteur Assessment Report | 17 February 2017 |
| PRAC Rapporteur Assessment Report | 1 March 2017 |
| PRAC members comments | n/a |
| PRAC Outcome | 9 March 2017 |
| CHMP members comments | n/a |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 17 March 2017 |
| Request for supplementary information (RSI) | 23 March 2017 |
| Submission of responses | 18 April 2017 |
| Re-start of procedure | 19 April 2017 |
| PRAC Rapporteur Assessment Report | 5 May 2017 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | n/a |
| CHMP Rapporteur Assessment Report | 5 May 2017 |
| PRAC Outcome | 5 May 2017 |
| CHMP members comments | 8 May 2017 |
| Updated CHMP Rapporteur Assessment Report | 12 May 2017 |
| Opinion | 18 May 2017 |

# 2. Scientific discussion

## 2.1. Introduction

**About the disease**

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). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al, 2013).

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 (epidermoid) carcinoma (Brambilla et al, 2014 and Schrump DS et al NSCLC; Principles and Practice of Oncology. 9th Edition. 2011). Recently, histology has emerged as a predictive factor for pemetrexed efficacy (Scagliotti G. et al 2011) and a determinant of toxicity with bevacizumab for patients with advanced NSCLC (Johnson DH. et al, 2004).

For the majority of patients, NSCLC is diagnosed at an advanced stage with an overall poor prognosis. The overall survival (OS) for metastatic NSCLC is dismal with 5-year survival of <5% (Lindsey A. et al, 2016).

In addition, over the past decade molecular subsets based on the presence of driver mutations have been identified. In particular, epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements were the first molecular alterations shown to confer sensitivity to specific targeted therapies.

According to the ESMO Clinical Practice Guidelines for metastatic NSCLC (Novello S. et al, 2016), in the absence of driver mutations first-line platinum-based doublet chemotherapy (four with a maximum of six cycles) is recommended in patients with good performance status, based on the observed prolonged survival and improved quality of life (QoL). A comparable efficacy has been observed with several regimens including cisplatin and carboplatin combinations with gemcitabine, paclitaxel and docetaxel (Schiller JH. et al, 2002). The addition of bevacizumab to platinum-based backbone regimen improved OS in non-squamous NSCLC patients with ECOG PS 0-1 (Sandler A. et al, 2006). Therefore, the combination of bevacizumab and platinum-based chemotherapy should be considered in eligible non-squamous NSCLC.

In case of epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, approved target therapy agents are available.

Crizotinib has been authorised on 23 November 2015 for the first-line treatment of adults with ALK-positive advanced NSCLC. In the full analysis population of study 1014, the median PFS was 10.9 months for crizotinib and 7.0 months for chemotherapy. The HR comparing crizotinib with chemotherapy was 0.454 (95% CI: 0.346, 0.596), with a p-value of <0.0001 (1-sided, based on a stratified log-rank test).

**About the product**

Ceritinib is a second-generation, orally, selective ALK-tyrosine kinase inhibitor (TKI), which inhibits auto-phosphorylation of ALK, ALK-mediated phosphorylation of downstream signalling proteins and proliferation of ALK-dependent cancer cells both in vitro and in vivo.

The recommended dosage and schedule as single agent therapy in NSCLC is 750 mg once daily (21 days cycle). Treatment should continue as long as clinical benefit is observed.

Ceritinib received conditional marketing authorisation in the EU on 6 May 2015 for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC previously treated with crizotinib.

This application for an extension of indication provides data from the randomised, open-label, multicentre, active-controlled Phase III study for the first-line treatment of ALK-positive patients with stage IIIb, or stage IV NSCLC (Study CLDK378A2301, referred to with abbreviated study code A2301).

Based on the results from this single pivotal study, the MAH is submitted an application for an extension of the indication as follows:

*Zykadia is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).*

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

To support this application, the MAH submitted a 26–week chronic toxicity study conducted with ceritinib in rats and a 39-week chronic toxicity study conducted with ceritinib in Cynomolgus monkeys.

### 2.2.2. Toxicology

***Repeat dose toxicity***

26-week rat study with an 8-week recovery period - Study 1370208 (GLP)

Administration of ceritinib was tolerated in rats when given daily by oral gavage for 26 weeks at doses up to 20 mg/kg/day. Slightly lower mean body weights and lower weekly mean body weight change were noted in males given 20 mg/kg/day. Ceritinib-related haematology effects consisted of minimally lower haemoglobin concentration and haematocrit for females given 20 mg/kg/day due to minimally lower mean corpuscular volume and mean corpuscular haemoglobin. Ceritinib-related clinical chemistry effects included minimally lower albumin:globulin ratio for males given 10 or 20 mg/kg/day and females given 20 mg/kg/day. Mildly lower triglyceride concentration for males and minimally lower magnesium and inorganic phosphorus concentrations for females were observed at 20 mg/kg/day.

As with previously conducted studies with ceritinib, microscopic findings were observed in the liver, duodenum, bile duct, lymph node, and lungs. Following an 8-week recovery phase, partial or full recovery was apparent for all findings in animals given 20 mg/kg/day. The no observed effect level (NOEL) was not attained because minimal changes in the bile duct and slight to minimal changes in the liver and lymph nodes were observed at the lowest dose (3 mg/kg/day). Corresponding Cmax and AUC0-24h values at 20 mg/kg/day were 1290 ng/mL and 22400 ng.hr/mL, respectively, for males, and 1260 ng/mL and 21800 ng.hr/mL, respectively, for females. These exposure values are similar to those observed clinically with ceritinib.

39-week monkey study with an 8-week recovery period – Study 1370280 (GLP)

Administration of ceritinib was well tolerated in cynomolgus monkeys as a daily gavage administration at dose levels up to 30 mg/kg/day for at least 39 weeks. Test article-related clinical findings were limited to excessive salivation at 30 mg/kg/day. In addition, mild (males) or moderate (females) reductions in body weight gain were observed at 30 mg/kg/day. Ceritinib-related effects on clinical pathology test results were limited to minimally to mildly increased ALT activity for animals given 30 mg/kg/day and minimally to mildly higher post-dose glucose concentrations, relative to controls, for animals given ⩾10 mg/kg/day. Neither of these findings were considered adverse. A mechanism for this modest effect on post-dose glucose concentration was undetermined, but because animals were not fasted before sample collections, differences in relative timing of food consumption between groups and/or individuals may have impacted the results. Serum glucose concentration appeared unaffected at the end of the recovery phase, but it was only assessed once during the day. Insulin and haemoglobin A1C concentrations appeared unaffected by ceritinib.

Ceritinib-related microscopic findings were present at doses ⩾10 mg/kg/day. Changes were similar to those observed in the 13-week toxicity study and included minimal to moderate increased mixed cell infiltrates in the common and cystic (extra-hepatic) bile ducts (males only), minimal to slight infiltrates of macrophages and minimal increased mixed cell infiltrates in the major duodenal papilla, and minimal sinus histiocytosis in the mesenteric lymph node. Ceritinib-related histological changes along the biliary tree were restricted to extra-hepatic bile ducts. At the end of recovery, macrophage infiltrates in the major duodenal papilla and

sinus histiocytosis in the mesenteric lymph node were noted but were of reduced incidence and severity, indicating partial recovery. Corresponding Cmax and AUC0-24h values at 30 mg/kg/day were 1350 ng/mL and 23,100 ng.hr/mL, respectively, for males, and 1340 ng/mL and 25,100 ng.hr/mL, respectively, for females, which are similar to the plasma exposures seen clinically. The no effect level in this study (NOEL) was considered to be 3 mg/kg/day, and the No Observable Adverse Effect Level (NOAEL) was considered to be 30 mg/kg/day.

## 2.2.3. Ecotoxicity / environmental risk assessment

The refined Fpen has been recalculated based on prevalence of the disease (complete prevalence of ALK-positive NSCLC). The predicted environmental concentration (PEC) of ceritinib (0.034 µg/L) was above the trigger value for a Phase II Tier A assessment.

Nevertheless, Phase II Tier A risk calculations based on available epidemiological data were performed and are presented below.

**Outcome of Tier A fate and effects analysis**

**Surface water assessment**

Refined PECsurface water = 0.034 µg/L

PNECsurface water = 4.5 µg/L

**PEC / PNECsurface water** = 0.034 µg/L / 4.5 µg/L = **0.00756**

**Microorganisms / sewage treatment plant assessment**

Refined PECmicroorg = 0.34 µg/L

PNELR microorg. $\geqslant$ 10000 µg/L

PNECmicroorg. $\geqslant$ 1350 µg/L (limit of water solubility / 10)

**PEC / PNECmicroorg**. = 0.34 µg/L / $\geqslant$ 1350 µg/L = $\leqslant$ **0.00025**

**Groundwater assessment**

PECgroundwater = 8.5 ng/L

PNECgroundwater = 41 µg/L

**PEC / PNECgroundwater** = 0.0085 µg/L / 41 µg/L = **0.00021**

The risk ratios of the Phase II Tier A risk assessment based on predicted environmental concentrations calculated with epidemiology data remain significantly below a risk ratio of 1.

## 2.2.4. Discussion and conclusion on non-clinical aspects

Two new repeat-dose toxicology studies (26-week study in rat and 39-week study in monkey) have been submitted. Increased treatment duration did not change the toxicity profile of ceritinib. The toxicological findings in these studies were similar to what has already observed in the previous shorter repeat-dose toxicology studies. Therefore, there are no changes to the conclusions from the previous non-clinical safety evaluation and to the SmPC in section 5.3.

According to the Q&A document on Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010) the refined Fpen has been recalculated based on prevalence of the disease (complete prevalence of ALK-positive NSCLC). The predicted environmental concentration (PEC) of ceritinib (0.034 µg/L) was above the tigger value for a Phase II Tier A assessment. The results of the

risk ratios of the Phase II Tier A risk bases on PEC calculated with prevalence data of the disease show that no risk for surface waters, microorganisms in sewage treatment plants and for groundwater is expected.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ceritinib. Considering the above data, ceritinib is not expected to pose a significant risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

This application is based primarily on a Phase III, open-label, randomised, active-controlled global study, CLDK378A2301 (ASCEND-4), for the first-line treatment of ALK positive advanced NSCLC patients.

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Study (Data cut-off) | Number of patients | Study details | Study status |
|---|---|---|---|
| **Registration study contributing to pivotal efficacy and safety data of ceritinib** | | | |
| [Study A2301] Registration study (24-Jun-2016) | N=376 (all 189randomized to ceritinib received ceritinib, and 175 out of 187 randomizedto chemotherapy received chemotherapy) | Phase III, open-label, randomized, active-controlled, global study of oral ceritinib (750 mg once daily, fasted) vs. standard first-line chemotherapy (platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after 4 cycles) in adult patients with advanced (stage IIIB; who were not candidates for definitive multimodality therapy) or metastatic (stage IV) non-squamous NSCLC (hereafter referred to as advanced NSCLC), harboring an ALK rearrangement (ALK-positive), that was confirmed using the VENTANA ALK (D5F3) CDx Assay (Ventana immunohistochemistry (IHC) test) by a Novartis designated central laboratory. Patients were previously not treated with any systemic anti-cancer therapy (including ALK inhibitor) with exception of neo-adjuvant or adjuvant therapyif progression/relapse had not occurred within 12 months after end of neo-adjuvant or adjuvant therapy.<br>The patients randomized to the chemotherapy treatment were allowed to crossover to receive ceritinib treatment in the extension treatment phase, only after BIRC-confirmed RECIST-defined PD was documented. | Ongoing, enrollment complete |
| **Additional studies contributing to key safety data of ceritinib (Pooled dataset)** | | | |
| [Study X2101] 03-May-2016 | N=255[a] | Phase I (in patients with ALK-positive tumors) with extension phase (in patients with ALK-positive NSCLC), multi-center, dose-escalation study of oral ceritinib including those patients who had received prior treatment with chemotherapy (any number of prior chemotherapies) and/or crizotinib. Ceritinib was administered at a dose of 50-750 mg once daily fasted in the dose-escalation phase, and 750 mg once daily fasted in the expansion phase. | Ongoing, enrollment complete |
| [Study X1101] 28-Jan-2016[c] | Dose-escalation phase: N=19[b]<br>Expansion phase: N=3<br>N=9 at 750 mg[b] | A Phase I, multi-center, dose-escalation study of oral ceritinib (300-750 mg once daily fasted in the dose-escalation phase; 750 mg once daily fasted in the expansion phase) in Japanese patients with ALK-positive tumors; prior ALK inhibitor therapy was allowed. | Completed |
| [Study A2201] 29-Mar-2016[d] | N=140 | A Phase II, multi-center, single-arm study of oral ceritinib (750 mg once daily, fasted) in adult patients with ALK-positive NSCLC previously treated with crizotinib, and 1-3 lines of chemotherapy. All patients received crizotinib as their last anti-neoplastic medication prior to their first dose of ceritinib as per the inclusion criteria. | Completed |
| [Study A2203] 15-Nov-2015 | N=124 | Phase II, multi-center, single-arm study of oral ceritinib (750 mg once daily, fasted)in crizotinib naïve patients with ALK-positive NSCLC, who had received up to 3 lines of chemotherapy. | Ongoing, enrollment complete |

| | | | |
|---|---|---|---|
| [Study A2109]<br>30-Oct-2015 | Phase I (5–day PK run-in): N=20<br>Phase II: N=103 | A Phase I/II, multicenter, open-label, single-arm study of oral ceritinib (single dose of 750 mg in the PK run-in Phase; 750 mg once daily fasted in Phase II) in adult Chinese patients with ALK-positive advanced NSCLC previously treated with crizotinib and/or chemotherapy (maximum 2 lines of chemotherapy). All the patients received crizotinib as the last regimen prior to study entry, although this was not a mandatory criterion for patient inclusion. | Ongoing, enrollment complete |
| [Study A2303]<br>26-Jan-2016 | N=231<br>Ceritinib=115<br>Chemotherapy=113 with 73 on docetaxel and 40 on pemetrexed[e] | A Phase III, global, randomized open-label study of oral ceritinib (750 mg once daily fasted) versus standard chemotherapy (based on Investigator's choice: pemetrexed/docetaxel) in adult patients with ALK-positive NSCLC previously treated with chemotherapy (one or two prior regimens, including one platinum-based doublet) and crizotinib. The patients randomized to the chemotherapy treatment were allowed to crossover to receive ceritinib treatment in the extension treatment phase, only after BIRC-confirmed RECIST-defined PD was documented. | Ongoing, enrollment complete |
| [Study A2301]<br>(Details mentioned above) | | | |

[a] 246 patients with NSCLC and 9 patients with another malignancy
[b]18 patients with NSCLC (5 treated at 750 mg) and 1 patient with another malignancy (treated at 750 mg)
[c] 1 patient was rolled-over to the extension protocol.
[d] 16 patients who were still benefitting from treatment with ceritinib per Investigator judgement continued to receive ceritinib outside of StudyCLDK378A2201 (e.g., through a separate protocol, patient support program).
[e] 116 patients randomized to chemotherapy arm; 113 patients actually treated with at least one dose.
NSCLC=non-small cell lung cancer; ALK=anaplastic lymphoma kinase; IHC=immunohistochemistry; BIRC=Blinded Independent Review Committee; RECIST=Response Evaluation Criteria In Solid Tumors; PD=disease progression/progressive disease; PK=pharmacokinetic
Source: [Study A2301], [Study X2101], [Study X1101], [Study A2201], [Study A2203], [Study A2109], [Study A2303].

## 2.3.2. Pharmacokinetics

### Population PK

A population PK analysis was performed to characterise the PK of ceritinib in ALK-positive cancer patients (NSCLC and non-NSCLC) and to investigate the effects of intrinsic and extrinsic factors on the PK of ceritinib.

The population PK analysis was performed with 9782 ceritinib concentration values from 973 patients (NSCLC and non-NSCLC) who were treated with at least one dose of ceritinib and had at least one post-dose PK sample from in the studies LDK378X2101, LDK378X1101, LDK378A2201, LD378A2203, LDK378A2109, LDK378A2301, and LDK378A2303.

The treatment period began on Day 1 of Cycle 1. All patients were treated with ceritinib 750 mg administered orally on a once-daily dosing schedule under fasting conditions. Each treatment cycle was 21 days. The study consisted of trough PK sampling in all patients who received ceritinib treatment on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, and Cycle 6 Day 1.

**Table 1: PK parameter-covariate relationships included in full model development**

| PK Parameter | Continuous Covariates | Categorical Covariates |
|---|---|---|
| $CL/F_{ss}$ | Baseline body weight (WT0)<br>Baseline albumin (BALB), time-varying albumin (ALB)<br>Baseline ALT (BALT), time-varying ALT (ALT) | Gender (female *vs.* male)<br>Ethnicity (Caucasian, Chinese, Japanese, Other Asian, and Other) |
| V/F | Baseline body weight (WT0) | |
| $k_{out}$ | | Ethnicity (Caucasian, Chinese, Japanese, Other Asian, and Other) |
| $k_a$ | | Proton pump inhibitors (PPI)<br>$H_2$ receptor antagonists ($H_2$RA) |
| $F_{rel}$ | | Proton pump inhibitors (PPI)<br>$H_2$ receptor antagonists ($H_2$RA) |

$CL/F_{ss}$: apparent clearance at steady-state;
V/F: apparent volume of distribution;
$k_{out}$: first-order enzyme turnover rate constant;
$k_a$: first-order absorption rate constant;
$F_{rel}$: relative bioavailability and its typical value is fixed to 1

### Methodology

The population PK model was developed following 3 steps.

- First, a base model consisting of structural, random effects, and residual error models was developed.
- Second, a full model was developed by incorporating covariate effects of intrinsic factors (body weight, ethnicity, and hepatic function) and extrinsic factors (concomitant medications with acid-reducing agents (ARAs)) on the structural model parameters.
- Third, the final parsimonious model was obtained using stepwise backward elimination of covariate-parameter relationships.

The population PK of ceritinib was described by a one-compartment model with delayed first order absorption and time-dependent elimination. An empirical exponential function was used to allow the apparent clearance to decrease asymptotically over time.

The final population PK model was evaluated by a non-parametric bootstrap technique and a prediction-corrected visual predictive check (pcVPC). The effects of covariates on ceritinib systemic exposure at steady state ($AUC_{ss}$, $C_{max,ss}$, and $C_{min,ss}$) were assessed using model-based simulation procedures.

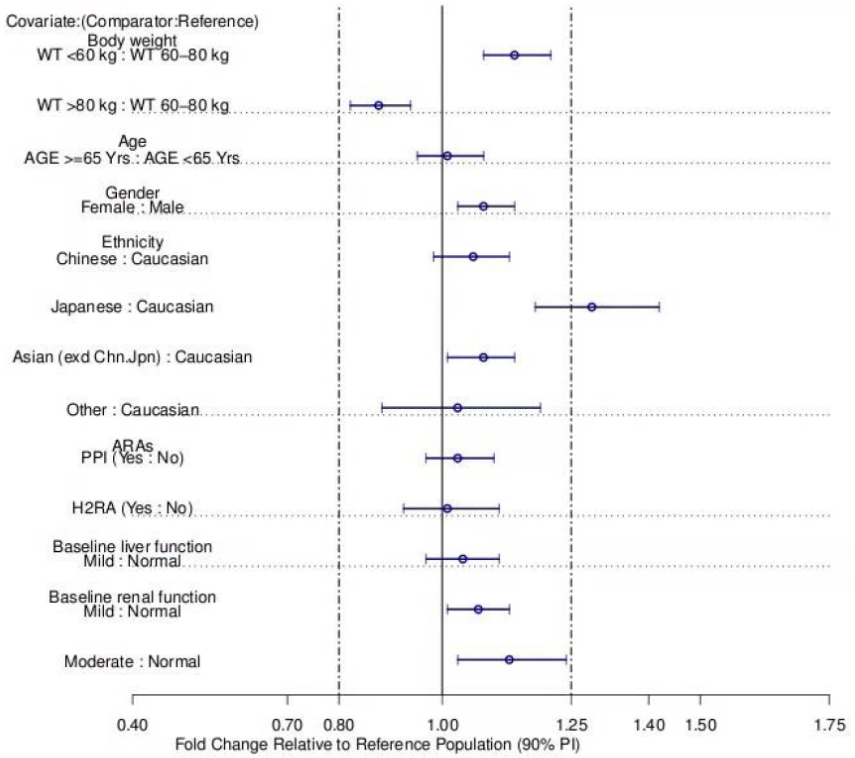
The final parameter estimates are given in Table 2.

**Table 2: Final pharmacokinetic model parameter estimates**

| Parameter | Original data | | 500 bootstrap replicates | | |
|---|---|---|---|---|---|
| | Estimate | RSE [%][a] | Estimate | RSE [%][a] | 95%CI |
| Fixed-effect | | | | | |
| $CL/F_{ss}$ ($\theta_1$) [L/hr] | 26.1 | 1.89 | 26.0 | 2.08 | 25.0, 27.1 |
| WT0 ~ $CL/F_{ss}$ ($\theta_{12}$) | 0.585 | 12.4 | 0.572 | 12.9 | 0.428, 0.709 |
| BALB ~ $CL/F_{ss}$ ($\theta_{13}$) | 0.264 | 36.4 | 0.265 | 36.1 | 0.0670, 0.469 |
| ALB ~ $CL/F_{ss}$ ($\theta_{14}$) | 0.250 | 37.6 | 0.254 | 38.1 | 0.0558, 0.437 |
| BALT ~ $CL/F_{ss}$ ($\theta_{15}$) | -0.107 | 24.0 | -0.110 | 24.7 | -0.169, -0.0627 |
| ALT ~ $CL/F_{ss}$ ($\theta_{16}$) | -0.0880 | 16.6 | -0.0880 | 16.8 | -0.116, -0.0574 |
| $\Delta CL/F$ ($\theta_2$) [L/hr] | 29.7 | 5.98 | 29.8 | 6.82 | 25.6, 33.7 |
| $k_{out}$ ($\theta_3$) [$day^{-1}$] | 0.148[c] | — | 0.148 | — | — |
| Japanese ~ $k_{out}$ ($\theta_{24}$) | 7.14 | 41.1 | 7.41[d] | —[e] | — |
| V/F ($\theta_4$) [L] | 3499 | 3.33 | 3485 | 3.62 | 3251, 3732 |
| WT0 ~ V/F ($\theta_{21}$) | 0.317 | 44.2 | 0.326 | 45.2 | 0.0075, 0.596 |
| $k_a$ ($\theta_5$) [$hr^{-1}$] | 0.450 | 5.07 | 0.450 | 4.55 | 0.415, 0.493 |
| $t_{lag}$ ($\theta_6$) [hr] | 0.759 | 1.30 | 0.759 | 1.33 | 0.738, 0.778 |
| $F_{rel}$ | 1[c] | — | — | — | — |
| $\sigma_{prop}$ ($\theta_7$) [%] | 22.0 | 2.43 | 21.8 | 2.79 | 20.5, 23.0 |
| $\sigma_{add1}$ ($\theta_8$) [ng/mL] | 10.6 | 12.6 | 10.7 | 10.8 | 8.46, 13.1 |
| $\sigma_{add2}$ ($\theta_9$) [ng/mL] | 80.6 | 18.6 | 80.1 | 21.5 | 42.3, 110 |
| $\sigma_{add3}$ ($\theta_{10}$) [ng/mL] | 8.15 | 59.9 | 18.5 | 101 | 2.55, 68.4 |
| Random-effect[b] | | | | | |
| $\omega CL_{ss}/F$ [%] | 29.9 | 14.9 | 30.0 | 18.1 | 24.5, 35.7 |
| $\omega \Delta CL/F$ [%] | 69.8 | 18.1 | 69.8 | 21.9 | 53.2, 85.2 |
| $\omega k_{out}$ [%] | 143 | 10.7 | 142 | 14.5 | 121, 161 |
| $\omega V/F$ [%] | 56.2 | 10.2 | 56.9 | 11.4 | 50.6, 63.1 |
| $\omega k_a$ [%] | 91.3 | 12.2 | 91.5 | 11.5 | 80.2, 102 |
| $\omega F_{rel}$ [%] | 22.5 | 29.6 | 22.0 | 31.6 | 14.1, 28.3 |

[a] Relative standard error is standard error as a percentage of population parameter estimates.
[b] Random-effect variability is reported as $\sqrt{\omega^2} \cdot 100$.
[c] Fixed; [d] Reported as median; [e] Standard error not reported by bootstrap.
Source: /vob/CLDK378X/pool/pkpd_002/pgm_04/C2001_2C2.nmctl
/vob/CLDK378X/pool/pkpd_002/pgm_04/calc.rse.R

The fold change of ceritinib geometric mean of steady-state exposure (AUCss) relative to reference groups is presented in Figure 1. Goodness-of-fit (GOF) plots are presented in Figure 2 and Figure 3, visual predictive checks (VPCs) in Figure 4, Figure 5, Figure 6 and conditional weighted residuals (CWRES) plots in Figure 7 and Figure 8, respectively.




Open circle is the fold change of $AUC_{ss}$ for a covariate group compared to $AUC_{ss}$ for its corresponding reference group, and horizontal line represents 90%PI of fold change.
Source: /vob/CLDK378X/pool/pkpd_002/pgm_04/plot.covEff.popauc.report.R

**Figure 1: Fold change of ceritinib geometric mean of steady-state exposure (*AUCss*) relative to reference groups**

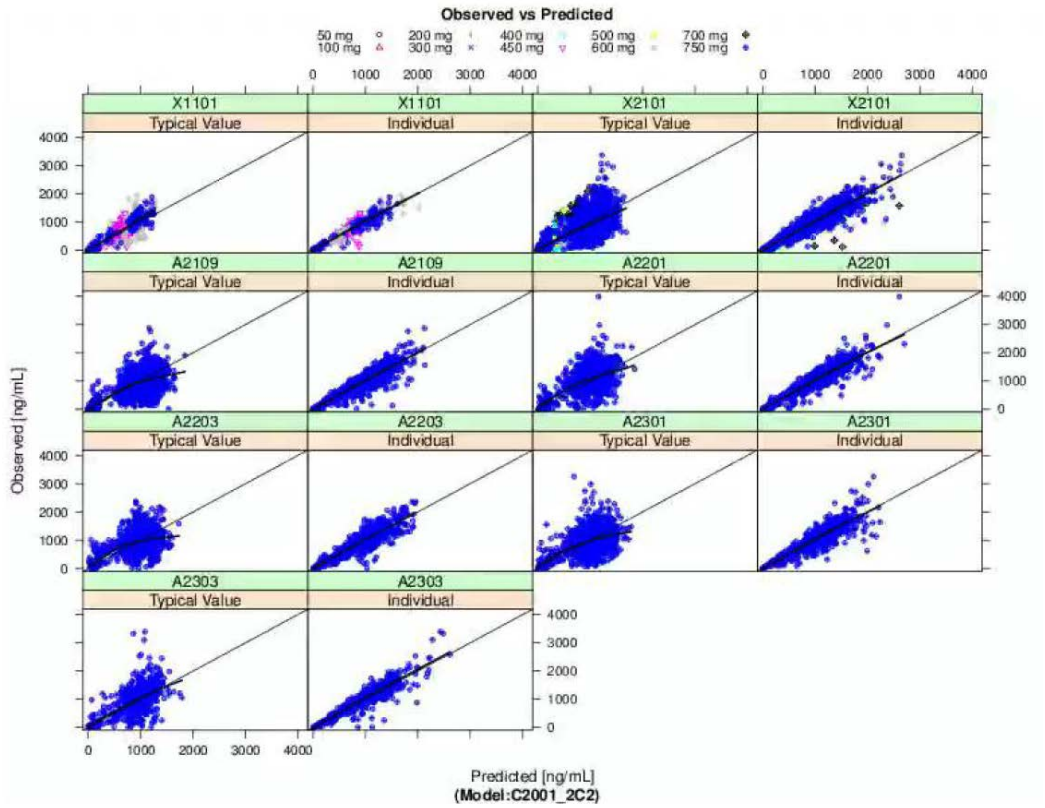



**Figure 2: Observed versus predicted for the final ceritinib population-PK model**

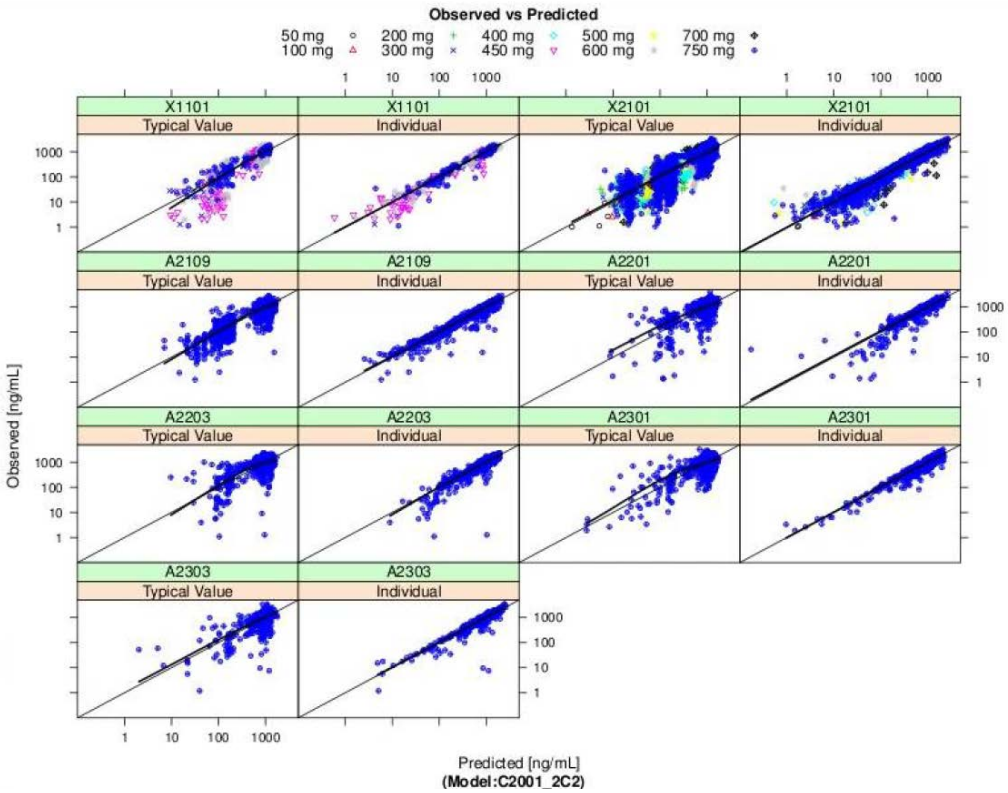
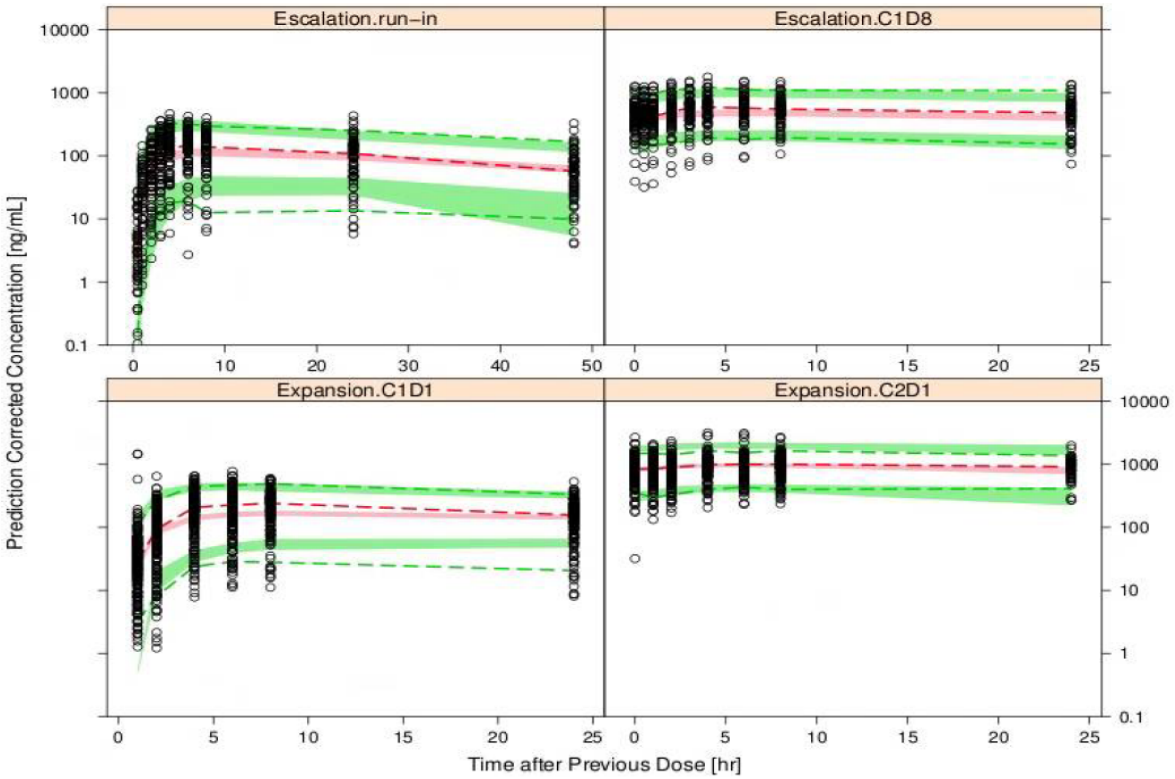
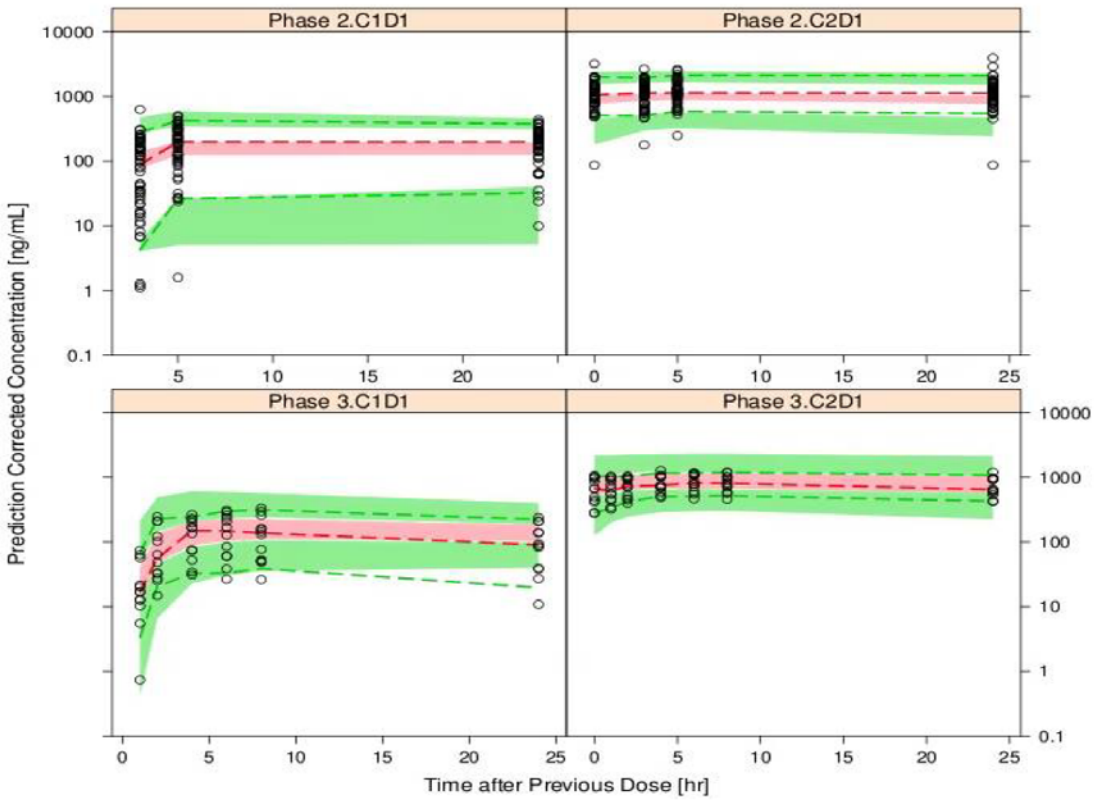



**Figure 3: Predictive check plot for the observed and simulated concentrations**



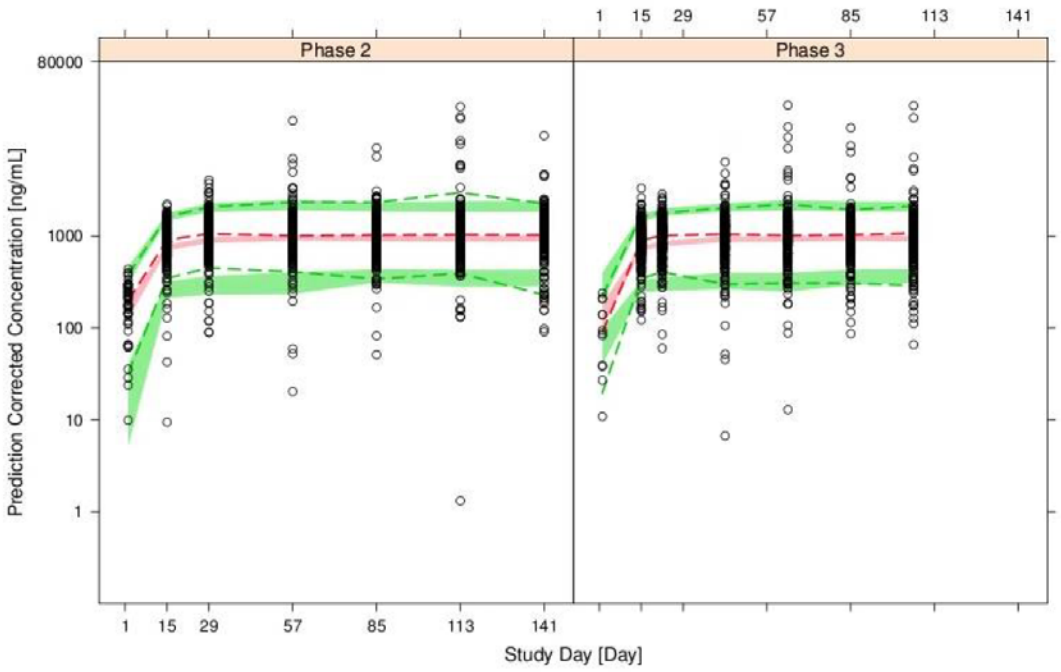

Prediction-corrected observed concentration is represented as open circle, and its 5th, 50th, and 95th percentiles are represented as dashed line. The shaded area is the 90% prediction interval of 5th, 50th, and 95th percentiles of prediction-corrected concentrations simulated by final model.

**Figure 4: Prediction-corrected visual predictive check for dense PK profiles in Study LDK378X2101 and Study LDK378X1101**



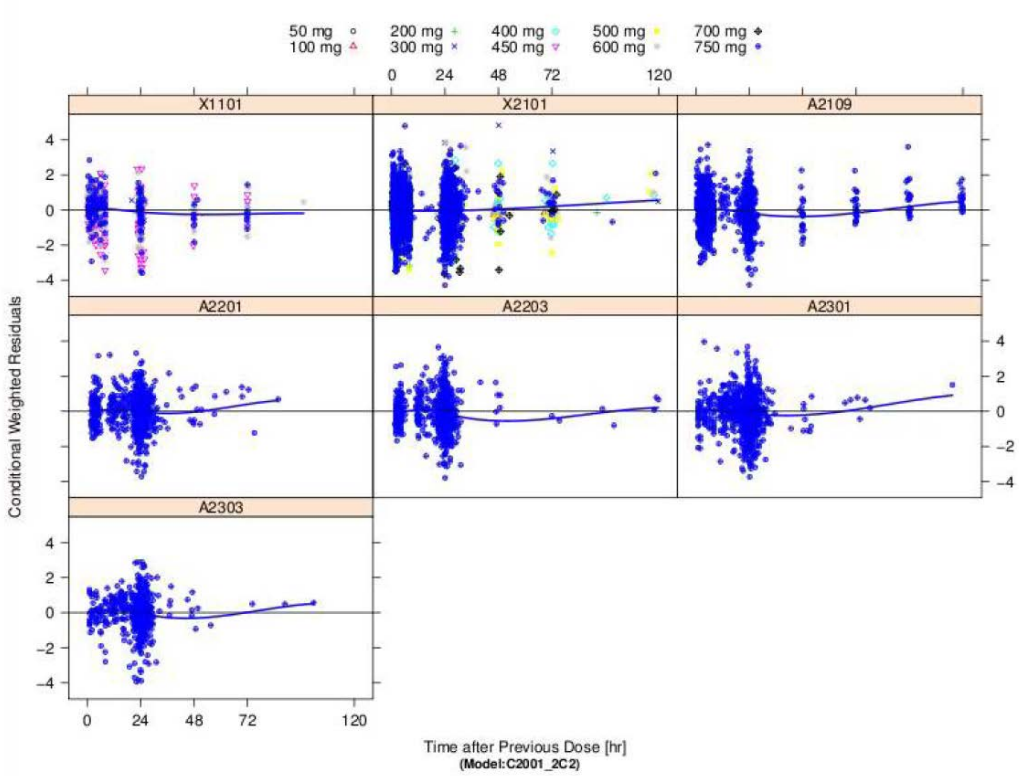

Prediction-corrected observed concentration is represented as open circle and its 5th, 50th, and 95th percentiles are represented as dashed line. The shaded area is the 90% prediction interval of 5th, 50th, and 95th percentiles of prediction-corrected concentrations simulated by final model.

**Figure 5: Prediction-corrected visual predictive check for sparse PK profiles in Studies LDK378A2201, LDK378A2203, LDK378A2301, and LDK378A2303**



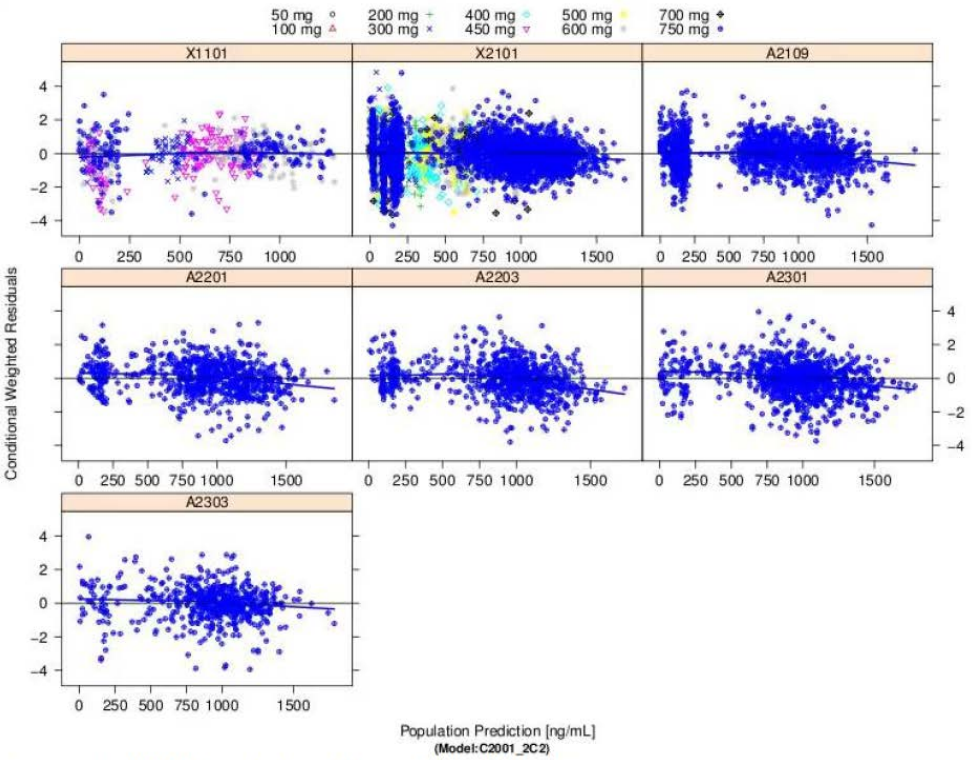

Prediction-corrected observed concentration is represented as open circle and its 5th, 50th, and 95th percentiles are represented as dashed line. The shaded area is the 90% prediction interval of 5th, 50th, and 95th percentiles of prediction-corrected concentrations simulated by final model.
Source: /vob/CLDK378X/pool/pkpd_002/pgm_04/plot.pcVPredCheck.R

**Figure 6: Prediction-corrected visual predictive check for trough data in Studies LDK378A2201, LDK378A2203, LDK378A2301, and LDK378A2303**




Source: /vob/CLDK378X/pool/pkpd_002/pgm_04/plot.CWRES.R

**Figure 7: CWRES, time after previous dose**




Source: /vob/CLDK378X/pool/pkpd_002/pgm_04/plot.CWRES.R

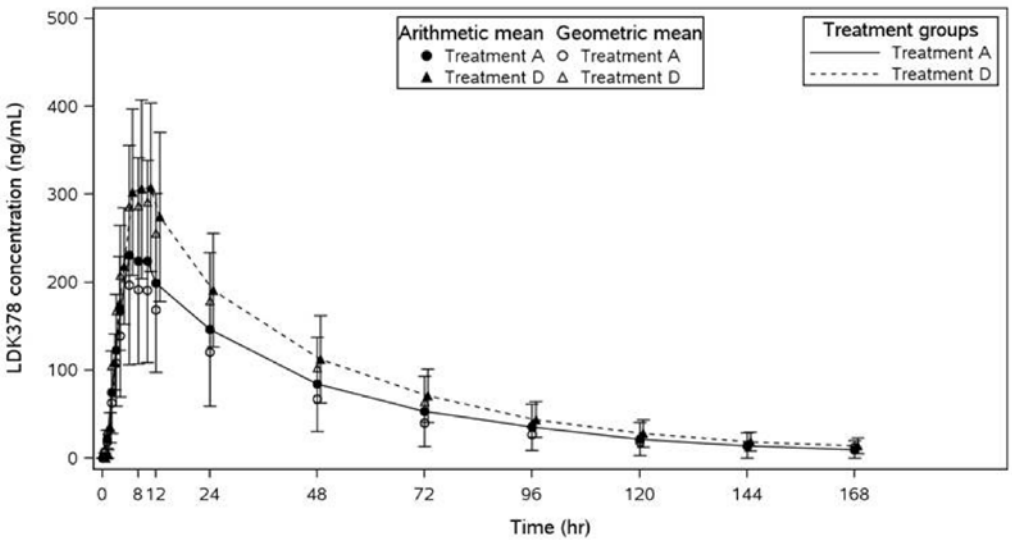
**Figure 8: CWRES, concentration (ng/ml)**

## *Absorption*

### *Food-drug interactions (A2108)*

Study LDK378A2108 was a randomised, open-label cross-over study to evaluate the relative bioavailability of a new tablet formulation of ceritinib in comparison to the reference ceritinib capsule formulation (Cohort 1) and to evaluate the effect of a light snack on the PK of ceritinib capsules (Cohort 3) in healthy subjects.

Compared to the fasted state, a light snack (containing approximately 100-300 calories and 1.5 grams of fat) increased $C_{max}$ and $AUC_{inf}$ following a single 750 mg oral dose of ceritinib in healthy subjects by 45% and 54%, respectively, in Study A2108 (Figure 9 and Table 3).




Note: Treatment A: ceritinib 750 mg under fasted condition, Treatment D: ceritinib 750 mg with a light snack.

Source: [Study LDK378A2113-Figure 11-1]

**Figure 9: Geometric mean and arithmetic mean (SD) concentration-time profiles for ceritinib after a single oral 750 mg dose under fasted condition or with a light snack**

**Table 3: Summary of statistical analysis of primary PK parameters for ceritinib Cohort 3 (Study A2108 – PAS)**

| | | | | | Treatment comparison | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 90% CI | |
| PK parameter (unit) | Treatment | n* | Adjusted geo-mean | Comparison(s) | Geo-mean ratio | Lower | Upper |
| AUClast (ng*hr/mL) | A | 11 | 8820 | | | | |
| | D | 12 | 13700 | D / A | 1.55 | 1.15 | 2.08 |
| AUCinf (ng*hr/mL) | A | 12 | 9390 | | | | |
| | D | 12 | 14500 | D / A | 1.54 | 1.19 | 1.99 |
| Cmax (ng/mL) | A | 12 | 213 | | | | |
| | D | 12 | 308 | D / A | 1.45 | 1.15 | 1.82 |
| Tmax (hr) | A | 12 | 6.02 | | | | |
| | D | 12 | 8.02 | D - A | 1.98 | -4.00 | 4.00 |

Treatment A = ceritinib 750 mg capsules under fasted condition; Treatment D = ceritinib 750 mg capsules with a light snack

n*=number of subjects with non-missing values.

For Tmax, median is presented under 'Adjusted Geo-mean', median of difference under 'Geo-mean ratio', minimum and maximum difference under 90% CI.

Source: [Study LDK378A2108-Table 14.2-1.1a]

The dosing recommendation for the pivotal study (A2301) was changed from fasting for at least 2 hours before and 2 hours after dosing to “at least two hours before and one hour after the dose is taken”.

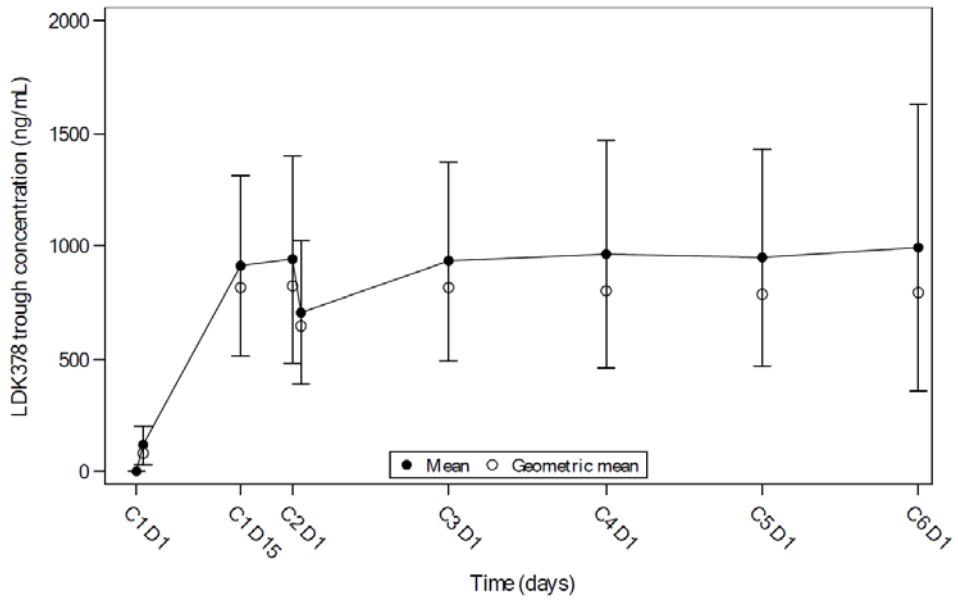
## *PK substudy of study A2301*

PK samples were collected in the phase III registration study A2301, which investigated efficacy and safety of ceritinib to standard first-line chemotherapy (platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after 4 cycles) in adult patients with ALK-positive advanced NSCLC.

The study consisted of trough PK sampling in all patients who received ceritinib treatment on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, and Cycle 6 Day 1.

Thirteen (13) patients in the ceritinib arm were enrolled to participate in the extensive PK sampling group with serial blood sample collections on Cycle 1 Day 1 and Cycle 2 Day 1. Only 7 and 6 patients had evaluable full PK data collected after single dose (Cycle 1 Day 1) and at steady-state (Cycle 2 Day 1), respectively, and were included in the pharmacokinetic analysis set (PAS).

Geometric and arithmetic mean trough concentration-time profiles for ceritinib at 750 mg/day are presented in Figure 10 and the temporal profiles of ceritinib trough concentrations in Figure 11. Geometric and arithmetic mean concentration at 750 mg for patients in the extensive ceritinib PK sampling group are presented in Table 4 and the time curve of the individual observations in Figure 12.




Note: There is an approximately 20% (geo-mean of 829 ng/mL vs. 649 ng/mL) drop in trough concentration from Cycle 2 Day 1 to Cycle 2 Day 2. The reason is likely due to the difference in sample size (n=109 at Cycle 2 Day 1 and n=6 at Cycle 2 Day 2. The latter sampling time point was only for patients with evaluable full PK).

Source: Figure 14.2-5.1

**Figure 10: Geometric mean and arithmetic mean (SD) trough concentration-time profiles for ceritinib (PAS)**

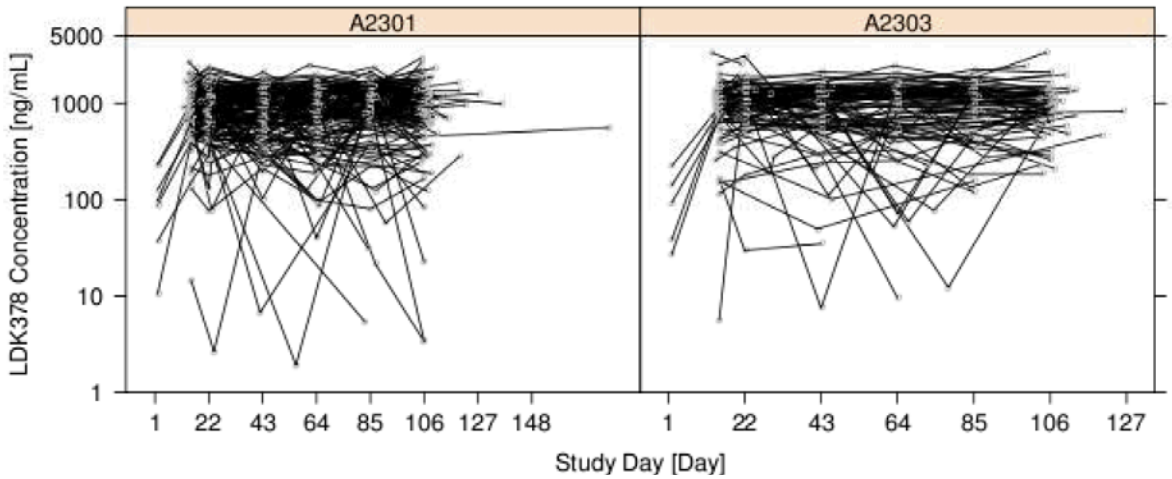



**Figure 11: Temporal profiles of ceritinib trough concentrations in Study LDK378A2301 and Study LDK378A2303**

In the extensive PK sampling group, after the first dose, peak plasma levels ($C_{max}$) of ceritinib were achieved approximately six hours after oral administration in these patients (Table 4). The geometric mean steady-state (at C2D1) $C_{max}$ (794 ng/mL) and AUC0-24h (16600 hr×ng/mL) were approximately 30% lower than that reported in the 750 mg dose group in LDK378X2101.

**Table 4: Summary of PK parameters for ceritinib by visit for patients in the extensive ceritinib PK sampling group (PAS)**

| Time point | Statistics | Cmax (ng/mL) | Tmax (hr) | Tlast (hr) | AUC0-24h (hr*ng/mL) | Racc | CLF_ss (L/hr) |
|---|---|---|---|---|---|---|---|
| C1 D1 | n | 7 | 7 | 7 | 7 | N/A | N/A |
| | Mean (SD) | 208 (122) | N/A | N/A | 3330 (2140) | | |
| | CV% mean | 58.6 | N/A | N/A | 64.4 | | |
| | Geo-mean | 162 | N/A | N/A | 2540 | | |
| | CV% geo-mean | 106.9 | N/A | N/A | 113.1 | | |
| | Median | 268 | 6.00 | 24.0 | 3310 | | |
| | [Min; Max] | [32.8; 329] | [4.00; 8.00] | [23.7; 24.2] | [469; 6250] | | |
| C2 D1 | n | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean (SD) | 846 (350) | N/A | N/A | 18000 (8330) | 8.85 (8.2) | 48.3 (17.4) |
| | CV% mean | 41.3 | N/A | N/A | 46.4 | 92.6 | 36.0 |
| | Geo-mean | 794 | N/A | N/A | 16600 | 6.94 | 45.2 |
| | CV% geo-mean | 39.2 | N/A | N/A | 44.0 | 78.1 | 44.0 |
| | Median | 687 | 6.00 | 24.0 | 14000 | 5.26 | 54.3 |
| | [Min; Max] | [573; 1440] | [6.00; 24.0] | [23.8; 24.3] | [11800; 32000] | [3.87; 25.2] | [23.4; 63.3] |

n: number of patients with non-missing values.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Visits: SCR=Screening, CxDy=Cycle x Day y, EOT=End of treatment, E-CxDy=Extension Cycle x Day y, Uns=Unscheduled, FUx=Post-treatment follow-up x, E-EOT=Extension phase end of treatment, EOS= End of post-treatment follow-up.

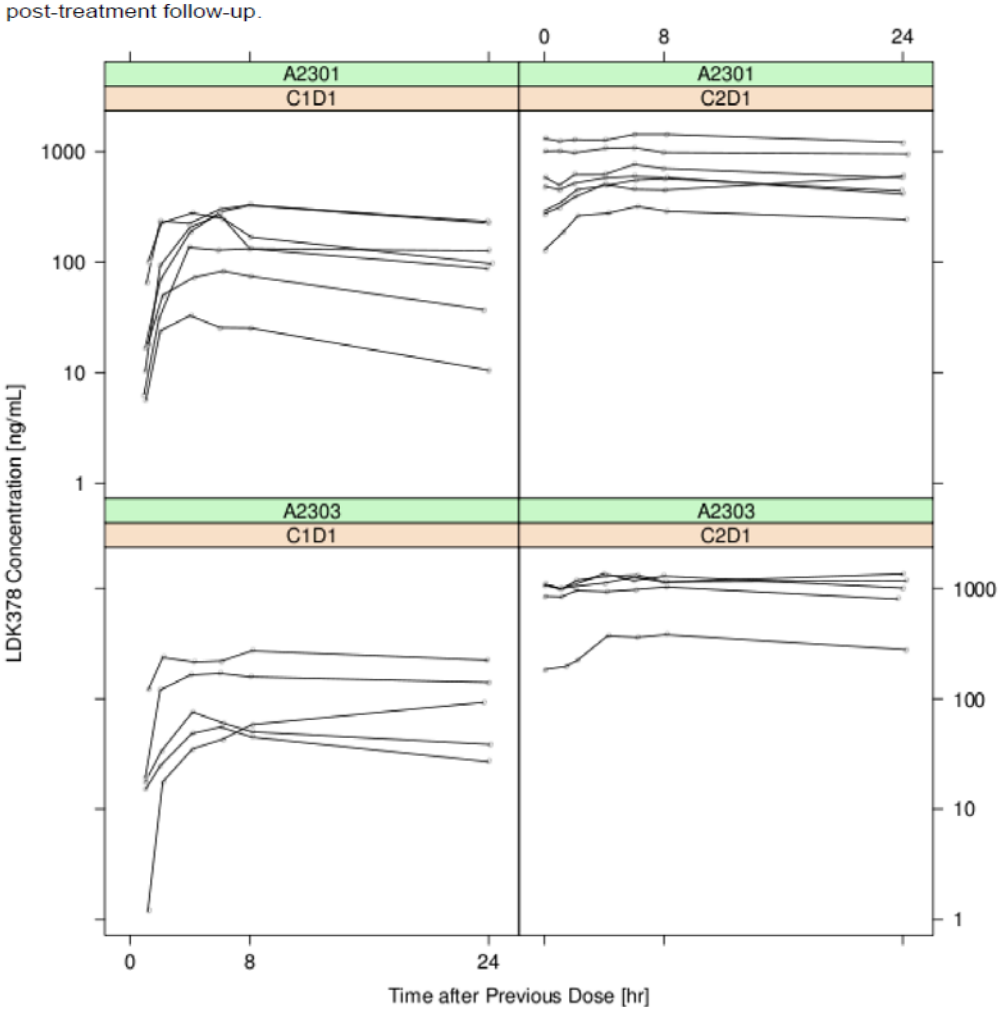



**Figure 12: Ceritinib concentration-time profiles on Cycle 1 Day 1 and Cycle 2 Day1 in Study LDK378A2301 and Study LDK378A2303**

Moderate inter-patient and intra-patient variabilities were observed (inter-patient CV%: 55.4%; intra-patient CV%: 30.3%) using evaluable steady-state trough concentrations.

## *Special populations*

### Body weight

Baseline body weight was evaluated in the population PK model and was identified as a significant covariate impacting ceritinib apparent oral clearance at steady-state ($CL/F_{ss}$) and apparent volume of distribution (V/F).

The steady-state $AUC_{tau}$ in patients with lower body weight (less than 60 kg) (26155 ng*h/mL [90% PI: 24846-27484 ng*h/mL]) was estimated to be only 14% higher compared to the reference patients (22981 ng*h/mL [90% PI: 22053- 23892 ng*h/mL]) with a body weight range of 60-80 kg (body weight cut-off values corresponded to the approximate 1st and 3rd quartiles of the body weight range in the study).

The systemic exposure to ceritinib in patients with higher body weight (greater than 80 kg) (20101 ng*h/mL [90% PI: 18829-21480 ng*h/mL]) was estimated to be only 12% lower compared with reference patients.

In a model-based simulation of exposure according to body weight as a continuous variable, the $AUC_{ss}$ tended to decrease with increasing body weight. The $AUC_{ss}$ at 40 kg (lower end of BW range encompassing 90% patients) was 1.25-fold (90%PI: 0.45-3.26) and 0.87- fold (90%PI: 0.33-2.30) at 90 kg (higher end of body weight range encompassing 90% patients) compared to the $AUC_{ss}$ at mean body weight 67 kg.

### Gender

Gender had no statistically significant effect on the systemic exposures of ceritinib.

### Ethnicity

Overall, the magnitude of exposure increase was considered to be modest in all Asian populations (including Chinese, Japanese, and Other Asian). No clinically meaningful difference in efficacy (ORR) and safety between these two populations were observed.

### Age

Ceritinib PK was not affected by age (age range: 22 to 82 years) in the population PK analysis.

### Impaired renal function

In the population PK analysis, the estimated steady-state ceritinib exposure was similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment were not included in the clinical trials.

### Impaired hepatic function

In the population PK, the steady-state $AUC_{tau}$ of ceritinib in patients with mild hepatic impairment is estimated to be comparable to that in patients with normal liver function. Only one patient included in the population PK analysis had pre-existing moderate hepatic impairment and no patients had severe impairment. A study in non-cancer patients with varying degrees of hepatic impairment (mild, moderate, severe based on Child-Pugh classification) (Study A2110) and matched subjects with normal hepatic function is ongoing.

## 2.3.3. PK/PD modelling

### Exposure-response analyses

Exposure-response (E-R) analyses for efficacy and safety were conducted in ALK-positive metastatic NSCLC treatment naïve (including ALK inhibitor) patients.

In these analyses, average ceritinib trough concentration ($C_{trough\_avg}$) was used as plasma PK exposure measure. This parameter is defined as the geometric mean of evaluable trough concentrations for each patient.

The incidences and 95% CI for efficacy and safety parameters were analysed according to the average $C_{trough}$ values that were categorised in four ascending quartile (Q) ranges as follows:

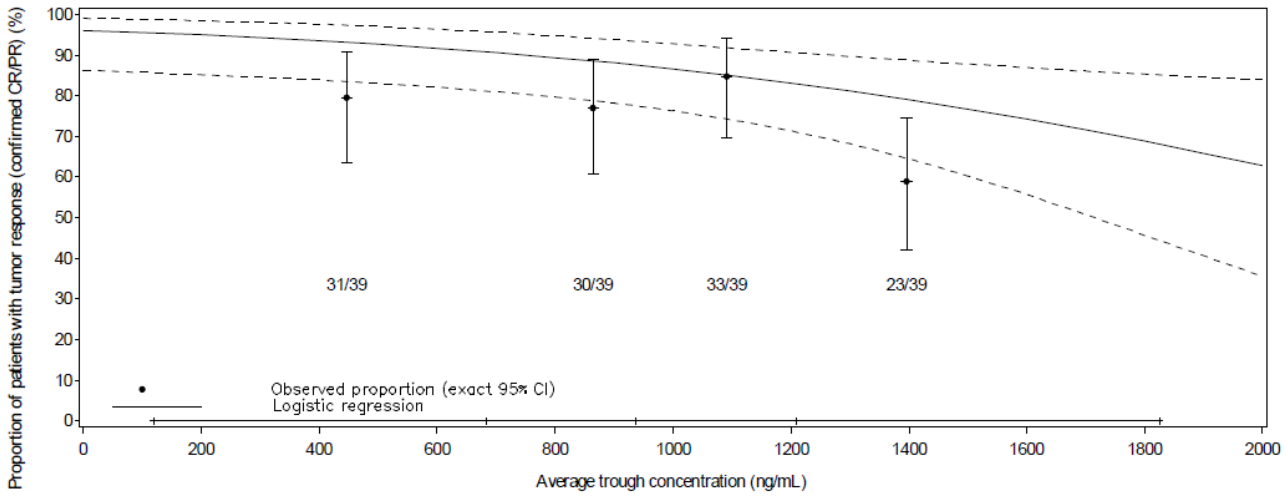
| <Q1 | Q1-Q2 | Q2-Q3 | ≥Q3 |
|---|---|---|---|
| 119-683 ng/ml | 683-936 ng/ml | 936-1210 ng/ml | 1210-1825 ng/ml |

### Results

E-R efficacy

A total of 116 patients from Study A2301 were included in these analyses, i.e. 39 patients in each quartile of $C_{trough}$. Based on these analyses, high and clinically meaningful response rates (confirmed CR/PR per BIRC assessment) were observed across all $C_{trough\_avg}$ quartiles, i.e. 79.5% (95 CI: 63.5, 90.7), 76.9% (60.7, 88.9), 84.6% (69.5, 94.1), and 59.0% (42.1, 74.4) for the ascending four quartiles.

The fitted curve based on the logistic regression model indicated a lack of relationship between tumour response vs. $C_{trough\_avg}$ along with the 95% CI (Figure 13). The logistic regression analysis showed that with a 200 ng/mL increase in ceritinib $C_{trough\_avg}$, there was a 23% decrease in the odds of having a confirmed CR/PR (OR=0.77; 95% CI: 0.62, 0.94).




- The model is log(p/(1-p)) = average trough concentration + gender + brain metastases at baseline, where p is the probability of tumor response status.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average trough concentration (i.e. <=25%, >25%-<=50%, >50%-<=75%, >75%).
- n/N is the number of patients with events/total number of patients in the quartile range.
- Data cutoff for A2301: 24-JUN-2016

**Figure 13: Logistic regression of tumour response status (confirmed CR/PR per BIRC assessment) vs. $C_{trough}$ of ceritinib, overlaid with observed data (PK-efficacy analysis set)**

Cox regression analyses indicated a lack of association between exposure level and DOR or PFS. Overall survival data was not mature enough and no clear trend can be identified.

The estimated PFS rates (95% CI) at 15 months were 50.9% (33.8%, 65.7%), 68.5% (51.3%, 80.7%), 60.3% (42.2%, 74.3%) and 35.7% (20.2%, 51.4%).

Baseline brain metastasis was a statistically significant covariate for efficacy in both the logistic regression and the Cox regression models, indicating that patients without baseline brain metastasis tend to have better efficacy outcome in terms of response rate, DOR and PFS. The estimated odds ratio for ORR in the absence vs. presence of brain metastasis was 3.39 (95% CI: 1.50, 7.64).

**Table 5: Summary of ORR, PFS and baseline brain metastasis by quartile of average Ctrough of ceritinib (PK-efficacy analysis set)**

| | <Q1 (119-<683 ng/mL) N=39 | Q1-<Q2 (683-936 ng/mL) N=39 | Q2-<Q3 (936-<1210 ng/mL) N=39 | >=Q3 (1210-1825 ng/mL) N=39 |
|---|---|---|---|---|
| No. of patients with baseline brain metastasis- n (%) | 15 (38.5) | 11 (28.2) | 6 (15.4) | 14 (35.9) |
| PFS within 3 months [a] | 1 (6.7) | 3 (27.3) | 0 | 8 (57.1) |
| Best overall response [b] | | | | |
| Stable Disease (SD) | 0 | 0 | 0 | 3 (37.5) |
| Progressive Disease (PD) | 0 | 3 (100.0) | 0 | 5 (62.5) |
| Unknown (UNK) | 1 (100.0) | 0 | 0 | 0 |
| No. of patients with PFS within 3 months – n (%) | 4 (10.3) | 8 (20.5) | 3 (7.7) | 13 (33.3) |
| Baseline brain metastasis - Absence [c] | 3 (75.0) | 5 (62.5) | 3 (100.0) | 5 (38.5) |
| Baseline brain metastasis - Presence [c] | 1 (25.0) | 3 (37.5) | 0 | 8 (61.5) |

[a] Percentage based on patients with baseline brain metastasis
[b] Percentage based on patients with baseline brain metastasis and PFS within 3 months
[c] Percentage based on patients with PFS within 3 months

E-R safety

Based on the pooled safety data, there were more newly occurring grade 2-4 transaminase elevations, and grade 2-4 hyperglycaemia in patients with higher ceritinib $C_{trough}$ values. However, no apparent association between ceritinib $C_{trough\_avg}$ and total bilirubin elevations was observed.

Logistic regression models suggested that with a 200 ng/mL increase in ceritinib $C_{trough\_avg}$, the risk of AST and ALT elevation increased by 28% (OR=1.28; 95% CI: 1.19, 1.38) and 37% (OR=1.37; 95% CI: 1.27, 1.49), respectively, while the risk of grade 2-4 hyperglycaemia increased by 14% (OR=1.14; 95% CI: 1.04, 1.24).

Using a linear mixed effects model, increased exposures of ceritinib were shown to be associated with increased QTcP changes from baseline (Figure 14).

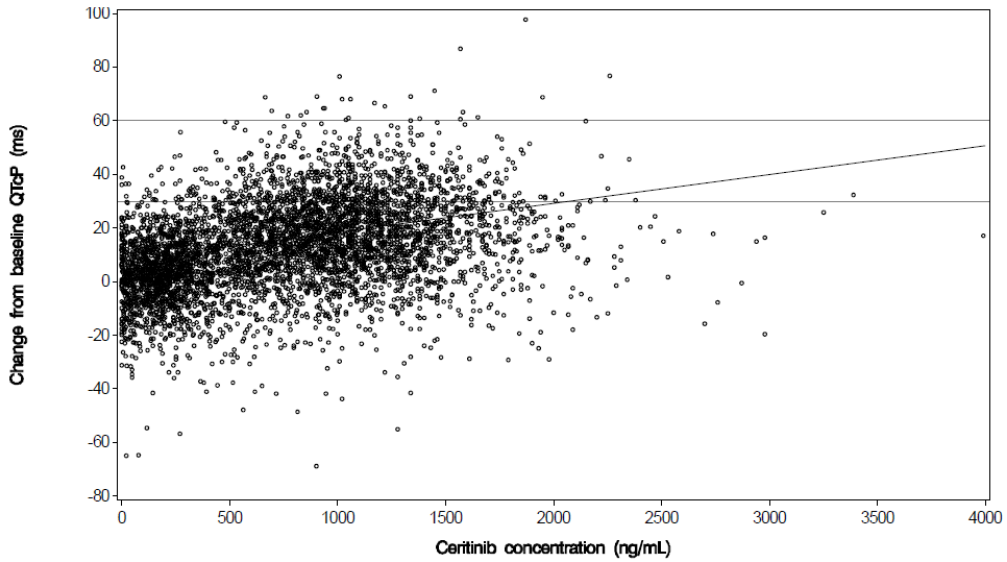



**Figure 14: QTcP change from baseline versus time-matched ceritinib PK concentration (PK-ECG analysis set)**

Grade 3-4 AEs were observed in 71.6%, 69.2%, 73.9% and 84.6% of patients across the exposure quartiles, i.e. more patients in the highest quartile range experienced grade 3-4 AEs. The median times (95% CI) to first grade 3-4 AEs using Kaplan-Meier method by quartiles of $C_{trough\_avg}$ were 2.2 months (1.4, 4.4), 5.4 months (3.7, 7.4), 3.8 months (3.0, 5.3) and 2.7 months (1.9, 3.4), respectively.

No apparent association was observed between ceritinib $C_{trough\_avg}$ and grade 2-4 GI events.

*Exposure-dose adjustment relationship*

Increasing $C_{trough}$ levels were associated with higher frequency of **dose reductions**, i.e. 48.6%, 56.1%, 61.0% and 72.6% of patients had dose reductions in the ascending four quartiles of $C_{trough}$.

A similar trend was observed for time to first dose interruption. Approximately 65%, 70%, 75% and 83% of patients had **dose interruptions** in the ascending four quartiles of $C_{trough\_avg}$.

There was no clear association between increased exposures and permanent discontinuation of study drug as 81.2%, 77.6%, 72.2% and 71.9% of patients discontinued study drug in the ascending four quartiles. Across exposure ranges, median times (95% CI) to study drug discontinuation were as follows: 7.9 months (6.1, 11.0), 12.5 months (10.6, 17.4), 12.4 months (9.9, 15.2) and 12.9 months (9.9, 17.1) for the ascending four quartiles.

## 2.3.4. Discussion on clinical pharmacology

No new clinical pharmacology studies have been conducted, however some PK data in the new patient population have been collected as part of the pivotal trial (A2301). In addition a PK vs. efficacy and safety relationship analysis based on study A2301 only, and a population-PK analysis based on the pooled dataset from 7 clinical studies have been included in this submission.

The submitted PK data are in general considered acceptable.

*Population-PK model*

A population-PK analysis has been performed using data from a new Phase III clinical trial (LDK378A2301) together with six clinical trials that were included in the initial Marketing Authorization Application submission. The modelling workflow is adequate and clearly justified.

Several covariates were selected regarding statistical and clinical criteria. The MAH concluded that none of the covariates had a clinically meaningful effect on the systemic exposure. The point estimate of the 90% prediction limit of the ethnicity effect (Japanese versus Caucasian population) is out of 1.25 limit, which indicates that at least part of Japanese population would have a clinically higher exposure with the recommended schedule (750 mg q.d.). This has been partially explained because of the reduced weight of the Japanese individuals and no ethnic differences were detected on ALT and AST levels, suggesting that liver enzymatic activity is unlikely to contribute to the increased exposure in Japanese patients relative to other ethnicity groups.

Study 2108 investigated the effect of a light snack on the PK of ceritinib. $C_{max}$ and $AUC_{inf}$ were increased with a light snack compared to fasted state. The magnitude of increase was similar to that caused by a low-fat meal. Based on the observations in Studies A2108 and A2101, an increase in exposure would be expected when ceritinib is taken with food.

The MAH proposed to change the fasting window in section 4.2 of the SmPC in line with the recommendation provided in the study protocols of pivotal study A2301 and study A2303 to indicate that “no food should be eaten for at least two hours before and one hour after the dose is taken”. However, no information on the precise food-effect when food is taken one hour after administration of ceritinib has been submitted and has been reflected in section 5.2 of the SmPC.

*Exposure-response efficacy analyses*

The E-R analyses indicated a lack of relationship between the increased exposure levels and efficacy endpoints of ORR, PFS and DOR. The logistic regression analysis showed that with a 200 ng/mL increase in ceritinib $C_{trough\_avg}$, there was a 23% decrease in the odds of having a confirmed CR/PR (OR=0.77; 95% CI: 0.62, 0.94).

The experimental trend observed between confirmed CR/PR per BIRC assessment is captured by the model. The logistic regression model included gender and baseline brain metastasis as covariates. Nevertheless, the model over-predicts the proportion of patients with tumour response along the range of average trough concentrations shown. The overall fit is adequate for the most representative group of individuals included in the study.

Patients in the fourth $C_{trough\_avg}$ quartile (i.e. the highest exposure level) appeared to have a lower response rate and a shorter PFS compared to the other quartiles. To better characterise the exposure-efficacy relationship, the applicant conducted an additional time-dependent cox regression analysis where the overall response was associated with its corresponding exposure within 2 cycles prior to each tumour assessment. Results of these analyses suggested lack of a relationship between PK exposure and overall tumour response, indicating that patients with the lowest and the highest exposure levels achieved similar response in terms of CR/PR. Although higher exposures to ceritinib do not seem to be associated with any detrimental effect based on the new exposure-response analysis, median times to dose reduction or interruption were shorter for patients in the upper exposure quartiles compared to the lowest quartile. Besides, the number of patients that needed dose reduction was 2-fold higher in the upper quartiles compared to the lowest quartile. However, as exposure-response analyses included only a limited data set of patients with $C_{trough\_average}$ values and with at least one efficacy record (n=116), no firm conclusions can be drawn based on these results.

Any particular imbalances in baseline demographics and disease characteristics between the 20 patients with baseline brain metastasis in the first and fourth quartiles who did not have a PFS event within 3 months was identified. A comparison could not be made for patients who had a PFS event < 3 months, as the number of patients with baseline brain metastasis was limited to one in the first quartile. For the 8 patients in the fourth quartile with PFS event < 3 months, no particular demographic or disease characteristics were identified that might have been associated with poor efficacy outcome.

The E-R efficacy analysis results showed that patients without brain metastasis at baseline had a higher chance of responding, i.e. estimated odds ratio for ORR was 3.39 (95% CI: 1.50, 7.64). Based on the Cox regression model of DOR per BIRC assessment with $C_{trough\_avg}$, patients without brain metastasis at baseline were 57% less likely to progress/die after the initial response, compared with those with brain metastasis (HR=0.43; 95% CI: 0.23, 0.78). However, these data should be interpreted with caution due to limited number of patients in these analyses.

*Exposure-response safety analyses*

E-R safety analyses were based on pooled safety data from 7 clinical studies (Studies X1101, X2101, A2201, A2203, A2109, A2301 and A2303) in all ALK-positive NSCLC patients at all dose levels. Safety endpoints included all grade 3-4 AEs, hepatotoxicity, hyperglycaemia, gastrointestinal AEs, QTc interval prolongation, dose reduction, dose interruption and study drug discontinuation.

These analyses showed a clear relationship between exposure level and increased frequency of AEs of ALT/AST elevations, hyperglycaemia and QTc prolongation.

Higher exposures, particularly in the fourth quartile with average $C_{trough}$ levels of 1210-1825 ng/ml, appeared to be associated with earlier and more frequent grade 3-4 AEs. Furthermore, increasing $C_{trough}$ levels were associated with higher frequency of dose reductions, i.e. 48.6%, 56.1%, 61.0% and 72.6% in the ascending four quartiles. A similar trend was also observed for time to first dose interruption, i.e. ~ 65%, 70%, 75% and 83% of patients had dose interruptions in the ascending four quartiles. The median time to dose reduction or interruption was also shorter for patients included in the fourth quartile. No clear association was found between high exposures and time to permanent discontinuation of ceritinib.

Due to the poor tolerability of high exposures to ceritinib and markedly increased need for dose adjustments in the ascending quartiles of $C_{trough}$ in conjunction with the lack of an exposure-response relationship with efficacy in terms of all parameters investigated, the proposed initial dose of 750 mg can be questioned. The Applicant justified the proposed initial dose of 750 mg due to the high and stable response observed within the PK exposure studied. Although the initial dose of 750 mg could primarily be associated with the observed efficacy, the average dose based on the patient exposure data was 626 mg. Considering that approximately 62% of the patients required dose reduction from 750 mg to 600 mg or lower doses, any favourable or unfavourable impact of the initial higher dose on the overall efficacy remains unknown.

Exposure-QT analysis has been adequately assessed and the QTcP change has been reported for the mean/median but also for 25 and 75% percentiles ($C_{max}$ and $C_{min}$). The maximal predicted change of QTcP from baseline was 22.4 (21.2; 23.6) (75% percentile of $C_{max}$). These results are in line with previous findings on QT investigations as well as with data included in SmPC which suggested that ceritinib causes concentration-dependent increases in QTc. Having said that, the prediction on change from baseline QTcP were performed assuming the most frequent individual in the database: age 52 years, weight 65 kg, median baseline QTcP 414.4 ms, female, non-Caucasian, and baseline WHO status ≥1.

### 2.3.5. Conclusions on clinical pharmacology

The new data provided do not impact the overall knowledge on PK/PD of ceritinib. However, the SmPC has been updated in section 4.2 and 5.2 in order to revise the fasting window for the administration of ceritinib.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

The tolerability of ceritinib was first evaluated in Phase I, open-label, dose-escalation and expansion study in adult patients with tumours characterized by genetic abnormalities in ALK, where patients received

continuous once daily administration of ceritinib, orally, fasted over the doses ranging from 50 to 750 mg [Study X2101].

Among the different doses tested, ceritinib 750 mg (highest dose evaluated) was determined as MTD/RD based on the number of DLTs, safety and clinical experience of individual patients observed during the first cycle of treatment [Study X2101].

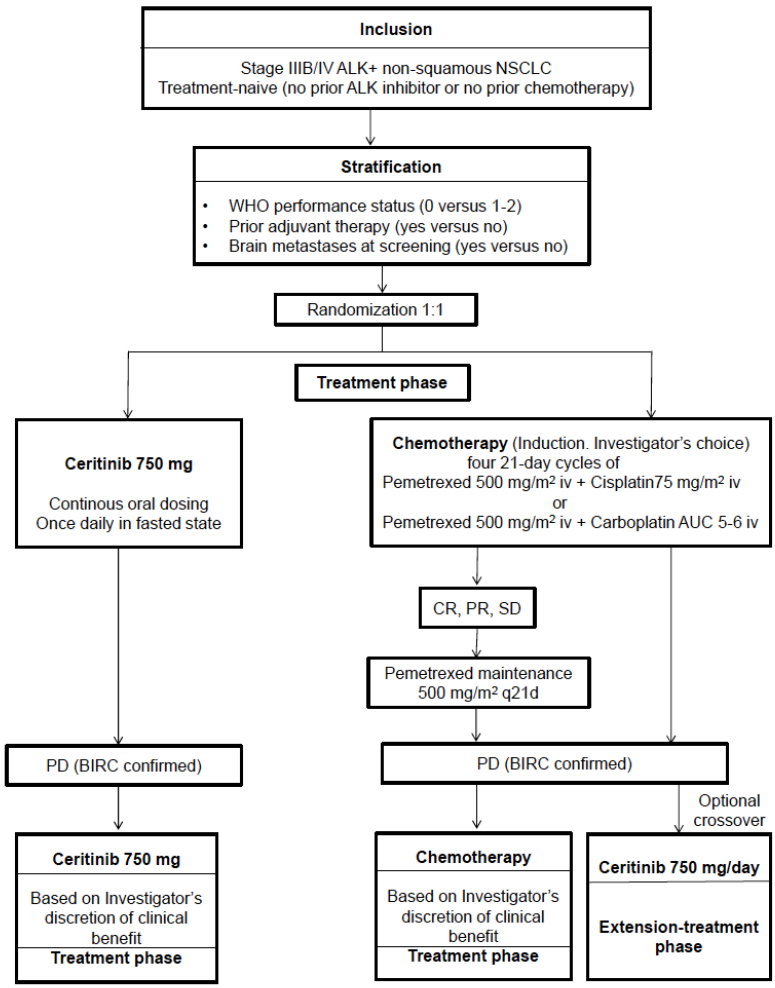
Ceritinib 750 mg dose was used in the expansion phase of the Study X2101 and it is the RD for ceritinib in the ongoing Phase II and III studies. This dose of ceritinib is also the registered dose in the countries ceritinib obtained marketing authorisation.

In Study A2301, ceritinib was administered orally, once-daily (fasted) at a planned dose of 750 mg.

## 2.4.2. Main study

**A Phase III multi-center, randomized study of oral LDK378 versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK -positive), stage IIIB or IV, non-squamous non-small cell lung cancer (ASCEND-4/A2301)**

### *Methods*




During screening and treatment, patients will receive standard pemetrexed premedication consisting of folic acid and vitamin $B_{12}$ starting 7 days prior to randomization and as well steroid premedication (or as per local product label and practice).

## Study participants

Main inclusion criteria:

- Histologically or cytologically confirmed diagnosis of non-squamous NSCLC that was ALK-positive as assessed by the Ventana IHC test. The test was performed at Novartis designated central laboratories.
- Newly diagnosed stage IIIB (and was not a candidate for definitive multimodality therapy) or had stage IV non-squamous NSCLC or relapsed locally advanced or metastatic NSCLC (per Protocol Amendment 1) not previously treated with any systemic anti -cancer therapy (e.g. cytotoxic drugs, monoclonal antibody therapy, crizotinib or other ALK inhibitors, or other targeted therapies, either experimental or not), with the exception of neo-adjuvant or adjuvant therapy.
- Patients with at least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion was only counted as a target lesion if there was clear sign of progression since the irradiation.
- Patients who received previous neo-adjuvant or adjuvant systemic therapy were eligible for enrolment only if relapse had occurred more than 12 months from the end of the neoadjuvant or adjuvant systemic therapy. Patients who had recovered from all toxicities related to prior (neo-) adjuvant systemic therapy to grade ≤ 1 (CTCAE v 4.03). Exception to this criterion: patients with any grade of alopecia were allowed to enter the study.
- WHO performance status 0-2

Main exclusion criteria

- History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
- Patients with symptomatic CNS metastases who were neurologically unstable or had required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms.
- Received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who had not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or had not recovered from radiotherapy -related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment was allowed.

## Treatments

**Table 6: Treatment and posology used in study A2301**

| | Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|---|
| Arm 1 | Ceritinib* | Hard gelatin capsule for oral use | 750 mg (5 x 150 mg capsule) | Once daily (21 day cycle) |
| Arm 2 | Pemetrexed | Intravenous use | 500 mg/m² | Every 21 days |
| | Cisplatin | Intravenous use | 75 mg/m² | Every 21 days |
| | OR | | | |
| | Pemetrexed | Intravenous use | 500 mg/m² | Every 21 days |
| | Carboplatin | Intravenous use | AUC 5-6 | Every 21 days |

* Administered in fasted state

Note: During screening and treatment, patients will receive standard pemetrexed premedication

Platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after 4 cycles was the control treatment (chemotherapy). During screening and treatment, patients received standard pemetrexed premedication consisting of folic acid and vitamin B12

starting 7 days prior to randomization and as well as steroid premedication (or as per local product label and practice).

## Objectives

Primary objective

- To compare the anti-tumour activity of ceritinib versus chemotherapy, as measured by PFS determined by a BIRC.

Secondary objectives

- To compare OS in patients treated with ceritinib versus chemotherapy.

- To assess the anti-tumour activity of ceritinib versus chemotherapy, as measured by ORR, DOR, disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigators.

- To assess the anti-tumour activity of ceritinib versus chemotherapy, as measured by PFS determined by Investigators.

- To assess the anti-tumour activity of ceritinib versus chemotherapy in the brain, as measured by overall intracranial response rate (OIRR), IDCR and duration of intracranial response (DOIR) as determined by BIRC neuro-radiologist per modified RECIST 1.1 (as per Protocol Amendment 3).

- To evaluate the safety profile of ceritinib versus chemotherapy.

- To assess the effect of ceritinib versus chemotherapy on patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

- To characterize the PK of ceritinib in this patient population.

## Outcomes / endpoints

Primary endpoint

The primary endpoint used to evaluate the anti-tumour activity of ceritinib versus chemotherapy was PFS, defined as the time from the date of randomisation to the date of the first radiologically documented disease progression per BIRC assessment or death due to any cause.

Tumour evaluation was performed at baseline and then every six weeks (two cycles) after C1D1 through Month 33, and then every nine weeks (three cycles) thereafter and at EOT for response determination.

Secondary endpoints

- The key secondary endpoint, OS, was defined as the time from date of randomisation to 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 data cut-off date.
- Overall response rate (ORR): The ORR was defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR).
- Duration of response (DOR): Among patients with a confirmed response (PR or CR), DOR 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 last adequate tumour assessment.
- Disease control rate (DCR): defined as the proportion of patients with BOR of CR, PR, SD, or Non-CR/Non-PD per RECIST 1.1.

- Time to response: The time to overall response of CR or PR (TTR), was defined as the time from the date of randomisation to the date of the first documented response (CR or PR, which was confirmed subsequently) for patients with confirmed CR or PR.
- Overall intracranial response rate (OIRR): The OIRR was calculated based on response assessments in the brain for patients having measurable or non-measurable BM at baseline. OIRR was defined as the ORR based on target and non-target lesions (and new lesions, if applicable) assessments in the brain and calculated as the proportion of patients with a best overall confirmed response of CR or PR in the brain per modified RECIST 1.1 as assessed by BIRC neuro-radiologist.
- Intracranial disease response rate (IDCR): The IDCR was calculated based on response assessments in the brain for patients having measurable or non-measurable BM at baseline. IDCR was defined as the DCR based on target and non-target lesions (and new lesions, if applicable) assessments in the brain and calculated as the proportion of patients with a best overall confirmed response of CR or PR or a response of SD (or non-CR/non-PD) in the brain per modified RECIST 1.1 as assessed by BIRC neuro-radiologist.
- Intracranial clinical benefit rate (ICBR): defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non -CR/Non-PD which lasts for a minimum time duration. This endpoint measures signs of activity taking into account duration of disease stabilization. ICBR was added as post-hoc analyses to be calculated at 12 weeks, 18 weeks and 24 weeks after randomisation among patients with measurable BM at baseline and separately in patients having measurable or non-measurable BM at baseline.
- Duration of intracranial response (DOIR): Among patients with a confirmed intracranial response (PR or CR), DOIR was defined as the DOR based on target, non-target lesion (and new lesion, if applicable) assessments in the brain and calculated from the time of first documented intracranial response (PR or CR) to the date of first documented intracranial PD or death due to any cause per modified RECIST 1.1 as assessed by BIRC neuro-radiologist. If a patient did not have an event, DOIR was censored at the date of last adequate intracranial tumour assessment.
- Patient reported outcomes: The European Organization for Research and Treatment of Cancer' score QoL questionnaire (EORTC-QLQC30, version 3.0) and lung cancer specific questionnaire (QLQ LC13, version 1.0) were used to explore PRO measures of health-related QoL, functioning, disease symptoms and treatment-related side effects. The Lung Cancer Symptom Scale (LCSS) measured physical and functional dimensions for individuals with lung cancer. The EuroQOL five dimensions questionnaire (EQ-5D) is a standardized measure of health status, was used to provide a simple, generic measure of health for clinical and economic appraisal.

## Sample size

In a randomized Phase III study in chemotherapy-naive patients with advanced-stage NSCLC, median PFS of approximately 7.7 months and median OS of approximately 16.5 months were observed in patients who received pemetrexed maintenance after induction with platinum-based chemotherapy (Ciuleanu 2009). In the randomised Phase III PARAMOUNT Study in chemotherapy-naive patients with advanced-stage NSCLC, median PFS of approximately 7 months was observed after treatment with pemetrexed/cisplatin followed by pemetrexed maintenance (Paz-Ares 2012). In the planned study, to be conservative, median PFS of 8 months and median OS of 17 months were assumed for the control arm.

Therefore, it was expected that treatment with ceritinib would result in a 38% reduction in the hazard rate (corresponding to an increase in median PFS from 8 months to 12.94 months under the exponential model assumption). If the true hazard ratio was 0.62 (under the alternative hypothesis), a total of approximately 205 PFS events were required to have 90% power at a one-sided 2.5% level of significance to reject the null

hypothesis (HR=1) using a log-rank test and a 2-look group sequential design. To be conservative, it was assumed that both futility and efficacy analyses were performed at the interim analysis. However, there was no plan to stop the study for efficacy at the interim analysis. Assuming a recruitment period of approximately 24 months at an increasing rate during the first 6 months and stabilizing at a uniform rate of 15 patient's/month after the first 6 months, along with an assumed 15% dropout rate, approximately 348 patients were needed to be randomised to the two treatment arms in a 1:1 ratio. Given the above assumptions, it was estimated that the 205th PFS event would occur approximately 32 months from the date of first patient randomised in the study.

Power for analysis of key secondary variables

With 253 deaths, the study would have 80% cumulative power (unadjusted for the pre -testing, in the hierarchical procedure, of PFS) to detect a hazard ratio of 0.70 using a log-rank test and a 4-look Lan-De Mets group sequential design with O'Brien-Fleming type boundary at one sided 2.5% level of significance. If the median OS in the control arm was 17 months, a 30% reduction in hazard rate corresponded to an increase in median OS from 17 months to 24.3 months under the exponential model assumption.

## Randomisation

Eligible patients were randomized via IRT to one of the treatment arms. Randomisation was stratified by factors including WHO PS (0 vs 1-2), presence or absence of BM, and with or without previous neo- or adjuvant chemotherapy.

## Blinding (masking)

Study A2301 was an open label study.

## Statistical methods

Statistical hypothesis, model, and method of analysis

The primary efficacy analysis was performed on the FAS according to the treatment arm and randomisation strata (WHO performance status: 0 vs. 1-2; presence or absence of BM, presence or absence of previous neo-/adjuvant chemotherapy) to which patients were assigned at randomisation.

The distribution of PFS was estimated using the Kaplan-Meier method. The median PFS along with 95% CI was presented by treatment arm using the method of Brookmeyer &Crowley (1982). The Kaplan-Meier curves were displayed by treatment arm. The number of patients at risk at certain time points was shown on the plots.

PFS was tested using the stratified log-rank test (stratified according to randomisation stratification factors). The statistical basis for a claim of efficacy was the statistical significance (at the 2.5% one-sided level of significance) for PFS in favour of the ceritinib arm.

Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (including at least 3, 6,12, 18 and 24 months) was summarised. The CIs were constructed using Greenwood's formula (Collett 1994) for the standard error of the Kaplan-Meier estimate.

A Cox regression model stratified by randomisation stratification factors was used to estimate the hazard ratio of PFS, along with 95% CI based on the Wald test.

Handling of missing values/censoring/discontinuations

PFS was censored at the date of the last adequate tumour assessment before an event or censoring reason occurred. Clinical deterioration was not considered as a qualifying event for progression. Patients without

baseline tumour assessment who died within 14 weeks from randomisation date were counted as having an event in the primary analysis of PFS.

The PFS censoring reasons included ongoing without event, lost to follow-up, withdrew consent, adequate assessment no longer available, new cancer therapy received prior to an event, event after >=2 missing tumour assessments.

Analysis of secondary variables

A hierarchical testing strategy, where OS was to be statistically evaluated and interpreted only if PFS was significantly different between treatment groups, was to be used to control the overall type-I error rate.

The distribution function of OS was to be estimated using Kaplan-Meier methodology. The two treatment groups were to be compared using a stratified log-rank test at an overall onesided2.5% level of significance. A stratified Cox regression was to be used to estimate the OS hazard ratio and the associated 95% CI.

OS was analysed based on the data from FAS, according to the treatment arm to which patients were randomised and the strata they were assigned at randomisation.

Interim analysis

Interim analysis for PFS: One interim analysis was planned to be performed when approximately 72 (35% of the 205) PFS events were documented by BIRC. The primary intent of the interim analysis was to stop early for lack of efficacy (futility). Approximately 203 patients were expected to be randomised at the time of the interim analysis. At the cut-off date of 23-Mar-2015 for interim analysis, 85 PFS events (41.4% information fraction) were observed. Upon data monitoring committee (DMC) recommendation, the decision was to continue the study without modification.

Interim analysis for OS: A maximum of four analyses were planned for OS: 1) an interim analysis at the time of the interim analyses for PFS (provided PFS is significant); 2) an interim analysis at the projected time of the final analysis for PFS (provided PFS is significant); 3) if OS is not significant at the time of final analysis for PFS, provided PFS is significant, the third interim analysis for OS will be conducted when approximately 215 deaths are observed and 4) If OS is not significant at third interim analysis, the final analysis for OS will be conducted when 253 deaths are observed.

## *Results*

## Participant flow

Overall, 425 patients signed the main study informed consent, among whom 49 (11.5%) patients discontinued from Screening phase without getting randomised. Of the 49 patients who discontinued, 45 patients failed screening assessment, one patient died, and three patients were not randomised due to the patient/guardian decision. A total of 376 patients completed the Screening phase and were randomised to either ceritinib or chemotherapy arm in the treatment phase.

**Table 7: Patient disposition by treatment arm (FAS)**

| Disposition/ reason | Ceritinib 750 mg N=189 n (%) | Chemotherapy N=187 n (%) | All patients N=376 n (%) |
|---|---|---|---|
| Patients randomized | | | |
| Untreated | 0 | 12( 6.4) | 12( 3.2) |
| Treated | 189( 100) | 175(93.6) | 364(96.8) |
| Treatment phase | | | |
| Ongoing [a] | 95(50.3) | 30(16.0) | 125(33.2) |
| Discontinued from treatment phase | 94(49.7) | 157(84.0) | 251(66.8) |
| Entered extension-treatment phase | 0 | 81(43.3) | 81(21.5) |
| Entered post-treatment follow-up phase | 10( 5.3) | 16( 8.6) | 26( 6.9) |
| Entered survival follow-up phase | 64(33.9) | 31(16.6) | 95(25.3) |
| Discontinued from study | 20(10.6) | 29(15.5) | 49(13.0) |
| Primary reason for discontinuation from treatment phase | | | |
| Adverse event | 15( 7.9) | 18( 9.6) | 33( 8.8) |
| Death | 9( 4.8) | 11( 5.9) | 20( 5.3) |
| Lost to follow-up | 2( 1.1) | 0 | 2( 0.5) |
| Non-compliance with study treatment | 2( 1.1) | 0 | 2( 0.5) |
| Physician decision | 7( 3.7) | 11( 5.9) | 18( 4.8) |
| Progressive disease | 51(27.0) | 94(50.3) | 145(38.6) |
| Protocol deviation | 1( 0.5) | 0 | 1( 0.3) |
| Subject/guardian decision | 7( 3.7) | 23(12.3) | 30( 8.0) |
| Post-treatment follow-up phase | | | |
| Ongoing [a] | 4( 2.1) | 4( 2.1) | 8( 2.1) |
| Discontinued post-treatment follow-up phase | 6( 3.2) | 12( 6.4) | 18( 4.8) |
| Entered extension-treatment phase after discontinuation from post-treatment follow-up phase | 0 | 4( 2.1) | 4( 1.1) |
| Entered survival follow-up phase after discontinuation from post-treatment follow-up phase | 5( 2.6) | 7( 3.7) | 12( 3.2) |
| Discontinued from study | 1( 0.5) | 1( 0.5) | 2( 0.5) |
| Primary reason for discontinuation from post-treatment phase | | | |
| Death | 1( 0.5) | 0 | 1( 0.3) |
| New therapy for study indication | 4( 2.1) | 1( 0.5) | 5( 1.3) |
| Progressive disease | 1( 0.5) | 10( 5.3) | 11( 2.9) |
| Subject/guardian decision | 0 | 1( 0.5) | 1( 0.3) |
| Extension-treatment phase [b] | | | |
| Ongoing [a] | 0 | 33 (17.6) | 33( 8.8) |
| Discontinued extension-treatment phase | 0 | 52(27.8) | 52(13.8) |
| Entered survival follow-up phase after discontinuation from extension-treatment phase | 0 | 41(21.9) | 41(10.9) |
| Discontinued from study | 0 | 11( 5.9) | 11( 2.9) |
| Primary reason for discontinuation from extension-treatment phase | | | |
| Adverse event | 0 | 9 (4.8) | 9 (2.4) |
| Death | 0 | 9 (4.8) | 9 (2.4) |
| Progressive disease | 0 | 28 (15.0) | 28 (7.4) |
| Subject/guardian decision | 0 | 6 (3.2) | 6 (1.6) |

[a] Patients ongoing at the time of the cut-off 24-Jun-2016

[b] Extension-treatment phase is for patients who crossed over from chemotherapy to LDK378 treatment.

Percentage is based on N.

Reasons for discontinuation are based on the 'End of Treatment Phase Disposition', 'End of Extension Treatment Phase Disposition' and 'Post-treatment Phase Completion' CRF pages.

Source: [Study A2301-Table 14.1-1.1b]

## Recruitment

The study is being conducted in 134 sites that randomised at least one patient across 27 countries excluding the US. The study was initiated on 09 July 2013 (first patient first visit) and completed enrolment on 1 April 2015 (last patient first visit). Between 19 August 2013 and 11 May 2015, a total of 376 patients with ALK-positive advanced non-squamous NSCLC who were previously untreated with systemic therapy (with the exception of adjuvant or neo adjuvant therapy if relapse had occurred at least 12 months after the end of therapy), were randomised to either ceritinib (n=189) or chemotherapy (n=187).

The data cut-off date for this primary analysis was 24 June 2016, when 202 PFS events had been

documented as per BIRC assessment and 218 PFS events per Investigator assessment were documented. The analyses are presented using data locked on 11 September 2016. The study is ongoing. The median duration between randomisation and data cut-off date for all patients was 19.7 months.

## Conduct of the study

The study protocol was amended three times.

Amendment 1 (27 August 2013): The most relevant change in the protocol was to limit the study population to stage IIIB patients who were not candidates for definitive multimodality therapy or stage IV, non-squamous NSCLC harbouring a confirmed ALK rearrangement.

Amendment 2 (29 May 2015): This amendment allowed radiotherapy and surgical resection as local palliative therapy of metastases for patients who developed progressive disease but were still deriving clinical benefit from ceritinib therapy as determined by the Investigator.

Amendment 3 (11 December 2015): This amendment provided follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize the patient safety, and clarified sections of the protocol where additional guidance was required. The secondary objectives and related endpoints were updated to include assessment of the anti-tumour activity of ceritinib versus chemotherapy in the brain, as measured by OIRR, IDCR and DOIR, as assessed by BIRC neuro-radiologist per modified RECIST 1.1 to allow selecting up to five measurable brain lesions as target lesions

**Table 8: Changes to protocol specified analysis or descriptions and rationale**

| Protocol section | Protocol Description | Change |
|---|---|---|
| 10.5.2 Other secondary efficacy objectives | BOR for each patient were determined based on the following rule:<br>• SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR).<br>• PD = progression ≤ 12 weeks after randomization (and not qualifying for CR, PR or SD). | BOR for each patient were determined based on the following rule:<br>• SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).<br>• PD = progression ≤ 13 weeks after randomization (and not qualifying for CR, PR or SD).<br>This update was made to account for the +/-1 week window for the tumor assessment protocol defined schedule of 6 weeks. Consequently, BOR of 'Unknown' derivations of 'SD too early' and 'PD too late' were based on the updated calculations:<br>• Stable disease (SD) too early (≤ 5 weeks after randomization date)<br>• PD too late (> 13 weeks after randomization date). |
| 10.1.6 Other analysis sets | All exploratory analyses discussed in the CSR were defined in the RAP. Additional analyses may have been performed on a program or company level. These were planned and reported separately from this study. | The crossover analysis set was pre-specified in the statistical analysis plan for the primary analysis CSR to conduct analyses pertaining to safety evaluations collected for patients who were randomized to the chemotherapy arm and crossed over to receive at least one dose of LDK378 in the extension-treatment phase. |
| 14.2.7 Best overall response | As a default, any assessments taken more than 30 days after the last dose of study treatment were not included in the best overall response derivation. | For the BOR calculation, the default option was not used, i.e., assessments taken more than the 30 days after the last dose of study treatment were included in the best overall response derivation for consistency with other time to event end-points. |

Protocol deviations

At least one protocol deviation was reported in 110 patients (58.2%) in the ceritinib arm and 103 patients (55.1%) in the chemotherapy arm.

The most frequently reported protocol deviations were due to treatment related deviation (39.2% patients in ceritinib arm and 37.4% of patients in chemotherapy arm).

Protocol deviations that led to exclusion from PPS set were infrequent with no imbalance evident across the two treatment arms. Two patients (1.1%) in the chemotherapy arm had protocol deviations leading to exclusion from the PPS; both these patients received prior neo-/adjuvant therapy and had a relapse <12 months from the end of neo -/adjuvant therapy. No patient in the ceritinib arm had protocol deviation that led to exclusion from the PPS.

**Table 9: Protocol deviations leading to exclusion from the per-protocol set (FAS)**

| Protocol deviation | Ceritinib 750 mg N=189 n (%) | Chemotherapy N=187 n (%) | All patients N=376 n (%) |
|---|---|---|---|
| Patients with at least one protocol deviation | 0 | 2 (1.1) | 2 (0.5) |
| Selection criteria not met | 0 | 2 (1.1) | 2 (0.5) |
| Previous neo-adjuvant or adjuvant systemic therapy with a relapse less than 12 months from the end of the neo-adjuvant or adjuvant systemic therapy | 0 | 2 (1.1) | 2 (0.5) |

A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.

Patients could have protocol deviations in more than one protocol deviation category.

A patient with multiple occurrences of a protocol deviation was counted only once in the protocol deviation row.

Source: Table 14.1-1.3

## Baseline data

**Table 10: Demographics by treatment arm (FAS)**

| Demographic variable | Ceritinib 750 mg N=189 | Chemotherapy N=187 | All patients N=376 |
|---|---|---|---|
| **Age (years)** | | | |
| n | 189 | 187 | 376 |
| Mean | 54.5 | 53.3 | 53.9 |
| SD | 12.76 | 12.49 | 12.62 |
| Median | 55.0 | 54.0 | 54.0 |
| Minimum | 22 | 22 | 22 |
| Maximum | 81 | 80 | 81 |
| **Age category (years) -n (%)** | | | |
| < 65 | 143 (75.7) | 152 (81.3) | 295 (78.5) |
| >= 65 | 46 (24.3) | 35 (18.7) | 81 (21.5) |
| **Sex -n (%)** | | | |
| Female | 102 (54.0) | 114 (61.0) | 216 (57.4) |
| Male | 87 (46.0) | 73 (39.0) | 160 (42.6) |
| **Race -n (%)** | | | |
| Asian | 76 (40.2) | 82 (43.9) | 158 (42.0) |
| Black | 3 (1.6) | 3 (1.6) | 6 (1.6) |
| Caucasian | 104 (55.0) | 98 (52.4) | 202 (53.7) |
| Native American | 3 (1.6) | 2 (1.1) | 5 (1.3) |
| Other | 3 (1.6) | 2 (1.1) | 5 (1.3) |
| **Ethnicity -n (%)** | | | |
| East Asian | 50 (26.5) | 52 (27.8) | 102 (27.1) |
| Hispanic or Latino | 14 (7.4) | 12 (6.4) | 26 (6.9) |
| Mixed ethnicity | 1 (0.5) | 0 | 1 (0.3) |
| Russian | 14 (7.4) | 12 (6.4) | 26 (6.9) |
| South Asian | 3 (1.6) | 2 (1.1) | 5 (1.3) |
| Southeast Asian | 21 (11.1) | 22 (11.8) | 43 (11.4) |
| West Asian | 5 (2.6) | 7 (3.7) | 12 (3.2) |

| | | | |
|---|---|---|---|
| Other | 64 (33.9) | 64 (34.2) | 128 (34.0) |
| Unknown | 5 (2.6) | 5 (2.7) | 10 (2.7) |
| Not reported | 12 (6.3) | 11 (5.9) | 23 (6.1) |
| **Body surface area (m2)** | | | |
| n | 189 | 187 | 376 |
| Mean | 1.733 | 1.693 | 1.713 |
| SD | 0.2257 | 0.2052 | 0.2164 |
| Median | 1.720 | 1.660 | 1.700 |
| Minimum | 1.26 | 1.17 | 1.17 |
| Maximum | 2.40 | 2.52 | 2.52 |
| **Body mass index (kg/m2)** | | | |
| n | 189 | 186 | 375 |
| Mean | 24.311 | 24.104 | 24.208 |
| SD | 4.5329 | 3.9021 | 4.2274 |
| Median | 23.847 | 23.308 | 23.665 |
| Minimum | 14.42 | 13.33 | 13.33 |
| Maximum | 38.27 | 39.34 | 39.34 |
| **WHO performance status -n (%)** | | | |
| 0 | 69 (36.5) | 70 (37.4) | 139 (37.0) |
| 1 | 107 (56.6) | 105 (56.1) | 212 (56.4) |
| 2 | 13 (6.9) | 11 (5.9) | 24 (6.4) |
| Missing | 0 | 1 (0.5) | 1 (0.3) |
| **Smoking history -n (%)** | | | |
| Current smoker | 15 (7.9) | 15 (8.0) | 30 (8.0) |
| Ex-smoker | 66 (34.9) | 50 (26.7) | 116 (30.9) |
| Never smoked | 108 (57.1) | 122 (65.2) | 230 (61.2) |

Body Mass Index: BMI [kg/m2] = weight[kg] / (height[m]**2)
Source: Table 14.1-3.1

**Table 11: Disease history by treatment arm (FAS)**

| Disease characteristics | Ceritinib 750 mg N=189 | Chemotherapy N=187 | All patients N=376 |
|---|---|---|---|
| **Primary site of cancer - n(%)** | | | |
| Lung | 189( 100) | 187( 100) | 376( 100) |
| **Histology/Cytology - n(%)** | | | |
| Adenocarcinoma | 180(95.2) | 183(97.9) | 363(96.5) |
| Adenosquamous cell carcinoma | 2( 1.1) | 2( 1.1) | 4( 1.1) |
| Large cell carcinoma | 3( 1.6) | 1( 0.5) | 4( 1.1) |
| Undifferentiated carcinoma | 1( 0.5) | 0 | 1( 0.3) |
| Other | 3( 1.6) | 1( 0.5) | 4( 1.1) |
| **Histological grade - n(%)** | | | |
| Well differentiated | 13( 6.9) | 17( 9.1) | 30( 8.0) |
| Moderately differentiated | 23(12.2) | 19(10.2) | 42(11.2) |
| Poorly differentiated | 38(20.1) | 52(27.8) | 90(23.9) |
| Undifferentiated | 3( 1.6) | 2( 1.1) | 5( 1.3) |
| Unknown | 112(59.3) | 97(51.9) | 209(55.6) |
| **Metastatic site of cancer - n(%)** | | | |
| Adrenal | 24(12.7) | 25(13.4) | 49(13.0) |
| Bone | 77(40.7) | 80(42.8) | 157(41.8) |
| Brain | 59(31.2) | 62(33.2) | 121(32.2) |
| Kidney | 4( 2.1) | 3( 1.6) | 7( 1.9) |
| Liver | 34(18.0) | 39(20.9) | 73(19.4) |
| Lung | 175(92.6) | 160(85.6) | 335(89.1) |

| | | | |
|---|---|---|---|
| Pleura | 67(35.4) | 77(41.2) | 144(38.3) |
| Skin | 3( 1.6) | 1( 0.5) | 4( 1.1) |
| Soft tissue | 7( 3.7) | 5( 2.7) | 12( 3.2) |
| Lymph nodes | 151(79.9) | 146(78.1) | 297(79.0) |
| Metastatic | 13( 6.9) | 13( 7.0) | 26( 6.9) |
| Axillary lymph nodes | 2( 1.1) | 6( 3.2) | 8( 2.1) |
| Cervical lymph nodes | 7( 3.7) | 4( 2.1) | 11( 2.9) |
| Retroperitoneal lymph nodes | 5( 2.6) | 3( 1.6) | 8( 2.1) |
| Local | 116(61.4) | 116(62.0) | 232(61.7) |
| Bronchiopulmonary lymph nodes | 20(10.6) | 22(11.8) | 42(11.2) |
| Mediastinum lymph nodes | 98(51.9) | 96(51.3) | 194(51.6) |
| Subclavicular lymph nodes | 3( 1.6) | 5( 2.7) | 8( 2.1) |
| Supraclavicular lymph nodes | 17( 9.0) | 24(12.8) | 41(10.9) |
| Other | 75(39.7) | 67(35.8) | 142(37.8) |
| Other | 42(22.2) | 47(25.1) | 89(23.7) |
| **Stage at initial diagnosis - n(%)** | | | |
| I | 1( 0.5) | 5( 2.7) | 6( 1.6) |
| IA | 0 | 5( 2.7) | 5( 1.3) |
| IB | 0 | 2( 1.1) | 2( 0.5) |
| IIA | 4( 2.1) | 2( 1.1) | 6( 1.6) |
| IIB | 0 | 1( 0.5) | 1( 0.3) |
| IIIA | 6( 3.2) | 8( 4.3) | 14( 3.7) |
| IIIB | 17( 9.0) | 7( 3.7) | 24( 6.4) |
| IV | 161(85.2) | 156(83.4) | 317(84.3) |
| Unk | 0 | 1( 0.5) | 1( 0.3) |
| **Stage at time of study entry - n(%)** | | | |
| IIIB | 9( 4.8) | 5( 2.7) | 14( 3.7) |
| IV | 180(95.2) | 182(97.3) | 362(96.3) |
| **Time from initial diagnosis of primary site to randomization (months)** | | | |
| n | 189 | 187 | 376 |
| Mean | 5.4 | 7.6 | 6.5 |
| SD | 14.97 | 23.85 | 19.89 |
| Median | 1.6 | 1.8 | 1.7 |
| Minimum | 0.5 | 0.4 | 0.4 |
| Maximum | 129.1 | 258.6 | 258.6 |
| **Time from most recent relapse/progression to randomization (months)** | | | |
| n | 22 | 27 | 49 |
| Mean | 2.0 | 2.1 | 2.0 |
| SD | 1.60 | 1.89 | 1.75 |

| Disease characteristics | Ceritinib 750 mg N=189 | Chemotherapy N=187 | All patients N=376 |
|---|---|---|---|
| Median | 1.5 | 1.7 | 1.5 |
| Minimum | 0.2 | 0.1 | 0.1 |
| Maximum | 6.4 | 9.3 | 9.3 |
| **Time from initial diagnosis of primary site to randomization for patients with initial diagnosis of stage < IIIB and with stage IIIB who received any prior treatment(months)[a]** | | | |
| n | 17 | 24 | 41 |
| Mean | 41.2 | 45.0 | 43.4 |
| SD | 33.34 | 53.60 | 45.83 |
| Median | 29.6 | 24.2 | 25.7 |
| Minimum | 2.2 | 2.0 | 2.0 |
| Maximum | 129.1 | 258.6 | 258.6 |
| **Time from initial diagnosis to first recurrence/progression for patients with initial diagnosis of stage < IIIB and with stage IIIB who received any prior treatment(months)[a]** | | | |
| n | 17 | 24 | 41 |
| Mean | 36.0 | 40.8 | 38.8 |
| SD | 32.60 | 52.90 | 45.17 |
| Median | 26.0 | 20.8 | 21.2 |
| Minimum | 1.5 | 1.8 | 1.5 |
| Maximum | 124.0 | 249.3 | 249.3 |
| **Type of Lesion at baseline based on Investigator assessment - n(%)** | | | |
| Target only | 8( 4.2) | 5( 2.7) | 13( 3.5) |
| Both target and non-target | 181( 95.8) | 182( 97.3) | 363( 96.5) |
| **Type of Lesion at baseline based on BIRC assessment - n(%)** | | | |
| Target only | 5( 2.6) | 4( 2.1) | 9( 2.4) |
| Non-target only | 4( 2.1) | 11( 5.9) | 15( 4.0) |
| Both target and non-target | 180( 95.2) | 172( 92.0) | 352( 93.6) |
| **Disease burden (sum of diameters for target lesions) at baseline based on BIRC assessment (mm)** | | | |
| n | 185 | 176 | 361 |
| Mean | 66.7 | 73.3 | 69.9 |
| SD | 41.46 | 47.09 | 44.36 |
| Median | 58.0 | 66.0 | 63.0 |
| Minimum | 11.0 | 12.0 | 11.0 |
| Maximum | 266.0 | 269.0 | 269.0 |

**Table 12: Prior anti-neoplastic therapy – Overall, by treatment arm (FAS)**

| | Ceritinib 750 mg N=189 n (%) | Chemotherapy N=187 n (%) | All patients N=376 n (%) |
|---|---|---|---|
| Any therapy | | | |
| No | 120 (63.5) | 119 (63.6) | 239 (63.6) |
| Yes | 69 (36.5) | 68 (36.4) | 137 (36.4) |
| Surgery | | | |
| No | 145 (76.7) | 144 (77.0) | 289 (76.9) |
| Yes | 44 (23.3) | 43 (23.0) | 87 (23.1) |
| Radiotherapy | | | |
| No | 152 (80.4) | 147 (78.6) | 299 (79.5) |
| Yes | 37 (19.6) | 40 (21.4) | 77 (20.5) |
| Medication: chemotherapy setting [a] | | | |
| Adjuvant | 10 (5.3) | 7 (3.7) | 17 (4.5) |
| Neoadjuvant | 0 | 2 (1.1) | 2 (0.5) |
| Number of prior regimens of chemotherapy | | | |
| 0 | 179 (94.7) | 178 (95.2) | 357 (94.9) |
| 1 | 10 (5.3) | 9 (4.8) | 19 (5.1) |
| Prior anti-cancer medications | | | |
| Carboplatin | 1 (0.5) | 3 (1.6) | 4 (1.1) |
| Cisplatin | 7 (3.7) | 5 (2.7) | 12 (3.2) |
| Docetaxel | 0 | 2 (1.1) | 2 (0.5) |
| Etoposide | 1 (0.5) | 1 (0.5) | 2 (0.5) |
| Gemcitabine | 2 (1.1) | 4 (2.1) | 6 (1.6) |
| Nedaplatin | 2 (1.1) | 0 | 2 (0.5) |
| Oxaliplatin | 0 | 1 (0.5) | 1 (0.3) |
| Paclitaxel | 0 | 2 (1.1) | 2 (0.5) |
| Pemetrexed | 2 (1.1) | 0 | 2 (0.5) |
| Vinorelbine | 5 (2.6) | 1 (0.5) | 6 (1.6) |

[ a] A patient may have multiple settings.
Any prior anti-neoplastic therapy included patients who have had medication, radiotherapy or surgery.
Prior surgery = YES excludes diagnostic biopsies.

## Numbers analysed

The Full Analysis Set (FAS) consisted of all patients to whom study treatment had been assigned by randomisation. According to the intent to treat principle, patients were analysed according to the treatment and strata to which they had been assigned during the randomisation procedure.

The Safety Set consisted of all patients who received at least one dose of study drug (ceritinib or pemetrexed or carboplatin or cisplatin). Patients were analysed according to the study treatment they received. Patients were classified according to treatment received, where treatment received was defined as (i) the intended treatment if it was received at least once, or (ii) the first treatment received when starting therapy with study medication if intended treatment was never received. Each patient was classified into and analysed consistently within one (and only one) treatment arm.

The Per-Protocol Set (PPS) consisted of a subset of patients in the FAS who had an adequate tumour assessment by the Investigator at baseline, a follow-up tumour assessment by the Investigator >5 weeks after starting treatment (unless disease progression was observed by the Investigator or death was observed, within 7 weeks), who received study drug only from the treatment arm they were randomized to prior to cross-over and had no protocol deviations that led to exclusion from PPS.

The Crossover Analysis Set consisted of patients randomized to the chemotherapy arm, and who crossed over to receive at least one dose of ceritinib. This analysis set was used for all safety evaluations collected after patients crossed over into the extension treatment phase.

A total of 376 patients were randomized in a 1:1 ratio to the ceritinib arm (n=189) or chemotherapy arm (platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after the first 4 cycles; n=187) and were included in the FAS. All efficacy analyses are

based on the FAS, unless specified otherwise. All 189 patients randomised to the ceritinib arm were treated whereas only 175 patients among the 187 patients randomised to chemotherapy were treated. Among the 187 patients randomized to chemotherapy: 87 patients started treatment with pemetrexed and cisplatin and 88 patients started treatment with pemetrexed and carboplatin and 12 patients were not treated (seven due to patient/guardian decision, two due to AEs, two due to physician's decision and one due to death). Further, 127 patients continued treatment with pemetrexed maintenance in the chemotherapy arm.

A total of 85 patients entered the extension treatment phase, among these 80 patients received at least one dose of ceritinib and were included in the cross-over analysis set (three patients did not receive ceritinib as of the data cut-off date and other two patients had died before start of first dose of ceritinib).

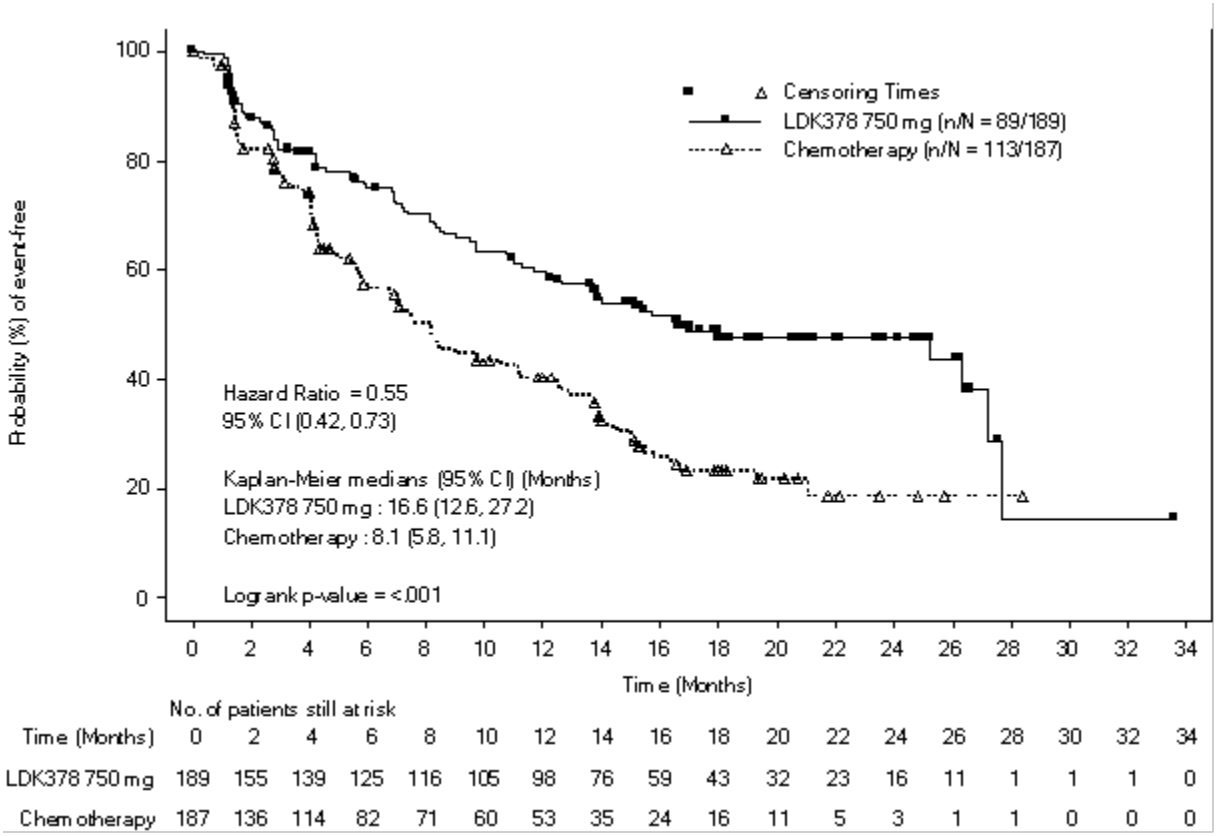
## Outcomes and estimation

Primary efficacy results PFS per BIRC assessment

**Table 13: Summary of progression-free survival per BIRC assessment by treatment arm (FAS)**

| | Ceritinib 750 mg N=189 | Chemotherapy N=187 |
|---|---|---|
| n/N (%) | 89/189 (47.1) | 113/187 (60.4) |
| Percentiles (95% CI) (months) | | |
| 25th | 6.8 (4.1, 8.2) | 3.6 (2.6, 4.1) |
| Median | 16.6 (12.6, 27.2) | 8.1 (5.8, 11.1) |
| 75th | 27.7 (26.3, NE) | 16.4 (13.9, NE) |
| % Event-free probability estimates (95% CI) | | |
| 3 months | 82.1 (75.7, 87.0) | 77.2 (70.1, 82.9) |
| 6 months | 75.0 (67.9, 80.8) | 56.8 (48.6, 64.1) |
| 9 months | 66.6 (59.0, 73.1) | 44.8 (36.7, 52.5) |
| 12 months | 59.9 (52.1, 66.8) | 40.4 (32.5, 48.2) |
| 15 months | 54.1 (46.2, 61.3) | 30.5 (23.0, 38.4) |
| 18 months | 48.7 (40.6, 56.4) | 23.3 (16.3, 31.2) |
| 21 months | 47.6 (39.3, 55.4) | 21.7 (14.5, 29.7) |
| 24 months | 47.6 (39.3, 55.4) | 18.6 (10.9, 27.9) |
| 27 months | 38.2 (24.8, 51.4) | 18.6 (10.9, 27.9) |

Percentiles with 95% CIs were calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). % Event-free probability estimate was the estimated probability that a patient remained event-free up to the specified time point. % Event-free probability estimates were obtained from the Kaplan-Meier survival estimates; Greenwood formula was used for CIs of KM estimates.
n: Total number of events included in the analysis.
N: Total number of patients included in the analysis.
Source: [Study A2301-Table 14.2-1.1]




No. of patients still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDK378 750 mg | 189 | 155 | 139 | 125 | 116 | 105 | 98 | 76 | 59 | 43 | 32 | 23 | 16 | 11 | 1 | 1 | 1 | 0 |
| Chemotherapy | 187 | 136 | 114 | 82 | 71 | 60 | 53 | 35 | 24 | 16 | 11 | 5 | 3 | 1 | 1 | 0 | 0 | 0 |

Both log-rank and Cox regression model were stratified by presence or absence of brain metastases, WHO status (0 versus 1-2) and presence or absence of prior adjuvant chemotherapy. P-value is one sided and is based on the stratified log rank test.

**Figure 15: Kaplan-Meier plot of progression-free survival per BIRC assessment by treatment arm (FAS)**

Hazard ratio for PFSs by BIRC in the different randomization strata are as follows: patients with brain metastases (HR=0.80; 95% CI: 0.50, 1.28); patients without brain metastases (HR=0.45; 95% CI: 0.32, 0.64); WHO status 0 (HR=0.60; 95% CI: 0.37, 0.98), WHO status 1-2 (HR=0.53; 95% CI: 0.37, 0.75), patients with prior adjuvant chemotherapy (HR=0.58; 95% CI: 0.04, 9.30) and patients without prior adjuvant chemotherapy (HR=0.55; 95% CI: 0.41, 0.73).

**Table 14: Summary of reasons for censoring patients in PFS analysis by treatment arm(Full analysis set)**

| Study analysis endpoints | Reason of censoring | LDK378 750 mg N=189 n (%) | Chemotherapy N=187 n (%) |
|---|---|---|---|
| PFS by BIRC assessment | Number of patients censored | 100 ( 52.9) | 74 ( 39.6) |
| | Reason of censoring | | |
| | Ongoing without event [a] | 76 ( 40.2) | 31 ( 16.6) |
| | Lost to follow-up [b] | 1 ( 0.5) | 0 |
| | Withdrew consent | 5 ( 2.6) | 12 ( 6.4) |
| | Initiation of new anticancer therapy | 11 ( 5.8) | 25 ( 13.4) |
| | Event documented after two or more missing tumor assessments | 5 ( 2.6) | 2 ( 1.1) |
| | Adequate assessment no longer available [c] | 2 ( 1.1) | 4 ( 2.1) |
| PFS by investigator assessment | Number of patients censored | 97 ( 51.3) | 61 ( 32.6) |
| | Reason of censoring | | |
| | Ongoing without event [a] | 78 ( 41.3) | 28 ( 15.0) |
| | Lost to follow-up [b] | 1 ( 0.5) | 0 |
| | Withdrew consent | 5 ( 2.6) | 12 ( 6.4) |
| | Initiation of new anticancer therapy | 6 ( 3.2) | 16 ( 8.6) |
| | Event documented after two or more missing tumor assessments | 5 ( 2.6) | 2 ( 1.1) |
| | Adequate assessment no longer available [c] | 2 ( 1.1) | 3 ( 1.6) |

[a] Patients without event and had adequate follow-up as of data cut-off.
[b] Recorded on the 'End of Treatment Phase Completion', 'End of Extension Treatment Phase Completion' and 'Post-treatment Phase Completion' CRF pages.
[c] Patients censored without adequate evaluations for a specified period prior to data cut-off or without adequate baseline assessment.

Supportive and sensitivity analyses of PFS by BIRC assessment

The results of the PFS analysis using the PPS were consistent with that of the primary analysis based on the FAS. The results yielded a HR of 0.56 (95% CI: 0.42, 0.75; p<0.001); the median PFS as assessed by BIRC (95% CI) was 16.6 months (95% CI: 12.6, 27.2) and 8.1 months (95% CI: 5.8, 11.1) for the ceritinib arm and chemotherapy arm, respectively.

The following baseline covariates were included in a stratified multivariate Cox proportional hazard regression model for PFS assessed by BIRC: stage of disease, geographic region, age, race and gender. The treatment effect hazard ratio (HR=0.50, 95% CI: 0.37, 0.66) after adjusting for the baseline covariates was similar to the stratified Cox regression model hazard ratio from the primary PFS analysis.

**Table 15: Sensitivity analyses – Study A2301**

Stratified log-rank test and Cox regression model for PFS, comparison of LDK378 750 mg with chemotherapy, including PD events assessed by either BIRC or investigator as PFS events
(Full analysis set)

| | | | Log-rank Test [a] | Cox Model [a] | |
|---|---|---|---|---|---|
| | Event/N (%) | Median Time (95% CI) (months) [b] | p-value | Hazard Ratio [c] | 95% CI [d] |
| All Patients | | | | | |
| LDK378 750 mg | 101/189 (53.4) | 13.9 (11.0, 19.1) | < 0.001 | 0.55 | (0.42, 0.72) |
| Chemotherapy | 129/187 (69.0) | 6.8 ( 4.3, 8.3) | | | |

Stratified log-rank test and Cox regression model for PFS per BIRC assessment, comparison of LDK378 750 mg with chemotherapy - stratified by randomization stratification factors as per clinical database at baseline
(Full analysis set)

| | | | Log-rank Test [a] | Cox Model [a] | |
|---|---|---|---|---|---|
| | Event/N (%) | Median Time (95% CI) (months) [b] | p-value | Hazard Ratio [c] | 95% CI [d] |
| All Patients | | | | | |
| LDK378 750 mg | 89/189 (47.1) | 16.6 (12.6, 27.2) | < 0.001 | 0.55 | (0.41, 0.73) |
| Chemotherapy | 113/186 (60.8) | 8.1 ( 5.8, 10.6) | | | |

Unstratified log-rank test and unstratified Cox regression model for PFS per BIRC assessment, comparison of LDK378 750 mg with chemotherapy
(Full analysis set)

| | Event/N (%) | Median Time (95% CI) (months) [b] | Log-rank Test [a] p-value | Cox Model [a] Hazard Ratio [c] | 95% CI [d] |
|---|---|---|---|---|---|
| All Patients | | | | | |
| LDK378 750 mg | 89/189 (47.1) | 16.6 (12.6, 27.2) | < 0.001 | 0.53 | (0.40, 0.70) |
| Chemotherapy | 113/187 (60.4) | 8.1 ( 5.8, 11.1) | | | |

Stratified log-rank test and Cox regression model for PFS per BIRC assessment, comparison of LDK378 750 mg with chemotherapy, excluding the start of anti-neoplastic therapy as a reason for censoring
(Full analysis set)

| | Event/N (%) | Median Time (95% CI) (months) [b] | Log-rank Test [a] p-value | Cox Model [a] Hazard Ratio [c] | 95% CI [d] |
|---|---|---|---|---|---|
| All Patients | | | | | |
| LDK378 750 mg | 91/189 (48.1) | 16.4 (12.5, 27.2) | < 0.001 | 0.56 | (0.43, 0.75) |
| Chemotherapy | 114/187 (61.0) | 8.1 ( 5.8, 11.1) | | | |

Stratified log-rank test and Cox regression model for PFS per BIRC assessment, comparison of LDK378 750 mg with chemotherapy, including the start of anti-neoplastic therapy as a PFS event
(Full analysis set)

| | Event/N (%) | Median Time (95% CI) (months) [b] | Log-rank Test [a] p-value | Cox Model [a] Hazard Ratio [c] | 95% CI [d] |
|---|---|---|---|---|---|
| All Patients | | | | | |
| LDK378 750 mg | 100/189 (52.9) | 15.4 (11.3, 25.2) | < 0.001 | 0.52 | (0.40, 0.67) |
| Chemotherapy | 138/187 (73.8) | 6.0 ( 4.3, 7.9) | | | |

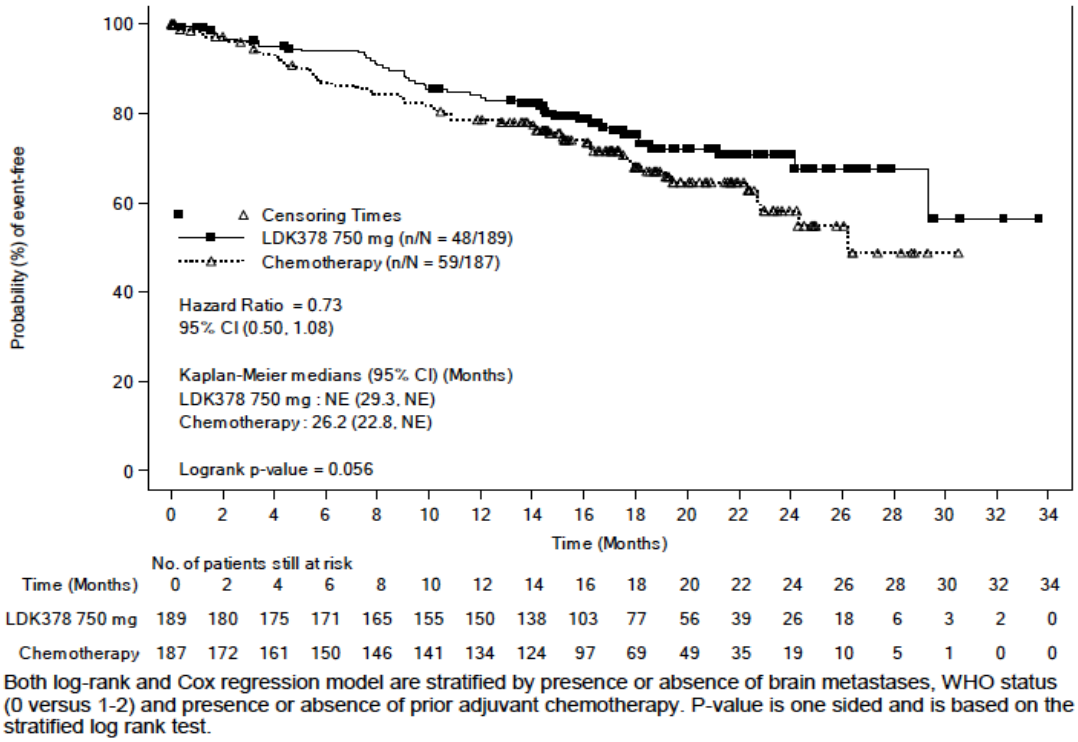
Stratified log-rank test and Cox regression model for PFS per BIRC assessment, comparison of LDK378 750 mg with chemotherapy, including events for patients with at least two tumor assessments missing prior to the PFS events
(Full analysis set)

| | Event/N (%) | Median Time (95% CI) (months) [b] | Log-rank Test [a] p-value | Cox Model [a] Hazard Ratio [c] | 95% CI [d] |
|---|---|---|---|---|---|
| All Patients | | | | | |
| LDK378 750 mg | 94/189 (49.7) | 16.4 (12.2, 27.2) | < 0.001 | 0.56 | (0.42, 0.74) |
| Chemotherapy | 115/187 (61.5) | 8.1 ( 5.8, 10.6) | | | |

Key secondary efficacy results - OS

As pre-specified in both the protocol and statistical analysis plan, statistical testing was performed on OS, based on a hierarchical testing procedure adopted for the study, as the primary efficacy endpoint PFS by BIRC assessment was statistically significant favouring the ceritinib arm. This is the second interim analysis OS.

The study did not cross the efficacy stopping boundary for OS at this second interim analysis. Testing was performed at a one-sided 0.0006 level of significance and the boundary was determined as per the predefined hierarchical testing procedure based on the planned 4-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary.




No. of patients still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDK378 750 mg | 189 | 180 | 175 | 171 | 165 | 155 | 150 | 138 | 103 | 77 | 56 | 39 | 26 | 18 | 6 | 3 | 2 | 0 |
| Chemotherapy | 187 | 172 | 161 | 150 | 146 | 141 | 134 | 124 | 97 | 69 | 49 | 35 | 19 | 10 | 5 | 1 | 0 | 0 |

Both log-rank and Cox regression model are stratified by presence or absence of brain metastases, WHO status (0 versus 1-2) and presence or absence of prior adjuvant chemotherapy. P-value is one sided and is based on the stratified log rank test.

**Figure 16: Kaplan-Meier plot of overall survival by treatment arm (FAS)**

**Table 16: Summary of reasons for censoring patients in OS analysis by treatment arm (Full analysis set)**

| Study analysis endpoint | Reason of censoring | LDK378 750 mg N=189 n (%) | Chemotherapy N=187 n (%) |
|---|---|---|---|
| OS | Number of patients censored | 141 ( 74.6) | 128 ( 68.4) |
| | Reason of censoring | | |
| | Alive [a] | 131 ( 69.3) | 110 ( 58.8) |
| | Lost to follow-up [b] | 10 ( 5.3) | 18 ( 9.6) |

The results of the OS analysis based on the PPS were similar to those assessed on the FAS (HR=0.81 with 95% CI: 0.55, 1.20; p=0.144) using stratified Cox model.

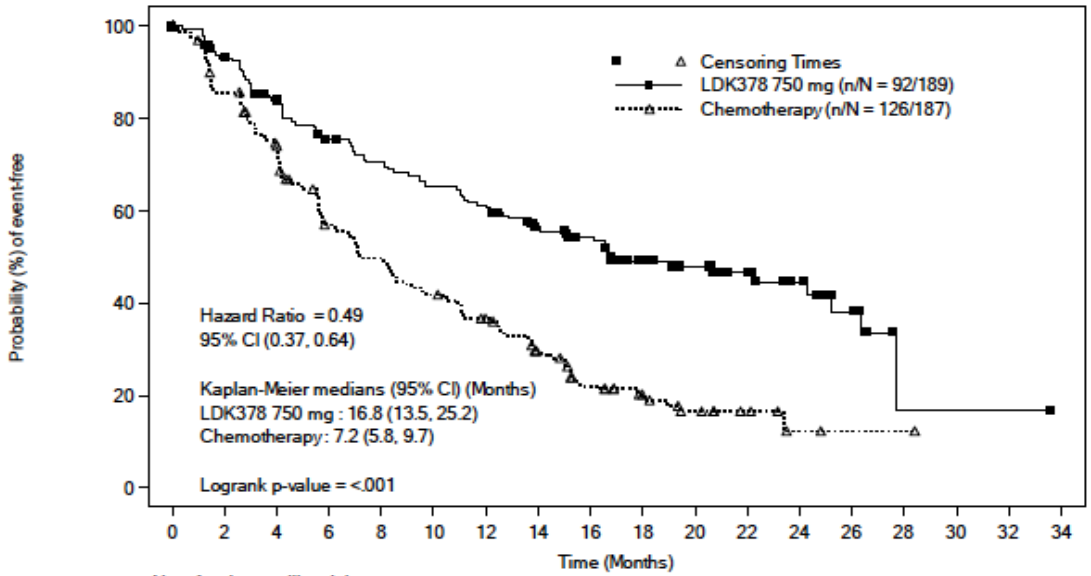
The following baseline covariates were included in a stratified multivariate Cox regression model for OS: stage of disease, geographic region, age, race, and gender. The treatment effect on the hazard ratio (HR=0.68, 95% CI: 0.46, 1.00) after adjusting for these baseline covariates was comparable to the stratified Cox regression model hazard ratio from the primary OS analysis.

Of note, at the time of interim analysis for OS, a total of 109 out of 175 patients treated in the chemotherapy arm received subsequent anti-neoplastic medication after discontinuation of chemotherapy. Of the 175 treated chemotherapy arm treated patients, 105 (60.0%) received a subsequent ALK-inhibitor as first treatment after discontinuation of chemotherapy including the 80 patients who received ceritinib in the extension treatment phase as per protocol. The additional 25 patients who did not cross-over received an ALK inhibitor as first treatment after discontinuation of chemotherapy. These ALK inhibitors received included crizotinib (23 patients), alectinib (one patient), and ceritinib (one patient). In addition, four patients received other chemotherapy as first treatment after discontinuation of study treatment with chemotherapy.

A sensitivity analysis using rank-preserving structural failure time (RPSFT) was performed to correct for confounding introduced by the change of treatment when patients crossed-over from chemotherapy arm to

ceritinib arm. After adjustment for cross-over with the RPSFT model, the HR estimate from the RPSFT analysis was similar to the one from the primary OS analysis (HR=0.73; 95% CI: 0.49, 1.10). However the data was immature at the time of this primary analysis.

PFS by Investigator assessment (secondary endpoint)




No. of patients still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDK378 750 mg | 189 | 167 | 146 | 129 | 120 | 111 | 104 | 80 | 67 | 46 | 37 | 27 | 17 | 11 | 1 | 1 | 1 | 0 |
| Chemotherapy | 187 | 143 | 119 | 87 | 76 | 64 | 53 | 38 | 25 | 17 | 11 | 6 | 2 | 1 | 1 | 0 | 0 | 0 |

Both log-rank and Cox regression model were stratified by presence or absence of brain metastases, WHO status and presence or absence of prior adjuvant chemotherapy as per randomization. P-value was one sided and was based on the stratified log rank test.

Source: Figure 14.2-1.2

**Figure 17: Kaplan-Meier plot of progression-free survival per Investigator assessment by treatment arm (FAS)**

As of the data cut-off date, the median follow-up time for PFS by Investigator assessment was 13.7 months (range: 0 to 33.6 months) for the ceritinib arm and 5.6 months (range: 0 to 28.4months) for the chemotherapy arm

Hazard ratio for patients in different stratifications were as follows: patients with BM (HR=0.66; 95% CI: 0.41, 1.05); patients without BM (HR=0.42; 95% CI: 0.30, 0.59); WHO status 0 (HR=0.51; 95% CI: 0.32, 0.80),WHO status 1-2 (HR=0.48; 95% CI: 0.34, 0.67), patients with prior adjuvant chemotherapy (HR=0.34; 95% CI: 0.03, 3.85) and patients without prior adjuvant chemotherapy (HR=0.49;95% CI: 0.37, 0.65).

The results of the PFS analysis by Investigator assessment using the PPS were consistent with those of the PFS analysis based on the FAS. The results yielded a HR of 0.50 (95% CI: 0.38, 0.65; p<0.001 one-sided, stratified log-rank test); the median PFS as assessed by Investigator assessment (95% CI) was 16.8 months (95% CI: 13.5, 25.2) and 7.2 months (95% CI: 5.8, 9.7) for the ceritinib arm and the chemotherapy arm, respectively.

High concordance rates in the assessment of PFS event type between BIRC and Investigator review was observed with 88.4% for the ceritinib arm and 86.6% for the chemotherapy arm.

**Table 17: Progression free survival as assessed by Investigator vs BIRC by treatment arm (FAS)**

| | Investigator assessment PFS results | | _BIRC assessment PFS results_ Death n (%) | PD n (%) | Censor n (%) |
|---|---|---|---|---|---|
| Ceritinib 750 mg (N=189) | Death (n=9) | [a] | 9 ( 100) | 0 | 0 |
| | | [b] | 9 (90.0) | 0 | 0 |
| | PD (n=83) | [a] | 1 ( 1.2) | 70 (84.3) | 12 (14.5) |
| | | [b] | 1 (10.0) | 70 (88.6) | 12 (12.0) |
| | Censor (n=97) | [a] | 0 | 9 ( 9.3) | 88 (90.7) |
| | | [b] | 0 | 9 (11.4) | 88 (88.0) |
| | Total | | 10 | 79 | 100 |
| Chemotherapy (N=187) | Death (n=8) | [a] | 5 (62.5) | 3 (37.5) | 0 |
| | | [b] | 5 (62.5) | 3 ( 2.9) | 0 |
| | PD (n=118) | [a] | 3 ( 2.5) | 99 (83.9) | 16 (13.6) |
| | | [b] | 3 (37.5) | 99 (94.3) | 16 (21.6) |
| | Censor (n=61) | [a] | 0 | 3 ( 4.9) | 58 (95.1) |
| | | [b] | 0 | 3 ( 2.9) | 58 (78.4) |
| | Total | | 8 | 105 | 74 |

N: The total number of patients in FAS. Death refers to death without PD.

n: Number of patients who were at the corresponding category.

[a] row percent rates were calculated as the number of patients in the corresponding cell (e.g. Death/Death) divided by the total number of patients corresponding to that particular row as per Investigator assessment (e.g. all patients with Investigator PFS result = Death).

[b] column percent rates were calculated as the number of patients in the corresponding cell (e.g. Death/Death) divided by the total number of patients corresponding to that particular column as per BIRC assessment (e.g. all patients with BIRC assessment PFS result = Death).

Overall response rate (secondary endpoint)

**Table 18: Best overall response per BIRC assessment by treatment arm (FAS)**

| | Ceritinib 750 mg N=189 | | | Chemotherapy N=187 | | |
|---|---|---|---|---|---|---|
| | n | (%) | 95% CI [a] | n | (%) | 95% CI [a] |
| Best overall response | | | | | | |
| Complete Response (CR) | 1 ( 0.5) | | | 0 | | |
| Partial Response (PR) | 136 (72.0) | | | 50 (26.7) | | |
| Stable Disease (SD) | 20 (10.6) | | | 79 (42.2) | | |
| Progressive Disease (PD) | 19 (10.1) | | | 26 (13.9) | | |
| Non-CR/Non-PD | 3 ( 1.6) | | | 9 ( 4.8) | | |
| Unknown (UNK) | 10 ( 5.3) | | | 23 (12.3) | | |
| Overall Response Rate (ORR: CR+PR) | 137 (72.5) | | (65.5, 78.7) | 50 (26.7) | | (20.5, 33.7) |
| Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD) | 160 (84.7) | | (78.7, 89.5) | 138 (73.8) | | (66.9, 79.9) |

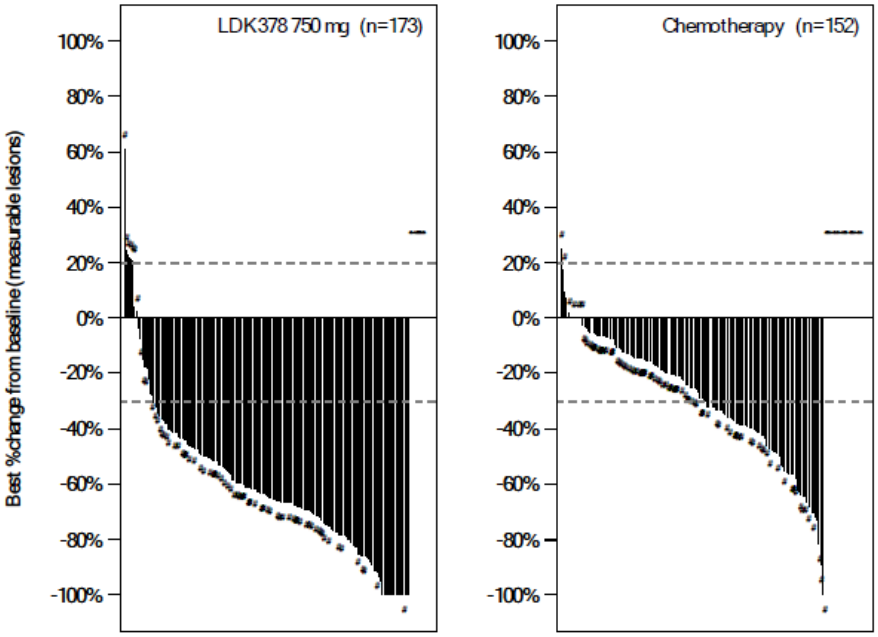
N: The total number of patients in the Full Analysis Set. It is the denominator for percentage (%) calculation.

n: Number of patients who were at the corresponding category.

[a] Exact binomial 95% Confidence Interval.

Non-CR/Non-PD refers to best overall responses that were neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.

Source: Table 14.2-3.1




| | LDK378 750 mg | Chemotherapy |
|---|---|---|
| Best percentage change from baseline<0 | 90.17% (156) | 80.26% (122) |
| Best percentage change from baseline>0 | 4.62% (8) | 3.29% (5) |
| Best percentage change from baseline=0 | 0.00% (0) | 3.95% (6) |

* %change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 5.20% (9) 12.50% (19)

**Figure 18: Waterfall plot for best percentage change from baseline in sum of diameters per BIRC assessment (FAS)**

**Table 19: Best overall response per Investigator assessment by treatment arm (FAS)**

| | Ceritinib 750 mg N=189 | | Chemotherapy N=187 | |
|---|---|---|---|---|
| | n (%) | 95% CI [a] | n (%) | 95% CI [a] |
| Best overall response | | | | |
| Complete Response (CR) | 5 ( 2.6) | | 0 | |
| Partial Response (PR) | 134 (70.9) | | 60 (32.1) | |
| Stable Disease (SD) | 30 (15.9) | | 82 (43.9) | |
| Progressive Disease (PD) | 11 ( 5.8) | | 21 (11.2) | |
| Unknown (UNK) | 9 ( 4.8) | | 24 (12.8) | |
| Overall Response Rate (ORR: CR+PR) | 139 (73.5) | (66.7, 79.7) | 60 (32.1) | (25.5, 39.3) |
| Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD) | 169 (89.4) | (84.1, 93.4) | 142 (75.9) | (69.2, 81.9) |

N: The total number of patients in the Full Analysis Set. It is the denominator for percentage (%) calculation.
n: Number of patients who were at the corresponding category.
[a] Exact binomial 95% Confidence Interval.
Non-CR/Non-PD refers to best overall responses that were neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.
Source: Table 14.2-3.2

Disease control rate

Disease control rate as assessed by BIRC was higher in the ceritinib arm compared to the chemotherapy arm (84.7%, 95% CI: 78.7, 89.5 and 73.8%, 95% CI: 66.9, 79.9, respectively).

Duration of response

Among patients with a confirmed CR or PR, the median DOR per BIRC assessment was longer in patients treated with ceritinib (23.9 months; 95% CI: 16.6, NE) compared to patients treated with chemotherapy (11.1 months; 95% CI: 7.8, 16.4).

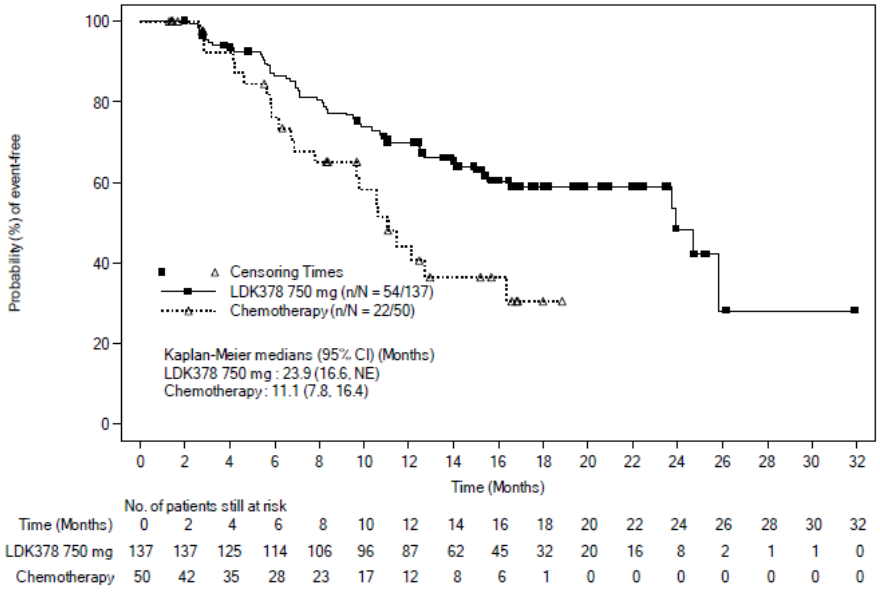



**Figure 19: Kaplan-Meier plot of duration of response per BIRC assessment by treatment arm (FAS – Patients with confirmed CR or PR)**

Time to response

Among patients with confirmed CR/PR, 124/137 (90.5%) patients achieved the first documented response during the first 12 weeks on treatment with ceritinib compared to 16/50(32%) patients treated with chemotherapy. The median time to first response for patients with confirmed CR or PR was 6.1 weeks (range: 5.1 to 61.7 weeks) in the ceritinib arm and 13.4 weeks (range: 5.1 to 90.1 weeks) in the chemotherapy arm.

Intracranial response

Of the 121 patients (61 patients in the ceritinib arm and 60 patients in the chemotherapy arm) who had measurable or non-measurable brain metastases at baseline as per BIRC neuro-radiologist review, 106 patients had at least one post-baseline assessment allowing the evaluation of the response to the study treatment. The proportion of patients with five or more number of brain lesions was 19/61 (31.1%) and was 15/60 (25.0%) in the ceritinib and chemotherapy arm respectively. Fifty-five of 121 patients had measurable disease in the brain at baseline, among whom 44 patients had measurable lesions and who had a baseline and at least one post-baseline assessment (22 patients each in the ceritinib arm and the chemotherapy arm). Of the 121 patients with brain metastasis, 24/61 patients in the ceritinib arm and 24/60 patients in the chemotherapy arm had received prior radiation therapy to brain, 22/24 patients in the ceritinib arm and 21/24 patients in the chemotherapy arm had radiation to the brain within 3 months prior to randomization.

**Table 20: Intracranial responses as per BIRC neuro-radiology review**

| Brain metastases at baseline | OIRR (CR+PR) n%, 95% CI[a] | | Median DOIR[b] Months, 95% CI[a] | | ICBR at 12 weeks n%, 95% CI[a] | | ICBR at 24 weeks n%, 95% CI[a] | | IDCR (CR+PR+SD+Non-CR/Non-PD) n%, 95% CI[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ceritinib | Chemotherapy | Ceritinib | Chemotherapy | Ceritinib | Chemotherapy | Ceritinib | Chemotherapy | Ceritinib | Chemotherapy |
| Measurable brain disease and at least one post-baseline assessment | N=22 | N=22 | N=16 | N=6 | N=22 | N=22 | N=22 | N=22 | N=22 | N=22 |
| | 72.7%, (49.8, 89.3) | 27.3%, (10.7, 50.2) | 16.6 (8.1, NE) | NE (1.5, NE) | 86.4% (65.1, 97.1) | 68.2% (45.1, 86.1) | 86.4% (65.1, 97.1) | 50.0% (28.2, 71.8) | 86.4% (65.1, 97.1) | 90.9%; (70.8, 98.9) |
| Measurable brain disease and at least one post-baseline assessment and without prior radiotherapy | N=13 | N=18 | N=9 | N=5 | - | - | - | - | N=13 | N=18 |
| | 69.2%, (38.6, 90.9) | 27.8%, (9.7, 53.5) | 16.6 (5.4, 16.6) | NE (1.5, NE) | - | - | - | - | 92.3% (64.0, 99.8) | 94.4% (72.7, 99.9) |
| Measurable or non-measurable brain disease and at least one post-baseline assessment | N=54 | N=52 | N[b]=25 | N[b]=11 | N=54 | N=52 | N=54 | N=52 | N=54 | N=52 |
| | 46.3%, (32.6, 60.4) | 21.2%, (11.1, 34.7) | 16.6 (8.1, 21.3) | 18.4 (1.5, 18.4) | 79.6% (66.5, 89.4) | 75.0% (61.1, 86.0) | 70.4% (56.4, 82.0 | 55.8% (41.3, 69.5 | 88.9% (77.4, 95.8) | 92.3% (81.5, 97.9) |
| Measurable or non-measurable brain disease and at least one post-baseline assessment, without prior radiotherapy | N=32 | N=31 | N=15 | N=9 | - | - | - | - | N=32 | N=31 |
| | 46.9%, (29.1, 65.3) | 29.0%, (14.2, 48.0) | 12.4, (6.5, NE)[c] | 9.9, (1.5, 18.4) | - | - | - | - | 90.6% (75.0, 98.0) | 96.8% (83.3, 99.9) |

N: Number of patients who were at the corresponding category.
[a] Exact binomial 95% Confidence Interval
[b] Patients with confirmed intracranial CR or PR.
[c] DOIR rate at 15 months for the ceritinib arm was 42.2% (95%CI:14.9, 67.7)

Patient reported outcomes

The compliance of patients completing the quality of life questionnaires was high with ≥ 80% of the patients in the ceritinib and chemotherapy arm completing the LCSS, EORTC QLQ C30, EORTC QLQ-LC13, and EQ-5D, questionnaires at most of the time points during the course of the study.

Improvements were reported for the majority of lung cancer specific symptoms in the ceritinib arm compared to the chemotherapy arm.

Specifically, time to deterioration for the composite endpoint of cough, pain and dyspnoea was prolonged in the LCSS (NE months vs 18.4 months, HR=0.61; 95% CI: 0.41, 0.90) and QLQ-LC13 (23.6 months vs 12.6 months, HR=0.48, 95% CI: 0.34, 0.69) instruments for ceritinib versus chemotherapy.

The probability of patients not having a definitive deterioration for the LCSS composite endpoint in the ceritinib arm at 24 months was 55.3% (95% CI: 43.6, 65.5) compared to 25.9% (95% CI: 6.8, 50.8) in the chemotherapy arm. The probability of patients not having a definitive deterioration for the QLQ-LC13 composite endpoint at 18 months was 60.8% (95% CI: 51.8, 68.7) compared to 34.4% (95% CI: 23.4, 45.7) for the ceritinib arm and chemotherapy arm respectively.

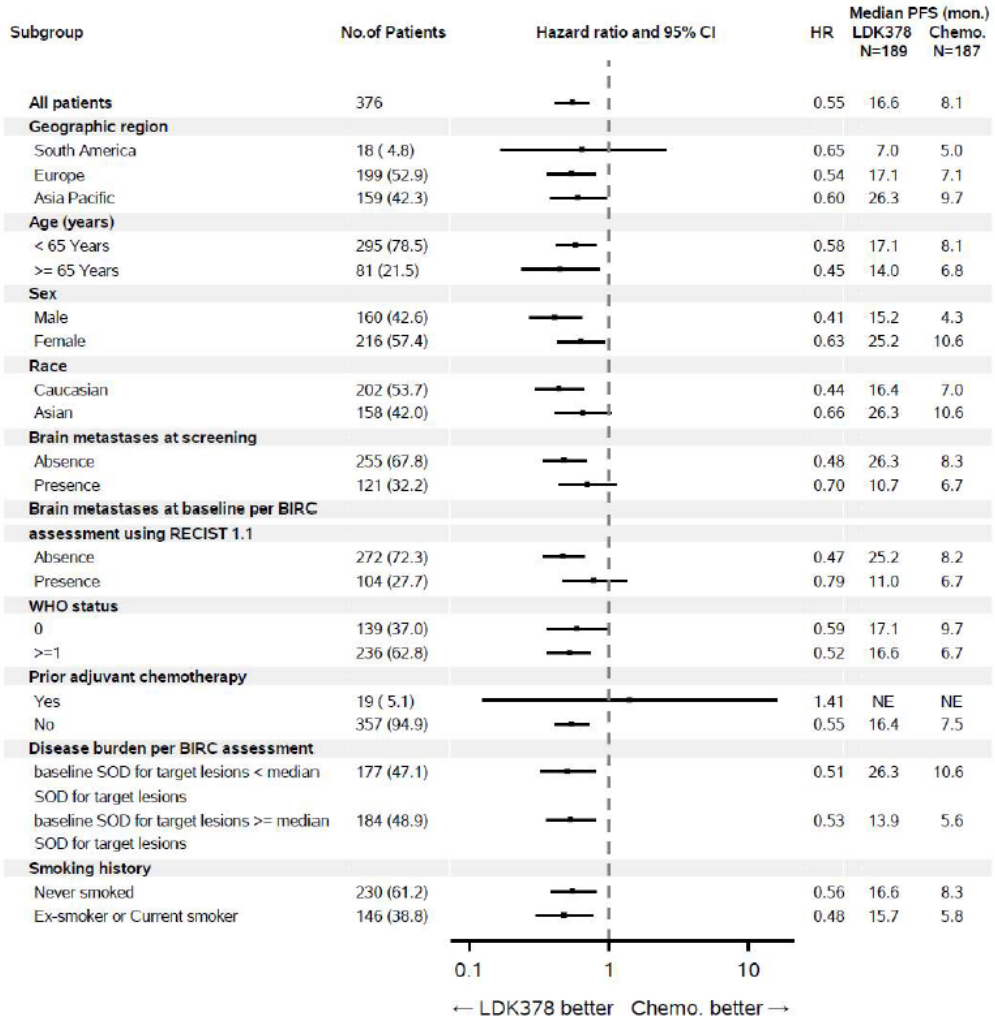
Four out of six LCSS symptom scales (pain, cough, shortness of breath and fatigues), LCSS total score, average symptom burden index, normal activity status, total symptom distress and overall quality of life were improved in the ceritinib arm compared to the chemotherapy arm. The symptom scales for appetite loss and haemoptysis showed no change in the ceritinib arm compared to chemotherapy.

Eight out of ten QLQ-LC13 scales (including the three item overall dyspnoea scale) showed improvements in the ceritinib arm compared to the chemotherapy arm. Improvements in the two scores for pain in arm or shoulder and haemoptysis were not significant.

The QLQ-C30 questionnaire on general cancer symptoms showed improvements in four (physical functioning, emotional functioning, social functioning and role functioning) out of five functional scales and six (fatigue, pain, dyspnoea, insomnia, constipation and financial difficulties) out of nine individual scales. Patients receiving ceritinib achieved less favourable outcomes than those on chemotherapy for diarrhoea as

well as for nausea and vomiting scales, however no deterioration in the overall Quality of Life for patients was observed despite the longer exposure to ceritinib. In addition, improvements were demonstrated for ceritinib versus chemotherapy with improvements in most symptom scores, functional domains and for Global Health Status / QoL in the same instrument.

## Ancillary analyses




Except for 'WHO status', 'Brain metastases at Screening' and 'Brain metastases at baseline per BIRC assessment using RECIST 1.1', 'Prior adjuvant chemotherapy' Cox regression model stratified by presence or absence of brain metastases, prior adjuvant chemotherapy and WHO status.

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

For 'Brain metastases at screening' and 'Brain metastases at baseline per BIRC assessment using RECIST 1.1' Cox regression model was stratified by WHO status and presence or absence of prior adjuvant chemotherapy.

For 'Prior adjuvant chemotherapy' Cox model was stratified by WHO status and presence or absence of brain metastases

**Figure 20: Forest plot for progression-free survival per BIRC assessment by subgroup (FAS)**

**Table 21: Efficacy of ceritinib by BIRC in subgroups of patients by WHO performance status (FAS)**

| | Ceritinib 750 mg N=189 | | | | Chemotherapy N=187 | | | |
|---|---|---|---|---|---|---|---|---|
| | WHO PS 0 N=69 | WHO PS 1 N=107 | WHO PS 2 N=13 | All patients N=189 | WHO PS 0 N=70 | WHO PS 1 N=105 | WHO PS 2 N=11 | All patients N=187 |
| ORR by BIRC, n (%) (95% CI) | 51 (73.9) (61.9, 83.7) | 77 (72.0) (62.5, 80.2) | 9 (69.2) (38.6, 90.9) | 137 (72.5) (65.5, 78.7) | 21 (30.0) (19.6, 42.1) | 28 (26.7) (18.5, 36.2) | 1 (9.1) (0.2, 41.3) | 50 (26.7) (20.5, 33.7) |
| DCR by BIRC, n (%) (95% CI) | 61 (88.4) (78.4, 94.9) | 89 (83.2) (74.7, 89.7) | 10 (76.9) (46.2, 95.0) | 160 (84.7) (78.7, 89.5) | 55 (78.6) (67.1, 87.5) | 77 (73.3) (63.8, 81.5) | 5 (45.5) (16.7, 76.6) | 138 (73.8) (66.9, 79.9) |
| Median DOR by BIRC- months (95% CI) | N*=51 24.7 (12.6, NE) | N*=77 23.9 (23.7, NE) | N*=9 8.2 (2.8, 15.0) | N*=137 23.9 (16.6, NE) | N*=21 11.4 (5.6, NE) | N*=28 11.1 (7.8, NE) | N*=1 5.9 (NE, NE) | N*=50 11.1 (7.8, 16.4) |
| Median PFS by BIRC - months (95% CI) | 17.1 (11.3, NE) | 25.2 (12.5, 27.7) | 8.8 (1.8, 16.4) | 16.6 (12.6, 27.2) | 9.7 (7.0, 14.2) | 6.7 (4.3, 9.7) | 6.1 (0.2, 15.1) | 8.1 (5.8, 11.1) |
| % Event-free probability (95% CI) at 15 months | 54.2 (40.8, 65.8) | 57.8 (47.2, 67.0) | 25.0 (6.0, 50.5) | 54.1 (46.2, 61.3) | 34.5 (21.8, 47.5) | 28.5 (19.1, 38.6) | 16.7 (0.9, 50.8) | 30.5 (23.0, 38.4) |

Source: [A2301 EMA Response-Table 17-1], [A2301 EMA Response-Table 17-3], [A2301 EMA Response-Table 17-9], [CSR Study A2301 CSR-Table 14.2-1.1], [CSR Study A2301 CSR-Table 14.2-3.1], [CSR Study A2301 CSR-Table 14.2-3.8]
N*: Number of responders

PFS in patients who continued to receive pemetrexed in maintenance

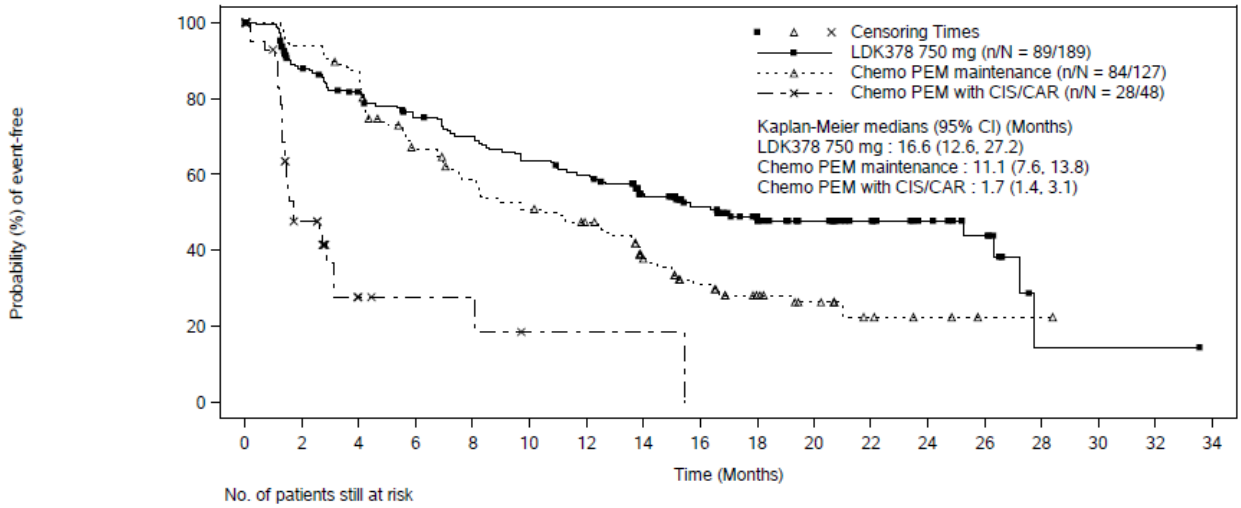
Out of the 376 patients with ALK-positive advanced non-squamous NSCLC who were included in Study A2301, 187 were randomized to the chemotherapy arm to receive pemetrexed-based platinum doublet therapy. Eighty-seven (87) patients started treatment with pemetrexed and cisplatin, 88 patients started treatment with pemetrexed and carboplatin. Twelve (12) patients were not treated (seven due to patient/guardian decision, two due to AEs, two due to physician's decision and one due to death). One hundred and twenty seven (127) patients entered the pemetrexed maintenance phase after induction therapy. Forty-eight (48) patients did not qualify for pemetrexed maintenance therapy at the end of the 4 cycles of induction. The primary reason for treatment discontinuation in these 48 patients was progressive disease in 25 (52.1%), physician decision in 8 (16.7%), subject guardian decision in 7 (14.6%) patients, deaths in 5 (10.4%) patients and AEs in 3 (6.25%) patients.

**Table 22: Summary of patients characteristics for patients with and without Pemetrexed maintenance treatment in study A2301 (FAS)**

| Patient characteristics | Ceritinib 750 mg N=189 | Chemotherapy + pemetrexed maintenance N=127 | Chemotherapy no maintenance N=48 |
|---|---|---|---|
| Age (years) | | | |
| Median (min, max) | 55.0 (22, 81) | 52.0 (22, 79) | 57.0 (29, 79) |
| Age category (years) – n (%) | | | |
| <65 years | 143 (75.7) | 109 (85.8) | 35 (72.9) |
| ≥ 65 years | 46 (24.3) | 18 (14.2) | 13 (27.1) |
| Gender – n (%) | | | |
| Female | 102 (54.0) | 86 (67.7) | 22 (45.8) |
| Male | 87 (46.0) | 41 (32.3) | 26 (54.2) |
| Race – n (%) | | | |
| Asian | 76 (40.2) | 58 (45.7) | 17 (35.4) |
| Black | 3 (1.6) | 2 (1.6) | 1 (2.1) |
| Caucasian | 104 (55.0) | 63 (49.6) | 30 (62.5) |
| Native American | 3 (1.6) | 2 (1.6) | 0 |
| Other | 3 (1.6) | 2 (1.6) | 0 |
| WHO Performance status – n (%) | | | |
| 0 | 69 (36.5) | 50 (39.4) | 15 (31.3) |
| 1 | 107 (56.6) | 71 (55.9) | 29 (60.4) |
| 2 | 13 (6.9) | 5 (3.9) | 4 (8.3) |
| Missing | 0 | 1 (0.8) | 0 |
| Metastatic site of cancer – n (%) | | | |
| Bone | 77 (40.7) | 49 (38.6) | 26 (54.2) |
| Brain | 59 (31.2) | 39 (30.7) | 19 (39.6) |
| Liver | 34 (18.0) | 22 (17.3) | 14 (29.2) |

Based on BIRC assessment, 89/189 (47.1%) PFS events were observed in the ceritinib arm compared to 84/127 (66.1%) PFS events observed in the subset of 127 patients in the chemotherapy arm who received pemetrexed maintenance. The median PFS was 16.6 months (95% CI: 12.6, 27.2) in the ceritinib arm and remain longer (+5.5 months) in favour of patients treated with ceritinib as compared to 11.1 months (95%

CI: 7.6, 13.8) in the subset of 127 patients who received pemetrexed maintenance, with an hazard ratio (HR) estimate of 0.68 (95% CI: 0.50, 0.92).




No. of patients still at risk

| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDK378 750 mg | 189 | 155 | 139 | 125 | 116 | 105 | 98 | 76 | 59 | 43 | 32 | 23 | 16 | 11 | 1 | 1 | 1 | 0 |
| Chemo PEM maintenance | 127 | 119 | 110 | 79 | 68 | 59 | 52 | 34 | 24 | 16 | 11 | 5 | 3 | 1 | 1 | 0 | 0 | 0 |
| Chemo PEM with CIS/CAR | 48 | 17 | 4 | 3 | 3 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- Chemo PEM maintenance denote patients in the chemotherapy arm who continued to receive at least a dose of pemetrexed as single agent (maintenance).
- Chemo PEM with CIS/CAR denote patients in the chemotherapy arm who did not continue to receive a dose of pemetrexed as single agent (maintenance).

**Figure 21: Kaplan-Meier plot of PFS per BIRC assessment by treatment arm and patients in the chemotherapy arm who continued to receive at least a dose of Pemetrexed as single agent maintenance and those who did not (safety analysis set)**

An analysis of PFS based on BIRC assessment including patients who continued treatment beyond 15 weeks in both treatment arms (127/175 patients in the chemotherapy arm and 156/189 patients in the ceritinib arm) showed a median PFS of 25.2 months (95% CI: 15.4, 27.7) in the ceritinib arm and 11.1 months (95% CI: 7.6, 13.8) in the chemotherapy arm (HR 0.53 95%CI 0.38-0.74).

## *Summary of main study*

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 23: Summary of Efficacy for trial A2301**

| **Title:** A phase III multicenter, randomized study of oral LDK378 versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer | | |
|---|---|---|
| Study identifier | CLDK378A2301 (ASCEND-4) | |
| Design | Open-label, randomised vs chemotherapy in first line | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | Study ongoing |
| Hypothesis | Superiority | |
| Treatments groups | Ceritinib | Ceritinib 750 mg once daily. 189 patients |
| | Chemotherapy | pemetrexed (500 mg/m2 iv q 21 days) plus cisplatin (75mg/m² iv q 21 days) or pemetrexed (500 mg/m2 iv q 21 days) plus carboplatin (AUC 5-6 iv q 21 days)for 4 cycles of treatment (Induction) followed by pemetrexed alone as single-agent (maintenance)every 21 days in patients without progressive disease after induction chemotherapy. 187 patients |

| | | | |
|---|---|---|---|
| | | | Treatment with ceritinib or chemotherapy was continued until the patient experienced PD, unacceptable toxicity, pregnancy, start of a new anti-cancer therapy, discontinues treatment at the discretion of the patient or Investigator, lost to follow-up, death,or study terminated by Sponsor |
| Endpoints and definitions | Primary endpoint | PFS by BIRC | time from the date of randomization to the date of the first radiologically documented disease progression per BIRC assessment or death due to any cause |
| | Secondary | OS | time from date of randomization to date of death due to any cause |
| | Secondary | ORR by BICR | proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) |
| Database lock | 11-Sep-2016 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat | | |
| Descriptive statistics and estimate variability | Treatment group | Ceritinib | Chemotherapy |
| | Number of subject | 189 | 187 |
| | PFS (median; months) | 16.6 | 8.1 |
| | 95% CI | 12.6, 27.2 | 5.8, 11.1 |
| | OS (median; months) | NE | 26.2 |
| | 95% CI | 29.3, NE | 22.8, NE |
| | ORR (%) | 72.5 | 26.7 |
| | 95% CI | 65.5, 78.7 | 20.5, 33.7 |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | PFS | Comparison groups | Ceritinib vs chemotherapy |
| | | HR | 0.55 |
| | | 95% CI | 0.42 0.73 |
| | | P-value | <0.001 |
| | OS | Comparison groups | Ceritinib vs chemotherapy |
| | | HR | 0.73 |
| | | 95% CI | 0.50, 1.08 |
| | | P-value | 0.056 |
| Notes | The data cut-off date for this primary analysis was 24-Jun-2016, when 202 PFS events had been documented as per BIRC assessment and 218 PFS events per Investigator assessment were documented. The analyses are presented using data locked on 11-Sep-2016. The study is ongoing. The median duration between randomization and data cut-off date for all patients was 19.7 months | | |

## *Analysis performed across trials (pooled analyses and meta-analysis)*

No analyses performed across trials have been performed.

## *Clinical studies in special populations*

As the laboratory eligibility criteria required patients to have adequate renal and hepatic function to be eligible for Study A2301, specific subgroup analyses of patients with renal or hepatic impairment in the targeted patient population were not feasible.

### *Supportive study*

No supportive study was submitted as part of this application.

## 2.4.3. Discussion on clinical efficacy

The MAH is seeking a new indication for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). For that purpose, a Phase III, open-label, randomized, active-controlled global study, CLDK378A2301 (ASCEND-4), for the first-line treatment of ALK positive advanced NSCLC patients, has been submitted.

Patients were randomized in a 1:1 ratio to receive either ceritinib (750 mg once daily fasted) or chemotherapy (pemetrexed [500 mg/$m^2$] plus cisplatin [75 mg/$m^2$] or carboplatin [AUC 5-6 iv q 21 days) in the Treatment Phase. Patients who completed 4 cycles of treatment (induction) without progressive disease subsequently received pemetrexed as single-agent (maintenance 500 mg/$m^2$) every 21 day. Patients in the chemotherapy arm were allowed to cross-over and receive ceritinib after BIRC-confirmed disease progression. Patients in either arm were allowed to continue the assigned study treatment beyond BIRC-confirmed disease progression in case of continued clinical benefit as per the Investigator.

Patients included in Study A2301 presented with locally advanced (not candidates for definitive multimodality therapy) or metastatic ALK-positive non-squamous NSCLC not previously treated with any systemic anti-cancer therapy for advanced disease. Patients who were previously treated with neo-adjuvant or adjuvant systemic therapy were eligible for enrolment only if relapse occurred more than 12 months from the end of the adjuvant or neo adjuvant systemic therapy.

This population seems to represent a first line ALK positive NSCLC. Of note, patients with symptomatic CNS metastases who were neurologically unstable or had required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms, were excluded from the study and reflected in section 5.1 of the SmPC.

Treatments administered in the control arm could be considered, from a regulatory point of view, as the SoC at the time of the first patient was recruited (July 2013) since crizotinib received a positive opinion for previously treated patients in July 2012. On 22 October 2015, the CHMP recommended the use of crizotinib in first line setting. Doses of chemotherapy, the possibility of choosing between cisplatin or carboplatin and maintenance option for those patients with at least SD after induction (4 cycles), reflected the clinical practice at that time.

Baseline characteristics are evenly balanced. The median age of the population recruited was 54 years, with a vast majority in WHO PS 0-1 (93%). Approximately, half of the population was Caucasian and 42% Asian. Never smoked patients represent 61% of the patients randomised, which is characteristic of ALK positive patients. Regarding the histology, adenocarcima, as expected, is the most frequent histology type in the study.

The primary objective was to compare the anti-tumour activity of ceritinib versus chemotherapy, as measured by PFS determined by a BIRC. Therefore, the primary endpoint was PFS per BIRC, which is acceptable in first line of NSCLC within the context of an open-label design. The cross-over was allowed from chemotherapy to ceritinib arm after BIRC-confirmed disease progression. The latter, from an ethical perspective is totally acceptable, even though from a methodological point of view will have an impact on the interpretability of the key secondary endpoint, OS.

The rest of secondary endpoints and exploratory variables appear adequate. Of note, the MAH did not follow the national scientific advice from AEMPS (March 2013) and MPA (April 2013) with respect to using PFS2 as an endpoint as recommended in the CHMP guideline. This is unfortunate as PFS2 results would have been of great interest, in order to evaluate the impact of ceritinib on next line therapies.

Sample size calculations and statistical methods are in principle agreeable, especially the fact that the study is powered to detect a hazard ratio of 0.70 in OS. The analysis of efficacy variables and the several sensitivity analyses pre-specified into the protocol will provide robustness to the main analysis.

The randomisation process, via IRT, and the stratification factors (WHO PS, BM and neo/adjuvant chemo) are deemed appropriated.

**Efficacy data and additional analyses**

All patients randomised in ceritinib arm were treated but there were 12 subjects in the chemo group who were randomised but untreated. More patients discontinued in chemotherapy arm than in ceritinib group during the treatment phase, being the main reason disease progression. Among the 85 patients (in the chemo arm) who entered the extension treatment phase, 80 had received a dose of ceritinib by the cut-off date in the extension treatment phase. At the time of the data cut -off, 33/85 patients in the extension treatment phase were still ongoing. In addition, 95 (50.3%) patients in the ceritinib arm and 30 (16.0%) in the chemotherapy arm were still on study treatment in the treatment phase.

Patients treated with ceritinib in first line of ALK+ NSCLC obtain a gain of 8 months in terms of median PFS (from 8 months to 16 months) with a HR of 0.55. From an efficacy point of view, the outcomes clearly point out the benefit of ceritinib over chemotherapy. The percentage of events is 47% and 60% in ceritinib and chemotherapy arms respectively. Reasons for censoring are mainly due to absence of event and initiation of new anticancer therapy, the former higher for ceritinib and the latter more frequently reported for chemotherapy. These results in terms of PFS seem robust enough as several sensitive analyses (including the PPS) do not show important dissimilar outcomes, and subgroup analyses results were supportive.

The investigator's assessment of PFS offers a similar result to the primary analysis based on BIRC. The delay in the tumor progression observed in the PFS results (79 events out of 89 were progression) seems to be a direct consequence of the antitumor activity, since the ORR associated to ceritinib (72.5%) are almost all due to PR, with only 1 CR and 20 patients with SD. On the contrary, SD was the most frequent (42.2%) response in the chemotherapy arm. The response rate offered by ceritinib seems durable, seeing as the median of the duration of the response was 23.9 months (vs. 11 months in chemo group) even though these data are not mature enough.

This superiority in progression free survival could be translated into a longer survival for patients treated with ceritinib in first line, however, despite the positive trend observed in the interim analysis OS (HR 0.73 95% CI: 0.50, 1.08;p=0.056), did not reach statistical significance at the pre-specified one-sided significance level of 0.0006. The final OS results could not show significant differences due to the cross-over from ceritinib and the use of subsequent anti-neoplastic medication (109 out of 175 patients) with 60% of patients in the chemotherapy arm treated with ALK inhibitors after progression (crizotinib in 23 patients).

In the subgroup of patients with brain metastases, ceritinib is showing a valuable OIRR, superior to chemotherapy. The same trend was seen in those patients with and without prior radiotherapy. Despite the exploratory nature of these analyses, the intracranial activity of ceritinib is deemed promising. Unfortunately, the efficacy of ceritinib to delay the onset of brain metastases was not investigated in study A2301, as only patients with identified brain lesions at baseline had subsequent scheduled brain assessment. However, according the MAH, the long median PFS (exceeding 2 years) in the subgroup of patients without brain lesions at baseline indicate that ceritinib may have delayed early or symptomatic brain progression. Considering that delaying the onset of brain metastases was not investigated in study A2301, it is considered impossible to draw any conclusion as regards whether ceritinib may delay the onset of brain metastases or not.

PROs questionnaires were completed by 80% of patients, overall in the majority of the time-points of the trial (Day 1 of each cycle). Results highlighted an improvement in overall health status over chemotherapy.

The results indicated significant improvements in lung cancer specific symptoms shown by significant improvements in most individual symptom scales and delay in time to deterioration of LCSS/QLQ-LC13 composite scores for patients receiving ceritinib versus chemotherapy. The QLQ-C30 showed improvements in four out of five functional scales and in six out of nine individual scales. Furthermore, ceritinib showed improvements versus chemotherapy in overall quality of life (LCSS), Global Health status/quality of life (QLQ-C30) and in the EQ-5D index and Visual analogue score (VAS) scores. These results demonstrate an overall health status benefit. However, due to the open-label design, and exploratory nature of these analyses, these results should be interpreted with caution.

The landscape of frontline ALK positive setting is characterised by the use of crizotinib. In study 1014, crizotinib significantly prolonged progression-free survival (PFS), the primary objective of the study, compared to chemotherapy (without maintenance) as assessed by IRR (HR 0.45 95%CI 0.35, 0.60; Median PFS 10.9 vs 7.0 crizotinib and chemotherapy respectively). ORR was 74% for crizotinib vs 45% in the chemotherapy arm. OS data were not mature enough, but a positive trend was shown (HR=0.82; 95%CI 0.54, 1.26). So, taking into consideration the results offered by ceritinib and despite the bias associated to indirect comparison, ceritinib does not seem inferior to crizotinib, which is reassuring.

### 2.4.4. Conclusions on the clinical efficacy

Ceritinib has shown a clinically meaningful gain in PFS over chemotherapy in the first line of ALK positive NSCLC. This improvement in the primary endpoint seems robust and supported by the secondary endpoint endpoints. Comparing the study results from both products in the first line treatment of patients with ALK positive NSCLC, it appears that ceritinib does not have a lower efficacy than that observed for crizotinib in a similar clinical setting.

## *2.5. Clinical safety*

### *Introduction*

The safety review is based primarily on the results of the Phase III Study A2301. At the time of the data cut-off date of 24 June 2016, the median duration of follow-up between the date of randomization to the cut-off date for all patients was 19.7 months.

Comprehensive safety assessment of ceritinib is also provided from the pooled dataset (N=925) that consists of all available safety data from the Study A2301 (excluding the safety data from the extension-treatment phase) and six other Novartis-sponsored studies that had completed enrolment at the time of data cut-off of 24 June 2016 (see Table 24).

Additional safety information (cumulative line listings of deaths and SAEs) reported in the Novartis global pharmacovigilance safety database (ARGUS) for all 21 ongoing and two completed studies consisting of 1927 enrolled patients received as of the 10-Aug-2016. For completeness, safety of patients who were treated in the lower dose groups from the two Phase I studies (Study X2101, N=44 and Study X1101, N=13) are also summarized; and key safety findings of the few patients that were ongoing since the original submission (Study X2101 [N=6] and Study X1101 [N=2]) are presented.

The latest Zykadia PSUR with a data lock point of 28 April 2016 provides additional information on estimated 3700 patients treated with ceritinib in post-marketing setting.

**Table 24: Studies contributing key safety data**

| Study<br>Data cut-off date<br>Status | Design | Ceritinib dose | Total No. of patients | Study subgroups | Number of patients treated with ceritinib | Pooling |
|---|---|---|---|---|---|---|
| Study X2101<br>03-May-2016<br>Study completed | Phase I with extension phase, multi-center, dose-escalation study in patients with ALK-positive tumors including those who had received prior treatment with chemotherapy (any number of prior chemotherapies) and/or crizotinib. | Dose-escalation phase: 50-750 mg once daily, fasted<br>Expansion phase: 750 mg once daily, fasted | Dose-escalation phase: 59<br>Expansion phase: 245<br>Total at 750 mg: 255[a] | ALK+ NSCLC with prior crizotinib | <750 mg: n=33 | No |
| | | | | | 750 mg: n=163 | Yes |
| | | | | ALK+ NSCLC ALKi naive | <750 mg: n=11 | No |
| | | | | | 750 mg: n=83 | Yes |
| | | | | ALK+ in non-NSCLC cancers | <750 mg: n=5 | No |
| | | | | | 750 mg: n=9 | No |
| Study X1101<br>28-Jan-2016<br>ongoing: enrollment complete (study ongoing) | Phase I, multi-center, dose-escalation study in Japanese patients with ALK-positive tumors; previously treated with any number of prior chemotherapies, and prior ALK inhibitor therapy was allowed | Dose-escalation phase: 300-750 mg, once daily, fasted<br>Expansion phase: 750 mg, once daily, fasted | Dose-escalation phase: 19[b]<br>Expansion phase: 0[c]<br>Total at 750 mg: 6[b] | ALK+ NSCLC with prior ALKi | <750 mg: n=11 | No |
| | | | | | 750 mg: n=6 | Yes |
| | | | | ALK+ NSCLC ALKi naive | <750 mg: n=2 | No |
| | | | | | 750 mg: n=2 | Yes |
| | | | | ALK+ in non-NSCLC cancers | 750 mg: n=1 | No |
| Study A2201<br>29-Mar-2016<br>Study completed | Phase II, multi-center, single-arm study in adult patients with ALK-positive NSCLC previously treated with crizotinib, and 1-3 lines of chemotherapy. | 750 mg once daily, fasted | 140 | ALK+ NSCLC with prior crizotinib | 750 mg: n=140 | Yes |
| Study A2203<br>15-Nov-2015<br>ongoing: enrollment complete | Phase II, multi-center, single-arm study in crizotinib naive patients with ALK-positive NSCLC, who had received up to 3 lines of chemotherapy | 750 mg once daily, fasted | 124 | ALK+ NSCLC crizotinib naive | 750 mg: n=124 | Yes |
| Study A2109<br>30-Oct-2015<br>ongoing: enrollment complete | Phase I/II, multicenter, open-label, single-arm study in adult Chinese patients with ALK-positive advanced NSCLC previously treated with crizotinib with or without chemotherapy | Phase I (5 day PK Run-in): single dose of 750 mg<br>Phase II: 750 mg once daily, fasted | Phase I: 20<br>Phase II: 103 | ALK+ NSCLC with prior crizotinib | 750 mg: n=103 | Yes |
| Study A2303<br>26-Jan-2016<br>ongoing: enrollment complete | Phase III, global, randomized, open-label study of oral ceritinib versus standard chemotherapy in adult patients with ALK-positive NSCLC previously treated with chemotherapy (one or two prior regimens, including one platinum-based doublet) and crizotinib. Patients randomized to the chemotherapy treatment were allowed to crossover to receive ceritinib treatment in the extension treatment phase, only after BIRC-confirmed RECIST-defined PD was documented. | 750 mg once daily, fasted | N=231<br>Ceritinib=115<br>Docetaxel=73<br>Pemetrexed=40 | ALK+ NSCLC with prior crizotinib | 750 mg: n=115 | Yes |
| Study A2301<br>24-Jun-2016<br>ongoing: enrollment complete | Phase III global, open-label, active-controlled, randomized study of ceritinib vs. standard first-line chemotherapy (platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after 4 cycles) in previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC. The patients randomized to the chemotherapy treatment were allowed to crossover to receive ceritinib treatment in the extension treatment phase, only after BIRC-confirmed RECIST-defined PD was documented. | 750 mg once daily, fasted | 376<br>Ceritinib: 189<br>Chemo: 187 | ALK+ NSCLC crizotinib and chemo naive | 750 mg: n=189 | Yes |

For studies X2101 and X1101, the 750 mg group includes patients from both the dose-escalation phase treated at that dose and from the expansion phase.
[a] 246 patients with NSCLC and 9 patients with another malignancy
[b] 18 patients with NSCLC (5 treated at 750 mg) and 1 patient with another malignancy (treated at 750 mg)
[c] Enrolment in the expansion phase is ongoing; 1 additional patient was enrolled in the expansion phase since the data cut-off for the CSR
Source: [Study X2101], [Study X1101], [Study A2201], [Study A2203], [Study A2109], [Study A2303], [Study A2301].

The database, analysis set, and treatment groups are presented in the table below.

**Table 25: Database, analysis sets and treatment groups**

| Analysis set | Studies | Treatment groups/columns in tables | Number of patients who received ceritinib 750 mg qd |
|---|---|---|---|
| Safety set – Registration study | A2301 | Ceritinib 750 mg and chemotherapy | 189 |
| Safety set – pool | X2101, X1101 | All NSCLC patients* treated with ceritinib 750 mg | 925 |
| | A2201, A2203, A2109 | | |
| | A2301, A2303 | | |
| Crossover analysis set** | A2301 and A2303 | Ceritinib 750 mg | 80 in A2301<br>74 in A2303 |

* Only data from the 750 mg dose groups were pooled.

** Crossover analysis set was assessed separately and is presented in Section 2.1.9.

## *Patient exposure*

### Patient disposition

For patient disposition in Study A2301, please see **Error! Reference source not found.**.

In the pooled dataset, 925 patients were treated with ceritinib. Of the 925 patients, 704 patients (76.1%) discontinued treatment and 221 patients (23.9%) were still ongoing in the studies at the time of the individual study data cut-off dates.

**Table 26: Patient disposition by treatment group (FAS)**

| | Study A2301 | | All patients |
|---|---|---|---|
| | Chemotherapy N=187 n (%) | Ceritinib 750 mg N=189 n (%) | Ceritinib 750 mg N=925 n (%) |
| **Patients randomized** | 187 (100) | 189 (100) | |
| **Patients treated** | 175 (93.6) | 189 (100) | 925 (100) |
| Treatment discontinued | 157 (84.0) | 94 (49.7) | 704 (76.1) |
| Treatment ongoing* | 30 (16.0) | 95 (50.3) | 221 (23.9) |
| **Primary reason for end of treatment** | | | |
| Adverse event | 18 (9.6) | 15 (7.9) | 78 (8.4) |
| Completed | 0 | 0 | 16 (1.7) |
| Death | 11 (5.9) | 9 (4.8) | 60 (6.5) |
| Lack of efficacy | 0 | 0 | 5 (0.5) |
| Lost to follow-up | 0 | 2 (1.1) | 7 (0.8) |
| No longer requires treatment | 0 | 0 | 1 (0.1) |
| Non-compliance with study treatment | 0 | 2 (1.1) | 2 (0.2) |
| Physician decision | 11 (5.9) | 7 (3.7) | 33 (3.6) |
| Progressive disease | 94 (50.3) | 51 (27.0) | 384 (41.5) |
| Protocol deviation | 0 | 1 (0.5) | 2 (0.2) |
| Study terminated by sponsor | 0 | 0 | 1 (0.1) |
| Subject/guardian decision | 23 (12.3) | 7 (3.7) | 80 (8.6) |
| Technical problems [a] | 0 | 0 | 35 (3.8) |

- Patients ongoing at the time of the individual study cutoff.
- Percentage is based on N.
- Reasons for discontinuation are from EOT completion CRF pages.
- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.
- [a] From Study X2101 – patients rolled over to another study to continue receiving ceritinib treatment and this was coded as 'technical problems' as the primary reason for end of treatment.

Source: [SCS Appendix 1-Table 14.1-1.1]

### Exposure to treatment

*Duration of exposure*

Duration of exposure is summarised in Table 27.

**Table 27: Duration of exposure to study treatment by treatment group (Safety set)**

| | Study A2301 | | | | | All patients |
|---|---|---|---|---|---|---|
| | Chemotherapy | | | | Ceritinib | Ceritinib |
| | Pemetrexed M=175 | Cisplatin M=87 | Carboplatin M=100 | Overall N=175 | 750 mg N=189 | 750 mg N=925 |
| **Exposure categories (weeks) - n (%)** | | | | | | |
| <3 | 2 (1.1) | 0 | 2 (2.0) | 2 (1.1) | 3 (1.6) | 40 (4.3) |
| 3 to <6 | 13 (7.4) | 12 (13.8) | 13 (13.0) | 13 (7.4) | 7 (3.7) | 35 (3.8) |
| 6 to <9 | 12 (6.9) | 5 (5.7) | 10 (10.0) | 12 (6.9) | 4 (2.1) | 47 (5.1) |
| 9 to <12 | 4 (2.3) | 10 (11.5) | 20 (20.0) | 4 (2.3) | 8 (4.2) | 29 (3.1) |
| 12 to <15 | 17 (9.7) | 57 (65.5) | 48 (48.0) | 17 (9.7) | 10 (5.3) | 44 (4.8) |
| 15 to <18 | 10 (5.7) | 3 (3.4) | 5 (5.0) | 10 (5.7) | 3 (1.6) | 26 (2.8) |
| 18 to <21 | 14 (8.0) | 0 | 2 (2.0) | 14 (8.0) | 3 (1.6) | 33 (3.6) |
| 21 to <24 | 9 (5.1) | - | 0 | 9 (5.1) | 3 (1.6) | 19 (2.1) |
| 24 to <27 | 7 (4.0) | - | - | 7 (4.0) | 5 (2.6) | 37 (4.0) |
| 27 to <30 | 8 (4.6) | - | - | 8 (4.6) | 1 (0.5) | 24 (2.6) |
| 30 to <33 | 6 (3.4) | - | - | 6 (3.4) | 5 (2.6) | 36 (3.9) |
| ≥ 33 | 73 (41.7) | - | - | 73 (41.7) | 137 (72.5) | 555 (60.0) |
| **Exposure (weeks)** | | | | | | |
| Mean | 36.7 | 10.9 | 10.5 | 36.7 | 61.3 | 56.1 |
| SD | 28.76 | 3.51 | 4.04 | 28.76 | 35.06 | 43.77 |
| Median | 26.9 | 12.0 | 12.0 | 26.9 | 66.4 | 44.9 |
| Minimum | 0.7 | 3.0 | 0.7 | 0.7 | 1.0 | 0.1 |
| Maximum | 126.7 | 15.1 | 18.0 | 126.7 | 144.4 | 200.1 |

M = number of patients who had at least one dose of the corresponding drug

- Duration of exposure (weeks) = (Last date of exposure to study drug – First date of exposure to study drug + 1)/7.

- For chemotherapy drug (pemetrexed, cisplatin or carboplatin), last date of exposure to study drug = min(last dosing date of study drug + 20 days, last contact date before lost to follow-up, date of death, date of data cutoff)

- For chemotherapy treatment (overall), last date of exposure to chemotherapy treatment = min(last dosing date of any chemotherapy drug with non-zero dose + 20 days, last contact date before lost to follow-up, date of death, date of data cutoff)

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3-1.1]

*Cumulative dose, dose intensity, and relative dose intensity*

**Table 28: Summary statistics of exposure by treatment group (Safety set)**

| | Study A2301 | | | | All patients |
|---|---|---|---|---|---|
| | Chemotherapy N=175 | | | | |
| Exposure variable | Pemetrexed M=175 | Cisplatin M=87 | Carboplatin M=100 | Ceritinib 750 mg N=189 | Ceritinib 750 mg N=925 |
| **Cumulative dose [a]** | | | | | |
| Mean | 5653.2 | 256.7 | 17.2 | 241581.0 | 222995.6 |
| SD | 4500.93 | 79.29 | 6.75 | 152600.90 | 178417.52 |
| Median | 4000.0 | 299.1 | 18.9 | 235800.0 | 185550.0 |
| Minimum | 400.0 | 72.9 | 3.4 | 5250.0 | 750.0 |
| Maximum | 19990.5 | 375.0 | 33.0 | 676500.0 | 906750.0 |
| **Average dose [b]** | | | | | |
| Mean | 489.3 | 74.3 | 5.1 | 626.0 | 643.2 |
| SD | 30.62 | 2.82 | 0.79 | 124.82 | 115.66 |
| Median | 500.0 | 75.0 | 5.1 | 643.7 | 662.8 |
| Minimum | 297.8 | 60.8 | 3.4 | 317.8 | 288.4 |
| Maximum | 524.7 | 78.7 | 7.3 | 750.7 | 750.7 |
| **Actual dose intensity [c]** | | | | | |
| Mean | 480.1 | 71.7 | 5.1 | 579.6 | 598.9 |
| SD | 149.56 | 6.24 | 1.61 | 143.68 | 133.62 |
| Median | 480.5 | 74.4 | 5.0 | 588.4 | 609.2 |
| Minimum | 248.0 | 48.4 | 3.3 | 228.1 | 226.7 |
| Maximum | 2100.0 | 79.7 | 16.4 | 750.0 | 750.0 |
| **Relative dose intensity [%]** | | | | | |
| Mean | 92.6 | 95.6 | 93.0 | 77.3 | 79.9 |
| SD | 9.42 | 8.33 | 12.73 | 19.16 | 17.83 |
| Median | 95.8 | 99.2 | 93.8 | 78.4 | 81.2 |
| Minimum | 48.5 | 64.5 | 54.6 | 30.4 | 30.2 |
| Maximum | 103.4 | 106.2 | 125.9 | 100.0 | 100.0 |

M = number of patients who had at least one dose of the corresponding drug

[a]- Cumulative dose is total dose of drug taken by a patient in the study (LDK378, mg; Pemetrexed and cisplatin, mg/m2; Carboplatin, mg/mL x min)

[b]- Average dose is the average daily dose for LDK378 (mg/day) and the average dose per cycle for chemotherapy drugs. (Pemetrexed and cisplatin, mg/m2/cycle; Carboplatin, mg/mL x min/cycle)

[c]- Actual dose intensity (LDK378, mg/day; Pemetrexed and cisplatin, mg/m2/cycle; Carboplatin, mg/mLxmin/cycle)

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3-1.2]

*Dose reductions and interruptions*

***Study A2301***

*Dose interruptions*: The proportion of patients requiring at least one dose interruption was 78.3% for ceritinib in study A2301. Dose interruption for ceritinib occurred over the treatment period, with the highest percentage of dose interruption occurring between weeks 3 to 6 of treatment (24.9%), followed by 12.2% between 6 to 9 weeks of treatment. Dose interruptions in the subsequent 3-week intervals were <10%. The proportion of patients requiring only one dose interruption was 14.3%for ceritinib, and the median time to first dose interruption was 6.1 weeks (range: 0.6 to 91.9).In the ceritinib group, the most frequently reported reason for dose interruptions was AEs(95.3%), and primarily due to AEs of liver enzyme elevations.

The proportion of patients requiring at least one dose interruption was 44.6% for pemetrexed, 16.1% for cisplatin, and 19.0% for carboplatin. The proportion of patients requiring only one dose interruption was 22.9% for pemetrexed, 9.2% for cisplatin, and 15.0% for carboplatin. The median time to first dose interruption was 10.1 weeks (range: 3.0 to 104.3) for pemetrexed, 6.2 weeks (range: 3.0 to 9.7) for cisplatin, and 6.1 weeks (3.1 to 10.6) for carboplatin. Among the patients with at least one dose interruption, the most frequently reported cause for dose interruption was the occurrence of AEs (pemetrexed: 73.1%, cisplatin:78.6%, and carboplatin: 78.9%. The dose interruptions/delays were primarily due to hematology related AEs.

*Dose reductions*: The proportion of patients requiring at least one dose reduction was 67.7% for ceritinib in study A2301. Dose reductions for ceritinib occurred throughout the treatment period with a higher percentage of dose reductions occurring during Week 3 to 6 (17.5%) and Week 6 to 9 (11.1%). Dose reduction in the subsequent 3-week intervals was <10%. The proportion of patients with only one dose reduction for ceritinib was 27.0%, and the median time to first dose reduction was 9.1 weeks (range: 0.9 to 85.1 weeks). The dose reductions were primarily due to AEs of liver enzyme elevations and GI AEs.

The proportions of patients requiring at least one dose reduction were 14.3%, 6.9%, and 15.0% for pemetrexed, cisplatin, and carboplatin, respectively. The proportion of patients requiring only one dose reduction was 12.0%, 6.9%, and 13.0% of for pemetrexed, cisplatin, and carboplatin. Among the patients with at least one dose reduction, the most frequently reported reason was the occurrence of AEs for pemetrexed (23/25, 92.0%), cisplatin (6/6, 100.0%) and carboplatin (13/15, 86.7%). The dose adjustments were primarily due to haematology related AEs.

***Pooled dataset***

*Dose interruptions*: The proportion of patients requiring at least one dose interruption of ceritinib treatment was 74.8%, and the dose interruptions occurred over the treatment period, with the highest percentage of dose interruption occurring during 3 to 6 weeks (20.3%). Dose interruptions in the other 3-week intervals were ≤ 15%.The proportion of patients requiring only one dose interruption was 18.8%; the median time to first dose interruption was 6.1 weeks (range: 0.3 to 122.9 weeks). Among the patients with at least one dose interruption, the most frequently reported reason for dose interruption was the occurrence of AEs (92.2%). The dose interruptions were primarily due to elevations in liver enzymes.

*Dose reductions*: In the pooled dataset, 575 patients (62.2%) required at least one dose reduction of ceritinib treatment. Dose reductions for ceritinib occurred throughout the treatment period with a higher percentage of dose reductions occurring during Week 3 and 6 of treatment (14.3%) and Week 6 and 9 of treatment (12.0%). Dose reductions in the other 3-week intervals were <10%.The proportion of patients requiring only one dose reduction was 29.7%, and the median time to first dose reduction was 7.4 weeks (range: 0.4 to 148 weeks). Among the patients with at least one dose reduction, the primary reason for dose reductions were AEs (531 patients, 92.3%), and the dose reductions were primarily due to elevations in liver enzymes and GI AEs.

*Demographic and other characteristics of study population*

Characteristics of patients enrolled in **study A2301** are summarised in the clinical efficacy section.

The **pooled dataset** is predominantly representative of previously treated ALK-positive advanced NSCLC patients including predominantly chemotherapy alone or chemotherapy and crizotinib, except for A2301; the demographics were similar in Study A2301 and pooled dataset, except for WHO performance status. Patients had a median age of 53 years (range: 22 to 82 years), 81.8% of the patients were<65 years old, and 53.5% were female patients. Majority of the patients were either Caucasians (51.1%) or Asians (46.1%). In addition, 90.6% of patients had WHO/ECOG PS score of 0-1. Smoking history was not collected in studies X1101, A2201 andA2203; therefore smoking history of the pooled dataset is not presented. The median time since initial diagnosis of primary site to start of study treatment in the pooled dataset was 14.3 (range: 0.5 to 283.1months) reflecting the more advanced disease of these patients with previous treatments (StudyA2301 - 1.6 months, range: 0.5 to 129.1 months). Adenocarcinoma was the predominant histology (94.9%), and majority of the patients (78.3%) presented with Stage IV disease at the time of diagnosis. Key sites of metastatic disease were typical of patients with metastatic or locally advanced NSCLC–brain (50.3%), bone (46.3%), and liver (32.4%). The patients in the pooled dataset were heavily pretreated (72.3% of patients received at least one prior systemic regimen for the treatment of ALK-positive advanced NSCLC).

### *Adverse events*

The overall summary of AEs by treatment group (Safety set) is presented in Table 29.

**Table 29: Overall summary of AEs by treatment group (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Category | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **All deaths** | 56 (32.0) | - | 48 (25.4) | - | 382 (41.3) | - |
| On-treatment deaths [a] | 6 (3.4) | - | 11 (5.8) | - | 139 (15.0) | - |
| **Adverse Events** | 170 (97.1) | 108 (61.7) | 189 (100) | 148 (78.3) | 925 (100) | 722 (78.1) |
| Suspected to be drug related | 156 (89.1) | 70 (40.0) | 184 (97.4) | 123 (65.1) | 898 (97.1) | 510 (55.1) |
| Serious adverse events | 62 (35.4) | 53 (30.3) | 70 (37.0) | 59 (31.2) | 409 (44.2) | 351 (37.9) |
| SAEs Suspected to be drug related | 27 (15.4) | 22 (12.6) | 30 (15.9) | 23 (12.2) | 123 (13.3) | 90 (9.7) |
| AEs leading to discontinuation | 29 (16.6) | 16 (9.1) | 21 (11.1) | 12 (6.3) | 112 (12.1) | 87 (9.4) |
| AE requiring dose adjustment | 27 (15.4) | 23 (13.1) | 109 (57.7) | 66 (34.9) | 305 (44.9) | 138 (20.3) |
| AE requiring dose interruption | 69 (39.4) | 31 (17.7) | 131 (69.3) | 78 (41.3) | 450 (66.3) | 282 (41.5) |
| AEs requiring dose adjustment or interruption | 78 (44.6) | 46 (26.3) | 152 (80.4) | 108 (57.1) | 715 (77.3) | 498 (53.8) |
| AEs requiring additional therapy | 160 (91.4) | 82 (46.9) | 180 (95.2) | 83 (43.9) | 887 (95.9) | 471 (50.9) |

- 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] Deaths occurring after on-treatment period are not included.

- Only AEs occurring during on-treatment period are reported.

- AEs will be graded according to the CTCAE V4.03. MedDRA version 19.0 is used.

- The denominator to calculate the percentages for AEs requiring dose adjustment and AEs requiring dose interruption in the 'All patients' column does not include only X2101.

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3.1-1.17]

**Common adverse events**

*Adverse events by System organ class (SOC)*

**Table 30: Adverse events by treatment group, regardless of study drug relationship, by primary system organ class, maximum grade (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Primary system organ class | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **-Total** | **170 (97.1)** | **108 (61.7)** | **189 (100)** | **148 (78.3)** | **925 (100)** | **722 (78.1)** |
| Gastrointestinal Disorders | 137 (78.3) | 16 (9.1) | 181 (95.8) | 29 (15.3) | 893 (96.5) | 156 (16.9) |
| Investigations | 102 (58.3) | 33 (18.9) | 149 (78.8) | 108 (57.1) | 726 (78.5) | 428 (46.3) |
| General Disorders And Administration Site Conditions | 118 (67.4) | 15 (8.6) | 132 (69.8) | 21 (11.1) | 628 (67.9) | 121 (13.1) |
| Metabolism And Nutrition Disorders | 85 (48.6) | 20 (11.4) | 95 (50.3) | 26 (13.8) | 539 (58.3) | 157 (17.0) |
| Respiratory, Thoracic And Mediastinal Disorders | 93 (53.1) | 22 (12.6) | 100 (52.9) | 14 (7.4) | 487 (52.6) | 109 (11.8) |
| Musculoskeletal And Connective Tissue Disorders | 77 (44.0) | 10 (5.7) | 93 (49.2) | 6 (3.2) | 474 (51.2) | 27 (2.9) |
| Infections And Infestations | 80 (45.7) | 16 (9.1) | 93 (49.2) | 15 (7.9) | 454 (49.1) | 101 (10.9) |
| Nervous System Disorders | 65 (37.1) | 8 (4.6) | 78 (41.3) | 7 (3.7) | 434 (46.9) | 82 (8.9) |
| Skin And Subcutaneous Tissue Disorders | 53 (30.3) | 1 (0.6) | 74 (39.2) | 6 (3.2) | 350 (37.8) | 11 (1.2) |
| Psychiatric Disorders | 30 (17.1) | 6 (3.4) | 34 (18.0) | 1 (0.5) | 206 (22.3) | 10 (1.1) |
| Blood And Lymphatic System Disorders | 87 (49.7) | 34 (19.4) | 43 (22.8) | 6 (3.2) | 205 (22.2) | 45 (4.9) |
| Cardiac Disorders | 18 (10.3) | 5 (2.9) | 28 (14.8) | 8 (4.2) | 139 (15.0) | 42 (4.5) |
| Eye Disorders | 29 (16.6) | 1 (0.6) | 21 (11.1) | 0 | 128 (13.8) | 4 (0.4) |
| Injury, Poisoning And Procedural Complications | 11 (6.3) | 0 | 18 (9.5) | 2 (1.1) | 112 (12.1) | 15 (1.6) |
| Renal And Urinary Disorders | 13 (7.4) | 1 (0.6) | 19 (10.1) | 2 (1.1) | 108 (11.7) | 15 (1.6) |
| Vascular Disorders | 31 (17.7) | 10 (5.7) | 16 (8.5) | 3 (1.6) | 84 (9.1) | 14 (1.5) |
| Ear And Labyrinth Disorders | 21 (12.0) | 1 (0.6) | 9 (4.8) | 0 | 58 (6.3) | 0 |
| Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps) | 4 (2.3) | 1 (0.6) | 14 (7.4) | 7 (3.7) | 56 (6.1) | 21 (2.3) |
| Hepatobiliary Disorders | 4 (2.3) | 1 (0.6) | 13 (6.9) | 5 (2.6) | 49 (5.3) | 20 (2.2) |
| Reproductive System And Breast Disorders | 9 (5.1) | 1 (0.6) | 10 (5.3) | 0 | 44 (4.8) | 1 (0.1) |
| Immune System Disorders | 4 (2.3) | 1 (0.6) | 5 (2.6) | 0 | 23 (2.5) | 0 |
| Endocrine Disorders | 2 (1.1) | 0 | 3 (1.6) | 0 | 15 (1.6) | 1 (0.1) |
| Congenital, Familial And Genetic Disorders | 0 | 0 | 1 (0.5) | 0 | 3 (0.3) | 0 |
| Product Issues | 0 | 0 | 0 | 0 | 1 (0.1) | 0 |
| Surgical And Medical Procedures | 0 | 0 | 0 | 0 | 1 (0.1) | 1 (0.1) |
| Social Circumstances | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |

- SOC terms are sorted by descending frequency of 'all grades' column, as reported in the All patients column.

- A patient with multiple occurrences of an AE is counted only once in the AE category.

- The event with maximum severity is counted for patients who experienced multiple episodes of an event. - Only AEs occurring during on-treatment period are reported.

- AEs are graded according to the CTCAE V4.03; MedDRA version 19.0 is used.

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3.1-1.1]

*Adverse events by Preferred Term (PT)*

**Table 31: Adverse events by treatment group, regardless of study drug relationship, by preferred term (with at least 5% incidence for all grades in any group) (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Preferred term | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| -Total | 170 (97.1) | 108 (61.7) | 189 (100) | 148 (78.3) | 925 (100) | 722 (78.1) |
| Diarrhoea | 19 (10.9) | 2 (1.1) | 160 (84.7) | 10 (5.3) | 759 (82.1) | 48 (5.2) |
| Nausea | 97 (55.4) | 9 (5.1) | 130 (68.8) | 5 (2.6) | 691 (74.7) | 49 (5.3) |
| Vomiting | 63 (36.0) | 10 (5.7) | 125 (66.1) | 10 (5.3) | 585 (63.2) | 52 (5.6) |
| Alanine Aminotransferase Increased | 38 (21.7) | 5 (2.9) | 114 (60.3) | 58 (30.7) | 472 (51.0) | 231 (25.0) |
| Aspartate Aminotransferase Increased | 34 (19.4) | 3 (1.7) | 100 (52.9) | 32 (16.9) | 401 (43.4) | 117 (12.6) |
| Decreased Appetite | 55 (31.4) | 2 (1.1) | 64 (33.9) | 2 (1.1) | 365 (39.5) | 20 (2.2) |
| Fatigue | 52 (29.7) | 5 (2.9) | 55 (29.1) | 8 (4.2) | 314 (33.9) | 46 (5.0) |
| Abdominal Pain | 13 (7.4) | 0 | 47 (24.9) | 4 (2.1) | 287 (31.0) | 15 (1.6) |
| Weight Decreased | 26 (14.9) | 1 (0.6) | 45 (23.8) | 7 (3.7) | 255 (27.6) | 26 (2.8) |
| Constipation | 38 (21.7) | 0 | 36 (19.0) | 0 | 222 (24.0) | 3 (0.3) |
| Cough | 28 (16.0) | 0 | 46 (24.3) | 0 | 216 (23.4) | 2 (0.2) |
| Blood Creatinine Increased | 17 (9.7) | 0 | 42 (22.2) | 4 (2.1) | 204 (22.1) | 5 (0.5) |
| Blood Alkaline Phosphatase Increased | 8 (4.6) | 1 (0.6) | 55 (29.1) | 14 (7.4) | 200 (21.6) | 52 (5.6) |
| Gamma-Glutamyltransferase Increased | 18 (10.3) | 3 (1.7) | 70 (37.0) | 54 (28.6) | 192 (20.8) | 141 (15.2) |
| Headache | 21 (12.0) | 2 (1.1) | 31 (16.4) | 0 | 191 (20.6) | 8 (0.9) |
| Dyspnoea | 35 (20.0) | 11 (6.3) | 29 (15.3) | 4 (2.1) | 187 (20.2) | 42 (4.5) |
| Abdominal Pain Upper | 10 (5.7) | 0 | 39 (20.6) | 3 (1.6) | 184 (19.9) | 9 (1.0) |
| Back Pain | 32 (18.3) | 4 (2.3) | 36 (19.0) | 3 (1.6) | 184 (19.9) | 11 (1.2) |
| Asthenia | 36 (20.6) | 6 (3.4) | 33 (17.5) | 5 (2.6) | 172 (18.6) | 26 (2.8) |
| Pyrexia | 24 (13.7) | 2 (1.1) | 34 (18.0) | 0 | 167 (18.1) | 8 (0.9) |
| Non-Cardiac Chest Pain | 17 (9.7) | 1 (0.6) | 38 (20.1) | 2 (1.1) | 148 (16.0) | 9 (1.0) |
| Anaemia | 62 (35.4) | 13 (7.4) | 28 (14.8) | 4 (2.1) | 141 (15.2) | 28 (3.0) |
| Rash | 11 (6.3) | 1 (0.6) | 28 (14.8) | 1 (0.5) | 140 (15.1) | 2 (0.2) |
| Musculoskeletal Pain | 11 (6.3) | 1 (0.6) | 21 (11.1) | 1 (0.5) | 116 (12.5) | 2 (0.2) |
| Dizziness | 17 (9.7) | 1 (0.6) | 22 (11.6) | 2 (1.1) | 115 (12.4) | 4 (0.4) |
| Arthralgia | 17 (9.7) | 1 (0.6) | 18 (9.5) | 0 | 102 (11.0) | 2 (0.2) |
| Insomnia | 17 (9.7) | 1 (0.6) | 17 (9.0) | 0 | 100 (10.8) | 1 (0.1) |
| Upper Respiratory Tract Infection | 16 (9.1) | 1 (0.6) | 18 (9.5) | 0 | 97 (10.5) | 0 |
| Electrocardiogram Qt Prolonged | 2 (1.1) | 1 (0.6) | 21 (11.1) | 4 (2.1) | 90 (9.7) | 19 (2.1) |
| Hyperglycaemia | 13 (7.4) | 5 (2.9) | 21 (11.1) | 12 (6.3) | 87 (9.4) | 50 (5.4) |
| Hypokalaemia | 9 (5.1) | 5 (2.9) | 11 (5.8) | 4 (2.1) | 84 (9.1) | 40 (4.3) |
| Pneumonia | 9 (5.1) | 5 (2.9) | 11 (5.8) | 6 (3.2) | 83 (9.0) | 44 (4.8) |
| Nasopharyngitis | 9 (5.1) | 0 | 12 (6.3) | 0 | 79 (8.5) | 0 |
| Dyspepsia | 9 (5.1) | 0 | 16 (8.5) | 1 (0.5) | 74 (8.0) | 2 (0.2) |
| Pain In Extremity | 13 (7.4) | 0 | 21 (11.1) | 0 | 74 (8.0) | 1 (0.1) |
| Musculoskeletal Chest Pain | 6 (3.4) | 0 | 12 (6.3) | 1 (0.5) | 73 (7.9) | 1 (0.1) |
| Pruritus | 8 (4.6) | 0 | 19 (10.1) | 1 (0.5) | 72 (7.8) | 2 (0.2) |
| Oedema Peripheral | 26 (14.9) | 1 (0.6) | 10 (5.3) | 0 | 71 (7.7) | 0 |
| Productive Cough | 8 (4.6) | 1 (0.6) | 10 (5.3) | 0 | 68 (7.4) | 0 |
| Amylase Increased | 9 (5.1) | 3 (1.7) | 19 (10.1) | 9 (4.8) | 65 (7.0) | 29 (3.1) |
| Dysgeusia | 10 (5.7) | 0 | 17 (9.0) | 0 | 54 (5.8) | 0 |
| Stomatitis | 19 (10.9) | 0 | 10 (5.3) | 1 (0.5) | 54 (5.8) | 3 (0.3) |
| Paraesthesia | 9 (5.1) | 0 | 11 (5.8) | 2 (1.1) | 53 (5.7) | 2 (0.2) |
| Creatinine Renal Clearance Decreased | 6 (3.4) | 0 | 13 (6.9) | 4 (2.1) | 50 (5.4) | 8 (0.9) |
| Dry Skin | 7 (4.0) | 0 | 7 (3.7) | 0 | 50 (5.4) | 0 |
| Neck Pain | 3 (1.7) | 0 | 7 (3.7) | 0 | 50 (5.4) | 1 (0.1) |
| Abdominal Distension | 4 (2.3) | 0 | 15 (7.9) | 1 (0.5) | 49 (5.3) | 1 (0.1) |
| Hyponatraemia | 11 (6.3) | 6 (3.4) | 11 (5.8) | 8 (4.2) | 49 (5.3) | 29 (3.1) |
| Hypophosphataemia | 0 | 0 | 8 (4.2) | 3 (1.6) | 49 (5.3) | 21 (2.3) |
| Anxiety | 5 (2.9) | 1 (0.6) | 5 (2.6) | 1 (0.5) | 48 (5.2) | 3 (0.3) |
| Influenza | 10 (5.7) | 1 (0.6) | 11 (5.8) | 0 | 48 (5.2) | 0 |
| Oropharyngeal Pain | 6 (3.4) | 0 | 11 (5.8) | 0 | 48 (5.2) | 0 |
| White Blood Cell Count Decreased | 31 (17.7) | 7 (4.0) | 7 (3.7) | 0 | 46 (5.0) | 1 (0.1) |
| Alopecia | 16 (9.1) | 0 | 9 (4.8) | 0 | 43 (4.6) | 1 (0.1) |
| Neutropenia | 38 (21.7) | 19 (10.9) | 9 (4.8) | 1 (0.5) | 41 (4.4) | 12 (1.3) |
| Haemoptysis | 13 (7.4) | 1 (0.6) | 10 (5.3) | 0 | 40 (4.3) | 3 (0.3) |
| Myalgia | 9 (5.1) | 1 (0.6) | 7 (3.7) | 0 | 39 (4.2) | 0 |
| Pleural Effusion | 6 (3.4) | 2 (1.1) | 12 (6.3) | 5 (2.6) | 36 (3.9) | 17 (1.8) |
| Rhinorrhoea | 5 (2.9) | 0 | 10 (5.3) | 0 | 36 (3.9) | 0 |
| Blood Bilirubin Increased | 1 (0.6) | 0 | 11 (5.8) | 1 (0.5) | 35 (3.8) | 4 (0.4) |
| Neutrophil Count Decreased | 26 (14.9) | 9 (5.1) | 5 (2.6) | 2 (1.1) | 30 (3.2) | 10 (1.1) |
| Platelet Count Decreased | 10 (5.7) | 2 (1.1) | 4 (2.1) | 1 (0.5) | 23 (2.5) | 9 (1.0) |
| Haemoglobin Decreased | 11 (6.3) | 3 (1.7) | 6 (3.2) | 2 (1.1) | 22 (2.4) | 6 (0.6) |
| Hypertension | 12 (6.9) | 4 (2.3) | 2 (1.1) | 2 (1.1) | 22 (2.4) | 7 (0.8) |
| Leukopenia | 16 (9.1) | 1 (0.6) | 6 (3.2) | 0 | 21 (2.3) | 1 (0.1) |
| Tinnitus | 16 (9.1) | 1 (0.6) | 4 (2.1) | 0 | 20 (2.2) | 0 |
| Thrombocytopenia | 18 (10.3) | 6 (3.4) | 3 (1.6) | 1 (0.5) | 18 (1.9) | 4 (0.4) |
| Pulmonary Embolism | 10 (5.7) | 7 (4.0) | 4 (2.1) | 3 (1.6) | 16 (1.7) | 12 (1.3) |
| Face Oedema | 10 (5.7) | 0 | 2 (1.1) | 0 | 6 (0.6) | 0 |

- Preferred terms are sorted in descending frequency of all grades column, 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 is counted only once in the total row.
- Only AEs occurring during on-treatment period are reported.
- AEs are graded according to the CTCAE V4.03; MedDRA version 19.0 is used.
- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

**Treatment related adverse events**

**Table 32: Adverse events by treatment group, suspected to be study drug related, by preferred term (greater than 5% for all grades in any group) (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Preferred term | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **-Total** | **156 (89.1)** | **70 (40.0)** | **184 (97.4)** | **123 (65.1)** | **898 (97.1)** | **510 (55.1)** |
| Diarrhoea | 12 (6.9) | 2 (1.1) | 152 (80.4) | 8 (4.2) | 728 (78.7) | 41 (4.4) |
| Nausea | 89 (50.9) | 8 (4.6) | 121 (64.0) | 5 (2.6) | 654 (70.7) | 42 (4.5) |
| Vomiting | 51 (29.1) | 8 (4.6) | 108 (57.1) | 9 (4.8) | 545 (58.9) | 44 (4.8) |
| Alanine Aminotransferase Increased | 30 (17.1) | 2 (1.1) | 112 (59.3) | 56 (29.6) | 452 (48.9) | 217 (23.5) |
| Aspartate Aminotransferase Increased | 26 (14.9) | 2 (1.1) | 96 (50.8) | 30 (15.9) | 378 (40.9) | 106 (11.5) |
| Decreased Appetite | 42 (24.0) | 1 (0.6) | 48 (25.4) | 1 (0.5) | 297 (32.1) | 14 (1.5) |
| Abdominal Pain | 3 (1.7) | 0 | 39 (20.6) | 4 (2.1) | 238 (25.7) | 9 (1.0) |
| Fatigue | 39 (22.3) | 3 (1.7) | 42 (22.2) | 5 (2.6) | 237 (25.6) | 28 (3.0) |
| Weight Decreased | 17 (9.7) | 1 (0.6) | 29 (15.3) | 4 (2.1) | 172 (18.6) | 9 (1.0) |
| Blood Alkaline Phosphatase Increased | 5 (2.9) | 1 (0.6) | 47 (24.9) | 12 (6.3) | 163 (17.6) | 45 (4.9) |
| Gamma-Glutamyltransferase Increased | 12 (6.9) | 3 (1.7) | 66 (34.9) | 50 (26.5) | 163 (17.6) | 118 (12.8) |
| Blood Creatinine Increased | 14 (8.0) | 0 | 37 (19.6) | 3 (1.6) | 161 (17.4) | 3 (0.3) |
| Abdominal Pain Upper | 6 (3.4) | 0 | 33 (17.5) | 2 (1.1) | 154 (16.6) | 5 (0.5) |
| Asthenia | 28 (16.0) | 4 (2.3) | 21 (11.1) | 5 (2.6) | 98 (10.6) | 15 (1.6) |
| Rash | 8 (4.6) | 1 (0.6) | 21 (11.1) | 1 (0.5) | 98 (10.6) | 2 (0.2) |
| Electrocardiogram Qt Prolonged | 2 (1.1) | 1 (0.6) | 19 (10.1) | 3 (1.6) | 84 (9.1) | 15 (1.6) |
| Constipation | 23 (13.1) | 0 | 18 (9.5) | 0 | 72 (7.8) | 0 |
| Anaemia | 50 (28.6) | 10 (5.7) | 13 (6.9) | 1 (0.5) | 51 (5.5) | 6 (0.6) |
| Amylase Increased | 6 (3.4) | 2 (1.1) | 14 (7.4) | 6 (3.2) | 49 (5.3) | 20 (2.2) |
| Dyspepsia | 5 (2.9) | 0 | 9 (4.8) | 0 | 46 (5.0) | 1 (0.1) |
| Creatinine Renal Clearance Decreased | 6 (3.4) | 0 | 11 (5.8) | 4 (2.1) | 45 (4.9) | 7 (0.8) |
| Dysgeusia | 9 (5.1) | 0 | 15 (7.9) | 0 | 42 (4.5) | 0 |
| White Blood Cell Count Decreased | 31 (17.7) | 7 (4.0) | 6 (3.2) | 0 | 36 (3.9) | 0 |
| Neutropenia | 36 (20.6) | 18 (10.3) | 6 (3.2) | 1 (0.5) | 32 (3.5) | 9 (1.0) |
| Stomatitis | 17 (9.7) | 0 | 7 (3.7) | 1 (0.5) | 31 (3.4) | 1 (0.1) |
| Oedema Peripheral | 12 (6.9) | 0 | 4 (2.1) | 0 | 24 (2.6) | 0 |
| Neutrophil Count Decreased | 26 (14.9) | 9 (5.1) | 5 (2.6) | 2 (1.1) | 23 (2.5) | 6 (0.6) |
| Alopecia | 16 (9.1) | 0 | 3 (1.6) | 0 | 18 (1.9) | 0 |
| Leukopenia | 15 (8.6) | 1 (0.6) | 3 (1.6) | 0 | 16 (1.7) | 1 (0.1) |
| Haemoglobin Decreased | 11 (6.3) | 3 (1.7) | 5 (2.6) | 1 (0.5) | 13 (1.4) | 3 (0.3) |
| Platelet Count Decreased | 10 (5.7) | 2 (1.1) | 2 (1.1) | 0 | 10 (1.1) | 1 (0.1) |
| Thrombocytopenia | 16 ( 9.1) | 5 ( 2.9) | 2 ( 1.1) | 0 | 7 ( 0.8) | 1 ( 0.1) |
| Tinnitus | 12 ( 6.9) | 1 ( 0.6) | 1 ( 0.5) | 0 | 4 ( 0.4) | 0 |

- Preferred terms are sorted in descending frequency of all grades column, 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 is counted only once in the total row.
- Only AEs occurring during on-treatment period are reported.
- AEs are graded according to the CTCAE V4.03; MedDRA version 19.0 is used.
- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3.1-1.7]

**Adverse events of special interest (AESIs)**

The AESIs for ceritinib are hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QTc prolongation, hyperglycaemia, bradycardia, GI toxicity (nausea, diarrhoea, vomiting) and pancreatitis.

The incidence of serious AESIs (regardless of study drug relationship) in the **Study A2301** ceritinib group included:

- Hepatotoxicity: six patients (3.2%)
- ILD/pneumonitis: one patient (0.5%)
- QT prolongation: one patient (0.5%)
- Bradycardia-related: one patient (0.5%)
- Hyperglycaemia: five patients (2.6%)
- GI toxicity: 12 patients (6.3%)
- Pancreatitis: None reported

One SAE of pneumonitis (grade 3) was reported that was not suspected related to ceritinib treatment, also mentioned under *Deaths*.

The incidence of serious AESIs (regardless of study drug relationship) in the **pooled dataset** was as follows:

- Hepatotoxicity: 23 patients (2.5%)
- ILD/pneumonitis: 16 patients (1.7%)
- QT prolongation: Seven patients (0.8%)
- Bradycardia-related: Four patients (0.4%)
- Hyperglycaemia: 20 patients (2.2%)
- GI toxicity: 46 patients (5.0%)
- Pancreatitis: Six patients (0.6%)

***Hepatotoxicity***

The incidence of hepatotoxicity AEs in Study A2301 ceritinib group was higher compared to the pooled dataset (68.8% and 60.5%, respectively) and the frequency of grade 3/4 hepatotoxicity was also higher in A2301 than in the pooled dataset, 49.2% vs 37.8%.

**Table 33: Hepatotoxicity events (Safety Set)**

| Hepatotoxicity | Study A2301 Chemotherapy N=175 n (%) | Study A2301 Ceritinib 750 mg N=189 n (%) | All patients Ceritinib 750 mg N=925 n (%) |
|---|---|---|---|
| **ALL AEs** | 53 (30.3) | 130 (68.8) | 560 (60.5) |
| Alanine Aminotransferase Increased | 38 (21.7) | 114 (60.3) | 472 (51.0) |
| Aspartate Aminotransferase Increased | 34 (19.4) | 100 (52.9) | 401 (43.4) |
| Gamma-Glutamyltransferase Increased | 18 (10.3) | 70 (37.0) | 192 (20.8) |
| Blood Bilirubin Increased | 1 (0.6) | 11 (5.8) | 35 (3.8) |
| Transaminases Increased | 2 (1.1) | 4 (2.1) | 23 (2.5) |
| Hepatic Function Abnormal | 1 (0.6) | 3 (1.6) | 19 (2.1) |
| Hepatic Enzyme Increased | 0 | 2 (1.1) | 12 (1.3) |
| Bilirubin Conjugated Increased | 1 (0.6) | 2 (1.1) | 6 (0.6) |
| Hepatotoxicity | 0 | 2 (1.1) | 6 (0.6) |
| Hepatocellular Injury | 1 (0.6) | 2 (1.1) | 3 (0.3) |
| Hypertransaminasaemia | 0 | 1 (0.5) | 2 (0.2) |
| Liver Function Test Abnormal | 0 | 1 (0.5) | 2 (0.2) |
| Liver Injury | 0 | 1 (0.5) | 2 (0.2) |
| Hepatitis Acute | 0 | 1 (0.5) | 1 (0.1) |
| Cholestasis | 1 ( 0.6) | 0 | 1 ( 0.1) |
| Hyperbilirubinaemia | 1 ( 0.6) | 0 | 1 ( 0.1) |
| **CTC grade 3/4 AEs** | 10 (5.7) | 93 (49.2) | 350 (37.8) |
| Alanine Aminotransferase Increased | 5 (2.9) | 58 (30.7) | 231 (25.0) |
| Gamma-Glutamyltransferase Increased | 3 (1.7) | 54 (28.6) | 141 (15.2) |
| Aspartate Aminotransferase Increased | 3 (1.7) | 32 (16.9) | 117 (12.6) |
| Hepatic Function Abnormal | 0 | 2 (1.1) | 9 (1.0) |
| Transaminases Increased | 1 (0.6) | 2 (1.1) | 9 (1.0) |
| Blood Bilirubin Increased | 0 | 1 (0.5) | 4 (0.4) |
| Hepatic Enzyme Increased | 0 | 1 (0.5) | 3 (0.3) |
| Hepatocellular Injury | 0 | 1 (0.5) | 2 (0.2) |
| Hepatitis Acute | 0 | 1 (0.5) | 1 (0.1) |
| Liver Injury | 0 | 1 (0.5) | 1 (0.1) |
| Hyperbilirubinaemia | 1 ( 0.6) | 0 | 0 |
| **AEs suspected to be drug related** | 41 (23.4) | 126 (66.7) | 524 (56.6) |
| Alanine Aminotransferase Increased | 30 (17.1) | 112 (59.3) | 452 (48.9) |
| Hepatitis | 0 | 0 | 1 (0.1) |
| Hepatitis Acute | 0 | 1 (0.5) | 1 (0.1) |
| Hepatocellular Injury | 0 | 0 | 1 (0.1) |
| Transaminases Increased | 1 (0.6) | 0 | 0 |
| **AE requiring dose interruption** | 2 (1.1) | 87 (46.0) | 249 (36.7) |
| Alanine Aminotransferase Increased | 2 (1.1) | 64 (33.9) | 194 (28.6) |
| Aspartate Aminotransferase Increased | 1 (0.6) | 43 (22.8) | 128 (18.9) |
| Gamma-Glutamyltransferase Increased | 1 (0.6) | 16 (8.5) | 35 (5.2) |
| Hepatic Function Abnormal | 0 | 3 (1.6) | 12 (1.8) |
| Blood Bilirubin Increased | 0 | 4 (2.1) | 9 (1.3) |
| Hepatic Enzyme Increased | 0 | 2 (1.1) | 8 (1.2) |
| Transaminases Increased | 0 | 2 (1.1) | 7 (1.0) |
| Hepatotoxicity | 0 | 0 | 3 (0.4) |
| Hepatitis | 0 | 0 | 2 (0.3) |
| Hepatocellular Injury | 0 | 2 (1.1) | 2 (0.3) |
| Hypertransaminasaemia | 0 | 1 (0.5) | 2 (0.3) |
| Bilirubin Conjugated Increased | 0 | 0 | 1 (0.1) |
| Liver Function Test Abnormal | 0 | 1 (0.5) | 1 (0.1) |
| Liver Injury | 0 | 1 (0.5) | 1 (0.1) |
| **AE requiring dose adjustment/interruption** | 3 (1.7) | 104 (55.0) | 376 (40.6) |
| Alanine Aminotransferase Increased | 2 (1.1) | 90 (47.6) | 322 (34.8) |
| Aspartate Aminotransferase Increased | 1 (0.6) | 64 (33.9) | 211 (22.8) |
| Gamma-Glutamyltransferase Increased | 1 (0.6) | 25 (13.2) | 52 (5.6) |
| Blood Bilirubin Increased | 0 | 4 (2.1) | 13 (1.4) |
| Hepatic Function Abnormal | 0 | 3 (1.6) | 13 (1.4) |
| Transaminases Increased | 1 (0.6) | 2 (1.1) | 12 (1.3) |
| Hepatic Enzyme Increased | 0 | 2 (1.1) | 8 (0.9) |
| Hepatocellular Injury | 0 | 2 (1.1) | 3 (0.3) |
| Hepatotoxicity | 0 | 0 | 3 (0.3) |
| Bilirubin Conjugated Increased | 0 | 0 | 2 (0.2) |
| Hepatitis | 0 | 0 | 2 (0.2) |
| Hypertransaminasaemia | 0 | 1 (0.5) | 2 (0.2) |
| Ascites | 0 | 0 | 1 (0.1) |
| Drug-Induced Liver Injury | 0 | 0 | 1 (0.1) |
| Hepatitis Acute | 0 | 1 (0.5) | 1 (0.1) |
| Liver Function Test Abnormal | 0 | 1 (0.5) | 1 (0.1) |
| Liver Injury | 0 | 1 (0.5) | 1 (0.1) |

***Interstitial lung disease (ILD)/pneumonitis***

***Study A2301***

In Study A2301, the ILD/pneumonitis AEs (all grades, regardless of study drug relationship) were reported in four patients (2.1%) treated in the ceritinib arm, with PTs of pneumonitis (three patients, 1.6%) and lung infiltration (one patient, 0.5%). One patient (0.5%) had grade ≥ 3 AE of pneumonitis (also reported as an SAE, assessed as not related to ceritinib by the Investigator, and required dose interruption). No other AEs requiring dose adjustment or interruptions were reported. Pneumonitis AEs led to study drug discontinuation in two patients (1.1%). SAE of pneumonitis was reported in one patient (0.5%), grade 3 pneumonitis on Day 272, study medication was interrupted, and the patient died two days later (on Day 274). The Investigator assessed the event as not related to ceritinib.

***Pooled dataset***

Interstitial lung disease/pneumonitis AEs (all grades, regardless of study drug relationship) were reported in 2.4% of patients – pneumonitis (1.6%), ILD (0.4%) and lung infiltration (0.3%). Grade 3/4 AEs were reported in 1.3% of patients – pneumonitis (1.0%), ILD (0.2%) and lung infiltration (0.1%). Pneumonitis events were assessed as related to ceritinib treatment by the Investigator in 16 patients (1.7%).The events required dose adjustment or interruption in 11 patients (1.2%) and led to discontinuation of ceritinib treatment in 10 patients (1.1%). Two deaths due to pneumonitis were reported. In patients who had grade <3 ILD/pneumonitis at baseline, the median time to onset of grade ≥ 3 ILD/pneumonitis was 18.57 weeks (range: 3.1 to 38.9 weeks).

***QT prolongation***

**Table 34: QT prolongation events**

| QT prolongation | Study A2301 Chemotherapy N=175 n (%) | Study A2301 Ceritinib 750 mg N=189 n (%) | All patients Ceritinib 750 mg N=925 n (%) |
|---|---|---|---|
| **ALL AEs** | 5 (2.9) | 21 (11.1) | 100 (10.8) |
| Electrocardiogram Qt Prolonged | 2 (1.1) | 21 (11.1) | 90 (9.7) |
| Syncope | 2 (1.1) | 0 | 7 (0.8) |
| Loss Of Consciousness | 0 | 0 | 2 (0.2) |
| Cardio-Respiratory Arrest | 0 | 0 | 1 (0.1) |
| Ventricular Arrhythmia | 0 | 0 | 1 (0.1) |
| Cardiac Arrest | 1 (0.6) | 0 | 0 |
| **CTC grade 3/4 AEs** | 3 (1.7) | 4 (2.1) | 26 (2.8) |
| Electrocardiogram Qt Prolonged | 1 (0.6) | 4 (2.1) | 19 (2.1) |
| Syncope | 1 (0.6) | 0 | 5 (0.5) |
| Cardio-Respiratory Arrest | 0 | 0 | 1 (0.1) |
| Loss Of Consciousness | 0 | 0 | 1 (0.1) |
| Cardiac Arrest | 1 (0.6) | 0 | 0 |
| **AEs suspected to be drug related** | 3 (1.7) | 19 (10.1) | 84 (9.1) |
| Electrocardiogram Qt Prolonged | 2 (1.1) | 19 (10.1) | 84 (9.1) |
| Ventricular Arrhythmia | 0 | 0 | 1 (0.1) |
| Syncope | 1 (0.6) | 0 | 0 |
| **SAEs** | 1 (0.6) | 1 (0.5) | 7 (0.8) |
| Electrocardiogram Qt Prolonged | 0 | 1 (0.5) | 3 (0.3) |
| Loss Of Consciousness | 0 | 0 | 2 (0.2) |
| Cardio-Respiratory Arrest | 0 | 0 | 1 (0.1) |
| Syncope | 0 | 0 | 1 (0.1) |
| Cardiac Arrest | 1 (0.6) | 0 | 0 |
| **AE leading to discontinuation** | 0 | 0 | 2 (0.2) |
| Electrocardiogram Qt Prolonged | 0 | 0 | 2 (0.2) |
| **AE requiring dose adjustment** | 0 | 3 (1.6) | 9 (1.3) |
| Electrocardiogram Qt Prolonged | 0 | 3 (1.6) | 9 (1.3) |
| **AE requiring dose interruption** | 1 (0.6) | 3 (1.6) | 10 (1.5) |
| Electrocardiogram Qt Prolonged | 1 (0.6) | 3 (1.6) | 9 (1.3) |
| Loss Of Consciousness | 0 | 0 | 1 (0.1) |
| **AE requiring dose adjustment/interruption** | 1 (0.6) | 4 (2.1) | 20 (2.2) |
| Electrocardiogram Qt Prolonged | 1 (0.6) | 4 (2.1) | 19 (2.1) |
| Loss Of Consciousness | 0 | 0 | 1 (0.1) |

***Study A2301***

**Table 35: Patients with notable ECG values in study A2301 and the pooled safety dataset (safety set)**

| | Study A2301 Ceritinib 750 mg N=189 | Pooled data set Ceritinib 750 mg N=925 |
|---|---|---|
| **QTcP (ms)** | **n=189** | **n=919** |
| New >480-500 – n (%) | 6 (3.2) | 40 (4.4) |
| New >500 – n (%) | 5 (2.6) | 12 (1.3) |
| Increase from Baseline >60 – n (%) | 15 (7.9) | 58 (6.3) |
| Source: [SCS Study A2301 Appendix 1-Table 14.3-5.2], [CSR Study A2301-Table 12-21] | | |

***Bradycardia***

***Study A2301***

AE of bradycardia was rarely reported in Study A2301 ceritinib group and pooled dataset (<2% of patients), all were grade 1-2, none were serious and none led to discontinuation of ceritinib treatment.

In the Study A2301, bradycardia events (all grades, regardless of study drug relationship) were reported in 29 patients (15.3%) in the ceritinib group. These included the AE of ECG QT prolonged reported in 21 patients (11.1%) which has also been reported under QT prolongation AESI category. An actual AE of bradycardia and sinus bradycardia was reported in three patients each (1.6%), none of which was grade 3/4 or serious or led to study treatment discontinuation. Two AEs of bradycardia were suspected to be study drug related, and two AEs of bradycardia required dose adjustment or interruption. One SAE of nodal rhythm was reported that was not suspected to study treatment.

Based on ECG data, ten (5.3%) patients in the ceritinib group had a decrease in the heart rate(HR) of >25% from baseline and to <50 beats per minute, of which it was reported as a no serious AE of sinus bradycardia in two patients and a non-serious AE of bradycardia in one patient. In the chemotherapy group, a decrease in the heart rate (HR) of >25% from baseline and to <50 beats per minute was reported in one (0.6%) patient.

***Pooled dataset***

In the pooled dataset, bradycardia events (all grades, regardless of study drug relationship) were reported in 121 patients (13.1%). These included the AEs of ECG QT prolonged in 90 patients (9.7%) and syncope in seven patients (0.8%) which have also been reported under QT prolongation AESI category. SAEs were reported in four patients, with ECG QT prolonged in three patients (0.3%),nodal rhythm and syncope in one patient each (0.1%). No deaths due to bradycardia AEs were reported.

The PTs ‘bradycardia’ and ‘sinus bradycardia’ were reported in 11 patients (1.2%) and 10 patients (1.1%), all grade 1-2, and none of these were serious. Other AEs that were reported were – right bundle branch block in three patients (0.3%); atrioventricular block and first degree atrioventricular block (each in two patients, 0.2%); ECG PR shortened, ECG QRS complex prolonged, and nodal rhythm (each in one patient, 0.1%) – all non-serious.

Two patients with PT of bradycardia (0.2%) and one patient with PT of nodal rhythm (0.1%) required dose adjustment/ interruption. None of the bradycardia related AEs required study drug discontinuation.

Based on ECG data, there were 40 patients (4.4%) in the ceritinib group having a decrease in the HR more than 25% and less than 50 beats per minute compared to baseline.

Asymptomatic cases of bradycardia (heart rate less than 60 bpm) have been observed in 21 out of 925 (2.3%) patients treated with ceritinib in clinical studies.

***Hyperglycaemia***

**Table 36: Hyperglycaemia events (Safety Set)**

| | Study A2301 | | All patients |
|---|---|---|---|
| Hyperglycemia | Chemotherapy N=175 n (%) | Ceritinib 750 mg N=189 n (%) | Ceritinib 750 mg N=925 n (%) |
| **ALL AEs** | 17 (9.7) | 24 (12.7) | 120 (13.0) |
| Hyperglycaemia | 13 (7.4) | 21 (11.1) | 87 (9.4) |
| Diabetes Mellitus | 3 (1.7) | 1 (0.5) | 21 (2.3) |
| Blood Glucose Increased | 2 (1.1) | 1 (0.5) | 14 (1.5) |
| Type 2 Diabetes Mellitus | 0 | 2 (1.1) | 3 (0.3) |
| Diabetic Ketoacidosis | 0 | 0 | 2 (0.2) |
| Blood Glucose Abnormal | 0 | 0 | 1 (0.1) |
| Glucose Tolerance Impaired | 0 | 0 | 1 (0.1) |
| Glycosuria | 1 (0.6) | 0 | 0 |
| **CTC grade 3/4 AEs** | 9 (5.1) | 15 (7.9) | 60 (6.5) |
| Hyperglycaemia | 5 (2.9) | 12 (6.3) | 50 (5.4) |
| Diabetes Mellitus | 2 (1.1) | 1 (0.5) | 4 (0.4) |
| Blood Glucose Increased | 2 (1.1) | 1 (0.5) | 2 (0.2) |
| Diabetic Ketoacidosis | 0 | 0 | 2 (0.2) |
| Glucose Tolerance Impaired | 0 | 0 | 1 (0.1) |
| Type 2 Diabetes Mellitus | 0 | 1 (0.5) | 1 (0.1) |
| **AEs suspected to be drug related** | 5 (2.9) | 10 (5.3) | 32 (3.5) |
| Hyperglycaemia | 2 (1.1) | 9 (4.8) | 26 (2.8) |
| Blood Glucose Increased | 2 (1.1) | 0 | 3 (0.3) |
| Diabetes Mellitus | 1 (0.6) | 0 | 2 (0.2) |
| Type 2 Diabetes Mellitus | 0 | 1 (0.5) | 1 (0.1) |
| Glycosuria | 1 (0.6) | 0 | 0 |
| **SAEs** | 1 (0.6) | 5 (2.6) | 20 (2.2) |
| Hyperglycaemia | 1 (0.6) | 5 (2.6) | 16 (1.7) |
| Diabetes Mellitus | 0 | 0 | 2 (0.2) |
| Diabetic Ketoacidosis | 0 | 0 | 2 (0.2) |
| **AE leading to discontinuation** | 0 | 0 | 1 (0.1) |
| Hyperglycaemia | 0 | 0 | 1 (0.1) |
| **AE requiring dose adjustment** | 0 | 4 (2.1) | 5 (0.7) |
| Hyperglycaemia | 0 | 4 (2.1) | 5 (0.7) |
| **AE requiring dose interruption** | 0 | 4 (2.1) | 8 (1.2) |
| Hyperglycaemia | 0 | 3 (1.6) | 4 (0.6) |
| Diabetes Mellitus | 0 | 0 | 2 (0.3) |
| Diabetic Ketoacidosis | 0 | 0 | 1 (0.1) |
| Type 2 Diabetes Mellitus | 0 | 1 (0.5) | 1 (0.1) |
| **AE requiring dose adjustment/interruption** | 0 | 6 (3.2) | 18 (1.9) |
| Hyperglycaemia | 0 | 5 (2.6) | 13 (1.4) |
| Diabetes Mellitus | 0 | 0 | 2 (0.2) |
| Diabetic Ketoacidosis | 0 | 0 | 2 (0.2) |
| Type 2 Diabetes Mellitus | 0 | 1 (0.5) | 1 (0.1) |

- Preferred terms are sorted within the AESI group in descending frequency, as reported in the All patients column.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- Only AEs occurring during on-treatment period are reported.
- AESIs are graded according to the CTCAE V4.03. MedDRA version 19.0 is used.
- The denominator to calculate the percentages for AEs requiring dose adjustment and AEs requiring dose interruption in the 'All patients' column does not include X2101.
- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

***GI toxicity***

**Table 37: GI toxicity events (safety set)**

| Gastrointestinal toxicity | Study A2301 Chemotherapy N=175 n (%) | Study A2301 Ceritinib 750 mg N=189 n (%) | All patients Ceritinib 750 mg N=925 n (%) |
|---|---|---|---|
| **ALL AEs** | 113 (64.6) | 179 (94.7) | 877 (94.8) |
| Diarrhoea | 19 (10.9) | 160 (84.7) | 759 (82.1) |
| Nausea | 97 (55.4) | 130 (68.8) | 691 (74.7) |
| Vomiting | 63 (36.0) | 125 (66.1) | 585 (63.2) |
| **CTC grade 3/4 AEs** | 14 (8.0) | 21 (11.1) | 116 (12.5) |
| Vomiting | 10 (5.7) | 10 (5.3) | 52 (5.6) |
| Nausea | 9 (5.1) | 5 (2.6) | 49 (5.3) |
| Diarrhoea | 2 (1.1) | 10 (5.3) | 48 (5.2) |
| **AEs suspected to be drug related** | 102 (58.3) | 175 (92.6) | 858 (92.8) |
| Diarrhoea | 12 (6.9) | 152 (80.4) | 728 (78.7) |
| Nausea | 89 (50.9) | 121 (64.0) | 654 (70.7) |
| Vomiting | 51 (29.1) | 108 (57.1) | 545 (58.9) |
| **SAEs** | 10 (5.7) | 12 (6.3) | 46 (5.0) |
| Nausea | 5 (2.9) | 6 (3.2) | 25 (2.7) |
| Vomiting | 6 (3.4) | 7 (3.7) | 25 (2.7) |
| Diarrhoea | 3 (1.7) | 3 (1.6) | 9 (1.0) |
| **AE leading to discontinuation** | 1 (0.6) | 3 (1.6) | 8 (0.9) |
| Nausea | 0 | 1 (0.5) | 5 (0.5) |
| Vomiting | 1 (0.6) | 1 (0.5) | 4 (0.4) |
| Diarrhoea | 0 | 1 (0.5) | 1 (0.1) |
| **AE requiring dose adjustment** | 5 (2.9) | 26 (13.8) | 114 (16.8) |
| Vomiting | 4 (2.3) | 14 (7.4) | 64 (9.4) |
| Diarrhoea | 0 | 11 (5.8) | 49 (7.2) |
| Nausea | 3 (1.7) | 8 (4.2) | 46 (6.8) |
| **AE requiring dose interruption** | 2 (1.1) | 36 (19.0) | 143 (21.1) |
| Vomiting | 1 (0.6) | 18 (9.5) | 84 (12.4) |
| Nausea | 0 | 15 (7.9) | 68 (10.0) |
| Diarrhoea | 1 (0.6) | 16 (8.5) | 60 (8.8) |
| **AE requiring dose adjustment/interruption** | 6 (3.4) | 52 (27.5) | 298 (32.2) |
| Vomiting | 4 (2.3) | 29 (15.3) | 178 (19.2) |
| Nausea | 3 (1.7) | 22 (11.6) | 155 (16.8) |

***Pancreatitis***

***Study A2301***

In the Study A2301, pancreatitis grouped AEs (all grades, regardless of study drug relationship) were reported in 22 patients (11.6%) in ceritinib treatment group, with grade 3/4 AEs reported in 15 patients (7.9%), all of them being laboratory pancreas function test abnormalities. The AEs reported were amylase increased in 19 patients (10.1%), and lipase increased in seven patients (3.7%). No AEs with PT of "pancreatitis" were reported. Majority of the reported laboratory pancreatic test abnormalities (15 patients, 7.9%) were suspected to be study drug-related. Six patients (3.2%) required dose adjustments or interruptions. Three patients (1.6%) required treatment discontinuation –lipase increased in two patients and amylase increased in two patients. No SAEs or deaths related to these events were reported.

*Amylase/lipase laboratory abnormalities:*

Based on the laboratory parameters, of the 189 patients treated with ceritinib the majority of patients (158 patients, 83.6%) had normal amylase (grade 0) at baseline. Post-baseline, 67patients (35.4%) had amylase increase, of which 43 patients had grade 1 (22.8%), 10 patients had grade 2 (5.3%), 13 patients had grade 3 (6.9%) and one patient had grade 4 (0.5%).

Lipase values were not available for the patients at baseline since this parameter was not routinely collected as part of the initial protocol. Post-baseline, 21 patients (11.1%) had lipase elevations of any grade, of which eight patients (4.2%), three patients (1.6%), nine patients (4.8%), and one patient (0.5%) had grade 1, grade 2, grade 3, and grade 4 lipase elevations, respectively.

***Pooled dataset***

In the pooled dataset, pancreatitis grouped AEs (all grades, regardless of study drug relationship) were reported in 89 patients (9.6%), with majority of the patients having laboratory pancreatic test abnormalities without reported evidence of pancreatitis. Pancreatitis as a PT was reported in five patients (all grade ≥ 3 and reported as SAEs) and one patient presented with pancreatitis pseudocyst. Grade 3/4 pancreatitis grouped AEs were reported in 54 patients (5.8%)– lipase increased in 32 patients (3.5%), amylase increased in 29 patients (3.1%), and pancreatitis in five patients (0.5%). Majority of the AEs (68 patients, 7.4%) were suspected to be study drug-related. Most of the AEs were managed with dose adjustments or interruptions (37 patients, 4.0%), and led to treatment discontinuation in five patients (0.5%) – lipase increased in three patients and amylase increased in two patients.

Adverse events with PT of “pancreatitis” were reported in five patients (0.5%), all of which were grade 3/4, and serious. Four of these events of pancreatitis were managed with dose adjustment or interruption, and treatment was discontinued in one patient. No deaths due to these events were reported.

*Amylase/lipase laboratory abnormalities:* Based on the laboratory parameters, of the 925 patients treated with ceritinib majority of the patients (84.5%) had normal amylase (grade 0) at baseline. Post-baseline, 35.8% of patients had amylase increase of any grade, of which 23.4%, 5.9%, 5.4% and 1.1% had grade 1, grade 2, grade 3, and grade 4amylase increase, respectively. Of note, 2.3% of patients and 0.3% had grade3 and grade 4 elevated amylase levels already at baseline.

**Other safety observations**

***AEs and laboratory abnormalities associated with creatinine increase and renal function***

***Study A2301***

In study A2301, 22.2% of patients in the ceritinib group had creatinine elevations based on AEs (PT of blood creatinine increased). Most of the AEs reported were suspected to be related to study drug (19.6%) and were of grade 1 or 2 in severity in 18% of patients and grade 3 in 1.6%. Events were reported as SAE in 1.6% of patients, and led to discontinuation of study drug 2.1%. Adverse events requiring dose adjustment or interruption were reported in 13.8% of patients. Further, decreased creatinine renal clearance was reported as AEs in 13 (6.9%) patients; of which two patients had grade 3 and two had grade 4 event. Most of the events were suspected to be study drug related in 11 (5.8%) patients. No SAEs were reported and led to discontinuation of study drug due to grade 4 event in one patient. Adverse events requiring dose adjustment or interruption were reported in four (2.1%) patients.

Based on laboratory assessments, most of the patients had normal creatinine value at baseline in the ceritinib group (95.8%). Post-baseline, 108 (57.1%) patients and eight (4.2%) patients had grade 2 and grade 3 increased creatinine values, respectively. No grade 4 increased creatinine value was reported.

Creatinine clearance was normal at baseline for most of the patients (91.5%). Post-baseline, grade 2, grade 3 and grade 4 decreased creatinine clearance were noted in 91 (48.1%), 8 (4.2%) and 2 (1.1%) patients, respectively.

Under the SOC of ‘renal and urinary disorders’ AEs were reported in 19 (10.1%) patients in the ceritinib group. Most of these events were grade 1 or 2 in severity (17/19) and only two patients had grade 3 AEs

(chronic kidney disease and hydronephrosis), both considered related to ceritinib treatment; there were no grade 4 events.

Analysis of mean/median blood creatinine levels at screening and during the course of the study showed an early increase after start of ceritinib (i.e. Day 15) with steady levels thereafter without further accumulation, and recovery upon treatment discontinuation.

***Pooled dataset***

The frequency and severity of creatinine increase reported in Study A2301 ceritinib group is consistent (<3% difference) with the pooled dataset. In the pooled dataset, 204 patients (22.1%) reported creatinine elevations based on AEs (PT of blood creatinine increased), majority of the AEs were grade 1 or 2, with grade 3 reported in five patients (0.5%), no grade 4 AEs were reported. The events were managed by ceritinib dose adjustment or interruption in 64 patients (6.9%), and led to discontinuation of ceritinib treatment in four patients (0.4%). Events were reported as SAE in six (0.6%) patients.

In the pooled dataset, under the SOC of 'renal and urinary disorders' AEs were reported in 108 (11.7%) patients, majority of the events were grade 1 or 2, with grade 3 reported in 15 patients (1.6%), no grade 4 events were reported. In 15 patients (1.6%), for AEs under SOC of 'renal and urinary disorders' ceritinib dose was adjusted or interrupted, and led to ceritinib discontinuation in two patients (0.2%, grade 3 acute kidney injury and grade 3 renal failure). Serious adverse events were reported in ten patients (1.1%). No deaths due to AEs under the SOC of 'renal and urinary disorders' were reported.

Six hundred and thirty eight patients (69.0%) had worst post-baseline any grade creatinine increase; 17 patients (1.8%) and one patient (0.1%) had grade 3 and grade 4 creatinine increase, respectively. The frequencies of grade 3/4 creatinine elevations were low despite prolonged treatment with ceritinib, indicating that creatinine elevations did not worsen over time with continued treatment.

## *Serious adverse event / deaths / other significant events*

### Serious adverse events

**Table 38: Serious adverse events by treatment group regardless of study drug relationship, by preferred term (with at least 1% incidence for all grades in any group) (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Preferred term | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| -Total | 62 (35.4) | 53 (30.3) | 70 (37.0) | 59 (31.2) | 409 (44.2) | 351 (37.9) |
| Pneumonia | 5 (2.9) | 5 (2.9) | 8 (4.2) | 6 (3.2) | 44 (4.8) | 37 (4.0) |
| Dyspnoea | 8 (4.6) | 8 (4.6) | 5 (2.6) | 4 (2.1) | 38 (4.1) | 30 (3.2) |
| Nausea | 5 (2.9) | 4 (2.3) | 6 (3.2) | 1 (0.5) | 25 (2.7) | 11 (1.2) |
| Vomiting | 6 (3.4) | 3 (1.7) | 7 (3.7) | 5 (2.6) | 25 (2.7) | 16 (1.7) |
| Pleural Effusion | 5 (2.9) | 2 (1.1) | 7 (3.7) | 4 (2.1) | 21 (2.3) | 16 (1.7) |
| Seizure | 1 (0.6) | 1 (0.6) | 0 | 0 | 21 (2.3) | 12 (1.3) |
| Pericardial Effusion | 2 (1.1) | 2 (1.1) | 4 (2.1) | 2 (1.1) | 19 (2.1) | 14 (1.5) |
| Pyrexia | 5 (2.9) | 2 (1.1) | 2 (1.1) | 0 | 18 (1.9) | 7 (0.8) |
| Hyperglycaemia | 1 (0.6) | 1 (0.6) | 5 (2.6) | 5 (2.6) | 16 (1.7) | 15 (1.6) |
| Respiratory Failure | 4 (2.3) | 4 (2.3) | 1 (0.5) | 1 (0.5) | 16 (1.7) | 16 (1.7) |
| General Physical Health Deterioration | 1 (0.6) | 1 (0.6) | 2 (1.1) | 2 (1.1) | 15 (1.6) | 14 (1.5) |
| Dehydration | 2 (1.1) | 1 (0.6) | 1 (0.5) | 1 (0.5) | 12 (1.3) | 10 (1.1) |
| Lung Infection | 4 (2.3) | 4 (2.3) | 3 (1.6) | 2 (1.1) | 12 (1.3) | 11 (1.2) |
| Pneumonitis | 0 | 0 | 1 (0.5) | 1 (0.5) | 12 (1.3) | 9 (1.0) |
| Pulmonary Embolism | 6 (3.4) | 6 (3.4) | 3 (1.6) | 3 (1.6) | 12 (1.3) | 12 (1.3) |
| Pericarditis | 0 | 0 | 0 | 0 | 11 (1.2) | 6 (0.6) |
| Alanine Aminotransferase Increased | 0 | 0 | 3 (1.6) | 1 (0.5) | 10 (1.1) | 8 (0.9) |
| Asthenia | 0 | 0 | 1 (0.5) | 1 (0.5) | 10 (1.1) | 7 (0.8) |
| Non-Cardiac Chest Pain | 0 | 0 | 2 (1.1) | 1 (0.5) | 10 (1.1) | 6 (0.6) |
| Diarrhoea | 3 (1.7) | 2 (1.1) | 3 (1.6) | 2 (1.1) | 9 (1.0) | 5 (0.5) |
| Aspartate Aminotransferase Increased | 0 | 0 | 4 (2.1) | 1 (0.5) | 8 (0.9) | 4 (0.4) |
| Fatigue | 2 (1.1) | 2 (1.1) | 2 (1.1) | 2 (1.1) | 8 (0.9) | 7 (0.8) |
| Back Pain | 2 (1.1) | 2 (1.1) | 3 (1.6) | 3 (1.6) | 7 (0.8) | 6 (0.6) |
| Atrial Fibrillation | 2 (1.1) | 2 (1.1) | 2 (1.1) | 1 (0.5) | 6 (0.6) | 3 (0.3) |
| Blood Creatinine Increased | 0 | 0 | 3 (1.6) | 1 (0.5) | 6 (0.6) | 1 (0.1) |
| Dizziness | 0 | 0 | 2 (1.1) | 1 (0.5) | 6 (0.6) | 3 (0.3) |
| Malaise | 1 (0.6) | 0 | 2 (1.1) | 1 (0.5) | 6 (0.6) | 2 (0.2) |
| Metastases To Central Nervous System | 0 | 0 | 3 (1.6) | 3 (1.6) | 5 (0.5) | 5 (0.5) |
| Anaemia | 4 (2.3) | 1 (0.6) | 1 (0.5) | 1 (0.5) | 4 (0.4) | 3 (0.3) |
| Paraesthesia | 0 | 0 | 2 (1.1) | 2 (1.1) | 4 (0.4) | 2 (0.2) |
| Sepsis | 2 (1.1) | 1 (0.6) | 0 | 0 | 4 (0.4) | 4 (0.4) |
| Hepatic Function Abnormal | 0 | 0 | 2 (1.1) | 2 (1.1) | 3 (0.3) | 3 (0.3) |
| Septic Shock | 2 (1.1) | 2 (1.1) | 0 | 0 | 3 (0.3) | 1 (0.1) |
| Urinary Tract Infection | 2 (1.1) | 2 (1.1) | 0 | 0 | 3 (0.3) | 3 (0.3) |
| Haemoptysis | 3 (1.7) | 1 (0.6) | 0 | 0 | 2 (0.2) | 1 (0.1) |
| Thrombocytopenia | 2 (1.1) | 2 (1.1) | 0 | 0 | 1 (0.1) | 1 (0.1) |
| Hypoglycaemia | 2 (1.1) | 1 (0.6) | 0 | 0 | 0 | 0 |
| Superior Vena Cava Syndrome | 2 (1.1) | 1 (0.6) | 0 | 0 | 0 | 0 |

- Preferred terms are sorted in descending frequency of all grades column, 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 is counted only once in the total row.
- Only AEs occurring during on-treatment period are reported.
- AEs are graded according to the CTCAE V4.03; MedDRA version 19.0 is used.
- Data cut-off for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3.1-1.9]

**Serious adverse events considered related to ceritinib treatment**

***Study A2301 ceritinib group***

Thirty patients (15.9%) from the ceritinib group experienced SAEs that were suspected by the Investigator to be related to study treatment. This was similar to the chemotherapy group (15.4%).

The most frequently reported (in ≥ 2% of patients) study drug-related SAEs in the ceritinib group were nausea and vomiting (each in six patients, 3.2%) and AST increased (2.1%). Majority of these SAEs suspected to be drug-related were grade 3/4 in severity (12.2%). There were no drug-related SAEs with fatal outcome in the ceritinib group.

Of note, one patient had QT-prolongation considered as a SAE related to ceritinib. There were no drug-related SAEs with fatal outcome in the ceritinib group.

***Pooled dataset***

Serious adverse events that were suspected by the Investigator to be related to ceritinib treatment were reported in 123 patients (13.3%). Suspected SAEs (by individual PT) were each reported in <1% of patients, with the exception of nausea and vomiting (each 18 patients, 1.9%), pericarditis (10 patients, 1.1%), and pneumonitis (nine patients, 1.0%).

One SAE of ILD (grade 4) was reported in one patient that was suspected to ceritinib treatment and led to death. Another SAE of pneumonitis (grade 3) reported in another patient was not suspected to ceritinib treatment and led to death. None of the other SAEs for these AESIs were the primary cause of death.

## Deaths

On-treatment deaths were defined as deaths while receiving study medication or up to 30 days after the last dose of study treatment.

**Table 39: On-treatment deaths by principal cause, primary system organ class, preferred term and treatment group (Safety Set)**

| Principal cause of death<br>Primary system organ class<br>Preferred term | Study A2301<br>Chemotherapy<br>N=175<br>n (%) | Study A2301<br>Ceritinib 750 mg<br>N=189<br>n (%) | All patients<br>Ceritinib 750 mg<br>N=925<br>n (%) |
|---|---|---|---|
| **Total** | 6 (3.4) | 11 (5.8) | 139 (15.0) |
| Study Indication [a] | 5 (2.9) | 7 (3.7) | 105 (11.4) |
| Other | 1 (0.6) | 4 (2.1) | 34 (3.7) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Total** | 5 (2.9) | 7 (3.7) | 96 (10.4) |
| Non-small cell lung cancer | 5 (2.9) | 7 (3.7) | 86 (9.3) |
| Malignant neoplasm progression | 0 | 0 | 4 (0.4) |
| Lung neoplasm malignant | 0 | 0 | 3 (0.3) |
| Lung cancer metastatic | 0 | 0 | 1 (0.1) |
| Malignant pleural effusion | 0 | 0 | 1 (0.1) |
| Metastases to central nervous system | 0 | 0 | 1 (0.1) |
| **Respiratory, thoracic and mediastinal disorders - Total** | 0 | 1 (0.5) | 16 (1.7) |
| Respiratory failure | 0 | 0 | 6 (0.6) |
| Pulmonary embolism | 0 | 0 | 3 (0.3) |
| Acute pulmonary oedema | 0 | 0 | 1 (0.1) |
| Acute respiratory distress syndrome | 0 | 0 | 1 (0.1) |
| Dyspnoea | 0 | 0 | 1 (0.1) |
| Interstitial lung disease | 0 | 0 | 1 (0.1) |
| Pneumonia aspiration | 0 | 0 | 1 (0.1) |
| Pneumonitis | 0 | 1 (0.5) | 1 (0.1) |
| Pneumothorax | 0 | 0 | 1 (0.1) |
| **General disorders and administration site conditions - Total** | 0 | 1 (0.5) | 11 (1.2) |
| Disease progression | 0 | 0 | 5 (0.5) |
| Death | 0 | 1 (0.5) | 2 (0.2) |
| General physical health deterioration | 0 | 0 | 2 (0.2) |
| Euthanasia | 0 | 0 | 1 (0.1) |
| Multiple organ dysfunction syndrome | 0 | 0 | 1 (0.1) |
| **Infections and infestations - Total** | 1 (0.6) | 1 (0.5) | 11 (1.2) |
| Pneumonia | 0 | 0 | 6 (0.6) |
| Atypical pneumonia | 0 | 0 | 1 (0.1) |
| Pulmonary tuberculosis | 0 | 0 | 1 (0.1) |
| Respiratory tract infection | 0 | 1 (0.5) | 1 (0.1) |
| Sepsis | 0 | 0 | 1 (0.1) |
| Septic shock | 0 | 0 | 1 (0.1) |
| Lung infection | 1 (0.6) | 0 | 0 |
| **Cardiac disorders - Total** | 0 | 1 (0.5) | 3 (0.3) |
| Cardiac tamponade | 0 | 0 | 2 (0.2) |
| Myocardial infarction | 0 | 1 (0.5) | 1 (0.1) |
| **Gastrointestinal disorders - Total** | 0 | 0 | 1 (0.1) |
| Gastric haemorrhage | 0 | 0 | 1 (0.1) |
| **Nervous system disorders - Total** | 0 | 0 | 1 (0.1) |
| Cerebrovascular accident | 0 | 0 | 1 (0.1) |

- Primary system organ classes are presented in descending frequency; preferred terms are sorted within primary system organ class in descending frequency, as reported in the All patients column.

- Only deaths occurring during on-treatment period are reported.

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

[a] Of the 105 deaths reported in the pooled dataset under study indication – 96 had PT under SOC of 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)', five with PT of disease progression, one each with PT of general physical health deterioration, respiratory failure, dyspnoea, and septic shock

Source: [SCS Appendix 1-Table 14.3.1-1.4]

## *Laboratory findings*

*Haematology*

In ceritinib-treated patients, haematological abnormalities were predominantly grade 1 or 2 in Study A2301 ceritinib group and pooled dataset. The frequency of any post-baseline grade changes in haematological parameters was similar (≤ 10% difference) in Study A2301 ceritinib group and pooled dataset. The most frequently occurring (>5%) grade 3/4 haematological abnormalities were seen for decreased lymphocytes.

In Study A2301 ceritinib group, of the 189 patients treated with ceritinib, majority of the patients (161 patients, 85.2%) had normal absolute lymphocytes (grade 0) at baseline. Post-baseline, 109 patients (57.7%) had decreased absolute lymphocytes of any grade, of which 45 patients (23.8%), 44 patients (23.3%), 15 patients (7.9%), and five patients (2.6%) had grade 1, grade 2, grade 3, and grade 4 decreased absolute lymphocytes, respectively. In the pooled dataset, of the 925 patients treated with ceritinib, majority of the patients (604 patients, 65.3%) had normal absolute lymphocytes (grade 0) at baseline. Post-baseline, 642 patients (69.4%) had decreased absolute lymphocytes of any grade, of which 184 patients (19.9%), 260 patients (28.1%), 167 patients (18.1%), and 31 patients (3.4%) had grade 1, grade 2, grade 3, and grade 4 decreased absolute lymphocytes, respectively.

In the A2301 chemotherapy group, the most frequently occurring (>5%) grade 3/4 haematological abnormalities were seen for decreased absolute lymphocytes (grade 3 in 17.7% and grade 4 in 1.7%), decreased absolute neutrophils (grade 3 in 12.0% and grade 4 in 7.4%), decreased haemoglobin (grade 3 in 10.9%, no grade 4), decreased platelet count (grade 3 in 3.4% and grade 4 in 1.7%), and decreased WBC (grade 3 in 5.7% and grade 4 in 1.1%).

*Clinical chemistry*

The frequency of any post-baseline grade changes in chemistry parameters was similar (≤ 10% difference) in Study A2301 ceritinib group and pooled dataset, except for decreased creatinine clearance (54.5% in Study A2301 ceritinib group, 39.2% in pooled dataset; grade 3/4 decrease were similar, 5.3% in A2301 ceritinib group and 3.1% in pooled dataset), decreased glucose (54.5% in Study A2301 ceritinib group, 38.6% in pooled dataset; grade 3/4 decrease were similar, 0.5% in A2301 ceritinib group and 0.9% in pooled dataset), and increased potassium (36% in Study A2301 ceritinib group, 25.3% in pooled dataset; grade 3/4 increases were similar, 3.2% in A2301 ceritinib group and 1.8% in pooled dataset).

The most frequent (>5%) post-baseline grade 3/4 chemistry increase in ceritinib treated patients in Study A2301 ceritinib group and pooled dataset were reported for liver enzymes (ALT, AST, ALP, and GGT), however there were no confirmed Hy's law cases, glucose and amylase (only in the pooled dataset).

The most frequent (>5%) post-baseline grade 3/4 chemistry decrease in ceritinib treated patients in Study A2301 ceritinib group were reported for:

- Sodium: In Study A2301 ceritinib group, of the 189 patients treated with ceritinib, majority of the patients (97.4%) had normal sodium (grade 0) at baseline. Post-baseline, 27% of patients had decreased sodium of any grade, of which 19.0%, 7.4%, and 0.5% had grade 1, grade 3, and grade 4 decreased sodium, respectively. In the pooled dataset, of the 925 patients treated with ceritinib, majority of the patients (93.3%) had normal sodium (grade 0) at baseline. Post-baseline, 33% of patients had decreased sodium of any grade, of which 25.2%, 7.7%, and 0.1% had grade 1, grade 3, and grade 4 decreased sodium, respectively.
- Potassium (only in the pooled dataset): In the pooled dataset, of the 925 patients treated with ceritinib, majority of the patients (97.9%) had normal potassium (grade 0) at baseline. Post-baseline, 21.6% of patients had decreased potassium of any grade, of which 15.7%, 5.2%, and 0.8% had grade 2, grade 3, and grade 4 decreased potassium, respectively.

- Phosphate (only in pooled dataset): In the pooled dataset, of the 925 patients treated with ceritinib, majority of the patients (89.9%) had normal phosphate (grade 0) at baseline. Post-baseline, 43.3% of patients had decreased phosphate of any grade, of which 9.2%, 27.7%, 6.4%, and 0.1% had grade 1, grade 2, grade 3, and grade 4 decreased phosphate, respectively.

In chemotherapy group, the most frequently reported (>5%) grade 3/4 chemistry parameters were seen for increased glucose (grade 3 in 10.3%, no grade 4) and decreased sodium (grade 3 in 5.1%, no grade 4).

*Special laboratory evaluations*

In Study A2301, testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone-binding globulin (SHBG) were measured in male patients to assess potential impact of ceritinib on male hormone levels. Analysis of total testosterone (free and bound), free testosterone index, LH, FSH and SHBG did not show significant changes between baseline and post-baseline measurement (i.e. D15).

## *Safety in special populations*

The subgroup analysis of safety by region, age, gender, race, presence or absence of brain metastases (based on CRF data), presence or absence of prior adjuvant chemotherapy, and WHO PS (0 vs. 1-2; based on CRF data) at baseline showed patterns that were generally consistent with those of the overall population and did not reveal any relevant clinically meaningful differences in the overall proportion of patients with AEs within subgroups.

No specific analyses were conducted to evaluate the use of other drugs, tobacco, alcohol on the tolerability and safety of ceritinib.

Ceritinib is eliminated primarily via the liver. So far, there is limited experience in patients with pre-existing moderate (only 1 patient) or no experience in patients with severe hepatic impairment. A PK study is currently ongoing to assess the effect of hepatic impairment in non-cancer patients.

No dose adjustment is necessary in patients with mild to moderate renal impairment since population pharmacokinetic analysis have shown that ceritinib exposure is similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trials.

## *Safety related to drug-drug interactions and other interactions*

No safety data regarding drug-drug interactions.

## *Discontinuation due to adverse events*

### Adverse events leading to discontinuation

**Table 40: Adverse events leading to discontinuation by treatment group, by preferred term and maximum grade regardless of study drug relationship (with AEs reported in more than one patient for all grades in any group) (Safety set)**

| | Study A2301 | | | | All patients | |
|---|---|---|---|---|---|---|
| | Chemotherapy N=175 | | Ceritinib 750 mg N=189 | | Ceritinib 750 mg N=925 | |
| Preferred term | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| -Total | 29 (16.6) | 16 (9.1) | 21 (11.1) | 12 (6.3) | 112 (12.1) | 87 (9.4) |
| Pneumonia | 1 (0.6) | 1 (0.6) | 0 | 0 | 6 (0.6) | 6 (0.6) |
| Respiratory Failure | 1 (0.6) | 1 (0.6) | 1 (0.5) | 1 (0.5) | 6 (0.6) | 6 (0.6) |
| Alanine Aminotransferase Increased | 1 (0.6) | 0 | 1 (0.5) | 1 (0.5) | 5 (0.5) | 5 (0.5) |
| General Physical Health Deterioration | 1 (0.6) | 1 (0.6) | 1 (0.5) | 1 (0.5) | 5 (0.5) | 5 (0.5) |
| Nausea | 0 | 0 | 1 (0.5) | 0 | 5 (0.5) | 2 (0.2) |
| Pneumonitis | 0 | 0 | 1 (0.5) | 0 | 5 (0.5) | 3 (0.3) |
| Aspartate Aminotransferase Increased | 0 | 0 | 0 | 0 | 4 (0.4) | 3 (0.3) |
| Blood Creatinine Increased | 6 (3.4) | 0 | 4 (2.1) | 1 (0.5) | 4 (0.4) | 1 (0.1) |
| Dyspnoea | 2 (1.1) | 2 (1.1) | 0 | 0 | 4 (0.4) | 2 (0.2) |
| Pulmonary Embolism | 1 (0.6) | 1 (0.6) | 0 | 0 | 4 (0.4) | 4 (0.4) |
| Vomiting | 1 (0.6) | 0 | 1 (0.5) | 0 | 4 (0.4) | 2 (0.2) |
| Decreased Appetite | 0 | 0 | 0 | 0 | 3 (0.3) | 2 (0.2) |
| Fatigue | 0 | 0 | 0 | 0 | 3 (0.3) | 3 (0.3) |
| Interstitial Lung Disease | 0 | 0 | 0 | 0 | 3 (0.3) | 2 (0.2) |
| Lipase Increased | 0 | 0 | 2 (1.1) | 2 (1.1) | 3 (0.3) | 3 (0.3) |
| Pericardial Effusion | 1 (0.6) | 1 (0.6) | 0 | 0 | 3 (0.3) | 2 (0.2) |
| Pleural Effusion | 1 (0.6) | 1 (0.6) | 0 | 0 | 3 (0.3) | 2 (0.2) |
| Respiratory Tract Infection | 0 | 0 | 1 (0.5) | 1 (0.5) | 3 (0.3) | 3 (0.3) |
| Amylase Increased | 0 | 0 | 2 (1.1) | 2 (1.1) | 2 (0.2) | 2 (0.2) |
| Asthenia | 0 | 0 | 1 (0.5) | 0 | 2 (0.2) | 0 |
| Cardiac Tamponade | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.2) |
| Electrocardiogram Qt Prolonged | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.2) |
| Gamma-Glutamyltransferase Increased | 0 | 0 | 1 (0.5) | 1 (0.5) | 2 (0.2) | 2 (0.2) |
| Lung Infiltration | 0 | 0 | 1 (0.5) | 0 | 2 (0.2) | 0 |
| Metastases To Central Nervous System | 0 | 0 | 1 (0.5) | 1 (0.5) | 2 (0.2) | 2 (0.2) |
| Metastases To Meninges | 0 | 0 | 0 | 0 | 2 (0.2) | 1 (0.1) |
| Pericarditis | 0 | 0 | 0 | 0 | 2 (0.2) | 1 (0.1) |
| Pneumonia Aspiration | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.2) |
| Creatinine Renal Clearance Decreased | 3 (1.7) | 0 | 1 (0.5) | 1 (0.5) | 1 (0.1) | 1 (0.1) |
| Tinnitus | 2 (1.1) | 1 (0.6) | 0 | 0 | 0 | 0 |

- Preferred terms are sorted by descending frequency of 'all grades' column, as reported in the All patients column. - A patient with multiple occurrences of an AE is counted only once in the AE category. - The event with maximum severity is counted for patients who experienced multiple episodes of an event. - Only AEs occurring during on-treatment period are reported.

- AEs are graded according to the CTCAE V4.03; MedDRA version 19.0 is used.

- Data cutoff for A2301: 24-Jun-2016, A2303: 26-Jan-2016, A2109: 30-Oct-2015, A2201: 29-Mar-2016, X2101: 03-May-2016, X1101: 28-Jan-2016, A2203: 15-Nov-2015.

Source: [SCS Appendix 1-Table 14.3.1-1.12]

### Adverse events requiring dose interruption

#### *Study A2301*

Adverse events (regardless of study drug relationship) requiring dose interruption in **ceritinib group** were reported in 131 patients (69.3%) in the Study A2301 ceritinib group. The most frequently occurring AEs (in ≥ 5% of patients) requiring dose interruption were: ALT increased (33.9%), AST increased (22.8%), blood creatinine increased (12.2%), vomiting (9.5%), diarrhoea (8.5%), GGT increased (8.5%), nausea (7.9%),

and blood alkaline phosphatase increased (5.3%). Grade 3/4 events regardless of study drug relationship requiring dose interruption were reported in 41.3% of patients in the Study A2301 ceritinib group; and the most frequently reported in ≥ 2% of patients were: ALT increased (12.2%), AST increased (7.4%), GGT increased (7.4%), vomiting (2.6%), blood alkaline phosphatase increased (2.6%), fatigue (2.6%), nausea (2.1%), pneumonia (2.1%).

Adverse events requiring study drug interruption in the **chemotherapy group** were reported in 39.4% of patients, and the most frequently occurring AEs (in ≥ 5% of patients) were neutropenia (8.0%), neutrophil count decrease (6.3%), WBC count decreased (6.3%), and anaemia (5.7%). Grade 3/4 AEs were reported in 17.7% of patients, and the most frequently reported (≥ 2%) was neutropenia (4.6%).

**Pooled dataset**

Adverse events requiring dose interruption regardless of study drug relationship were reported in 450 patients (66.3%); 282 patients (41.5%) had a grade 3/4 AE requiring dose interruption.

The most frequently occurring (any grade, ≥ 5% of patients) AEs regardless of study drug relationship requiring dose interruption were ALT increased (28.6%), AST increased (18.9%), vomiting (12.4%), nausea (10.0%), diarrhoea (8.8%), blood creatinine increased (6.8%), and GGT increased (5.2%).

The most frequently occurring (≥ 2%) grade 3/4 AEs regardless of study drug relationship requiring dose interruption were ALT increased (13.3%), AST increased (6.5%), GGT increased (4.6%), nausea (3.2%), fatigue (2.8%), vomiting (2.7%), diarrhoea and pneumonia (each 2.1%).

***Adverse events requiring dose adjustment***

***Study A2301***

Adverse events regardless of study drug relationship requiring dose adjustment in **ceritinib group** were reported in 109 patients (57.7%). The most frequently occurring AEs (in ≥ 5% of patients) that required dose adjustments were: ALT increased (29.6%); AST increased (16.4%); vomiting 7.4%); GGT increased (6.3%); blood creatinine increased and diarrhoea (each 5.8%). Grade 3/4 events regardless of study drug relationship requiring dose adjustments were reported in 34.9% patients in the ceritinib group; and the incidence of individual grade 3/4 AEs requiring a dose adjustment was low other than ALT increased that was reported in 21.2% of patients. The most frequent AEs (in ≥ 2% of patients) requiring a dose adjustment were ALT increased (21.2%), AST increased (9.5%), GGT increased (5.3%), and vomiting (2.6%).

Adverse events requiring dose adjustment in the **chemotherapy group** were reported in 15.4% of patients, and none of the AEs were reported in ≥ 5% of patients. Grade 3/4 AEs were reported in 13.1% of patients, and the most frequently occurring (in ≥ 2% of patients) were neutropenia (4.0%), anaemia (2.9%), and vomiting (2.3%).

**Pooled dataset**

Adverse events leading to dose adjustment regardless of study drug relationship were reported in 305 patients (44.9%), and 138 patients (20.3%) had a grade 3/4 AE leading to dose adjustment.

The most frequently occurring (any grade, ≥ 5% of patients) AEs regardless of study drug relationship requiring dose adjustment were ALT increased (15.5%), vomiting (9.4%), AST increased (8.5%), diarrhea (7.2%), and nausea (6.8%).

The most frequently occurring (≥ 2% of patients) grade 3/4 AEs requiring dose adjustment regardless of study drug relationship were ALT increased (9.1%), AST increased (4.1%), and vomiting (2.5%).

**Adverse events requiring significant additional therapy**

***Study A2301***

Adverse events requiring additional therapy in **ceritinib group** were reported in 95.2% patients in the ceritinib group; and the most frequently reported AEs (≥ 10% of patients) were: diarrhoea (62.4%), nausea (45.0%), vomiting (36.5%), ALT increased (19.0%), AST increased (18.5%), cough (16.4%), abdominal pain upper (11.1%), constipation (11.1%), decreased appetite (11.1%), rash (10.6%), abdominal pain (10.6%), back pain (10.1%). Grade 3/4 events requiring additional therapy were reported in 43.9% of patients in the ceritinib group; and the most frequently reported (≥ 2% of patients) were: ALT increased (7.4%), hyperglycemia (4.8%), AST increased (4.2%), vomiting (4.2%), GGT increased (3.2%), diarrhoea (3.2%), pneumonia (3.2%), nausea (2.6%), hypokalemia (2.1%).

Adverse events requiring additional therapy in the **chemotherapy group** were reported in 91.4% of patients, and the most frequently reported AEs (≥ 10% of patients) were nausea (41.1%), vomiting (25.7%), anaemia (18.9%), constipation (15.4%), cough (11.4%), pyrexia (10.3%). Grade 3/4 AEs were reported in 46.9% of patients, and the most frequently reported (≥ 2%) were anaemia (5.7%), dyspnoea (4.6%), nausea (4.0%), vomiting (4.0%), pulmonary embolism (4.0%), pneumonia (2.9%), neutrophil count decreased (2.9%), neutropenia (2.9%), lung infection (2.3%), back pain (2.3%), respiratory failure (2.3%), hyperglycaemia (2.3%).

**Pooled dataset**

Adverse events requiring additional therapy (which included all non-drug therapy in addition to concomitant medications, regardless of study drug relationship) were reported in 95.9% patients in the ceritinib group.

The most frequently reported AEs (≥ 10% of patients) requiring additional therapy were diarrhoea (57.1%), nausea (53.6%), vomiting (35.8%), constipation (15.8%), abdominal pain (14.8%), cough (14.4%), back pain and decreased appetite (each 12.5%), abdominal pain upper (12.0%), ALT increased (11.9%), pyrexia (11.1%), and headache (10.3%).

Grade 3/4 events requiring additional therapy were reported in 50.9% of patients treated with ceritinib. The most frequently reported grade 3/4 AEs (≥ 2% of patients) that required additional therapy regardless of study drug relationship were nausea (4.6%), ALT increased (4.4%), vomiting and pneumonia (each 4.3%), diarrhoea (3.9%), hyperglycemia (3.7%), hypokalemia (3.4%), dyspnoea (2.7%), and AST increased (2.2%).

**Analysis of safety after crossover in Phase III studies**

**Safety in the subgroup of patients who crossed over to ceritinib in Study A2301**

Among the 85 patients who crossed over, 80 patients received ceritinib in the extension treatment phase (three patients did not receive ceritinib as of the data cut-off date and other two patients had died before start of first dose of ceritinib). At the time of the data cut-off, 33/80 patients were still ongoing in the extension treatment phase.

The most frequently reported all grade AEs (regardless of study drug relationship) in the extension treatment phase (≥ 20% of patients) were: diarrhoea (75.0%), vomiting (52.5%), nausea and ALT increased (each 51.3%), AST increased (46.3%), blood creatinine increased (37.5%), fatigue (25.0%), GGT increased (23.8%), blood alkaline phosphatase increased (21.3%), and decreased appetite (20.0%).

The AEs in the extension treatment phase were similar (<10% difference) to the treatment phase ceritinib group except for: nausea (51.3% vs. 68.8%), vomiting (52.5% vs. 66.1%), GGT increased (23.8% vs. 37.0%), decreased appetite (20.0% vs. 33.9%), cough (13.8% vs. 24.3%), blood creatinine increased (37.5% vs. 22.2%), and pyrexia (7.5% vs. 18.0%), respectively.

Blood creatinine AE increased was reported more frequently in patients treated in the extension treatment phase than in the treatment phase (37.5% and 22.2%, respectively), and an AE of decreased creatinine clearance was reported in 6.9% patients in treatment phase and in 7.5% of patients in the extension treatment phase. Blood creatinine AE increased was reported more frequently in patients treated in the extension treatment phase than in the treatment phase (37.5% and 22.2%, respectively).

Fifty-five (68.8%) patients had grade 3/4 AEs, and the most frequently reported grade 3/4 AEs (>5% of patients) included: ALT increased and GGT increased (each 20.0%); fatigue (13.8%); AST increased (11.3%); blood alkaline phosphatase increased, decreased appetite, and back pain (each 6.3%). The grade 3/4 AEs in the extension treatment phase were similar (<5% difference) to the treatment phase ceritinib group except for: ALT increased (20.0 vs. 30.7), AST increased (11.3 vs. 16.9), fatigue (13.8 vs. 4.2), GGT increased (20.0 vs. 28.6), decreased appetite (6.3 vs. 1.1), respectively.

Serious adverse events were reported in 34 (42.5%) patients, of which was suspected to be drug related in 11 patients (13.8%).

Nine patients (11%) discontinued due to AEs (acute kidney injury, creatinine renal clearance decreased, pneumonia, blood creatinine increased, ALT increased, ILD – all suspected) and cancer pain, and lung infection (not suspected).

Among the 11 patients who died on-treatment in the extension treatment phase, six patients died due to study indication and five patients died due to other causes: pneumonia, septic shock, metabolic acidosis, pulmonary embolism, and respiratory failure in one patient each; none of these AEs were suspected to be study drug related except for metabolic acidosis.

**Table 41: Overall summary of AEs by treatment group (Cross-over Analysis Set)**

| | LDK378 750 mg N=80 | |
|---|---|---|
| **Category** | **All grades n (%)** | **Grade 3/4 n (%)** |
| **All deaths [a]** | 31 (38.8) | - |
| Extension treatment phase on-treatment deaths | 11 (13.8) | - |
| **Adverse Events** | 79 (98.8) | 55 (68.8) |
| Suspected to be drug related | 75 (93.8) | 41 (51.3) |
| **Serious adverse events** | 34 (42.5) | 27 (33.8) |
| Suspected to be drug related | 11 (13.8) | 7 (8.8) |
| **AEs leading to discontinuation** | 17 (21.3) | 12 (15.0) |
| Suspected to be drug related | 8 (10.0) | 3 (3.8) |
| **AEs requiring dose adjustment** | 38 (47.5) | 21 (26.3) |
| Suspected to be drug related | 36 (45.0) | 20 (25.0) |
| **AEs requiring dose interruption/delay** | 49 (61.3) | 22 (27.5) |
| Suspected to be drug related | 40 (50.0) | 16 (20.0) |
| **AEs requiring dose adjustment or interruption/delay** | 56 (70.0) | 34 (42.5) |
| Suspected to be drug related | 51 (63.8) | 31 (38.8) |
| **AEs requiring additional therapy** | 73 (91.3) | 36 (45.0) |
| Suspected to be drug related | 62 (77.5) | 19 (23.8) |

Categories are not mutually exclusive. Patients with multiple events in the same category were counted only once in that category.

Patients with events in more than one category were counted once in each of those categories.

[a] All deaths, including those after the end of the extension treatment period.

Only AEs occurring during on-treatment period were summarized.

AEs were graded according to the CTCAE V4.03.

Source: [Study A2301-Table 14.3.1-1.21c]

**Study A2303**

Study A2303, was an open-label, randomized, global Phase III study to compare the efficacy and safety of ceritinib to standard second-line chemotherapy (pemetrexed or docetaxel) in patients with advanced ALK-positive NSCLC who were previously treated with chemotherapy (including a platinum-based doublet) and crizotinib, and had demonstrated disease progression at study entry. Patients randomized to the chemotherapy arm were allowed to crossover to receive ceritinib therapy in the Extension Treatment Phase only after BIRC confirmed RECIST defined disease progression.

Seventy five patients from the chemotherapy arm crossed over to ceritinib, and entered the extension treatment phase.

The overall safety profile for the patients who crossed-over to ceritinib in the extension treatment phase was similar to the safety profile of patients in the ceritinib group in the treatment phase.

**Table 42: Overall summary of AEs (Cross-over analysis set)**

| | Ceritinib 750 mg N=74 | |
|---|---|---|
| Category | All grades n (%) | Grade 3/4 n (%) |
| All deaths[a] | 32 (43.2) | |
| Extension-treatment phase on-treatment deaths | 16 (21.6) | |
| Adverse Events | 73 (98.6) | 55 (74.3) |
| Suspected to be drug-related | 68 (91.9) | 37 (50.0) |
| Serious adverse events | 38 (51.4) | 38 (51.4) |
| Suspected to be drug-related | 17 (23.0) | 14 (18.9) |
| AEs leading to discontinuation | 8 (10.8) | 8 (10.8) |
| AEs requiring dose adjustment | 27 (36.5) | 11 (14.9) |
| AEs requiring dose interruption/delay | 42 (56.8) | 31 (41.9) |
| AEs requiring additional therapy | 68 (91.9) | 41 (55.4) |

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 one category are counted once in each of those categories.

[a] All deaths, including those after the end of the extension-treatment period.

Only AEs occurring during extension-treatment period are summarized.

AEs are graded according to the CTCAE V4.03.

Source: [Study A2303-Table 14.3.1-1.21c]

The most frequently reported all grade AEs (regardless of study drug relationship) in the extension treatment phase (≥ 20% of patients) were: diarrhoea (71.6%), nausea (56.8%), vomiting (47.3%), ALT increased (29.7%), decreased appetite (27.0%), AST increased (25.7%), blood creatinine increased (24.3%), abdominal pain (23.0%), constipation and fatigue (each 21.6%), and GGT increased (20.3%). The AEs in the extension treatment phase were similar (<10% difference) to the treatment phase ceritinib arm except for: ALT increased (29.7% vs. 42.6%), AST increased (25.7% vs. 36.5%), weight decreased (16.2% vs. 29.6%), decreased appetite (27.0% vs. 41.7%), and back pain (9.5% vs. 21.7%), respectively.

Fifty-five (74.3%) patients had grade 3/4 AEs, and the most frequently reported grade 3/4 AEs (>5% of patients) included: ALT increased (17.6%); nausea, AST increased, and GGT increased (each 10.8%); vomiting (9.5%); fatigue and dyspnoea (each 6.8%); diarrhoea, pleural effusion, and pneumonia (each 5.4%). The grade 3/4 AEs in the extension treatment phase were similar (<5% difference) to the treatment phase ceritinib group except for GGT increased (10.8% vs. 20.9%), respectively.

Serious adverse events were reported in 38 patients (51.4%); pneumonia, pleural effusion, and nausea were reported in >5% of patients.

No Hy's law case was observed in the extension treatment phase (i.e. concurrent AT >3xULN and TBILI >2xULN, and ALP <2xULN).

### *Post marketing experience*

The latest Zykadia PSUR (PSUR 4) with a data lock point of 28 April 2016 provides additional information on estimated 3700 patients treated with ceritinib in post-marketing setting.

Additional safety information (cumulative line listings of deaths and SAEs) reported in the Novartis global pharmacovigilance safety database (ARGUS) for 21 ongoing and two completed Novartis-sponsored studies including healthy volunteer studies consisting of 1927 enrolled patients based on the data cut-off date of 10 August 2016 is provided. The evaluation did not reveal any new safety concern or any meaningful change in frequency or severity. The safety data is consistent with the known safety profile of ceritinib described above.

## 2.5.1. Discussion on clinical safety

This safety review of ceritinib in first-line treatment of ALK positive NSCLC is based on the results of the pivotal phase III Study A2301 and a pooled dataset of seven clinical studies, which includes data on ceritinib from the pivotal trial.

With the pivotal trial of this application, the safety database for ceritinib in the treatment of ALK positive NSCLC now includes 925 patients and more data on long-term exposure to ceritinib is available. In study A2301, 72.5% of patients were treated for $\geqslant$ than 33 weeks and median exposure was 66.4 weeks. In the pooled dataset, the median exposure is 44.9 weeks.

As observed in previous trials with ceritinib, the rate of dose reductions and interruptions are high in study A2301, 67.7% and 78.3% respectively. This is even higher than in phase III trial A2303 conducted in previously treated ALK positive NSCLC patients. Most of the dose reductions and interruptions for ceritinib are due to AEs, 57.7% and 44.9% in study A2301 and the pooled dataset, respectively. The main reason for dose adjustments and dose interruptions is liver toxicity, i.e. increased ALT and AST.

The toxicity profile of ceritinib compared with the toxicity profile of the platinum doublets used in the pivotal study A2301 seems acceptable. The higher frequency of GI toxicity with ceritinib is mainly due to grade 1/2 AEs, and managed with additional therapies. The liver toxicity observed with ceritinib is mainly managed with dose adjustments.

Overall, the safety profile of ceritinib is considered similar to previous experience and AEs. However, compared to previous studies, there is an increase in liver toxicity in terms of increased frequencies of ALT and AST increase and also GGT increase. In addition, a higher frequency of decreased creatinine clearance than in previous studies is observed. These AEs lead to a higher rate of dose reductions and interruptions than previously reported. Based on exposure-response analyses, the applicant has concluded that there is a clear relationship between exposure level and AEs of ALT/AST elevations while no exposure efficacy relationship has been found. The high rate of dose reductions/interruptions may indicate that a lower dose of ceritinib from start of treatment could be more appropriate from a safety perspective.

No fatal outcome associated with any of the AESIs was reported with the exception of two deaths with pneumonitis in the pooled dataset (one patient with grade 4 ILD that was suspected to be related to ceritinib treatment, and another patient with grade 3 pneumonitis that was assessed as not related to ceritinib treatment).

There was a high rate of AE suspected to be drug-related (97.4%, grade ≥3, 65.1%) and AEs that requiring dose adjustment (57.7%, grade ≥3 34.9%) or interruption (69.3%, grade ≥3, 41.3%) of ceritinib. AEs suspected to be study drug related and Grade 3/4 AEs suspected to be study drug related were more frequent among patients receiving ceritinib than patients in the pooled dataset.

Dose interruption and dose reductions for ceritinib occurred over the treatment period, with the highest percentage of dose interruption and dose reductions occurring between weeks 3 to 6 of treatment (24.9% and 17.5% respectively). In the ceritinib group, the most frequently reported reason for dose interruptions was AEs (95.3%), and primarily due to AEs of liver enzyme elevations. The dose reductions were primarily due to AEs of liver enzyme elevations and GI AEs. Many patients requiring dose adjustment, interruption or reduction.

The proportion of patients requiring at least one dose interruption was 78.3% for ceritinib. In the ceritinib group, the dose interruptions were primarily due to AEs of liver enzyme elevations while dose reductions were primarily due to AEs of liver enzyme elevations and GI AEs.

In line with the current safety profile of ceritinib, hepatotoxicity AEs regardless of study drug relationship were the second most frequently reported AESIs (>60% of patients treated with ceritinib in Study A2301 and pooled dataset), with majority of them being elevation of liver function tests. Grade 3/4 hepatotoxicity AEs regardless of study drug relationship were reported in 49.2% of patients in Study A2301 and in 37.8% of patients in pooled dataset. Also, elevations of liver enzymes were the only grade 3/4 AEs requiring dose adjustment or interruption that were more frequently reported (≥ 5% difference) in the Study A2301 ceritinib group vs. pooled dataset. The review of the overall safety profile of ceritinib in patients with hepatic impairment versus patients without hepatic impairment in Study A2301 did not reveal any clinically relevant differences or new safety concerns, and is consistent with the known safety profile of ceritinib.

The incidence of QT prolongation AEs in Study A2301 ceritinib group and pooled safety dataset was 11.1% and 10.8%, respectively; grade 3 QT prolongation AEs were reported in 2.1% of patients, there were no grade 4 QT prolongations AEs; AEs requiring discontinuation of ceritinib treatment were none in Study A2301 ceritinib group and 0.2% in pooled safety dataset. SAEs of QT prolongation were 0.5% in Study A2301 ceritinib group and 0.8% in pooled safety dataset. No torsade de pointes, sudden death, or deaths due to QT prolongation AEs were reported. No patients with QT prolongation had syncope/loss of consciousness.

QTcP increases of > 60 ms baseline were reported in 7.9% of patients in Study A2301 and 6.3% of patients in the pooled safety dataset. QTcP interval >500 ms was reported at similar frequencies in Study A2301 and the pooled safety dataset (2.6% and 1.3%, respectively).

An analysis of patients with a heart rate below 60 bpm as observed on the baseline ECG treated with ceritinib compared to the patients with a normal heart rate at baseline and treated with ceritinib, and compared to similar groups of patients in the pooled safety dataset did not reveal any clinically meaningful differences between the groups.

Hyperglycaemia events regardless of study drug relationship were reported in 13% of patients treated with ceritinib in Study A2301 and pooled dataset, of which were grade 3/4 AEs in 7-8% of patients. The hyperglycaemia events were managed by dose interruption or reduction. Post-baseline any grade increase of glucose was noted in approximately half of the patients in the Study A2301 ceritinib group and pooled dataset.

Creatinine elevations based on AEs regardless of study drug relationship were reported in 22% of patients treated with ceritinib in Study A2301 and pooled dataset. The AEs were managed by dose interruption or reduction. 69.0% of patients had creatinine increase of any grade post-baseline, of which 17 patients (1.8%) and one patient (0.1%) had grade 3 and grade 4 creatinine increase, respectively.

The frequency of any post-baseline grade changes in chemistry parameters was similar (≤10% difference) in Study A2301 ceritinib group and pooled dataset, except for decreased creatinine clearance, decreased glucose and increased potassium.

No new information has emerged based on post-marketing usage of Zykadia that would substantially alter

the known safety profile of ceritinib.

### 2.5.2. Conclusions on clinical safety

There are no new safety concerns that have been identified in the safety database. The safety and tolerability of ceritinib remain the same. However, sections 4.4 and 4.8 of the SmPC have been updated accordingly with the new frequencies based on the pooled safety dataset.

### 2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

## *2.6. Risk management plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 is acceptable.

The CHMP endorsed this advice with the following changes:

to also include the due dates of the planned interim and final analysis of overall survival (OS) from the study CLDK378A2303.

The applicant implemented the changes in the RMP as requested by CHMP.
The CHMP endorsed the Risk Management Plan version 10.0 with the following content:

### *Safety concerns*

| | |
|---|---|
| Important identified risks | Hepatotoxicity<br>QT prolongation<br>Interstitial Lung Disease/Pneumonitis<br>Hyperglycemia<br>GI toxicity (nausea, vomiting, diarrhea)<br>Bradycardia<br>Pancreatitis |
| Important potential risks | Neuropathy<br>Concomitant use of ceritinib and strong CYP3A inhibitors or strong CYP3A inducers |
| Missing information | Patients with hepatic impairment<br>Patients with severe renal impairment<br>Patients with severe cardiac impairment<br>Elderly patients<br>Paediatric patients<br>Pregnant and lactating women, and women of childbearing potential<br>Long-term safety<br>Concomitant use of ceritinib and CYP3A, CYP2C9, CYP2A6 or CYP2E1 substrates; ceritinib and drugs that may prolong the QT interval<br>Concomitant use of ceritinib and gastric acid reducing agents such as PPIs |

No changes to the summary of safety concerns were deemed necessary with the current application.

## *Pharmacovigilance plan*

**Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan**

| **Study / activity** Type, title and category (1-3) | **Objectives** | **Safety concerns addressed** | **Status** (planned, started) | **Date for submission of interim or final reports** (planned or actual) |
|---|---|---|---|---|
| LDK378A2110/ A Phase I, open label, multi-center, single dose study to evaluate the PK of ceritinib in subjects with hepatic impairment compared to subjects with normal hepatic function (3). | To evaluate the PK of a single oral dose of ceritinib in subjects with impaired hepatic function as compared to healthy subjects with normal hepatic function. | Use in patients with hepatic impairment | Started | Final study report Jun-2016 (planned) |
| LDK378A2103/ A Phase I, multi-center, open label, drug-drug interaction study to assess the effect of ceritinib on the pharmacokinetics of warfarin and midazolam administered as a two- drug cocktail in patients with ALK-positive advanced tumors including non-small cell lung cancer (3) | To assess the effect of ceritinib on the PK of warfarin and midazolam administered as a two-drug cocktail in patients with ALK-positive advanced tumors including NSCLC | Concomitant use of ceritinib and CYP2C9 and CYP3A substrates | Planned | Final study report Mar-2017 (planned) |
| LDK378A2113 / A Phase I, single center, open-label, two-period, single-sequence study to assess the effect of esomeprazole (proton pump inhibitor) on the pharmacokinetics of ceritinib in healthy volunteers (3) | To assess the effect of esomeprazole on the PK of a single 750 mg ceritinib in healthy adult subjects. | Concomitant use of ceritinib and gastric acid reducing agents such as PPIs | Planned | Final study report Mar-2016 – under EMA evaluation |

There are no changes proposed to the PhV plan within this procedure which is considered acceptable.

### *Risk minimisation measures*

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| Hepatotoxicity | Dose modification recommendations provided in SmPC Section 4.2 Posology and method of administration.<br>Description of frequency and severity of events, and guidelines on monitoring of liver laboratory tests (including ALT, AST and total bilirubin) prior to and after start of treatment are provided in SmPC Section 4.4 Special warnings and precautions for use.<br>Abnormal liver function tests (including hepatic function abnormal, hyperbilirubinaemia), hepatotoxicity (including DILI, hepatitis cholestatic, hepatocellular injury, hepatotoxicity), and Liver laboratory test abnormalities (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal) are listed as ADRs in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| QT prolongation | Dose modification recommendations in SmPC Section 4.2 Posology and method of administration.<br>SmPC Section 4.4 Special warnings and precautions for use provides recommendations on avoiding use of Zykadia in patients with congenital long QT syndrome; consideration of benefits and potential risks of ceritinib before beginning therapy in patients who have pre-existing bradycardia, history or predisposition for QTc prolongation, taking medicinal products known to prolong QT interval, and in patients with relevant pre-existing cardiac disease and/or electrolyte disturbance; and recommendation on periodic monitoring of ECGs and electrolytes in these patients. It also provides dose modification recommendations, correction of electrolytes as clinically indicated.<br>SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions: Provides caution with use in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation; recommendations for monitoring of QTc interval in case of combinations of such medicinal products.<br>Electrocardiogram QT prolonged is listed as an ADR in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Interstitial lung disease/ pneumonitis | Dose modification recommendations in SmPC Section 4.2 Posology and method of administration<br>Dose modification recommendations and guideline on periodic monitoring of pulmonary symptoms indicative of | None. |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| | pneumonitis in SmPC Section 4.4 Special warnings and precautions for use.<br>Pneumonitis (including ILD, pneumonitis) is listed as an ADR in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | |
| Hyperglycemia | Dose modification recommendations in SmPC Section 4.2 Posology and method of administration<br>SmPC Section 4.4 Special warnings and precautions for use provides details regarding the description of frequency and severity of events, guidance on monitoring of fasting glucose prior to and after start of Zykadia treatment, use of anti-hyperglycaemic medication, and risk of hyperglycaemia being higher in patients with diabetes mellitus and/or concurrent steroid use.<br>Hyperglycaemia is listed as an ADR in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| GI toxicity (nausea, vomiting, diarrhea) | Dose modification recommendations in SmPC Section 4.2 Posology and method of administration.<br>Description of frequency and severity of events, dose modification recommendations and recommendations for supportive treatment using standards of care in SmPC Section 4.4 Special Warnings and Precautions for use.<br>Nausea, vomiting, and diarrhea are listed as very common ADRs in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Bradycardia | Dose modification recommendations in SmPC Section 4.2 Posology and method of administration.<br>SmPC Section 4.4 Special warnings and precautions for use provides dose modification recommendations, guidelines on regular monitoring of heart rate and blood pressure, and instructions on avoiding use Zykadia in combination with other agents known to cause bradycardia.<br>Bradycardia (including bradycardia, sinus bradycardia) is listed as an ADR in SmPC Section 4.8 Undesirable effects. Description of events as observed in clinical trials is also presented in SmPC Section 4.8 Undesirable effects.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Pancreatitis | Dose modification recommendations are provided in SmPC Section 4.2 Posology and method of administration.<br>SmPC Section 4.4 Special warnings and precautions for use provides guidelines on periodic monitoring of lipase and | None |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| | amylase levels before and after the start of treatment with ceritinib.<br>Pancreatitis, lipase increased and amylase increased are listed as ADRs in SmPC Section 4.8 Undesirable effects | |
| Neuropathy | Currently available data do not support the need for risk minimization.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Concomitant use of ceritinib and strong CYP3A inhibitors or strong CYP3A inducers | SmPC Sections 4.2 and 4.5 provide recommendations to avoid concomitant use of strong CYP3A inhibitors during treatment with ceritinib. Dose modification guidelines provided, if concomitant use with strong CYP3A inhibitors cannot be avoided.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.<br>The Patient Leaflet provides detailed instructions to the patients on the drugs that may interact with ceritinib and to notify the doctor or pharmacist if using any of these drugs. | None. |
| Patients with hepatic impairment | SmPC Section 4.2 Posology and method of administration states that no dose adjustment is necessary in patients with mild hepatic impairment, and that ceritinib is not recommended in patients with moderate and severe hepatic impairment.<br>PK information in SmPC Section 5.2 Pharmacokinetic properties.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Patients with severe renal impairment | Caution of use in patients with severe renal impairment in SmPC Section 4.2 Posology and method of administration.<br>PK information in SmPC Section 5.2 Pharmacokinetic properties.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Patients with severe cardiac impairment | Currently available data do not support the need for risk minimization.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Elderly patients | Paucity of data and that no dose modification is required in this patient population is detailed in SmPC Section 4.2 Posology and method of administration.<br>SmPC Section 4.8 Undesirable effects that the safety profile in patients aged 65 years or older was similar to that in patients less than 65 years of age. There are no available data on patients over 85 years of age.<br>SmPC Section 5.2 Pharmacokinetic properties details that the PK analyses showed that age had no clinically meaningful influence on ceritinib exposure.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| Paediatric patients | SmPC Section 4.2 Posology and method of administration details that there is no data in this patient population.<br>SmPC Section 5.1 pharmacodynamics properties details that The European Medicines Agency has waived the obligation to submit the results of studies with Zykadia in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma).<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Pregnant and lactating women, and women of childbearing potential | Adequate information and guidance to help the prescriber and the patient is provided in Section 4.6 (Fertility, pregnancy, and lactation) of the SmPC.<br>Preclinical safety data on reproductive toxicology studies (i.e. embryo-foetal development studies) and the potential effects of ceritinib on fertility are detailed in SmPC Section 5.3 (Preclinical safety data).<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Long-term safety | Currently available data do not support the need for risk minimization.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |
| Concomitant use of ceritinib and CYP3A, CYP2C9, CYP2A6 or CYP2E1 substrates; ceritinib and drugs that may prolong the QT interval | Guidelines on periodic monitoring of ECGs and electrolytes in patients taking medications known to prolong QT interval in SmPC Section 4.4 Special warning and precaution for use<br>SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions cautions on the concomitant use.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.<br>The Patient Leaflet provides detailed instructions to the patients on the drugs that may interact with ceritinib and to notify the doctor or pharmacist if using any of these drugs. | None. |
| Concomitant use of ceritinib and gastric acid reducing agents such as PPIs | SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions states that gastric acid reducing agents may alter the solubility of ceritinib and reduce its bioavailability.<br>Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. | None. |

No changes to the risk minimisation measures were introduced with this procedure. Routine risk minimisation measures are considered adequate.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes introduced in the context of this application are not considered to have a relevant impact on the readability of the package leaflet.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The MAH has applied for a new indication for Zykadia the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Approximately 85% of all lung cancers are NSCLC, further divided into squamous and non-squamous (including adenocarcinoma). Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer. Frequency of ALK-positive NSCLC is low; present in approximately 2 to 7% of tumours, which represents about 60,000 patients annually worldwide.

### 3.1.2. Available therapies and unmet medical need

Currently approved first-line therapies for ALK-positive advanced NSCLC are either crizotinib or chemotherapy. Nevertheless, crizotinib has shown to significantly prolong the progression-free survival, offering more profound and durable responses than chemotherapy. OS data were not mature enough, but a positive trend was shown.

### 3.1.3. Main clinical studies

The pivotal study was a phase III (study A2301; ASCEND-4), open-label, randomised, active-controlled, global study of oral ceritinib (750 mg once daily, fasted) vs. standard first-line chemotherapy (platinum-based doublet with pemetrexed followed by pemetrexed maintenance in patients without progressive disease after 4 cycles) in adult patients with advanced or metastatic non-squamous NSCLC, harbouring an ALK rearrangement. Patients enrolled were previously not treated with any systemic anti-cancer therapy (including ALK inhibitor) with exception of patients that received neo-adjuvant or adjuvant therapy if progression/relapse had not occurred within 12 months after end of neo-adjuvant or adjuvant therapy. Crossover of patients in the chemotherapy treatment arm was allowed to ceritinib treatment arm in the extension treatment phase, only after BIRC-confirmed RECIST-defined PD was documented.

## *3.2. Favourable effects*

Study A2301 met its primary objective showing a statistically significant benefit of ceritinib over chemotherapy in delaying disease progression (PFS as per BIRC). Patients treated with ceritinib in first line ALK+ NSCLC obtained a median PFS gain of 8 months (16 months ceritinib vs 8 months chemotherapy) and with a HR of 0.55 (95% CI: 0.42, 0.73).

PFS results by investigator's assessment (secondary endpoint) offer similar results to the primary analysis based on BIRC (HR=0.49; 95% CI: 0.37, 0.64). The estimated median PFS was 16.8 months (95% CI: 13.5, 25.2) in the ceritinib arm vs. 7.2 months (95% CI: 5.8, 9.7) in chemotherapy.

The ORR by BIRC was higher in the ceritinib arm compared to the chemotherapy arm, i.e. 72.5% (95% CI 65.5, 78.7) ceritinib vs 26.7%(95% CI 20.5, 33.7) chemotherapy. Investigator-based ORR revealed similar results.

Tumour responses were durable; the median DOR per BIRC assessment was longer in patients treated with ceritinib (23.9 months; 95% CI: 16.6, NE) compared to patients treated with chemotherapy (11.1 months; 95% CI: 7.8, 16.4).

Intracranial response: In patients with measurable disease in the brain at baseline, ceritinib led to a greater improvement in OIRR than chemotherapy; 72.7% (95% CI: 49.8, 89.3, n= 16) vs. 27.3% (95% CI: 10.7, 50.2, n=6). Corresponding figures for those with measurable and/or non-measurable brain metastases were 46.3% (95% CI: 32.6, 60.4, n=25) vs. 21.2% (95% CI: 11.1, 34.7, n=11). The same trend was seen in those with and without prior radiotherapy. Additionally, in patients with measurable or non-measurable disease in the brain at baseline, a total of 11 patients in the ceritinib arm and 7 in the chemotherapy arm had CRs.

## *3.3. Uncertainties and limitations about favourable effects*

The superiority in progression free survival is expected to translate into a longer survival in patients treated with ceritinib in first line. However, despite the positive trend observed in the interim analysis OS (HR 0.73 95% CI: 0.50, 1.08;p=0.056), results did not reach statistical significance at the pre-specified one sided significance level of 0.0006. However, due to switch to subsequent anti-neoplastic therapies (109 out of 175 patients in ceritinib and 60% in the chemotherapy arm treated with ALK inhibitors after progression (crizotinib in 23 patients), statistically significant differences in the final OS analysis are not expected, which raises questions about the tumour's drug resistance. Further, PFS2 data is lacking and the impact of ceritinib on next line therapies remains unknown. In this regard, biopsies collected from patients that were enrolled in the trial, and consented, will be used for additional exploratory biomarker assessments and to explore acquired resistance to ceritinib. These studies will be carried out firstly on a genetic based approach. The results from these exploratory biomarker analyses will be submitted when available.

PROs questionnaires were completed by 80% of patients, overall in the majority of the time-points of the trial (Day 1 of each cycle). Results highlighted an improvement in overall health status over chemotherapy. However, due to the open-label design, and exploratory nature of these analyses, these results should be interpreted with caution.

Patients with WHO PS 2 were limited to around 6% of the total studied population. Efficacy data in terms of ORR seem comparable to those patients with a better performance status. Conversely, the duration of the response and the PFS are shorter in this subpopulation, slightly superior to chemotherapy though significantly inferior to WHO PS 0-1 ceritinib subsets.

## *3.4. Unfavourable effects*

The safety review is based primarily on the results of the Phase III Study A2301, comprising of 364 patients among whom all 189 randomized patients received ceritinib 750 mg once daily and 175/187 patients received chemotherapy.

The most frequently reported AEs regardless of study drug relationship (>25% of patients) in Study A2301 ceritinib group were: diarrhoea (84.7%), nausea (68.8%), vomiting (66.1%), ALT increased (60.3%), AST increased (52.9%), GGT increased (37.0%), blood ALP increased (29.1%), and decreased appetite and fatigue (33.9% and 29.1% patients, respectively). The most frequently reported grade 3/4 AEs regardless of study drug relationship (> 10% of patients) in the ceritinib group were elevations in liver enzymes - ALT increased (30.7%), GGT increased (28.6%), and AST increased (16.9%).

Incidence of AEs leading to discontinuation in Study A2301 ceritinib group and pooled dataset were 11.1% and 12.1%, respectively, grade 3-4 in severity were 6.3% and 9.4%, respectively.

The safety and tolerability profiles of ceritinib remain the same.

## *3.5. Uncertainties and limitations about unfavourable effects*

Dose interruption and dose reductions for ceritinib occurred over the treatment period, with the highest percentage of dose interruption and dose reductions occurring between weeks 3 to 6 of treatment (24.9% and 17.5% respectively). In the ceritinib group, the most frequently reported reason for dose interruptions was AEs (95.3%), and primarily due to AEs of liver enzyme elevations. The dose reductions were primarily due to AEs of liver enzyme elevations and GI AEs. Many patients requiring dose adjustment, interruption or reduction.

Among 152 patients with post-baseline ALT or AST elevation of grade 1 or higher based on laboratory tests in study A2301, more than 60% had the first occurrence within the first 6 weeks of treatment and then 25% in the next 6 weeks. Considering that most cases are found within the first three months, the SmPC advice has been revised to every 2 weeks for the first three months and monthly thereafter to early capture patients with elevations.

## *3.6. Effects Table*

**Table 43: Effects Table for Zykadia in first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) (data cut-off: 24-Jun-2016)**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PFS by BIRC | time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause. | Median (months) | 16.6 | 8.1 | Supported by several sensitivity analyses and by investigator's assessment. | |
| OS by BIRC | time from the date of randomization to death due to any cause | Median (months) | NE | 26.2 | Data not mature enough | |
| ORR by BIRC | proportion of patients with abest overall response (BOR) of complete response (CR) or partial response (PR) | % | 72.5 | 26.7 | Patients still on response at the data cut-off | |
| **Unfavourable Effects Study A2301** | | | | | | |
| AEs | | % | AEs 100%<br>G3/4= 78.3% | AEs 97.1%<br>G3/4= 61.7% | | |
| AEs suspected to be drug related | | % | AEs 97.4%<br>G3/4= 65.1% | AEs 89.1%<br>G3/4= 40.0% | | |
| SAEs | | % | AEs 37.0% | AEs 35.4% | | |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| | | | G3/4= 31.2% | G3/4= 30.3% | | |
| SAEs suspected to be drug related | | % | AEs 15.9%<br>G3/4= 12.2% | AEs 15.4%<br>G3/4= 12.6% | | |
| AEs leading to discontinuation | | % | AEs 11.1%<br>G3/4= 6.3% | AEs 16.6%<br>G3/4= 9.1% | | |
| AEs requiring dose adjustment or interruption | | % | AE 80.4%<br>G3/4 57.1% | AE 44.6%<br>G3/4 26.3% | | |
| All Deaths | | % | 5.8 | 3.4 | | |
| GI disorders(nausea, diarrhea, vomiting, and constipation) | | % | GI AEs 95.8%<br>G3/4= 15.3%<br><br>Diarrhea:84.7%<br>G3/4= 5.3%<br><br>Nausea 68.8%<br>G3/4= 2.6%<br><br>Vomiting 66.1%<br>G3/4= 5.3% | GI AEs 78.3%<br>G3/4= 9.1%<br><br>Diarrhea:10.9%<br>G3/4= 1.1%<br><br>Nausea 55.4%<br>G3/4= 5.1%<br><br>Vomiting 36.0%<br>G3/4= 5.7% | | |
| Hepatic enzyme elevations | | % | ALT AEs 60.3%<br>G3/4= 30.7%<br><br>AST AEs 52.9%<br>G3/4= 16.9%<br><br>GGT AEs 37.0%<br>G3/4= 28.6% | ALT AEs 21.7%<br>G3/4= 2.9%<br><br>AST AEs 19.4%<br>G3/4= 1.7%<br><br>GGT AEs 10.3%<br>G3/4= 1.7% | | |
| Blood ALP increased | | % | AE 29.1%<br>G3/4 7.4% | AE 4.6%<br>G3/4 0.6% | | |
| Hyperglycaemia | | % | AE 11.1%<br>G3/4 6.3% | AE 7.4%<br>G3/4 2.9% | | |
| ECG QT prolonged | | % | AEs11.1%<br>G3/4= 2.1% | AEs1.1%<br>G3/4= 0.6% | | |
| Cardiac disorders | | % | AE 14.8%<br>G3/4 4.2% | AE 10.3%<br>G3/4 2.9% | | |
| Blood And Lymphatic System Disorders | | % | AEs22.8%<br>G3/4= 3.2% | AEs49.7%<br>G3/4= 19.4% | | |

Abbreviations: AE: Adverse event; ALP: Alkaline Phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG Electrocardiogram; GGT Gamma-glutamyltransferase; GI Gastrointestinal; ILD Interstitial Lung Disease; SAE Serious adverse event

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Results from the ASCEND-4 study are considered robust, since several sensitivity and subgroup analyses (including the Per protocol Set) show consistent outcomes.

The benefit observed in terms of antitumour activity (higher and long-lasting responses) and the delay in disease progression in patients with NSCLC with ALK rearrangement is considered clinically meaningful. The median 8 months gain in PFS is highly clinically relevant. Survival results also favour ceritinib, which is reassuring, but due to the high cross-over to subsequent effective therapies, results did not reach statistical significance.

The use of chemotherapy as comparator, even though is appropriate from a regulatory perspective since it was considered SoC at the time of the initiation of the study, is not the most adequate from the current clinical perspective, where the use of ALK inhibitors in frontline is widely accepted in patients with ALK rearrangement. Nonetheless, the results from study 1014 with crizotinib appear comparable to the ceritinib outcomes from study A2301.

Given the high prevalence of brain metastases in ALK-positive advanced NSCLC patients (around 50%) and the low bioavailability of crizotinib (the only ALK inhibitor currently approved as first-line therapy in ALK-positive patients with advanced NSCLC) in the cerebrospinal fluid, the promising intracerebral efficacy results of ceritinib over chemotherapy is considered of added clinical value.

The safety of ceritinib seems acceptable and manageable.

### 3.7.2. Balance of benefits and risks

The evidence provided in support of the efficacy of ceritinib in the first line treatment of NSCLC patients with ALK rearrangement is considered robust and the differences observed over chemotherapy treatment are deemed clinically relevant. The effect is consistent with what has been observed with other ALK inhibitors in the same class of products. The benefits associated to ceritinib outweigh the toxicity and ADRs observed with the treatment, which are considered well known and overall manageable.

## *3.8. Conclusions*

The overall benefit risk balance of Zykadia is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of Indication to include new indication/population for Zykadia as first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC); as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect the information based primarily on the supporting study, CLDK378A2301 (ASCEND-4). The Package Leaflet is updated in accordance. The Risk Management Plan version 10.0 was agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan.