18 May 2017
EMA/367341/2017
Committee for Medicinal Products for Human use (CHMP)

Assessment report

Zykadia

International non-proprietary name: ceritinib

Procedure No. EMEA/H/C/003819/II/0010

Note

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

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 9 November 2016 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC based on safety and efficacy results of the primary analysis from the Specific Obligation study A2303 (SOB 004). The Package Leaflet and Labelling are updated accordingly. The Annex II and the Risk Management Plan are also proposed to be updated to reflect the potential fulfilment the only outstanding specific obligation and the efficacy and safety results of Study A2303, respectively.

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

1.2. Rationale for the proposed change

The European Commission granted conditional approval to Zykadia on 6 May 2015. Currently, only one of the two specific obligations agreed upon at the time of the initial conditional marketing authorisation is still outstanding, for which Novartis committed to submitting the final results of a study by September 2018:

"*In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy*" (SOB004, due date 30 September 2018).

With this Type II variation, the MAH provided an update on the results of the progression free survival (PFS) from the study A2303 (not the final results of the Study). The MAH, nevertheless, asked the CHMP whether the data provided can be considered to fulfil SOB004.

Annex II and the Risk Management Plan were proposed to be updated to reflect fulfilment of the only outstanding specific obligation and the efficacy and safety results of Study A2303, respectively.

2. Overall conclusion and impact on the benefit/risk balance

In the EU, Zykadia was granted conditional marketing authorisation on 6 May 2015 for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib, with the original dossier supplemented at Day 120 based on data from the Phase II Study A2201 and Study CLDK378A2203 (referred to as Study A2203) and updated data from the Phase I Study X2101.

On July 2016, the MAH submitted the final analysis of the study A2201. Results from this final analysis were in line with those previously known from the primary analysis. Both the outcome from primary endpoint and values from the secondary endpoints, were maintained.

The MAH has now submitted a clinical study report from study A2303, which could fulfil the remaining Specific Obligation in Annex II.

Study A2303 is a Phase III, global, randomized, open-label study of oral ceritinib (750 mg qd fasted) versus standard chemotherapy (pemetrexed/docetaxel) in adult patients with ALK positive NSCLC previously treated with chemotherapy and crizotinib.

The inclusion/exclusion criteria allowed the recruitment of patients with locally advanced or metastatic ALK-positive NSCLC, previously treated with crizotinib and one or two chemotherapy lines for advanced disease (including a platinum-based doublet).

In terms of primary endpoint (PFS by BIRC), the use of ceritinib is associated to a longer PFS, with a HR of 0.49 (95% CI 0.36, 0.67). The almost 4 months in the delay of tumour progression or death is considered clinically meaningful. Results for OS are not conclusive, with no differences between groups (HR 1.00 95%CI 0.67, 1.49). Objective Response Rate (ORR) was higher for those patients treated with ceritinib, with almost 40% of responders vs 7% in the chemotherapy arm.

Overall, the results from this phase III confirmatory trial are in line with those obtained from previous studies. ORR seems similar to response rate seen in the study A2201 (35.7%) and the median PFS by BIRC was 7.1 months in the A2201 trial and 5.4 months according to investigator's assessment.

From an efficacy perspective, data from the phase III study A2303, show a clinically meaningful result, both in terms of PFS and ORR.

OS data were immature at the time of the primary PFS analysis. With an event rate of 42% and 43% for ceritinib and chemotherapy arm respectively, no conclusive results in terms of OS were observed (HR 1.00 95% CI 0.67, 1.49). The high cross-over rate (65% of patients had crossed over to ceritinib arm along with the subsequent therapy with ALK inhibitors) likely impacted study results, however a sensitivity analysis carried out as an attempt to correct for crossover, showed similar results (HR 0.97, 95% CI 0.65, 1.45). The second OS interim analysis will not be available until the end of 2018 and final OS analysis is expected around May 2021. However, final OS data are not expected to modify the benefit/risk balance, given the likely absence of relevant findings in survival due to the high rate of crossover. For this reason, the final CSR is only requested as a recommendation for information and completeness.

The safety profile of ceritinib in patients with ALK-positive NSCLC characterised in study A2303 seems consistent with the known safety of ceritinib in this patient population. The adverse events (AEs) are manageable and reversible within the clinical setting with dose reduction/interruption and/or use of concomitant medication; only very few patients discontinued study treatment due to ceritinib associated AEs. No new safety signals or concerns have been identified in Study A2303 except one new ADR (weight decreased) and one additional term for the already existing ADR of liver laboratory test abnormalities was identified (i.e, GGT and ALP increased). In support of this risk assessment of ceritinib, the evaluation of the information received from the MAH global pharmacovigilance safety database until 10 August 2016 in 22 ongoing studies did not reveal any new safety concern or a change in frequency or severity of AEs, and does not suggest an update to the characterisation of the risks is needed. No new information has emerged based on post-marketing usage of ceritinib that would substantially alter the known safety profile. In conclusion, the safety data is consistent with the known safety profile of ceritinib. No untoward effects have been reported in ongoing trials and pharmacovigilance activities that would alter the established safety profile of ceritinib. Routine pharmacovigilance activities, including regular targeted follow-up, should continue to be performed.

In summary, results from the phase III study A2303, have shown a clinically meaningful result both in PFS and ORR. These results are in line with data from the previous studies which were the basis of the conditional MA and appear sufficient so as to positively conclude about the benefit/risk of ceritinib.

The MAH´s request to switch from a CMA to a full marketing authorisation based on the results presented is accepted. Since these are primarily PFS and ORR, a recommendation to present the two pending analyses for OS is proposed. This is based on the fact that no new safety concerns have been identified and that

results from the phase III trial (including the primary endpoint) are consistent with the efficacy results supporting the initial MA and by complementing the previously available data constitute comprehensive data for the currently approved indication.

In conclusion, the SOB004 could be considered fulfilled at this point in time as the primary analysis of the phase III study A2303 has been submitted, confirming the positive Benefit/Risk of ceritinib for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib. The clinical data package supporting the B/R of ceritinib can now be considered comprehensive even though final results for OS data are not yet available (secondary endpoint) and the Conditional marketing authorisation can be switched to a full MA.

The MAH should provide the results of the foreseen second interim analysis and final analysis for the secondary endpoint of overall survival which are expected by the end of 2018 (interim analysis) and 2022 (final OS analysis), respectively.

Scientific Summary for the EPAR

Please refer to the Scientific Discussion Zykadia EMEA/H/C/003819/II/0010

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC based on safety and efficacy results of the primary analysis from the Specific Obligation study A2303 (SOB 004). The Package Leaflet and Labelling are updated accordingly. The Annex II and the Risk Management Plan are also proposed to be updated to reflect the potential fulfilment the only outstanding specific obligation and the efficacy and safety results of Study A2303, respectively. SOB004 is considered fulfilled.

Furthermore, the CHMP is of the opinion that all specific obligations have been fulfilled following submission of the results of study A2303 and in light of the data generated and the evidence of compliance with the specific obligations, the CHMP recommends the granting of a marketing authorisation in accordance with Article 14(1) of Regulation No 726/2004.

☒ is recommended for approval.

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

Description	**Due date**
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.	30 September 2018

4. Scientific discussion

4.1. Introduction

Ceritinib was granted accelerated approval in the USA under the trade name of Zykadia on 29 Apr 2014 for the treatment of patients with ALK positive metastatic NSCLC who have progressed or are intolerant to crizotinib. In the EU/ European Economic Area, Zykadia was granted conditional marketing authorization on 6 May 2015 for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib, with the original dossier supplemented at Day 120 based on data from the Phase II Study A2201 and Study CLDK378A2203 (referred to as Study A2203) and updated data from the Phase I Study X2101. These data were also submitted to other countries worldwide. To date, Zykadia has been approved in more than 50 countries worldwide.

This clinical assessment report presents and discusses clinical data from the Phase III, multi-center, randomized, open-label, confirmatory Phase III Study CLDK378A2303 (referred to as Study A2303) supporting the use of ceritinib (LDK378, Zykadia) for the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed or are intolerant to crizotinib.

Study Purpose	Number of patients	Study details	Study status
[Study A2303] Confirmatory, randomized Phase III study	N=231 Ceritinib: n=115 Chemotherapy: n=116	A Phase III, global, randomized, open-label study of oral ceritinib (750 mg qd fasted) versus standard chemotherapy (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.	Ongoing, enrollment complete

Abbreviations: ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; qd = once daily

4.2. Clinical Efficacy aspects

Study CLDK378A2303. A Phase III, multi-center, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with anaplastic lymphoma kinase (ALK) rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) who have been treated previously with chemotherapy (platinum doublet) and crizotinib

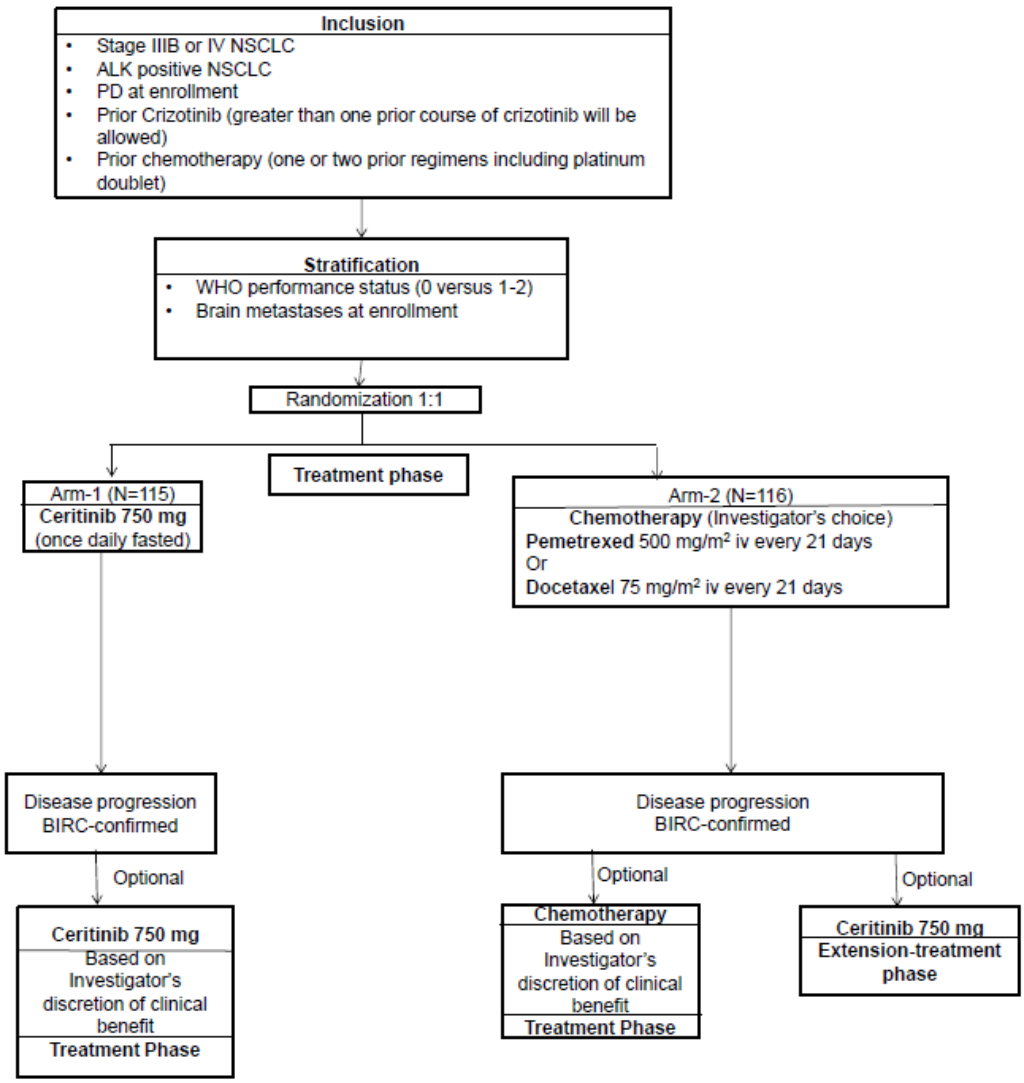


Figure 1 - Study design

4.2.1. Methods – analysis of data submitted

- **Study participants**

Main inclusion criteria

- Histologically or cytologically confirmed diagnosis of NSCLC carrying an ALK rearrangement as assessed by the FDA-approved FISH test using Vysis break-apart probes (Abbott Molecular Inc) test and scoring algorithm (including positivity criteria).
- Stage IIIB or IV NSCLC.
- World Health Organization performance status (PS) of 0-2.
- Patients who had received previous treatment with crizotinib for the treatment of locally advanced or metastatic NSCLC.
    - A minimum of 21 days of treatment with crizotinib was required to qualify as one prior course of crizotinib (unless crizotinib was discontinued due to PD after a shorter treatment course). Greater than one prior course of crizotinib was allowed.

- Patients might have had discontinued crizotinib therapy for disease progression, intolerance or other reason.
- No particular sequence of prior crizotinib and chemotherapy was required for enrollment, and either could comprise the last treatment received by the patient.

- Patients who had received one or two prior regimens (including platinum-based doublet) of cytotoxic chemotherapy to treat their locally advanced or metastatic NSCLC:
  - Prior therapy with bevacizumab was allowed if it was a component of the previous platinum-based regimen.
  - Prior maintenance therapy (e.g., bevacizumab, pemetrexed) was allowed if it was a component of the previous platinum-based regimen.
  - For chemotherapy regimens given every 21 or 28 days, a minimum of two cycles was required to qualify as a prior chemotherapy regimen (unless chemotherapy was discontinued due to PD after one cycle). If chemotherapy were discontinued for a reason other than PD after only one cycle, then this regimen did not count as a prior line of chemotherapy.
  - Prior cytotoxic chemotherapy was to include a platinum-based doublet.
  - If patients received two prior chemotherapy regimens, patients must not have received both pemetrexed and docetaxel.
  - No particular sequence of prior crizotinib and chemotherapy was required for enrollment, and either could comprise the last treatment received by the patient.
- Patients who had documented disease progression at study enrollment.
- At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion was counted as a target lesion only if there was clear sign of progression since the irradiation.

Main exclusion criteria

- Patients with symptomatic CNS metastases who were neurologically unstable or had required increasing doses of steroids within the two weeks prior to study entry to manage CNS symptoms.
- Prior therapy with other ALK-inhibitor investigational or approved agents with the exception of crizotinib.
- Prior systemic anti-cancer (including investigational) therapy aside from crizotinib and one-two regimens of previous cytotoxic chemotherapy for locally advanced or metastatic NSCLC.
- Patients who had thoracic radiotherapy to lung fields $\leqslant$ four 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 $\leqslant$ two weeks prior to starting the study treatment or patients who had not recovered from side effects of such procedure. Palliative radiotherapy for bone lesions $\leqslant$ two weeks prior to starting study treatment was allowed.
- Clinically significant, uncontrolled heart disease and/or recent cardiac event (within six months), such as:
  - Unstable angina within six months prior to Screening
  - Myocardial infarction within six months prior to Screening

- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ⩾ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ⩾ 100 mm Hg, with or without antihypertensive medication.
- Initiation or adjustment of antihypertensive medications was allowed prior to Screening
- Ventricular arrhythmias; supraventricular and nodal arrhythmias not controlled with medication
- Other cardiac arrhythmia not controlled with medication
- Corrected QT (QTc) >470 msec using Fridericia correction (QTcF) on the Screening ECG (as mean of triplicate)

- Patients treated with medications that met one of the following criteria and that could not be discontinued at least one week prior to the start of treatment with ceritinib and for the duration of the study:
  - Strong inhibitors or strong inducers of Cytochrome P450 (CYP) 3A4/5.
  - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9.
  - Medication with a known risk of prolonging the QT interval or inducing Tors ades de Pointes.

- **Treatments**

In this study, ceritinib was administered orally (fasted), once-daily at a planned dose of 750 mg. This dose was selected based on the results from the dose-escalation phase of the ongoing Phase I study X2101 wherein the maximum tolerated dose and recommended dose for the expansion phase were determined to be 750 mg once-daily fasted. This recommended dose 750 mg was used in subsequent Phase II and III studies. Pemetrexed and docetaxel was administered to the patient as per label instructions by the Investigator's designated staff.

Table 1: Dose and treatment schedule

	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 fasted (21-day cycle)
Arm 2	Pemetrexed	Solution reconstituted IV administration	500 mg/m^2 (iv infusion over 10 min)	Once every 21 days
	or			
	Docetaxel	Solution reconstituted IV administration	75 mg/m^2 (iv infusion over 1 hour)	Once every 21 days

CYP3A enzymes, thereby increasing the risk of reducing ceritinib drug exposure to sub-therapeutic levels. If possible, systemic corticosteroid treatment was not allowed during the study, except for: Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular); Stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g., for tumor associated symptoms) were permitted during the course of the study. The corticosteroid dose was stabilized (or decreasing) for at least five days before resuming the next dose of study treatment.

Concomitant treatment of ceritinib with weak inhibitors or inducers of CYP3A4/5 was permitted. Caution was advised when ceritinib was co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5. Duration of concomitant treatment was kept as short as possible, or completely avoided

whenever possible. Patients receiving such medications were monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and might require dose titration or adjustment. Co-administration of ceritinib with strong inhibitors or inducers of CYP3A4/5 was prohibited.

Concomitant treatment of ceritinib with medications known to be metabolized by CYP2C9 and CYP3A4 was allowed with caution, except for drugs which have narrow therapeutic index/sensitive substrates for this CYP isoform.

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors were allowed. However proton pump inhibitors were used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing ceritinib absorption. When the concurrent use of a H2-antagonist or an antacid with ceritinib was necessary, the H2 blocker was administered 10 hours before or two hours after the ceritinib dose, and the antacid was administered two hours before or two hours after the ceritinib dose

- **Objectives**

Primary objective

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

Secondary Objectives

To compare overall survival (OS) in patients treated with ceritinib versus chemotherapy

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

To assess the antitumor activity of ceritinib versus chemotherapy in the brain, as measured by overall intracranial response rate (OIRR), intracranial disease control rate (IDCR) and duration of intracranial response (DOIR), as determined by BIRC neuro-radiologist

PFS determined by Investigators.

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.

Pharmacokinetics (PK) of ceritinib

Exploratory objectives included exposure/response relationships including plasma concentration- QTc, and biomarker analysis. Exploratory biomarker analyses were not performed at the time of this CSR, and are planned to be performed subsequently and documented in a separate report.

- **Outcomes/endpoints**

Primary endpoint

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

The primary efficacy analysis was performed on the FAS according to the treatment arm and randomization strata (WHO performance status: 0 vs. 1-2; presence or absence of brain metastases) to which patients were assigned at randomization.

PFS and tumor response was assessed locally and by BIRC based on (RECIST) 1.1. Patients had to have at least one documented measurable lesion at study entry (by local assessment). Tumor evaluation was performed at baseline and then every six weeks (two cycles) after randomization during the first 18 months, and every nine weeks (three cycles) thereafter and at end of treatment (EOT) for response determination.

Intracranial efficacy was assessed by an independent central neuro-radiologist (intracranial BIRC) for all patients with known baseline brain metastasis using modified RECIST 1.1 (up to five target lesions allowed).

PFS was censored at the date of the last adequate tumor evaluation before the cut -off date or before the start of the new anticancer therapy date, whichever was earlier. Clinical deterioration was not considered as a qualifying event for progression. In particular, PFS was censored at the last adequate tumor assessment if one of the following occurred: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments.

Patients were treated until progression of disease (PD, BIRC assessed), unacceptable toxicity, or other discontinuation criteria were met (treatment phase). Patients randomized to chemotherapy (pemetrexed or docetaxel) treatment were allowed to cross-over to receive ceritinib treatment after BIRC-confirmed RECIST-defined PD (extension phase).

Table 2: Outcome and event dates for PFS and DOR analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of randomization [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given (including LDK378 for patients who crossover from the chemotherapy arm.)	Date of last adequate assessment	Censored

[a] The rare exception to this was if the patient died no later than the time of the second scheduled assessment as defined in the protocol in which case this was a PFS event at the date of death

Secondary endpoints

The key secondary endpoint, OS, was defined as the time from date of randomization 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. Patients who discontinued study treatment, were assessed for survival status every three months; OS follow-up will continue until the final OS analysis (when approximately 196 deaths are observed).

Other secondary endpoints included ORR, duration of response (DOR), DCR, time to response (TTR), OIRR, IDCR, DOIR and were evaluated by BIRC and Investigator assessment per RECIST 1.1, PFS by Investigator assessment per RECIST 1.1, and patient reported outcomes using the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30)/lung cancer specific questionnaire (LC13), lung cancer symptom scale (LCSS), and EuroQOL five dimensions index (EQ-5D) questionnaires

- **Sample size**

PFS

Under the assumption that the median PFS in the control arm was three months, it was expected that treatment with ceritinib would result in at least a 40% reduction in the hazard rate (corresponding to an increase in the median PFS from three months to five months under the exponential model assumption). Assuming that the true hazard ratio was 0.60 (under the alternative hypothesis), a total of 161 progression 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. Assuming a recruitment period of approximately 17 months, with a six-month accrual ramp-up period (where the accrual rate increases as additional sites initiate recruitment) followed by a steady accrual period (where the accrual rate stabilizes at a uniform rate of 15 patients/month after the first six months), along with an assumed 15% dropout rate, approximately 236 patients were needed to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions it was estimated that the 161st progression event would occur approximately 21 months from the date of when the first patient randomized in the study.

OS

With 196 deaths the study had 80% cumulative power to detect a hazard ratio of 0.667 using a log-rank test and a 3-look Lan-DeMets 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 8 months (Hanna et al 2004), a 33.3% reduction in hazard rate corresponded to an increase in median OS from 8 months to 12 months under the exponential model assumption.

- **Randomisation**

Randomization (1:1) was stratified by:

World health Organization performance status: 0 vs. 1-2.

Brain metastases at Screening: presence vs. absence.

- **Blinding (masking)**

This is an open label study

- **Statistical methods**

Analysis sets

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

The Per-Protocol Set (PPS) consisted of a subset of patients in the FAS who had an adequate tumor assessment by Investigator at Baseline, a follow-up tumor assessment by Investigator greater than five weeks after starting treatment (unless disease progression assessed by Investigator or death was observed before that time), 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.

The Cross-over Analysis set consisted of patients randomized to the chemotherapy arm 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.

Statistical hypothesis, model, and method of analysis

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 and Crowley 1982. Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (including at least 3, 6, 12, 18 and 24 months) were summarized. The CIs were constructed using Greenwood's formula (Kalbfleisch and Prentice 2002) for the standard error of the Kaplan-Meier estimate. The Kaplan-Meier curves were displayed by treatment.

PFS was tested using the stratified log-rank test (stratified according to randomization 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 favor of the ceritinib arm. A Cox regression model stratified by randomization stratification factors was used to estimate the HR of PFS, along with 95% CI based on the Wald test.

Interim analysis

No interim analysis was planned for PFS.

Three analyses were planned for OS: 1) an interim analysis at the projected time of the final analysis for PFS (provided PFS is significant); 2) an additional interim analysis when approximately 171 deaths were observed; 3) a final analysis for OS when approximately 196 deaths were observed.

An α-spending function for OS according to Lan-DeMets (O'Brien-Fleming) along with the testing strategy outlined below was to be used to maintain the overall type-I error rate (Lan and DeMets 1983). This guaranteed the protection of the overall level α=2.5% across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm 2010). The trial allowed for the stopping of the study for a superior OS result, provided the primary endpoint PFS had already been shown to be statistically significant favoring the ceritinib treatment arm. Further, the exact nominal p-values that was needed to be observed to declare statistical significance at the time of these analyses for OS depended on the number of OS events that had been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

If OS was tested alone, independent of the testing strategy for PFS,. At the time of final PFS analyses, both PFS and interim OS analysis were performed by the Sponsor's clinical team. All patients continued to be followed for OS until the final OS analysis (or earlier if OS reached statistical significance at any of the interim analysis).

Results

- **Participant flow**

Overall, 326 patients were screened, of which 95 (29.1%) patients did not complete the Screening phase. Of the 95 patients who did not complete the screening, 84 patients failed the screening, six patients died, and five patients were not randomized due to the physician's or patient's decision. A total of 231 patients completed the Screening phase and were randomized into the treatment phase.

Disposition/ reason	Ceritinib 750 mg N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
Patients randomized			
Untreated	0	3 (2.6)	3 (1.3)
Treated	115 (100)	113 (97.4)	228 (98.7)
Treatment phase			
Ongoing[a]	33 (28.7)	8 (6.9)	41 (17.7)
Discontinued from treatment phase	82 (71.3)	108 (93.1)	190 (82.3)
Entered extension treatment phase	0	74 (63.8)	74 (32.0)
Entered post-treatment follow-up phase	7 (6.1)	5 (4.3)	12 (5.2)
Entered survival follow-up phase	61 (53.0)	19 (16.4)	80 (34.6)
Discontinued from study	14 (12.2)	10 (8.6)	24 (10.4)
Primary reason for discontinuation from treatment phase			
Adverse event	6 (5.2)	8 (6.9)	14 (6.1)
Death	9 (7.8)	5 (4.3)	14 (6.1)
Physician decision[c]	5 (4.3)	5 (4.3)	10 (4.3)
Progressive disease	56 (48.7)	82 (70.7)	138 (59.7)
Subject/guardian decision	6 (5.2)	8 (6.9)	14 (6.1)
Post-treatment follow-up phase			
Ongoing[a]	1 (0.9)	1 (0.9)	2 (0.9)
Discontinued post-treatment follow-up phase	6 (5.2)	4 (3.4)	10 (4.3)
Entered extension treatment phase after discontinuation from post-treatment follow-up phase	0	1 (0.9)	1 (0.4)
Entered survival follow-up phase after discontinuation from post treatment follow-up phase	1 (0.9)	3 (2.6)	4 (1.7)
Discontinued from study	5 (4.3)	0	5 (2.2)
Primary reason for discontinuation from post-treatment phase			
Adverse event	0	1 (0.9)	1 (0.4)
Death	3 (2.6)	0	3 (1.3)
Lost to follow-up	2 (1.7)	0	2 (0.9)
Physician decision	0	1 (0.9)	1 (0.4)
Progressive disease	1 (0.9)	1 (0.9)	2 (0.9)
Subject/guardian decision	0	1 (0.9)	1 (0.4)
Extension treatment phase[b]			
Ongoing[a]	0	28 (24.1)	28 (12.1)
Discontinued extension treatment phase	0	47 (40.5)	47 (20.3)
Entered survival follow-up phase after discontinuation from extension treatment phase	0	28 (24.1)	28 (12.1)
Discontinued from study	0	19 (16.4)	19 (8.2)
Primary reason for discontinuation from extension treatment phase			
Adverse event	0	3 (2.6)	3 (1.3)
Death	0	15 (12.9)	15 (6.5)
Physician decision	0	1 (0.9)	1 (0.4)
Progressive disease	0	24 (20.7)	24 (10.4)
Subject/guardian decision	0	4 (3.4)	4 (1.7)

[a] Patients ongoing at the time of the cut-off 26-Jan-2016.
[b] Extension treatment phase is for patients who crossed-over from chemotherapy to ceritinib treatment.
[c] Includes eight patients with local disease progression by RECIST not confirmed by BIRC, or clinical disease progression.
Percentage is based on N.
Reasons for discontinuations are based on the 'End of Treatment Phase Disposition', 'End of Extension Treatment Phase Disposition' and 'Post-treatment Phase completion' CRF pages.

- **Recruitment**

This study is being conducted in 99 centers across 20 countries. Betwe en 2-Jul-2013 and 2-Nov- 2015, a total of 231 patients with advanced ALK-positive NSCLC were randomized to either ceritinib (n=115) or chemotherapy (n=116), stratified by WHO performance status [“0”: n=109 (47.2%); “1-2”: n=122 (52.8%)] and brain metastases at Screening [“Absence”: n=99 (42.9%); “Presence”: n=132 (57.1%)]. The cut-off date for this primary analysis was 26-Jan-2016 when 172 PFS events had been documented by BIRC and all randomized patients had completed at least 12 weeks of follow-up or had discontinued earlier. The analyses are presented using data locked on 22-Apr-2016. The study is ongoing.

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

- **Conduct of the study**

The study protocol was amended four times.

Amendment 1 (27-Aug-2013). At the time of the release of this amendment, two patients had been screened for enrollment and treated. The amendment had been implemented to address the availability of new safety data, to amend the eligible study population, and to clarify sections of the protocol where additional guidance was required.

Amendment 2 (20-May-2014). At the time of the release of this amendment, 88 patients had been screened for enrollment and 67 patients had been randomized. This amendment was updated to change prior one platinum-based doublet to one or two prior chemotherapy regimens (including one platinum-based doublet). It was implemented to expand the inclusion criteria to allow for one or two prior regimens of cytotoxic chemotherapy (one regimen must include a platinum-based doublet) for the treatment of locally advanced or metastatic ALK - positive NSCLC and to allow more than one course of prior crizotinib treatment. Additional amendment items include updated safety information and clarification of sections of the protocol where additional guidance was required. Also clarified that no particular sequence of prior crizotinib and chemotherapy was required for enrollment, and either could comprise the last treatment received by the patient.

Amendment 3 (23-Apr-2015). At the time of the release of this amendment, 257 patients had been screened for enrollment and 191 patients had been randomized. Included the following key items: Delete the requirement for patients randomized to the chemotherapy arm to wait 31 days before crossing over to the ceritinib treatment arm and provided guidance on ceritinib treatment initiation for cross-over patients to allow patients to cross-over earlier if eligible. The time window for cross-over to ceritinib treatment arm was increased from 56 days to 84 days, to allow for resolution of any AEs to grade $\leqslant$ 1 (CTCAE v 4.03). In addition, patients who had a WHO performance status above two or a history of interstitial lung disease or interstitial pneumonitis was not allowed to cross-over. Remove “start of new anti-cancer therapy” as an allowable reason to stop collecting tumor assessments to enable sensitivity analysis of PFS following a pure intent -to-treat principle where start of new antineoplastic therapy did not result in censoring for PFS. Include an additional condition for the final analysis of PFS, requiring that all randomized patients had to complete at least 12 weeks of follow-up or had discontinued earlier.

Amendment 4 (11-Dec-2015). As of 18 November 2015, 327 patients had been screened for enrollment and 231 patients had been randomized. The primary purpose of this amendment provides 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.

At least one protocol deviation was reported in 48.7% of patients in the ceritinib arm and 47.4% of patients in the chemotherapy arm.

Table 3: Protocol deviations leading to exclusion from Per-Protocol Set by treatment arm (FAS)

Protocol deviation	Ceritinib 750 mg N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
Patients with at least one protocol deviation	2 (1.7)	3 (2.6)	5 (2.2)
Selection criteria not met	2 (1.7)	3 (2.6)	5 (2.2)
Patient was ALK translocation negative per FDA-approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc) test and scoring algorithm prior to first dose	1 (0.9)	2 (1.7)	3 (1.3)
Patient has received systemic anti- cancer therapy (incl. investigational) aside from crizotinib and more than 2 regimens of cytotoxic chemotherapy for local advanced or metastatic NSCLC.	0	1 (0.9)	1 (0.4)
Patient was not treated with or received less than 2 cycles (unless chemotherapy was discontinued due to progressive disease after 1 cycle) of previous platinum-based doublet, cytotoxic chemotherapy	1 (0.9)	0	1 (0.4)

- **Baseline data**

The demographic characteristics of the patients in this study were consistent with those observed in patients with ALK-positive advanced NSCLC previously treated with multiple lines of therapy. The two treatment arms were well-balanced for the demographic characteristics except for race (70.4% vs. 58.6% Caucasian in the ceritinib arm vs. the chemotherapy arm, respectively) and ex-smokers (33.9% vs. 44.0% in the ceritinib arm vs. the chemotherapy arm, respectively).

The disease characteristics of patients in this study were representative of the population of ALK-positive advanced NSCLC patients previously treated with multiple lines of therapy including crizotinib. Baseline disease characteristics were well-balanced between the two treatment arms.

All except two patients (0.9%) had metastatic disease at study entry (two patients had Stage IIIB disease at study entry), with a metastatic pattern typical of patients with NSCLC. The most frequent metastasis sites were similar between treatment arms with lung metastases (100% vs. 99.1%), brain metastases (56.5% vs. 59.5%), bone metastases (53.9% vs. 50.9%), lymph nodes metastases (51.3% vs. 53.4%) in the ceritinib arm vs. chemotherapy arm, respectively

Table 4: Demographics by treatment arm (FAS)

Demographic variable	Ceritinib 750 mg N=115	Chemotherapy N=116	All patients N=231
Age (years)			
N	115	116	231
Mean	53.1	54.4	53.7
SD	11.96	11.61	11.78
Median	54.0	54.0	54.0
Minimum	30	28	28
Maximum	77	84	84
Age category (years) -n (%)			
<65	89 (77.4)	89 (76.7)	178 (77.1)
≥ 65	26 (22.6)	27 (23.3)	53 (22.9)
Sex -n (%)			
Female	68 (59.1)	61 (52.6)	129 (55.8)
Male	47 (40.9)	55 (47.4)	102 (44.2)
Race -n (%)			
Asian	30 (26.1)	38 (32.8)	68 (29.4)
Black	0	1 (0.9)	1 (0.4)
Caucasian	81 (70.4)	68 (58.6)	149 (64.5)
Other	2 (1.7)	4 (3.4)	6 (2.6)
Unknown	2 (1.7)	5 (4.3)	7 (3.0)
Body surface area (m^2)			
N	106	115	221
Mean	1.765	1.771	1.768
SD	0.2160	0.2473	0.2323
Median	1.750	1.740	1.750
Minimum	1.29	1.32	1.29
Maximum	2.35	2.46	2.46
Body mass index (kg/m^2)			
N	113	116	229
Mean	25.170	24.907	25.037
SD	5.0734	4.7555	4.9059
Median	24.977	24.376	24.562
Minimum	17.30	15.39	15.39
Maximum	41.52	40.51	41.52
WHO performance status -n (%)[a]			
0	56 (48.7)	51 (44.0)	107 (46.3)
1	50 (43.5)	60 (51.7)	110 (47.6)
2	9 (7.8)	5 (4.3)	14 (6.1)
Smoking history -n (%)			
Current smoker	4 (3.5)	1 (0.9)	5 (2.2)
Ex-smoker	39 (33.9)	51 (44.0)	90 (39.0)
Never smoked	71 (61.7)	61 (52.6)	132 (57.1)
Missing	1 (0.9)	3 (2.6)	4 (1.7)

Body Mass Index: BMI [kg/m^2]=weight [kg] / (height [m]**2)
[a] WHO PS is based on data from CRF

Table 5: Disease characteristics by treatment arm (FAS)

Disease characteristics	Ceritinib 750 mg N=115	Chemotherapy N=116	All patients N=231
Primary site of cancer – n (%)			
Lung	115 (100)	116 (100)	231 (100)
Histology/Cytology – n (%)			
Adenocarcinoma	111 (96.5)	113 (97.4)	224 (97.0)
Squamous cell carcinoma	0	2 (1.7)	2 (0.9)
Undifferentiated carcinoma	3 (2.6)	1 (0.9)	4 (1.7)
Other	1 (0.9)	0	1 (0.4)
Histological grade – n (%)			
Well differentiated	9 (7.8)	10 (8.6)	19 (8.2)
Moderately differentiated	12 (10.4)	10 (8.6)	22 (9.5)
Poorly differentiated	24 (20.9)	34 (29.3)	58 (25.1)
Undifferentiated	2 (1.7)	1 (0.9)	3 (1.3)
Unknown	68 (59.1)	61 (52.6)	129 (55.8)
Metastatic site of cancer – n (%)[a]			
Adrenal	12 (10.4)	10 (8.6)	22 (9.5)
Bone	62 (53.9)	59 (50.9)	121 (52.4)
Brain	65 (56.5)	69 (59.5)	134 (58.0)
Kidney	2 (1.7)	5 (4.3)	7 (3.0)
Liver	44 (38.3)	38 (32.8)	82 (35.5)
Lung	115 (100)	115 (99.1)	230 (99.6)
Pleura	40 (34.8)	41 (35.3)	81 (35.1)
Soft tissue	5 (4.3)	0	5 (2.2)
Lymph nodes	59 (51.3)	62 (53.4)	121 (52.4)
Metastatic	9 (7.8)	9 (7.8)	18 (7.8)
Local	36 (31.3)	42 (36.2)	78 (33.8)

Disease characteristics	Ceritinib 750 mg N=115	Chemotherapy N=116	All patients N=231
Other	26 (22.6)	30 (25.9)	56 (24.2)
Other	28 (24.3)	22 (19.0)	50 (21.6)
Stage at initial diagnosis – n (%)			
I	1 (0.9)	0	1 (0.4)
IA	1 (0.9)	1 (0.9)	2 (0.9)
II	0	1 (0.9)	1 (0.4)
IIA	1 (0.9)	2 (1.7)	3 (1.3)
IIB	1 (0.9)	2 (1.7)	3 (1.3)
III	0	2 (1.7)	2 (0.9)
IIIA	7 (6.1)	10 (8.6)	17 (7.4)
IIIB	7 (6.1)	3 (2.6)	10 (4.3)
IV	97 (84.3)	95 (81.9)	192 (83.1)
Stage at time of study entry – n (%)			
IIIB	1 (0.9)	1 (0.9)	2 (0.9)
IV	114 (99.1)	115 (99.1)	229 (99.1)
Time from initial diagnosis of primary site to randomization (months)			
N	115	116	231
Mean	24.1	24.9	24.5
SD	20.4	18.8	19.6
Median	19.4	19.8	19.5
Minimum	5.5	6.5	5.5
Maximum	153.3	115.9	153.3
Time from initial diagnosis to first recurrence/progression prior to randomization (months)			
N	114	113	227
Mean	11.6	12.0	11.8
SD	16.8	14.4	15.6
Median	8.3	8.0	8.1
Minimum	0.2	0.5	0.2
Maximum	122.2	94.6	122.2
Time from most recent relapse/progression to randomization (months)			
N	115	116	231
Mean	1.0	1.2	1.1
SD	0.67	1.43	1.12
Median	0.8	0.8	0.8
Minimum	0.1	0.1	0.1
Maximum	4.8	11.1	11.1
Type of Lesion at baseline based on Investigator assessment, n (%)			
Target only	7 (6.1)	6 (5.2)	13 (5.6)
Non-target only	1 (0.9)	0	1 (0.4)
Both target and non-target	107 (93.0)	110 (94.8)	217 (93.9)
Type of Lesion at baseline based on BIRC assessment, n (%)			
Target only	2 (1.7)	2 (1.7)	4 (1.7)
Non-target only	11 (9.6)	12 (10.3)	23 (10.0)
Both target and non-target	102 (88.7)	101 (87.1)	203 (87.9)
Unknown	0	1 (0.9)	1 (0.4)
Disease burden (sum of diameters for target lesions) at baseline based on BIRC assessment (mm)			
N	104	103	207
Mean	52.1	51.3	51.7
SD	33.5	34.8	34.1
Median	42.5	42.0	42.0
Minimum	11.0	11.0	11.0
Maximum	180.0	191.0	191.0

[a] Metastatic sites involved are derived from CRF page of diagnosis and extent of cancer.

All patients were treated with at least one prior regimen of crizotinib for advanced disease as per the inclusion criteria, of which three (1.3%) patients had received crizotinib more than once. A total of 189 (81.8%) patients took crizotinib as their last treatment prior to study enrollment. All patients except one (protocol deviation, excluded from the PPS) received chemotherapy including platinum-based doublet for

advanced NSCLC as per the inclusion criteria; 11.7% of all patients had two prior lines of chemotherapy for advanced disease and no patient received greater than two lines of prior chemotherapy for advanced disease. All patients had disease progression prior to study entry.

Table 6: Prior antineoplastic therapy – Overall, by treatment arm (FAS)

Antineoplastic Therapy	Ceritinib N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
Any therapy	115 (100)	116 (100)	231 (100)
Any surgery	35 (30.4)	33 (28.4)	68 (29.4)
Any radiotherapy	61 (53.0)	67 (57.8)	128 (55.4)
Radiotherapy to the brain	41 (35.7)	42 (36.2)	83 (35.9)
Any chemotherapy[a]			
Neo-adjuvant setting	3 (2.6)	1 (0.9)	4 (1.7)
Adjuvant setting	5 (4.3)	9 (7.8)	14 (6.1)
Advanced disease[b]	112 (97.4)	113 (97.4)	225 (97.4)[c]
Crizotinib	115 (100)	116 (100)	231 (100)
>1 prior regimen	1 (0.9)	2 (1.7)	3 (1.3)
As last treatment	94 (81.7)	95 (81.9)	189 (81.8)
Best response = CR-n%	3 (2.6)	2 (1.7)	5 (2.2)
Best response = PR-n%	51 (44.3)	40 (34.5)	91 (39.4)
Best response = PD-n%	16 (13.9)	19 (16.4)	35 (15.2)
Best response = SD-n%	25 (21.7)	30 (25.9)	55 (23.8)
Best response = Other response-n%[d]	1 (0.9)	1 (0.9)	2 (0.8)
Best response = Not applicable-n%	11 (9.6)	12 (10.3)	23 (10.0)
Best response = None-n%	1 (0.9)	0	1 (0.4)
Unknown response n%	7 (6.1)	12 (10.3)	19 (8.2)
Number of prior systemic therapy regimens			
Any setting (including neo-/adjuvant)			
1	1 (0.9)[e]	0	1 (0.4)
2	98 (85.2)	95 (81.9)	193 (83.5)
3	15 (13.0)	18 (15.5)	33 (14.3)
>3	1 (0.9)	3 (2.6)	4 (1.7)

Antineoplastic Therapy	Ceritinib N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
In advanced disease[b]			
1	3 (2.6)	3 (2.6)	6 (2.6)[c]
2	98 (85.2)	96 (82.8)	194 (84.0)
3	13 (11.3)	15 (12.9)	28 (12.1)
>3	1 (0.9)	2 (1.7)	3 (1.3)
Number of prior chemotherapy regimens			
Any setting (including neo-/adjuvant)			
0	1 (0.9)[e]	0	1 (0.4)
1	99 (86.1)	99 (85.3)	198 (85.7)
2	15 (13.0)	16 (13.8)	31 (13.4)
3	0	1 (0.9)	1 (0.4)
In advanced disease[b]			
0	3 (2.6)[e]	3 (2.6)	6 (2.6)[c]
1	99 (86.1)	99 (85.3)	198 (85.7)
2	13 (11.3)	14 (12.1)	27 (11.7)
Prior anti-cancer medications			
Bevacizumab	12 (10.4)	19 (16.4)	31 (13.4)
Carboplatin	48 (41.7)	50 (43.1)	98 (42.4)
Cisplatin	76 (66.1)	71 (61.2)	147 (63.6)
Crizotinib	115 (100)	116 (100)	231 (100)
Docetaxel	4 (3.5)	5 (4.3)	9 (3.9)
Erlotinib	0	3 (2.6)	3 (1.3)
Etoposide	2 (1.7)	1 (0.9)	3 (1.3)
Gefitinib	1 (0.9)	1 (0.9)	2 (0.9)
Gemcitabine	16 (13.9)	23 (19.8)	39 (16.9)
Investigational drug	2 (1.7)	1 (0.9)	3 (1.3)
Irinotecan	0	1 (0.9)	1 (0.4)
Paclitaxel	13 (11.3)	20 (17.2)	33 (14.3)
Pemetrexed	82 (71.3)	81 (69.8)	163 (70.6)
Vinorelbine	11 (9.6)	8 (6.9)	19 (8.2)
Prior platinum-based doublet therapies			
Any setting (including neo-/adjuvant)	114 (99.1)[f]	116 (100)	230 (99.6)
cisplatin or carboplatin + pemetrexed	80 (69.6)	76 (65.5)	156 (67.5)
cisplatin or carboplatin + paclitaxel	13 (11.3)	19 (16.4)	32 (13.9)
cisplatin or carboplatin + docetaxel	2 (1.7)	4 (3.4)	6 (2.6)
cisplatin or carboplatin + gemcitabine	14 (12.2)	22 (19.0)	36 (15.6)
cisplatin or carboplatin + vinorelbine	10 (8.7)	6 (5.2)	16 (6.9)
cisplatin or carboplatin + other[g]	2 (1.7)	2 (1.7)	4 (1.7)
In advanced disease[b]	111 (96.5)	113 (97.4)	224 (97.0)[h]
cisplatin or carboplatin + pemetrexed	78 (67.8)	76 (65.5)	154 (66.7)
cisplatin or carboplatin + paclitaxel	13 (11.3)	18 (15.5)	31 (13.4)
cisplatin or carboplatin + docetaxel	2 (1.7)	1 (0.9)	3 (1.3)
cisplatin or carboplatin + gemcitabine	14 (12.2)	20 (17.2)	34 (14.7)
cisplatin or carboplatin + vinorelbine	8 (7.0)	5 (4.3)	13 (5.6)
cisplatin or carboplatin + other[g]	2 (1.7)	1 (0.9)	3 (1.3)

CR=complete response, PR=partial response, PD=progressive disease, SD= stable disease
[a] A patient may have received prior therapy in multiple settings.
[b] Includes therapeutic, metastatic or palliative setting and neo-/adjuvant setting with relapse ≤ 12 months from end of therapy
[c] 5 out of 6 patients with "0" chemotherapy regimen in the metastatic setting were confirmed after database lock to have received chemotherapy for metastatic disease (not protocol deviations) and one patient in the ceritinib arm had no prior chemotherapy which was a protocol deviation (excluded from Per-Protocol Set)
[d] Other responses includes major and moderate responses
[e] Includes one patient who had no prior chemotherapy and which was a protocol deviation.
[f] Excludes one patient who had no prior chemotherapy and which was a protocol deviation.
[g] Other includes etoposide and irinotecan.
[h] 6/7 patients with "0" platinum-based chemotherapy regimen in the metastatic setting were confirmed after database lock to have received the treatment for metastatic disease (not protocol deviations) and one patient in the ceritinib arm had no prior chemotherapy which was a protocol deviation (excluded from Per-Protocol set).
Any prior antineoplastic therapy includes patients who have had medication, radiotherapy or surgery
Prior surgery=Yes, excludes diagnostic biopsies.

- **Numbers analysed**

Table 7: Analysis sets by treatment arm and stratum

Analysis set		Ceritinib 750 mg N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
Full Analysis Set		**115 (100)**	**116 (100)**	**231 (100)**
WHO performance status	Brain metastases			
0	Absence	28 (24.3)	27 (23.3)	55 (23.8)
0	Presence	26 (22.6)	28 (24.1)	54 (23.4)
1-2	Absence	22 (19.1)	22 (19.0)	44 (19.0)
1-2	Presence	39 (33.9)	39 (33.6)	78 (33.8)
Safety Set		**115 (100)**	**113 (97.4)**	**228 (98.7)**
WHO performance status	Brain metastases			
0	Absence	28 (24.3)	27 (23.3)	55 (23.8)
0	Presence	26 (22.6)	28 (24.1)	54 (23.4)
1-2	Absence	22 (19.1)	21 (18.1)	43 (18.6)
1-2	Presence	39 (33.9)	37 (31.9)	76 (32.9)
Per-Protocol Set		**112 (97.4)**	**108 (93.1)**	**220 (95.2)**
WHO performance status	Brain metastases			
0	Absence	27 (23.5)	26 (22.4)	53 (22.9)
0	Presence	25 (21.7)	27 (23.3)	52 (22.5)
1-2	Absence	22 (19.1)	20 (17.2)	42 (18.2)
1-2	Presence	38 (33.0)	35 (30.2)	73 (31.6)
Pharmacokinetic Analysis Set		**107 (93.0)**	**0**	**107 (46.3)**
WHO performance status	Brain metastases			
0	Absence	27 (23.5)	0	27 (11.7)
0	Presence	24 (20.9)	0	24 (10.4)
1-2	Absence	20 (17.4)	0	20 (8.7)
1-2	Presence	36 (31.3)	0	36 (15.6)
Cross-over Analysis Set		**0**	**74 (63.8)**	**74 (32.0)**

Strata information is from IRT. Full Analysis Set includes all patients to whom study treatment has been assigned by randomization.

- **Outcomes and estimation**

A summary overview of key efficacy results by BIRC and Investigator assessment is provided.

Table 8: Efficacy results by BIRC and Investigator assessment and by treatment arm (FAS)

Efficacy parameter	Ceritinib N=115	Chemotherapy N=116		
Primary analysis endpoint				
Progression-free survival (BIRC) (median; 95% CI) (months)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)	Log-rank test p-value <0.001	Cox model HR (95% CI) 0.49 (0.36,0.67)
Key secondary analysis endpoint				
Overall survival (median; 95% CI) (months)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)	Log-rank test p-value 0.496	Cox model HR (95% CI) 1.00 (0.67,1.49)
Other secondary analysis endpoints				
Progression-free survival (Investigator) (median; 95% CI) (months)	6.7 (4.4, 7.9)	1.6 (1.4, 2.6)	Log-rank test p-value <0.001	Cox model HR (95% CI) 0.40 (0.29, 0.54)

	Ceritinib N=115		Chemotherapy N=116	
	BIRC	Investigator	BIRC	Investigator
Overall Response Rate (CR+PR): % (95% CI)	39.1, (30.2, 48.7)	42.6 (33.4, 52.2)	6.9 (3.0, 13.1)	6.0 (2.5, 12.0)
DCR: % (95% CI)	76.5 (67.7, 83.9)	80.0; (71.5, 86.9)	36.2 (27.5, 45.6)	37.9 (29.1, 47.4)
Time to response (median; range), weeks[a]	N=45 6.7 (5.3 to 52.3)	N=49 6.4 (4.9 to 45.4)	N=8 7.4 (5.4 to 12.1)	N=7 12.1 (6.3 to 22.9)
DOR (CR+PR+SD): (median; 95% CI) (months)[a]	N=45 6.9 (5.4, 8.9)	N=49 5.9 (5.4, 9.7)	N=8 8.3 (3.5, NE)	N=7 4.3 (2.8, NE)
Intracranial Response	**In patients with measurable disease at baseline**		**In patients with measurable disease at baseline**	
OIRR % (95% CI)[b]	N=23 26.1 (10.2, 48.4)		N=23 4.3 (0.1, 21.9)	
DOIR (median; 95% CI), months[c]	N=6 6.9 (2.7, 8.3)		N=1 NE	

N=no. of patients; DOR=Duration of Response; DCR= Disease control rate
[a] Patients with a best overall response of CR or PR
[b] Patients with measurable disease in the brain at baseline as per an independent neuro-radiology review

Primary efficacy endpoint – Progression-free survival

The study met its primary objective showing a statistically significant and clinically meaningful benefit of ceritinib over chemotherapy in PFS by BIRC.

Ceritinib was associated with a 51% PFS risk reduction (HR=0.49; 95% CI: 0.36, 0.67); this result was statistically significant (log-rank test stratified by WHO performance status and baseline brain metastases, p-value <0.001, one-sided)

The median PFS as assessed by BIRC was 5.4 months (95% CI: 4.1, 6.9) and 1.6 months (95% CI: 1.4, 2.8) for the ceritinib arm and chemotherapy arm, respectively. There were 83 patients (72.2%) with events in the ceritinib arm and 89 patients (76.7%) with events in the chemotherapy arm.

Table 9: Summary of progression-free survival by BIRC assessment (FAS)

	Ceritinib 750 mg N=115	Chemotherapy N=116
n/N (%)	83/115 (72.2)	89/116 (76.7)
Events	83	89
PD	75	84
Death	8	5
Censored	32	27
Percentiles (95% CI) (months)		

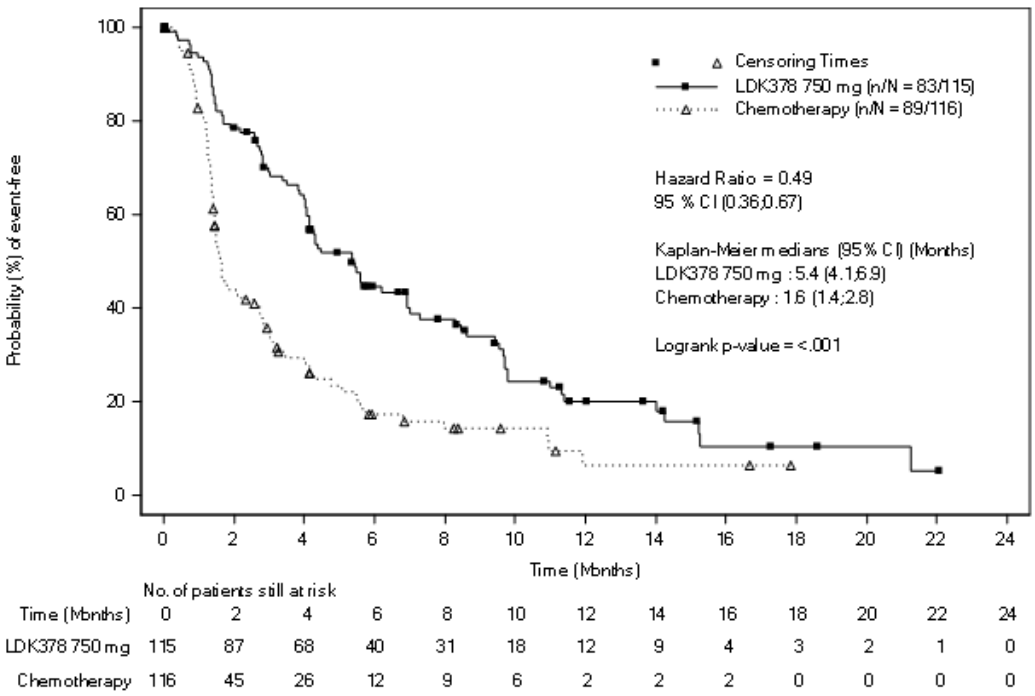
25th	2.7 (1.5, 3.5)	1.2 (1.0, 1.4)
50th (Median)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
75th	9.8 (8.6,15.2)	4.3 (3.0, 6.8)
% Event-free probability estimates (95% CI)		
3 months	69.1 (59.5, 76.8)	34.7 (25.7, 43.9)
6 months	44.6 (34.9, 53.8)	17.3 (10.4, 25.8)
9 months	33.8 (24.5, 43.3)	14.3 (7.8, 22.6)
12 months	19.9 (12.0, 29.2)	6.3 (1.6, 15.8)
15 months	15.7 (8.3, 25.2)	6.3 (1.6, 15.8)
18 months	10.4 (4.1, 20.3)	NE
21 months	10.4 (4.1, 20.3)	NE
24 months	NE	NE

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment arms; Greenwood formula is used for CIs of KM estimates.
n: Total number of events included in the analysis.
N: Total number of patients included in the analysis.

Table 10: Summary of reasons for censoring patients in progression-free survival analysis by treatment arm (full analysis set)

Study analysis endpoints	Reason of censoring	LDK378 750 mg N=115 n (%)	Chemotherapy N=116 n (%)
PFS by BIRC assessment	Number of patients censored	32 (27.8)	27 (23.3)
	Reason of censoring		
	Ongoing without event [a]	22 (19.1)	7 (6.0)
	Lost to follow-up [b]	2 (1.7)	0
	Withdrew consent	0	3 (2.6)
	Initiation of new anticancer therapy	3 (2.6)	14 (12.1)
	Event documented after two or more missing tumor assessments	4 (3.5)	0
	Adequate assessment no longer available [c]	1 (0.9)	3 (2.6)
PFS by investigator assessment	Number of patients censored	32 (27.8)	20 (17.2)
	Reason of censoring		
	Ongoing without event [a]	25 (21.7)	7 (6.0)
	Lost to follow-up [b]	2 (1.7)	0
	Withdrew consent	0	3 (2.6)
	Initiation of new anticancer therapy	3 (2.6)	9 (7.8)
	Event documented after two or more missing tumor assessments	2 (1.7)	1 (0.9)

[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.



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

Both log-rank and Cox regression model are stratified by presence or absence of brain metastases and World Health Organization Performance status (WHO PS) as per randomization. p-value is one sided and is based on the stratified log-rank test.

Figure 2 - Kaplan-Meier curve for progression-free survival by BIRC assessment (FAS)

- Supportive analyses

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 0.50 (95% CI: 0.36, 0.69; p<0.001); the median PFS as assessed by BIRC (95% CI) was 5.4 months (95% CI: 4.1, 7.0) and 1.6 months (95% CI: 1.4, 2.8) for the ceritinib arm and chemotherapy arm, respectively.

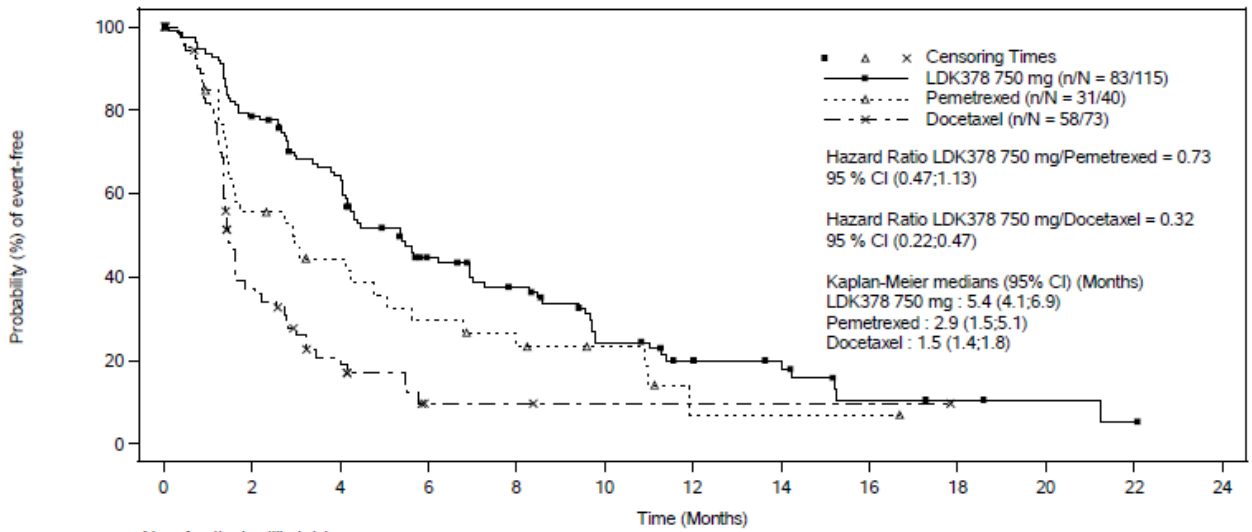
The following baseline covariates were included in a stratified multivariate Cox proportional hazard regression model for PFS by BIRC: stage of disease, geographic region, age, race, gender and previous response to crizotinib. The treatment effect hazard ratio (HR=0.49, 95% CI: 0.35, 0.68) after adjusting for the baseline covariates was similar to the stratified Cox regression model hazard ratio from the primary PFS analysis

Table 11: Stratified log-rank test and Cox regression model for PFS per BIRC assessment, comparison of ceritinib 750 mg with chemotherapy – overall and by randomization stratification factors as per randomization (FAS)

	Events/N (%)	Median Time (95% CI) (months)[c]	Log-rank Test[a] p-value	Cox Model[a] Hazard Ratio[d]	95% CI[e]
All Patients[a]					
Ceritinib 750 mg	83/115 (72.2)	5.4 (4.1, 6.9)	<0.001[f]	0.49	(0.36,0.67)
Chemotherapy	89/116 (76.7)	1.6 (1.4, 2.8)			
Brain metastases=Absence[b]					
Ceritinib 750 mg	32/ 50 (64.0)	8.3 (4.1,14.0)		0.41	(0.24,0.67)
Chemotherapy	36/ 49 (73.5)	2.8 (1.4, 4.1)			
Brain metastases=Presence[b]					
Ceritinib 750 mg	51/ 65 (78.5)	4.4 (3.5, 6.2)		0.55	(0.37,0.82)
Chemotherapy	53/ 67 (79.1)	1.5 (1.3, 1.7)			
WHO status=0[b]					
Ceritinib 750 mg	40/ 54 (74.1)	6.9 (4.1, 9.4)		0.41	(0.26,0.64)
Chemotherapy	45/ 55 (81.8)	1.8 (1.4, 2.9)			
WHO status=1-2[b]					
Ceritinib 750 mg	43/ 61 (70.5)	4.3 (2.8, 6.2)		0.59	(0.38,0.91)
Chemotherapy	44/ 61 (72.1)	1.5 (1.3, 2.8)			

[a] Both log-rank and Cox regression model are stratified by presence or absence of brain metastases and WHO status as per randomization. P-value was one tailed and was based on the stratified log-rank test.
[b] For "WHO status", Cox regression model was stratified by presence or absence of brain metastases as per randomization (IRT). For "Brain metastases", Cox regression model was stratified by WHO status as per randomization (IRT).
[c] Median PFS and its 95% CI were generated by KM estimation.
[d] Hazard ratio of ceritinib versus chemotherapy.
[e] Based on a Wald test from Cox model.
[f] Indicates statistical significance (one-sided) at the 0.025 level.

(safety set)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Pemetrexed	40	21	15	10	7	5	1	1	1	0	0	0	0
Docetaxel	73	24	11	2	2	1	1	1	1	0	0	0	0

Cox regression model is stratified by presence or absence of brain metastases and WHO status as per randomization.

Figure 3 - Kaplan-Meier plot of progression-free survival per BIRC assessment by LDK378 and chemotherapy

- Sensitivity analyses

Pre-defined sensitivity analyses were performed for PFS by BIRC assessment using the stratum derived from the clinical database, using an unstratified log-rank test, and unstratified Cox model for HR, including the

start of anti-neoplastic therapy as a PFS event, excluding the start of anti-neoplastic therapy as a reason for censoring, including events for patients with at least two consecutive tumor assessments missing prior to the PFS events. PFS was also compared between the treatment arms including PD events assessed by either BIRC or Investigator as PFS events (whichever occurred earlier). The results of the predefined sensitivity analyses were consistent with the primary analysis.

Secondary endpoints (OS)

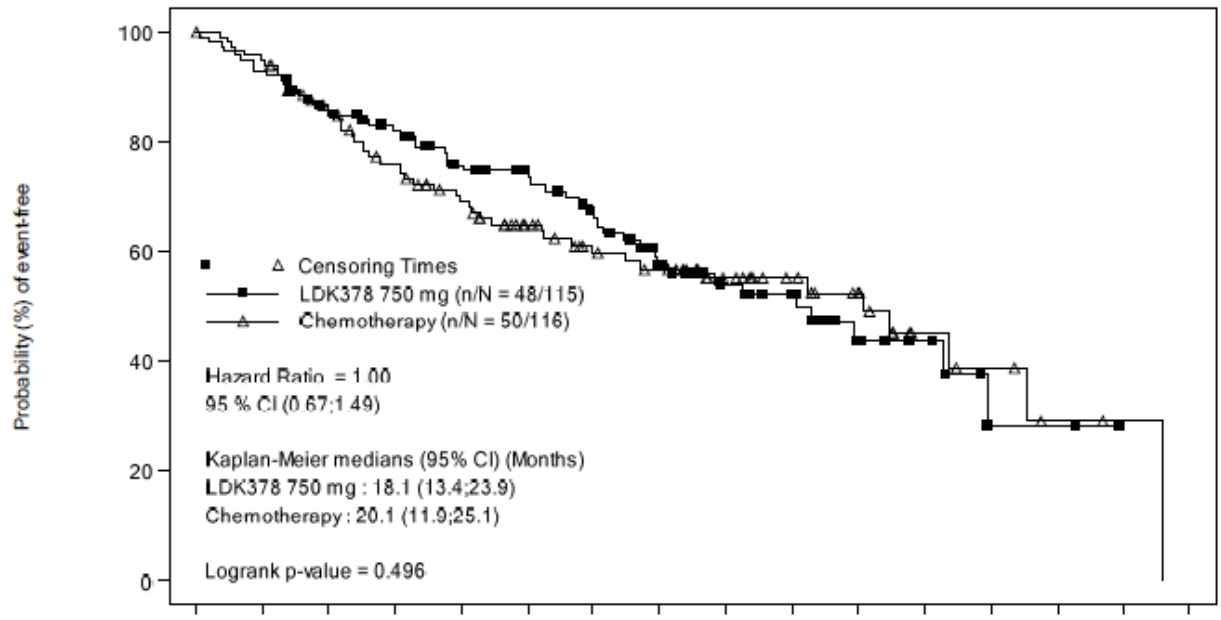
As pre-specified in both the protocol and the statistical analysis plan, OS was formally tested, based on a 50% information fraction, as the primary efficacy endpoint PFS by BIRC assessment was statistically significant favoring the ceritinib arm.

As of the data cut-off date, the median follow-up time for OS (from randomization to last contact date on or prior to the data cut-off date) was 10.9 months (range: 0.1 to 27.9 months) for the ceritinib arm and 9.3 months for the chemotherapy arm (range: 0 to 29.2 months).

Table 12: Stratified log-rank test and Cox regression model for overall survival, comparison of ceritinib 750 mg with chemotherapy (FAS)

			Log-rank Test[a]	Cox Model[a]	
	Events/N (%)	Median Time (95% CI) (months)[b]	p-value	Hazard Ratio[c]	95% CI[d]
All Patients[a]					
Ceritinib 750 mg	48/115 (41.7)	18.1 (13.4, 23.9)	0.496	1.00	(0.67, 1.49)
Chemotherapy	50/116 (43.1)	20.1 (11.9, 25.1)			

[a] Both log-rank and Cox regression model are stratified by presence or absence of brain metastases and WHO status as per randomization.
P-value was one tailed and was based on the stratified log-rank test.
[b] Median OS and its 95% CI are generated by KM estimation.
[c] Hazard ratio of Ceritinib versus chemotherapy.
[d] Based on a Wald test from Cox model.
Source: Table 14.2-2.4



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
LDK378 750 mg	115	107	92	83	71	61	52	37	28	23	13	8	2	2	0	0
Chemotherapy	116	109	91	78	66	53	43	39	29	22	17	7	5	2	1	0

Both log-rank and Cox regression model are stratified by presence or absence of brain metastases and WHO status as per randomization.

P-value was one sided and was based on the stratified log-rank test.

Figure 4 - Kaplan-Meier plot of overall survival by treatment arm (FAS)

A total of 67 patients (58.3%) in the ceritinib arm were censored for survival including 60 patients who were alive and seven patients who were lost to follow-up as of the data cut-off date. In the chemotherapy arm, 66 patients (56.9%) were censored for survival including 55 patients who were alive and 11 patients who were lost to follow-up as of the data cut-off date.

The results for the supportive analysis for OS based on the PPS were similar to those assessed on the FAS (HR=0.99 with 95% CI: 0.65, 1.49; p=0.474) using stratified log-rank test and 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, gender and previous response to crizotinib. The treatment effect hazard ratio after adjusting for these baseline covariates was comparable to the stratified Cox regression model hazard ratio from the primary OS analysis.

A final analysis for OS is planned to be conducted when approximately 196 deaths are observed.

Table 13: Overall survival by treatment arm (FAS)

	Ceritinib 750 mg N=115	**Chemotherapy N=116**
n/N (%)	48/115 (41.7)	50/116 (43.1)
Percentiles (95% CI) (months)		
25th	8.1 (5.2,12.0)	6.2 (4.4, 8.5)
Median	18.1 (13.4,23.9)	20.1 (11.9,25.1)
75th	NE (22.6, NE)	29.2 (22.8,29.2)
% Event-free probability estimate (95% CI)		
3 months	89.5 (82.3, 93.9)	89.5 (82.2, 93.9)

	Ceritinib 750 mg N=115	Chemotherapy N=116
6 months	82.0 (73.5, 88.0)	76.2 (67.0, 83.1)
9 months	74.7 (65.3, 82.0)	64.9 (54.8, 73.2)
12 months	67.3 (56.9, 75.7)	59.6 (49.2, 68.7)
15 months	55.9 (44.7, 65.8)	56.8 (46.1, 66.2)
18 months	52.1 (40.5, 62.6)	55.1 (44.2, 64.7)
21 months	43.8 (30.8, 56.1)	45.2 (31.6, 57.8)
24 months	28.2 (11.0, 48.4)	38.7 (22.7, 54.5)
27 months	28.2 (11.0, 48.4)	29.1 (11.2, 49.8)
30 months	NE	0

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
n: Total number of events included in the analysis.
N: Total number of patients included in the analysis.

Seventy-five (65%) patients from the chemotherapy arm crossed-over to the ceritinib arm after BIRC-confirmed PD as part of the extension treatment phase, one patient died before receiving the first dose of ceritinib. In addition, nine patients who did not cross-over received an ALK-inhibitor as their first therapy after treatment discontinuation (seven ceritinib, two crizotinib). Thus, overall 83 patients (71.6%) in the chemotherapy arm have received an ALK-inhibitor as their first antineoplastic medication after discontinuation of the chemotherapy. After discontinuation of ceritinib, 17 patients (14.8%) received chemotherapy, of which eight patients (7.0%) received pemetrexed and six patients (5.2%) received docetaxel.

Table 14: Selected first antineoplastic medications since treatment discontinuation

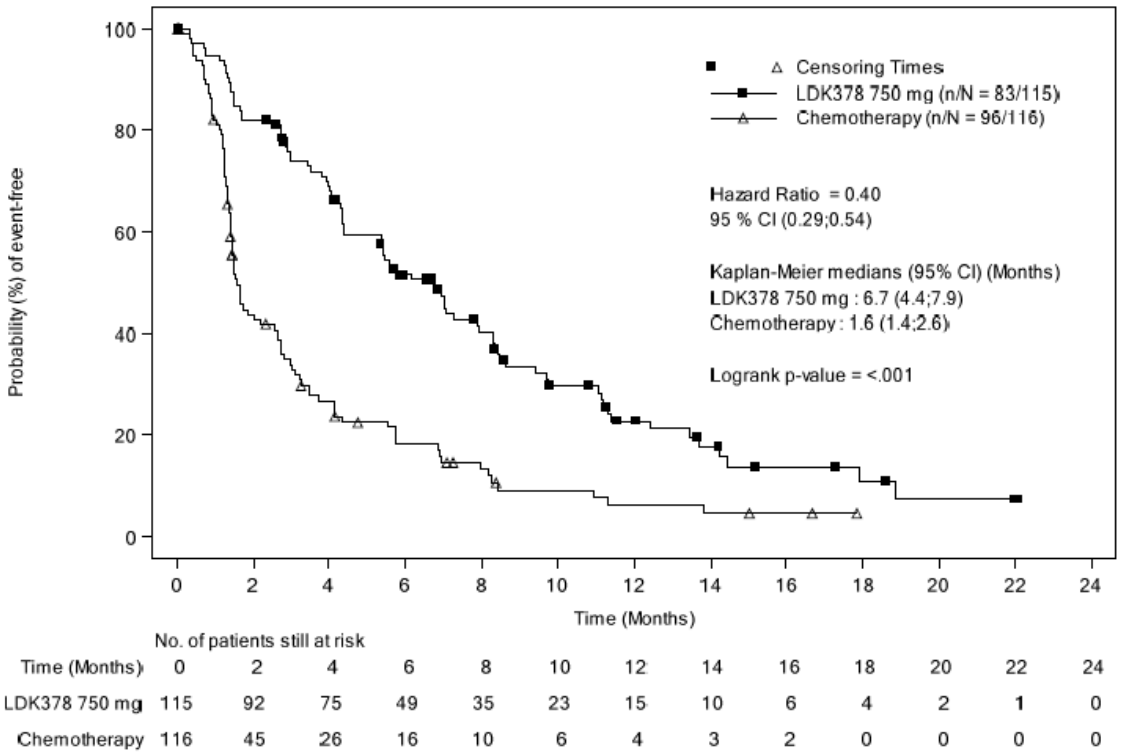
Type of therapy	Ceritinib 750 mg N=115 n (%)	Chemotherapy N=116 (including ceritinib in extension treatment phase) n (%)
Any	40 (34.8)	85 (73.3)
Chemotherapy	17 (14.8)	2 (1.7)
Pemetrexed	8 (7.0)	0
Taxane[a]	7 (6.1)	0
Platinum	4 (3.5)	0
Cytarabine	0	1 (0.9)
TS-1	0	1 (0.9)
Gemcitabine	2 (1.7)	0
Vinorelbine	1 (0.9)	0
ALK-inhibitor	17 (14.8)	83 (71.6)
Alectinib	15 (13.0)	0
Ceritinib	2 (1.7)	81 (69.8)
Crizotinib	0	2 (1.7)
Bevacizumab	1 (0.9)	1 (0.9)
EGFR TKI	4 (3.5)	0
Anti-PD1	1 (0.9%)	0

[a] Six patients received docetaxel
TKI=tyrosine kinase inhibitor, EGFR=epidermal growth factor receptor; PD1= programmed cell death protein 1

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. 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=0.97; 95% CI: 0.65, 1.45).

Progression-free survival by Investigator assessment

With a median follow-up for PFS of 5.4 months for the ceritinib arm and 1.5 months for the chemotherapy arm (range: 0.0 to 22.1) by Investigator assessment, the results of this PFS analysis corroborated the primary PFS analysis based on BIRC assessment. Ceritinib treatment demonstrated a statistically and clinically meaningful benefit over chemotherapy in prolonging PFS based on Investigator assessment (HR=0.40; 95% CI: 0.29, 0.54; stratified log-rank test, one-sided p<0.001). The estimated median PFS was 6.7 months (95% CI: 4.4, 7.9) in the ceritinib arm vs. 1.6 months (95% CI: 1.4, 2.6) in the chemotherapy arm. The concordance rate for PFS between Investigator and BIRC assessments was a high (87.4%). Subgroup and sensitivity analyses of PFS by Investigator assessment were similar to those by BIRC.



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	92	75	49	35	23	15	10	6	4	2	1	0
Chemotherapy	116	45	26	16	10	6	4	3	2	0	0	0	0

Both log-rank and Cox regression model are stratified by presence or absence of brain metastases and WHO PS as per randomization. P-value is one sided and is based on the stratified log-rank test.
WHO PS=World Health Organization performance status
Source: [Study A2303-Figure 14.2-1.2]

Figure 5 - Kaplan-Meier plot of progression-free survival per Investigator assessment by treatment arm (FAS)

Overall response rate (BIRC and Investigator assessment)

The ORR as assessed by BIRC was higher in the ceritinib arm compared to the chemotherapy arm (39.1% vs. 6.9%). Of the eight responders in the chemotherapy arm, seven patients were on pemetrexed and one patient was on docetaxel. The ORR was also higher in the ceritinib arm compared to the pemetrexed group (17.5%), and compared to the docetaxel group (1.4%). The BOR in both arms included PRs and no CRs. Of note, 16.5% and 51.7% of patients in the ceritinib and chemotherapy arm, respectively, had PD as BOR.

Similar results were obtained for ORR when tumor responses were assessed by the Investigator. Of the seven responders in the chemotherapy arm, five patients were on pemetrexed and two patients were on docetaxel.

Table 15: Best overall response per BIRC assessment by treatment arm (FAS)

	Ceritinib 750 mg N=115		Chemotherapy N=116	
	n (%)	95% CI[a]	n (%)	95% CI[a]
Best overall response				
Partial Response (PR)	45 (39.1)		8 (6.9)	
Stable Disease (SD)	35 (30.4)		28 (24.1)	
Progressive Disease (PD)	19 (16.5)		60 (51.7)	
Non-CR/Non-PD	8 (7.0)		6 (5.2)	
Unknown (UNK)	8 (7.0)		14 (12.1)	
Overall Response Rate (ORR: CR+PR)	45 (39.1)	(30.2, 48.7)	8 (6.9)	(3.0, 13.1)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	88 (76.5)	(67.7, 83.9)	42 (36.2)	(27.5, 45.6)

N: The total number of patients in the Full Analysis Set. It was the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
[a] Exact binomial 95% Confidence Interval.
CR=complete response
Non-CR/Non-PD refers to best overall responses that are neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.
Source: [Study A2303-Table 14.2-3.1]

	Pemetrexed N=40			Docetaxel N=73		
	n	(%)	95% CI [a]	n	(%)	95% CI [a]
Best overall response						
Partial Response (PR)	7	(17.5)		1	(1.4)	
Stable Disease (SD)	12	(30.0)		16	(21.9)	
Progressive Disease (PD)	17	(42.5)		43	(58.9)	
Non-CR/Non-PD	2	(5.0)		4	(5.5)	
Unknown (UNK)	2	(5.0)		9	(12.3)	
Overall Response Rate (ORR: CR+PR)	7	(17.5)	(7.3, 32.8)	1	(1.4)	(0.0, 7.4)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	21	(52.5)	(36.1, 68.5)	21	(28.8)	(18.8, 40.6)

Disease control rate (BIRC and Investigator assessment)

Disease control rate (CR+PR+stable disease+Non-CR/Non-PD) as assessed by BIRC was nearly twice as high in the ceritinib arm compared to the chemotherapy arm (76.5% vs. 36.2%). Disease control rate was also higher in the ceritinib arm compared to the pemetrexed group (52.5%), and compared to the docetaxel group (28.8%).

Similar results were obtained for DCR when tumor responses were assessed by the Investigator.

Duration of response (BIRC and Investigator assessment)

The responses were durable with a median DOR per BIRC assessment of 6.9 months (95% CI: 5.4, 8.9) in the ceritinib arm and 8.3 months (95% CI: 3.5, NE) in the chemotherapy arm in patients with a BOR of confirmed CR or PR (N=45 in the ceritinib arm, N=8 in the chemotherapy arm). Of these patients, 64.4% and 50.0% (ceritinib arm and chemotherapy arm, respectively) had an event (progression or death) at the date of the last tumor assessment prior to the data cut-off.

The median DOR based on Investigator assessment was 5.9 months (95% CI: 5.4, 9.7) in the ceritinib arm and 4.3 months (95% CI: 2.8, NE) in the chemotherapy arm in patients with a BOR of confirmed CR or PR (N=45 in the ceritinib arm, N=8 in the chemotherapy arm). 71.4% patients in both treatment arms achieved a response of confirmed CR or PR had an event (progression or death) prior to the data cut-off.

Of note, the number of responders in the chemotherapy arm was very small, and consequently the 95% CI for the estimate of median DOR was wide.

Time to response (BIRC and Investigator assessment)

The onset of response was rapid; in patients with confirmed PR by BIRC, 80% of patients achieved the response during the first 12 weeks on treatment with ceritinib. The median time to first response was 6.7 weeks in the ceritinib arm and 7.4 weeks in the chemotherapy arm. Using the Kaplan-Meier approach, the estimated probability of having a response within the first 18 weeks of treatment was 36.2% (95% CI: 28.1, 46.0) for the ceritinib arm and 7.6% (95% CI: 3.9, 14.7) for the chemotherapy arm.

Similar results were observed with Investigator's assessed responses. Of note, the number of responders in the chemotherapy arm was very small, and consequently the 95% CI for the estimate of median DOR was wide.

Table 16: Overview of additional secondary endpoints by BIRC and Investigator assessment (FAS)

	Ceritinib 750 mg N=115		Chemotherapy N=116	
	BIRC	**Investigator**	**BIRC**	**Investigator**
Median PFS, months (95% CI)	5.4 (4.1, 6.9) [a]	6.7 (4.4, 7.9)	1.6 (1.4, 2.8) [a]	1.6 (1.4, 2.6)
ORR (CR+PR), % (95% CI)	39.1 (30.2, 48.7)	42.6 (33.4, 52.2)	6.9 (3.0, 13.1)	6.0 (2.5, 12.0)
DCR (CR+PR+SD), % (95% CI)	76.5 (67.7, 83.9)	80.0 (71.5, 86.9)	36.2 (27.5, 45.6)	37.9 (29.1, 47.4)
Median TTR, N [b] weeks (range)	N=45 6.7 (5.3 to 52.3)	N=49 6.4 (4.9 to 45.4)	N=8 7.4 (5.4 to 12.1)	N=7 12.1 (6.3 to 22.9)
Median DoR, N [b] months (95% CI)	N=45 6.9 (5.4, 8.9)	N=49 5.9 (5.4, 9.7)	N=8 8.3 (3.5, NE)	N=7 4.3 (2.8, NE)

N=no. of patients
BIRC=Blinded Independent Review Committee; BOR=best overall response; CI=confidence interval; CR=complete response; DCR=disease control rate; DoR=duration of response; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; SD=stable disease; TTR=time to response.
[a] Primary endpoint (see Section 4.2.3.1)
[b] Patients with a BOR of CR or PR

Responses in patients with brain metastases

Overall intracranial response rate, intracranial disease control rate (IDCR) and duration of intracranial response (DOIR) were assessed by an independent neuro-radiologist (intracranial BIRC) in a subset of patients with baseline brain metastases, and were calculated based on modified RECIST 1.1 to assess activity in the brain.

- Patients with brain metastases at baseline

Of a total of 133 patients with ALK-positive NSCLC and brain metastases at baseline, 66 patients (49.6%) were randomized in the ceritinib arm and 67 patients (50.4%) in the chemotherapy arm. Baseline and disease characteristics, relevant medical history, current medical conditions, prior anti-neoplastic therapies in this sub-population were consistent with the overall population and were well-balanced between the two treatment arms. Approximately 56% of patients in each treatment arm had received prior radiation to the brain. The median time from end of radiation to the brain to randomization was 3.9 months (range: 0.2 to 44.7 months) in the ceritinib arm vs. 5.5 months (range: 0.0 to 23.8 months) in the chemotherapy arm.

Two patients in the chemotherapy arm were randomized but not treated. Forty-six patients (34.6%) had measurable lesions at baseline (23 patients each arm). Ten out of 46 patients (21.7%) with measurable disease had no valid post-baseline tumor assessment (6/23 in the ceritinib arm, 4/23 in the chemotherapy arm).

- Overall intracranial response

The OIRR in patients with measurable disease (at least one target lesion) in the brain at baseline was higher in the ceritinib arm (26.1%, 95% CI: 10.2, 48.4) as compared to the chemotherapy arm (4.3%, 95% CI: 0.1, 21.9). A high number of patients had unknown response, 26.1% in both the ceritinib arm and in the chemotherapy arm, mostly due to missing post-BL assessments. Excluding patients with no post-BL assessments from the analysis (n=6 in the ceritinib arm and n=3 in the chemotherapy arm), the OIRR was 35.3% (95% CI: 14.2, 61.7) in the ceritinib arm and 5.0% (95% CI: 0.1, 24.9) in the chemotherapy arm.

- Intracranial disease control rate

The IDCR (ceritinib vs the chemotherapy) was 56.5% (95% CI: 34.5, 76.8) vs. 52.2% (95% CI: 30.6, 73.2) in patients with measurable disease. However, in the chemotherapy arm, only one patient had a PR in the brain, therefore, the IDCR was primarily driven by stable disease. Moreover, the median PFS in patients with baseline brain metastases (as per case report form [CRF] data) was much shorter in the chemotherapy arm compared to the ceritinib arm (1.5 months vs. 4.4 months) suggesting disease control in the brain was not durable with chemotherapy.

Table 17: Best overall intracranial response by intracranial BIRC (FAS-patients with measurable disease in the brain at baseline)

	Ceritinib 750 mg N=23		Chemotherapy N=23	
	n (%)	95% CI[a]	n (%)	95% CI[a]
BOIR				
PR	6 (26.1)		1 (4.3)	
SD	7 (30.4)		11 (47.8)	
PD	4 (17.4)		5 (21.7)	
UNK	6 (26.1)		6 (26.1)	
OIRR (CR+PR)	6 (26.1)	(10.2, 48.4)	1 (4.3)	(0.1, 21.9)
IDCR (CR+PR+SD+Non-CR/Non-PD)	13 (56.5)	(34.5, 76.8)	12 (52.2)	(30.6, 73.2)

N=The total number of patients in the FAS with measurable and/or non-measurable disease in the brain at baseline as per BIRC neuro-radiology review
n=Number of patients who are at the corresponding category.
BOIR=best overall intracranial response; CR=complete response; IDCR=intracranial disease control rate; OIRR=overall intracranial response rate; PD=progressive disease; PR=partial response; SD=stable disease; UNK=unknown
[a] Exact binomial 95% Confidence Interval.
Non-CR/Non-PD refers to BOR that are neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline

- Duration of intracranial response

Intracranial responses with ceritinib were durable, with a median DOIR of 6.9 months (95% CI: 2.7, 8.3) in the ceritinib arm in patients with measurable disease in the brain at baseline. The DOIR was not reached in the chemotherapy arm as the only patient eligible for analysis was censored (patient was ongoing without an event).

Of note, the number of patients in subgroups and number of events (i.e. number of responders and number of intracranial PD events) were small. Since no tumor assessments were required after BIRC confirmed PD, this might have led to censoring of patients (in the DOIR analysis) who had extracranial but no intracranial progression, and did not die. Thus, the DOIR results have to be interpreted with caution.

- Progression-free survival in patients with brain metastases

In the subgroup of patients with brain metastases (based on CRF data) and the subgroup of patients without brain metastases at baseline, a positive treatment effect (based on median PFS) was demonstrated in favor of ceritinib vs. chemotherapy with the estimated HR of 0.54 and 0.41, respectively. The median PFS by BIRC and Investigator was longer in the ceritinib arm compared to the chemotherapy arm both in patients with brain metastases (based on CRF data) and without brain metastases.

Patient reported outcomes

Two instruments (LCSS and EORTC QLQ-C30/LC13) frequently used in clinical lung cancer studies and specifically designed to analyze lung cancer symptom changes were used to assess patient reported outcomes in Study A2303. In addition, EQ-5D, a simple, generic measure of health for clinical and economic appraisal was used to further assess patient reported outcomes.

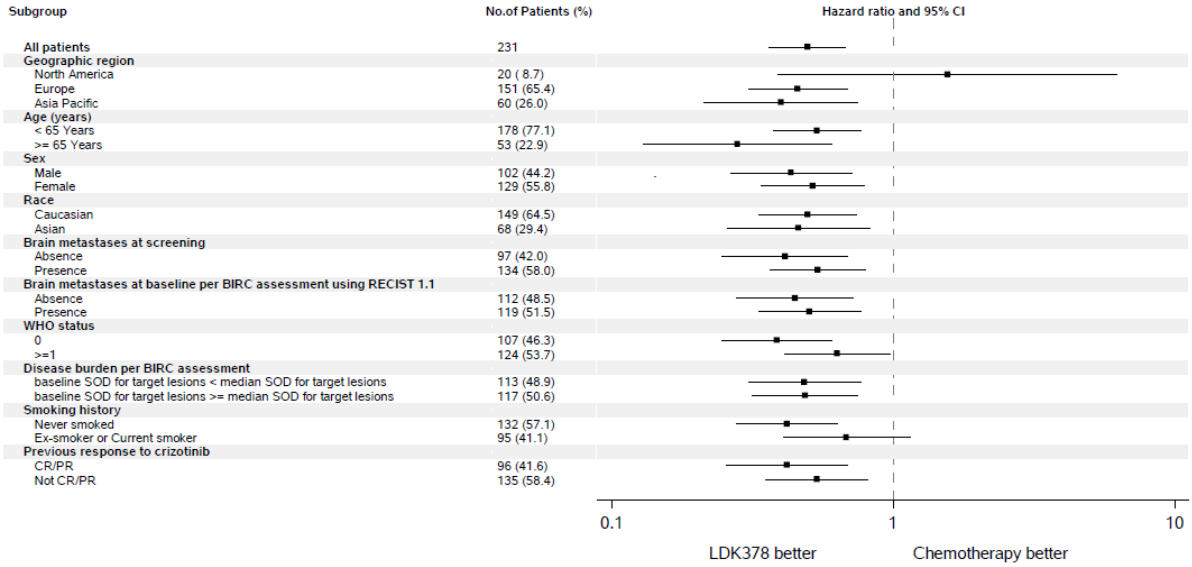
The compliance of patients completing the LCSS was high, ≥ 75% of patients in the ceritinib and chemotherapy arms completed the LCSS questionnaires at most of the time points during the course of the study. Significant improvements were reported for the majority of lung cancer specific symptoms for Zykadia compared to chemotherapy (four out of six LCSS and 10 out of 12 QLQ-LC13 symptom scores). Ceritinib significantly prolonged time to deterioration for the lung cancer specific symptoms of interest of cough, pain and dyspnoea (composite endpoint LCSS: HR=0.40; 95% CI: 0.25, 0.65, median Time to Deterioration [TTD] 18.0 months [95% CI: 13.4, NE] in the ceritinib arm versus 4.4 months [95% CI: 1.6, 8.6] in the chemotherapy arm; LC13: HR=0.34; 95% CI: 0.22, 0. 52, median TTD 11.1 months [95% CI: 7.1, 14.2] in the ceritinib arm versus 2.1 months [95% CI: 1.0, 5.6] in the chemotherapy arm). The EQ-5D questionnaire showed a significant overall health status improvement for Zykadia in comparison to the chemotherapy.

Results for QLQ-LC13 questionnaire are consistent with the findings of the LCSS and show significant improvements in most symptoms.

The QLQ-C30 questionnaire revealed improvements in half of its scales (7 out of 15) in patients treated with ceritinib; two scores related to nausea and vomiting as well as diarrhea showed better outcomes for chemotherapy arm.

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

- **Ancillary analyses**



Except for 'WHO PS', 'Brain metastases at screening' and 'Brain metastases at baseline per BIRC assessment using RECIST 1.1', hazard ratios are based on Cox regression model stratified by presence or absence of brain metastases and WHO PS as per randomization IRT at randomization.
Brain metastases at screening is as per case report form data at baseline
For 'Brain metastases at screening' and 'Brain metastases at baseline per BIRC assessment using RECIST 1.1', Cox regression model was stratified by WHO PS as per randomization (IRT).
For 'WHO PS', Cox regression model was stratified by presence or absence of brain metastases as per randomization (IRT).
The subgroup of ex-smokers or current smokers includes five patients who were current smokers.
WHO PS=World Health Organization performance status; IRT= Interactive response technology

Figure 6 - Forest plot for progression-free survival by BIRC assessment (FAS, Study A2303)

4.2.2. Discussion

Design

In the EU, Zykadia was granted conditional marketing authorisation on 6 May 2015 for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib, based on data from the Phase II Study A2201 and Study CLDK378A2203 (referred to as Study A2203) and updated data from the Phase I Study X2101.

On July 2016, the MAH submitted the final analysis of the study A2201. Results from this final analysis were in line with those previously known from the primary analysis. Both the outcome from primary endpoint and values from the secondary endpoints, were maintained.

Now, the MAH has submitted the data of the study A2303, which could fulfil the remaining Specific Obligation in Annex II.

Study A2303 is a Phase III, global, randomized, open-label study of oral ceritinib (750 mg qd fasted) versus standard chemotherapy (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 inclusion/exclusion criteria allowed the recruitment of Patients ⩾ 18 years with locally advanced or metastatic ALK-positive (confirmed by fluorescent in situ hybridization test) NSCLC, prior therapy with crizotinib and one or two chemotherapy lines for advanced disease (including a platinum-based doublet), WHO PS 0-2, documented disease progression at study entry with at least one measurable lesion, adequate organ and bone marrow function; patients with symptomatic brain metastasis or carcinomatous meningitis

were excluded. Importantly, no particular sequence of prior crizotinib and chemotherapy was required for enrollment, and either could comprise the last treatment received by the patient. Even though, the inclusion criteria overall seem to reproduce someway the wording of the indication granted to ceritinib, would not be the clear reflection of the current clinical practice, given the treatments algorithms for stage IV ALK NSCLC, with crizotinib in first line and ceritinib after progression.

Regarding the comparators used, pemetrexed (500 mg/m2 as an iv infusion over 10 minutes on Day 1 of each 21-day cycle) or docetaxel (75 mg/m2 infused iv over one hour on Day 1 of each 21-day cycle) can be considered as acceptable comparators as there seem to be a non-inferiority between pemetrexed and docetaxel in OS, even though pemetrexed would have a better tolerability with a significantly lower rate of neutropaenia and gastrointestinal AEs. Apparently, the choice of pemetrexed or docetaxel treatment in the chemotherapy arm was made by the Investigator taking into account prior therapy.

The primary endpoint, PFS by BIRC, was evaluated (tumour evaluation) every six weeks (two cycles) after randomization during the first 18 months, and every nine weeks (three cycles) thereafter and at end of treatment. This approach is considered acceptable, seeing as response evaluation is recommended after 2–3 cycles of chemotherapy (Novello et al. Ann Oncol 2016). PFS as primary endpoint with OS as key secondary endpoint, are agreeable, especially bearing in mind, firstly, the already known results from the phase II study A2201 and the cross-over design used in the A2303 study.

Randomisation (1:1) was stratified by performance status and presence of brain metastases. Performance status and brain metastases are two well-known prognostic factors.

According to the statistical analysis plan, the final PFS analysis was to be conducted when approximately 161 BIRC-confirmed PFS events had been documented and all randomized patients completed at least 12 weeks of follow-up or discontinued earlier.

Results

From the 326 patients who were screened, 29.1% did not complete that phase, mainly due to screen failure. 231 patients were randomised. One hundred and fifteen (115) patients received ceritinib and 116 patients received chemotherapy; among the 116 patients randomized to chemotherapy, 40 patients received pemetrexed, 73 patients received docetaxel. It is reassuring that at the time of the main analysis (PFS) more patients were ongoing in the ceritinib arm than in the chemotherapy group (28.7% vs 6.9%). Looking at the reasons for discontinuations, progressive disease was the main reason, followed by death and subject/physician's decision. However, the latter, is not considered representative enough due to the relatively low number of deaths.

The protocol was amended four times. Of them the most important when it comes to assessing the primary endpoint was the third one. In this one, after 191 patients had been randomised, the criterion to stop collecting tumor assessment, "start of new anti-cancer therapy", was removed. The aim of this amendment was to enable sensitivity analysis of PFS following a pure intent -to-treat principle where start of new antineoplastic therapy did not result in censoring for PFS.

Regarding the baseline characteristics (demographics), overall they seem to be evenly balanced, with a few imbalances in race and smoking status. All patients but two had metastatic disease, with brain metastases in half of patients approximately. Adenocarcinoma was the more predominant histology. Crizotinib was received by all patients, and 82% of them as last treatment. There is a slight imbalance in the response obtained from crizotinib; 46.9% vs 36.2% in ceritinib arm and chemotherapy group respectively showed response.

In terms of primary endpoint (PFS by BIRC), the use of ceritinib is associated to a longer PFS, with a HR of 0.49 (95%CI 0.36, 0.67). There is a clear separation of the curve from the beginning. The almost 4 months in the delay of tumour progression or death is considered clinically meaningful. These results seem robust

enough, both in number of events (72% for ceritinib arm and 76% for chemotherapy) and supportive-sensitivity analyses. More patients were censored in the ceritinib arm (27.8% vs 23.3%) with ongoing without event as main reason of censoring (19.1% vs 6.0% ceritinib vs chemotherapy respectively). Initiation of new anticancer therapy was the main reason for censuring in the control group. The PFS by investigator, in the PP population and in all the sensitivity analyses carried out by the MAH were consistent with the BIRC analysis. Even the stratified multivariate Cox proportional hazard regression model for PFS by BIRC, did not show any dissimilar result. On splitting the control group in the two different regimens used (pemetrexed and docetaxel) a better results seems to observe vs docetaxel (HR 0.32 95%CI 0.22, 0.47) than with pemetrexed (HR 0.73 95%CI 0.47, 1.13) although the study was not designed to find differences with each regimen. The median PFS as assessed by BIRC was 2.9 months (95% CI: 1.5, 5.1) and 1.5 months (95% CI: 1.4, 1.8) for pemetrexed and docetaxel, respectively, versus 5.4 months (95% CI: 4.1, 6.9) for ceritinib. Finally, the PFS results in the different subgroups analysed (including the stratifications strata) were consistent with the whole population

Results for OS are not conclusive, with no differences between groups (HR 1.00 95%CI 0.67, 1.49). The percentage of events (42% and 43%) and number of patients (75 [65%]) who crossed-over to ceritinib along with the subsequent therapy with ALK inhibitors (71.6% vs 14.8% ceritinib vs chemotherapy respectively), are likely to have influenced the absence of differences in OS. Nevertheless, after a sensitivity analysis with the aim of correcting for crossover was carried out, the HR remained similar to the original (HR 0.97 95%CI 0.65, 1.45). The latter warrants even more an update of the OS data.

ORR was higher for those patients treated with ceritinib, with almost 40% of responders vs 7% in the chemotherapy arm. Of note, no complete responses were observed in any arm. Despite this higher ORR, the duration of the response was pretty similar between groups with 7 and 8 months in ceritinib and chemotherapy groups respectively. A more interesting fact of the antitumor activity of ceritinib is the effect on brain metastases. The overall intracranial response by BIRC was 26% vs 4 % in ceritinib vs control group. Despite the limited sample size of this subset of patients (46) this is considered an added value, since the high prevalence of brain metastases in those patients with ALK positive (around 50%) and the low bioavailability of crizotinib in the cerebrospinal fluid.

Overall, results from this phase III confirmatory trial are in line with those obtained from previous studies. ORR seems similar to response rate seen in the study A2201 (35.7%) and the median PFS by BIRC was 7.1 months in the A2201 trial and 5.4 months according to investigator's assessment.

In conclusion, data from the phase III trial, study A2303, show a clinically meaningful result, both in PFS and ORR. OS data are not mature enough and the applicant is recommended to submit updates. These results confirm the preliminary data from the previous studies which were the basis of the conditional MA and constitute a comprehensive data package.

4.3. Clinical Safety aspects

This Summary of Clinical Safety (SCS) is primarily based on data from Phase III Study A2303 to further confirm the safety of ceritinib in the target population of patients with locally advanced or metastatic ALK-positive NSCLC disease previously treated with cytotoxic chemotherapy and crizotinib.

The SCS reviews the safety data from the confirmatory, randomized Phase III Study A2303 comprising of 231 patients, which were randomized (1:1 ratio) to receive either ceritinib 750 mg once daily fasted (n=115, consisted of all patients who received at least one dose of study drug) or chemotherapy (n=116; including 40 patients and 73 patients treated with pemetrexed and docetaxel respectively, three patients were not treated). Additional safety information (cumulative line listings of deaths and SAEs) were reported in the Applicant global pharmacovigilance safety database (ARGUS) for the other ongoing studies in the ceritinib program until 10-Aug-2016. There was no pooling of safety data.

Patients randomized to chemotherapy were allowed to cross-over and receive ceritinib after BIRC-confirmed disease progression (extension-treatment phase). Seventy-five patients crossed over to ceritinib, and entered the extension-treatment phase. One patient died before starting the first dose of ceritinib in the extension-treatment phase and 74 received ceritinib.

The median duration of follow-up (from randomization to data cut-off date 26-Jan-2016) for all patients was 16.5 months for Study A2303, and the median duration of exposure to ceritinib was 30.3 weeks (range: 0.3 to 122.9) and to chemotherapy was 6.3 weeks (range: 3.0 to 69.1), more patients discontinued treatment with chemotherapy (108 patients, 93.1%) than with ceritinib (82 patients, 71.3%) at the time of the data cut-off (26-Jan-2016). Treatment was ongoing for 33 patients (28.7%) in the ceritinib group and for eight patients (6.9%) in the chemotherapy group at the time of the data cut-off.

No specific long-term studies were conducted, and there is limited information regarding prolonged exposure of patients to ceritinib in clinical trials. In Study A2303, 47% of patients were exposed to ceritinib for a period of ≥ 33 weeks.

4.3.1. Methods – analysis of data submitted

Study A2303 is an open-label, randomized, active-controlled, global Phase III study to compare the efficacy and safety of ceritinib to standard, second-line, chemotherapy (pemetrexed or docetaxel) in patients with ALK-positive advanced NSCLC (harboring a confirmed ALK rearrangement). Patients were previously treated with chemotherapy (one or two prior regimens, including one platinum-based doublet) and crizotinib. No particular sequence of prior chemotherapy and crizotinib was required for enrollment, and either could comprise the last treatment received by the patient.

Patients were treated until Response Evaluation Criteria In Solid Tumors (RECIST) confirmed disease progression by BIRC, unacceptable toxicity, or other discontinuation criteria were met. Patients in the chemotherapy arm were allowed to cross -over and receive ceritinib after BIRC-confirmed disease progression (extension-treatment phase). Moreover, patients in either arm of the study with BIRC-confirmed disease progression were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion.

Safety data in the present SCS was analysed using the Safety set consisting of all patients who received at least one dose of study drug. Patients were analyzed as applicable according to the study treatment or the study drug they 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 analyzed consistently within one (and only one) treatment group.

The Cross-over analysis set consisted of patients randomized to the chemotherapy 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.

The key study design features and safety endpoints are summarized in Table 18.

Table 18: Phase III study in patients with ALK-positive advanced NSCLC – Study A2303

Study Data cut-off data Status	Design	Ceritinib dose	Total no. of patients treated	Safety endpoints
Study A2303 26-Jan-2016 Ongoing: enrollment complete.	Phase III, global, randomized, open-label study of oral ceritinib versus standard chemotherapy (pemetrexed or docetaxel) in adult patients with ALK-positive NSCLC previously treated with chemotherapy (one or two prior regimens, including one platinum-based doublet) and crizotinib.	750 mg once daily, fasted	228 Ceritinib=115 Docetaxel=73 Pemetrexed=40	Toxicity was assessed according to the NCI-CTCAE version 4.03. Reporting of all AEs and SAEs Routine vital signs and laboratory evaluations

Source: [Study A2303]

The analysis set, and treatment groups are presented in Table 19.

The **Safety set** (ceritinib group: N=115; chemotherapy group: N=113) consisted of all patients who received at least one dose of study drug. Patients were analyzed as applicable according to the study treatment or the study drug they received.

The **Cross-over analysis set** (N=74) consisted of patients randomized to the chemotherapy 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.

Table 19: Database, analysis sets and treatment groups

Analysis set	Study	Treatment groups/columns in tables	Number of patients who received ceritinib 750 mg qd
Safety set	A2303	Ceritinib 750 mg and chemotherapy	115
Cross-over analysis set	A2303	Ceritinib 750 mg	74

*Cross-over data using the cross-over analysis set was assessed separately (presented in Section 2.1.8).

Additional safety information (cumulative line listings of deaths and SAEs) reported in the Novartis global pharmacovigilance safety database (ARGUS) for the other ongoing studies received as of the 10-Aug-2016 are also provided.

The latest [Zykadia PSUR 4] provides additional information in post-marketing setting as follows:

- A review of post-marketing data, including the spontaneous reports, the reports received directly from the worldwide regulatory authorities.
- A review of SAE reported from ongoing studies submitted to the Novartis Drug Safety and Epidemiology department.
- A worldwide literature search, to capture any Investigator published reported on safety aspects not included in the study reports.

4.3.2. Results

This overall safety evaluation is based on data from 228 patients (115 received ceritinib and 113 patients received chemotherapy) from the comparative Study A2303. Patients treated with ceritinib have been exposed to the drug at the recommended dosing regimen of 750 mg once daily (fasted condition).

In addition, the analysis of safety data (n=74) after cross-over from chemotherapy to ceritinib was conducted separately, based on extension-treatment period i.e., from day of first dose of extension ceritinib treatment to 30 days after the last dose of extension ceritinib treatment. This allows an informed assessment of the safety profile of ceritinib and a judgment of the overall benefit-risk of ceritinib in patients with ALK-positive NSCLC.

Exposure to treatment - Patient disposition

Overall, 231 patients were randomized; 115 were randomized to treatment with ceritinib and 116 to treatment with chemotherapy. Three patients in the chemotherapy group (two patients due to Investigators decision and one due to subject/guardian's decision) were not treated. With a median duration of follow-up of 16.5 months (from randomization to data cut-off date) for Study A2303, more patients discontinued treatment with chemotherapy (108 patients, 93.1%) than with ceritinib (82 patients, 71.3%) at the time of the data cut-off (26-Jan-2016). Treatment was ongoing for 33 patients (28.7%) in the ceritinib group and for eight patients (6.9%) in the chemotherapy group at the time of the data cut-off.

In the treatment phase, the primary reason for treatment discontinuation in both the treatment groups was disease progression, although there were a greater proportion of discontinuations in chemotherapy group attributable to progression (82 patients (70.7%) in chemotherapy vs. 56 patients (48.7%) in the ceritinib group). Treatment discontinuation attributable to AEs was comparable between the chemotherapy and ceritinib groups (eight patients (6.9%) in chemotherapy vs. six patients (5.2%) in ceritinib group) (Table 20). Overall 14 patients (nine patients (7.8%) in ceritinib group, and five patients (4.3%) in the chemotherapy group) discontinued due to death; 12 of these 14 deaths were attributed to the underlying malignancy. Causes of death for the remaining two cases (both in ceritinib group) included respiratory failure and cerebrovascular accident, were consistent with what would be expected in a population with advanced cancer and with other comorbid conditions, and were not study drug-related. In addition, more than half of the ceritinib patients continued the treatment beyond BIRC –confirmed PD (for more than 6 weeks) while none of chemotherapy patients did continue beyond PD (for more than 6 weeks).

Seventy-five patients (74 patients from treatment phase and one from post-treatment followup phase) from the chemotherapy group (48 patients from the docetaxel group and 27 patients from the pemetrexed group) crossed over to ceritinib, and entered the extension-treatment phase. All the 75 patients who crossed-over had BIRC-confirmed PD at the time of cross-over, except for one patient who was reported as a protocol deviation. One of these 75 patients died before starting the first dose of ceritinib in the extension-treatment phase, and 74 received ceritinib. At the time of the data cut-off, 28/75 patients (37.3%) in the extension-treatment phase were still ongoing. Forty-seven of the 75 patients discontinued the extension-treatment phase, and the primary reasons for discontinuation were disease progression (24 patients) or deaths (15 patients) (Table 20).

Table 20: Patient disposition by treatment group (FAS)

Disposition/reason	Ceritinib750 mg N=115 n (%)	Chemotherapy N=116 n (%)	All patients N=231 n (%)
Patients randomized			
Treated	115 (100)	113 (97.4)	228 (98.7)
Untreated	0	3 (2.6)	3 (1.3)
Treatment phase			
Ongoing[a]	33 (28.7)	8 (6.9)	41 (17.7)
Discontinued from treatment phase	82 (71.3)	108 (93.1)	190 (82.3)
Entered extension-treatment phase	0	74 (63.8)	74 (32.0)

Entered post-treatment follow-up phase	7 (6.1)	5 (4.3)	12 (5.2)
Entered survival follow-up phase	61 (53.0)	19 (16.4)	80 (34.6)
Discontinued from study	14 (12.2)	10 (8.6)	24 (10.4)
Primary reason for discontinuation from treatment phase			
Progressive disease	56 (48.7)	82 (70.7)	138 (59.7)
Adverse event	6 (5.2)	8 (6.9)	14 (6.1)
Death	9 (7.8)	5 (4.3)	14 (6.1)
Subject/guardian decision	6 (5.2)	8 (6.9)	14 (6.1)
Physician decision[c]	5 (4.3)	5 (4.3)	10 (4.3)
Post-treatment follow-up phase			
Ongoing[a]	1 (0.9)	1 (0.9)	2 (0.9)
Discontinued post-treatment follow-up phase	6 (5.2)	4 (3.4)	10 (4.3)
Entered extension-treatment phase after discontinuation post-treatment follow-up phase	0	1 (0.9)	1 (0.4)
Entered survival follow-up phase after discontinuation post-treatment follow-up phase	1 (0.9)	3 (2.6)	4 (1.7)
Discontinued from study	5 (4.3)	0	5 (2.2)
Primary reason for discontinuation from post-treatment phase			
Death	3 (2.6)	0	3 (1.3)
Lost to follow-up	2 (1.7)	0	2 (0.9)
Progressive disease	1 (0.9)	1 (0.9)	2 (0.9)
Adverse event	0	1 (0.9)	1 (0.4)
Physician decision	0	1 (0.9)	1 (0.4)
Subject/guardian decision	0	1 (0.9)	1 (0.4)
Extension-treatment phase[b]			
Ongoing[a]	0	28 (24.1)	28 (12.1)
Discontinued extension-treatment phase	0	47 (40.5)	47 (20.3)
Entered survival follow-up phase	0	28 (24.1)	28 (12.1)
Discontinued from study	0	19 (16.4)	19 (8.2)
Primary reason for discontinuation from extension-treatment phase			
Adverse event	0	3 (2.6)	3 (1.3)
Death	0	15 (12.9)	15 (6.5)
Physician decision	0	1 (0.9)	1 (0.4)
Progressive disease	0	24 (20.7)	24 (10.4)
Subject/guardian decision	0	4 (3.4)	4 (1.7)

[a] Patients ongoing at the time of the cut-off 26-Jan-2016.
[b] Extension-treatment phase is for patients who crossed-over from chemotherapy to ceritinib treatment.
[c] Includes eight patients with local disease progression by RECIST not confirmed by BIRC, or clinical disease progression.
Percentage is based on N.
Reasons for discontinuations are based on the 'End of Treatment Phase Disposition', 'End of Extension Treatment Phase Disposition' and 'Post-treatment Phase completion' CRF pages.
Source: [Study A2303-Table 14.1-1.1b] and [Study A2303-Listing 16.2.1-1.1a]

Dose reductions and interruptions

The dose interruptions and dose reductions were more frequent among patients receiving ceritinib than for the chemotherapy group. These dose adjustments were primarily attributable to AEs.

Overall, 70 patients (60.9%), seven patients (17.5%), and 19 patients (26.0%) required at least one dose reduction for ceritinib, pemetrexed, and docetaxel, respectively; with 29.6%, 15.0%, and 21.9% of patients requiring only one dose reduction for ceritinib, pemetrexed, and docetaxel. Among the patients with at least one dose reduction, the primary reason for dose reductions were AEs (ceritinib group: 90.0%, pemetrexed group: 100%, and docetaxel group: 94.7%). In the ceritinib group, the dose adjustments were primarily due to hepatotoxicity and GI AEs.

Dose reductions occurred throughout the treatment period with a higher percentage of dose reductions occurring during Weeks 3 to 6. The median time to first dose reduction in the ceritinib group was 7.0 weeks (range: 0.4 to 46.0 weeks), in pemetrexed group was 6.0 weeks (range: 3.3 to 45.1 weeks), and in docetaxel group was 3.1 weeks (range: 2.9 to 15.1 weeks).

Overall, 88 patients (76.5%), 10 patients (25.0%), and four patients (5.5%) required at least one dose interruption/delay of ceritinib, pemetrexed, and docetaxel, respectively; with 26.1%, 22.5%, and 5.5% of patients requiring only one dose interruption/delay for ceritinib, pemetrexed, and docetaxel. Among the patients with at least one dose interruption/delay, the primary reason were AEs (ceritinib group: 96.6%, pemetrexed group: 90.0%, and docetaxel group: 75.0%). In the ceritinib group, the dose interruptions or delay were primarily due to hepatotoxicity and GI AEs. The median time to first dose interruption was 5.9 weeks (range: 0.3 to 75.1 weeks) in the ceritinib group and 6.4 weeks (range: 3.1 to 33.4 weeks) in the pemetrexed group and 8.4 weeks (range: 3.1 to 18.0 weeks) in the docetaxel group.

Demographic and other characteristics of study population

The demographic, disease, and other baseline characteristics of patients recruited into Study A2303 are consistent with the targeted population of patients with ALK-positive advanced NSCLC previously treated chemotherapy and crizotinib.

The two treatment groups were well-balanced for the demographic characteristics assessed except for race and smoking history. There were a higher proportion of Caucasian in the ceritinib group vs. chemotherapy group (70.4% vs. 58.6%). Ex-smokers were lower in the ceritinib group vs. chemotherapy group (33.9 vs. 44.0%).

In the ceritinib group, the median age was 54.0 years (range: 30 -77 years) and 77.4% of the patients were <65 years old. In line with the geographical location of the enrolling sites, the majority of the patients were Caucasian (70.4%) followed by Asian (26.1%), and a broad representation of ethnicities reflects the countries who participated in this study. In addition, 48.7% of the patients entered the study with a WHO PS score of 0 and 51.3% with a WHO PS score of 1-2. The proportion of patients who had never smoked was 61.7%; 3.5% patients were current smokers at the time of study entry. The demographic characteristics were generally similar between each of the chemotherapy types (pemetrexed and docetaxel) with some difference noted with respect to age, gender and ex-smokers.

- Age: There were a higher proportion of patients with ≥ 65 years in the docetaxel group vs. pemetrexed group (27.4% vs. 15.0%).
- Gender: Females were higher in pemetrexed vs. docetaxel group (62.5% vs. 49.3%).
- Ex-smokers: 52.5% of patients in the pemetrexed group vs. 41.1% of patients in the docetaxel group.

The demographic characteristics of the patients in the chemotherapy group who crossed–over to ceritinib treatment in the extension-treatment phase were consistent with those observed in patients in the treatment phase, except for the WHO PS which was worse at the time of crossover as compared to at the time of enrollment into the chemotherapy group. The proportion of patients with WHO PS at start of extension-treatment phase vs. at the time of enrollment into chemotherapy group was as follows:

- WHO PS 0: 21.6% vs 44.0%
- WHO PS 1: 63.5% vs. 51.7%
- WHO PS 2: 10.8% vs. 4.3%
- WHO PS >2: 4.1% vs. 0

Disease characteristics were representative of the population of ALK-positive NSCLC patients with metastatic disease previously treated with chemotherapy (one or two prior regimens, including one platinum-based doublet) and crizotinib. Baseline disease characteristics were well-balanced between the two treatment groups. Almost all patients (99.1%) presented with Stage IV disease at the time of study entry, two patients (0.9%) had Stage IIIB disease. All patients had metastatic disease, with a metastatic pattern typical of patients with NSCLC – lung metastases (100% vs. 99.1%), brain metastases (56.5% vs. 59.5%), bone metastases (53.9% vs. 50.9%), lymph nodes metastases (51.3% vs. 53.4%), and liver metastasis (38.3% vs. 32.8%) in ceritinib arm vs chemotherapy arm. The median time from initial diagnosis of the primary site was 19.4 months (range: 5.5 to 153.3) and for chemotherapy was 19.8 months (range: 6.5 to 115.9). The median time since the most recent recurrence/relapse to randomization was same for both the treatment groups (0.8 months).

Previous antineoplastic treatments administered were representative of those routinely used for the treatment of NSCLC, and were generally well-balanced between treatment arms. All patients were treated with at least one prior regimen of crizotinib for advanced disease as per the inclusion criteria, of which three patients (1.3%) had received crizotinib more than once. A total of 189 (81.8%) patients took crizotinib as their last treatment prior to study enrollment. All patients received chemotherapy including a platinum-based doublet (one patient did not received prior platinum-based doublet therapy) for advanced

NSCLC as per the inclusion criteria; 11.7% of patients had received two lines of prior chemotherapy, and none of the patient received three lines of prior chemotherapy for advanced disease. Most patients had received approved/commonly used drugs for the treatment of NSCLC, the most frequently (in ≥ 10% of patients) used medications included: crizotinib (100%), pemetrexed (70.6%), cisplatin (63.6%), carboplatin (42.4%), gemcitabine (16.9%), paclitaxel (14.3%), and bevacizumab (13.4%).

A total of 29.4% patients had prior surgery and 55.4% patients had been treated with prior radiotherapy, 35.9% of the patients had received prior radiation therapy to the brain. The median time from the end date of radiotherapy to the brain to randomization was 6.4 months (range: 0.0 to 44.7). With the exception of prior taxanes and pemetrexed, prior antineoplastic therapies (including surgery, radiation and medication) in the patients who were treated with pemetrexed or docetaxel were similar and consistent with the overall population.

Adverse events

The overall incidence of AEs was similar for ceritinib (100%) and chemotherapy group (99.1%); however, grade 3/4 AEs, suspected AEs, SAEs, AEs requiring dose adjustments, interruptions/delay were reported more frequently in the ceritinib group (with a difference of ≥ 10% relative to chemotherapy group).

The AEs by treatment group are presented in Table 21.

Table 21: Overall summary of AEs by treatment group (Safety set)

	Ceritinib750 mg N=115		Chemotherapy N=113		Pemetrexed N=40		Docetaxel N=73	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths[a]	48 (41.7)		50 (44.2)		16 (40.0)		34 (46.6)	
On-treatment deaths	15 (13.0)		5 (4.4)		2 (5.0)		3 (4.1)	
Adverse events	115 (100)	89 (77.4)	112 (99.1)	72 (63.7)	40 (100)	18 (45.0)	72 (98.6)	54 (74.0)
Suspected to be drug--related	110 (95.7)	60 (52.2)	89 (78.8)	41 (36.3)	31 (77.5)	8 (20.0)	58 (79.5)	33 (45.2)
Serious adverse events	49 (42.6)	45 (39.1)	36 (31.9)	34 (30.1)	11 (27.5)	10 (25.0)	25 (34.2)	24 (32.9)
Suspected to be drug-related	13 (11.3)	12 (10.4)	12 (10.6)	11 (9.7)	2 (5.0)	2 (5.0)	10 (13.7)	9 (12.3)
AEs leading to discontinuation	18 (15.7)	15 (13.0)	11 (9.7)	9 (8.0)	4 (10.0)	4 (10.0)	7 (9.6)	5 (6.8)
AEs requiring dose adjustment	42 (36.5)	11 (9.6)	24 (21.2)	21 (18.6)	6 (15.0)	5 (12.5)	18 (24.7)	16 (21.9)
AEs requiring dose interruption/delay	84 (73.0)	58 (50.4)	27 (23.9)	12 (10.6)	13 (32.5)	5 (12.5)	14 (19.2)	7 (9.6)
AEs requiring additional therapy	106 (92.2)	55 (47.8)	100 (88.5)	56 (49.6)	34 (85.0)	13 (32.5)	66 (90.4)	43 (58.9)

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 one category are counted once in each of those categories.
[a] All deaths, including those after the end of the on-treatment period.
Only AEs occurring during on-treatment period are summarized.
AEs are graded according to the CTCAE V4.03.
Source: [Study A2303-Table 14.3.1-1.21]

Common adverse events

Adverse events regardless of study drug relationship were experienced by 100% of patients ceritinib group and 99.1% of the chemotherapy group. The SOCs where AEs were reported in ≥ 30% of patients in either of the treatment groups included (Table 22):

- **Ceritinib group**: gastrointestinal disorders (93.9%), investigations (73.9%), general disorders and administrative site conditions (61.7%), metabolism and nutrition disorders (56.5%), musculoskeletal and connective tissue disorders (43.5%), respiratory, thoracic and mediastinal disorders (41.7%), infections and infestations (39.1%), nervous system disorders (39.1%), and skin and subcutaneous tissue disorders (33.9%).
- **Chemotherapy group**: general disorders and administrative site conditions (62.8%), gastrointestinal disorders (57.5%), respiratory, thoracic and mediastinal disorders (53.1%), and musculoskeletal and connective tissue disorders (41.6%), blood and lymphatic system disorders (39.8%), nervous system disorders (39.8%), skin and subcutaneous tissue disorders (34.5%), investigations (34.5%), metabolism and nutrition disorders (30.1%).

System organ classes where there were higher proportions of the ceritinib-treated patients reported events (≥ 20% difference relative to chemotherapy group) included:

- Investigations (+39.4%) (primarily transaminitis (ALT increased and AST increased), ALP increased, GGT increased, creatinine increased)
- Gastrointestinal disorders (+36.4%) (primarily diarrhea, nausea, and vomiting)
- Metabolism and nutrition disorders (+26.4%) (primarily decreased appetite)

These toxicities are manageable in clinical setting and treatment discontinuation due to these was low: only two patients (1.7%) discontinued the treatment due to transaminitis (suspected to be study drug-related) and one patient (0.9%) due to vomiting (not suspected to be study drug-related).

As expected, AEs of the SOC blood and lymphatic system disorders were reported more frequently in the chemotherapy group compared to the ceritinib group (+29.4% of patients).

The SOCs where grade 3/4 AEs were reported in ≥ 10% of patients in either of the treatment groups included (Table 22):

- **Ceritinib group:** gastrointestinal disorders (16.5%), investigations (43.5%), general disorders and administrative site conditions (18.3%), metabolism and nutrition disorders (12.2%), and respiratory, thoracic and mediastinal disorders (12.2%).
- **Chemotherapy group:** blood and lymphatic system disorders (24.8%), general disorders and administrative site conditions (13.3%), investigations (16.8%), and respiratory, thoracic and mediastinal disorders (11.5%).

Table 22: Adverse events by treatment group, regardless of study drug relationship, by primary system organ class, maximum grade (Safety set)

Primary SOC	Ceritinib 750 mg N=115		Chemotherapy N=113		Pemetrexed N=40		Docetaxel N=73	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade ¾ n (%)
Any primary SOC	**115 (100)**	**89 (77.4)**	**112 (99.1)**	**72 (63.7)**	**40 (100)**	**18 (45.0)**	**72 (98.6)**	**54 (74.0)**
Gastrointestinal disorders	108 (93.9)	19 (16.5)	65 (57.5)	6 (5.3)	23 (57.5)	2 (5.0)	42 (57.5)	4 (5.5)
Investigations	85 (73.9)	50 (43.5)	39 (34.5)	19 (16.8)	13 (32.5)	5 (12.5)	26 (35.6)	14 (19.2)
General disorders and administration site conditions	71 (61.7)	21 (18.3)	71 (62.8)	15 (13.3)	25 (62.5)	6 (15.0)	46 (63.0)	9 (12.3)
Metabolism and nutrition disorders	65 (56.5)	14 (12.2)	34 (30.1)	7 (6.2)	9 (22.5)	0	25 (34.2)	7 (9.6)
Musculoskeletal and connective tissue disorders	50 (43.5)	5 (4.3)	47 (41.6)	9 (8.0)	16 (40.0)	4 (10.0)	31 (42.5)	5 (6.8)
Respiratory, thoracic and mediastinal disorders	48 (41.7)	14 (12.2)	60 (53.1)	13 (11.5)	21 (52.5)	2 (5.0)	39 (53.4)	11 (15.1)
Infections and infestations	45 (39.1)	10 (8.7)	30 (26.5)	7 (6.2)	15 (37.5)	1 (2.5)	15 (20.5)	6 (8.2)
Nervous system disorders	45 (39.1)	8 (7.0)	45 (39.8)	10 (8.8)	15 (37.5)	3 (7.5)	30 (41.1)	7 (9.6)
Skin and subcutaneous tissue disorders	39 (33.9)	0	39 (34.5)	1 (0.9)	10 (25.0)	0	29 (39.7)	1 (1.4)
Cardiac disorders	21 (18.3)	7 (6.1)	8 (7.1)	2 (1.8)	2 (5.0)	1 (2.5)	6 (8.2)	1 (1.4)
Psychiatric disorders	16 (13.9)	1 (0.9)	23 (20.4)	2 (1.8)	7 (17.5)	1 (2.5)	16 (21.9)	1 (1.4)
Blood and lymphatic system disorders	12 (10.4)	1 (0.9)	45 (39.8)	28 (24.8)	10 (25.0)	4 (10.0)	35 (47.9)	24 (32.9)
Eye disorders	12 (10.4)	1 (0.9)	13 (11.5)	1 (0.9)	6 (15.0)	1 (2.5)	7 (9.6)	0
Vascular disorders	12 (10.4)	2 (1.7)	11 (9.7)	2 (1.8)	4 (10.0)	0	7 (9.6)	2 (2.7)
Renal and urinary disorders	10 (8.7)	2 (1.7)	6 (5.3)	0	4 (10.0)	0	2 (2.7)	0
Hepatobiliary disorders	9 (7.8)	1 (0.9)	4 (3.5)	2 (1.8)	1 (2.5)	0	3 (4.1)	2 (2.7)
Injury, poisoning and procedural complications	8 (7.0)	0	6 (5.3)	2 (1.8)	1 (2.5)	0	5 (6.8)	2 (2.7)
Ear and labyrinth disorders	6 (5.2)	0	6 (5.3)	0	4 (10.0)	0	2 (2.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (3.5)	2 (1.7)	5 (4.4)	2 (1.8)	3 (7.5)	1 (2.5)	2 (2.7)	1 (1.4)
Reproductive system and breast disorders	2 (1.7)	0	2 (1.8)	0	1 (2.5)	0	1 (1.4)	0
Surgical and medical procedures	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Immune system disorders	0	0	4 (3.5)	0	0	0	4 (5.5)	0

Primary SOC are sorted in decreasing frequency of all grades column, as reported for the ceritinib treatment group.
A patient with multiple occurrences of an AE was counted only once in the AE category.
A patient with multiple adverse events within a primary system organ class was counted only once in the total row.
The event with maximum severity was counted for patients who experienced multiple episodes of an event
Only AEs occurring during on-treatment period are summarized.
Missing grades are included under 'All grades' column.
MedDRA version 18.1 was used. AEs are graded according to the CTCAE V4.03.
Source: [Study A2303-Table:14.3.1-1.2]

The most frequently reported AEs (in ≥ 20% of patients) regardless of study drug relationship by PTs in either of the treatment groups included:

- **Ceritinib group**: diarrhea (72.2%), nausea (66.1%), vomiting (52.2%), ALT increased (42.6%), decreased appetite (41.7%), AST increased (36.5%), weight decreased (29.6%), fatigue (27.0%), asthenia (22.6%), ALP increased (22.6%), GGT increased (22.6%), abdominal pain (21.7%), and back pain (21.7%).
- **Chemotherapy group**: nausea (23.0%), fatigue (28.3%), alopecia (21.2%) and neutropenia (20.4%).

- Fatigue, nausea (each in 35.0%), asthenia, ALT increased (each in 20%) were the most frequently reported AEs (in ≥ 20% of patients) in the patients receiving pemetrexed.
- Alopecia (31.5%), neutropenia (27.4%), diarrhea (26.0%), fatigue (24.7%), and decreased appetite (23.3%) were the most frequently reported AEs (in ≥ 20% of patients) in the patients receiving docetaxel.

The majority of patients (77.4%) receiving ceritinib therapy had grade 3/4 AEs regardless of study drug relationship; of these, 61.7% and 15.7% of patients had a grade 3 event and a grade 4 event, respectively. In comparison, grade 3/4 events were reported in 63.7% of patients in the chemotherapy treatment group; of these, 38.9% and 24.8% had a grade 3 event and a grade 4 event, respectively.

The most frequently reported (in ≥ 10% of patients) grade 3/4 events in patients treated with ceritinib included ALT increased (20.9%), GGT increased (20.9%), and AST increased (13.9%); whereas neutropenia (15.0%) was the most frequently reported grade 3/4 AE in the chemotherapy group (Table 23).

Twenty-two (19.1%) patients had creatinine elevations in the ceritinib group and none in the chemotherapy group.

Table 23: Adverse events by treatment group, regardless of study drug relationship, by preferred term, maximum grade, and treatment group (with at least 10% incidence for all grades in either group) (Safety set)

	Ceritinib N=115		Chemotherapy N=113		Pemetrexed N=40		Docetaxel N=73	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade ¾
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**115 (100)**	**89 (77.4)**	**112 (99.1)**	**72 (63.7)**	**40 (100)**	**18 (45.0)**	**72 (98.6)**	**54 (74.0)**
Diarrhoea	83 (72.2)	5 (4.3)	20 (17.7)	1 (0.9)	1 (2.5)	0	19 (26.0)	1 (1.4)
Nausea	76 (66.1)	9 (7.8)	26 (23.0)	2 (1.8)	14 (35.0)	1 (2.5)	12 (16.4)	1 (1.4)
Vomiting	60 (52.2)	9 (7.8)	6 (5.3)	1 (0.9)	2 (5.0)	1 (2.5)	4 (5.5)	0
ALT increased	49 (42.6)	24 (20.9)	10 (8.8)	2 (1.8)	8 (20.0)	2 (5.0)	2 (2.7)	0
Decreased appetite	48 (41.7)	2 (1.7)	22 (19.5)	3 (2.7)	5 (12.5)	0	17 (23.3)	3 (4.1)
AST increased	42 (36.5)	16 (13.9)	5 (4.4)	1 (0.9)	3 (7.5)	1 (2.5)	2 (2.7)	0
Weight decreased	34 (29.6)	3 (2.6)	7 (6.2)	1 (0.9)	1 (2.5)	0	6 (8.2)	1 (1.4)
Fatigue	31 (27.0)	6 (5.2)	32 (28.3)	5 (4.4)	14 (35.0)	2 (5.0)	18 (24.7)	3 (4.1)
Asthenia	26 (22.6)	6 (5.2)	21 (18.6)	7 (6.2)	8 (20.0)	4 (10.0)	13 (17.8)	3 (4.1)
Blood ALP increased	26 (22.6)	7 (6.1)	1 (0.9)	0	0	0	1 (1.4)	0
GGT increased	26 (22.6)	24 (20.9)	2 (1.8)	1 (0.9)	0	0	2 (2.7)	1 (1.4)
Abdominal pain	25 (21.7)	1 (0.9)	11 (9.7)	1 (0.9)	5 (12.5)	0	6 (8.2)	1 (1.4)
Back pain	25 (21.7)	1 (0.9)	8 (7.1)	3 (2.7)	3 (7.5)	1 (2.5)	5 (6.8)	2 (2.7)
Blood creatinine increased	22 (19.1)	0	0	0	0	0	0	0
Constipation	22 (19.1)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Headache	22 (19.1)	1 (0.9)	17 (15.0)	2 (1.8)	6 (15.0)	1 (2.5)	11 (15.1)	1 (1.4)
Dyspnoea	20 (17.4)	6 (5.2)	21 (18.6)	7 (6.2)	7 (17.5)	2 (5.0)	14 (19.2)	5 (6.8)
Pyrexia	19 (16.5)	2 (1.7)	17 (15.0)	0	4 (10.0)	0	13 (17.8)	0
Abdominal pain upper	18 (15.7)	1 (0.9)	5 (4.4)	0	1 (2.5)	0	4 (5.5)	0
Cough	16 (13.9)	0	18 (15.9)	1 (0.9)	6 (15.0)	0	12 (16.4)	1 (1.4)
Non-cardiac chest pain	15 (13.0)	1 (0.9)	4 (3.5)	0	2 (5.0)	0	2 (2.7)	0
Electrocardiogram QT prolonged	13 (11.3)	1 (0.9)	0	0	0	0	0	0
Rash	13 (11.3)	0	12 (10.6)	0	6 (15.0)	0	6 (8.2)	0
Arthralgia	12 (10.4)	0	13 (11.5)	3 (2.7)	3 (7.5)	2 (5.0)	10 (13.7)	1 (1.4)
Nasopharyngitis	12 (10.4)	0	1 (0.9)	0	1 (2.5)	0	0	0
Alopecia	6 (5.2)	0	24 (21.2)	0	1 (2.5)	0	23 (31.5)	0
Anaemia	6 (5.2)	0	19 (16.8)	5 (4.4)	5 (12.5)	4 (10.0)	14 (19.2)	1 (1.4)
Stomatitis	5 (4.3)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Myalgia	4 (3.5)	0	13 (11.5)	0	2 (5.0)	0	11 (15.1)	0
Neutropenia	4 (3.5)	1 (0.9)	23 (20.4)	17 (15.0)	3 (7.5)	0	20 (27.4)	17 (23.3)

ALT=alanine aminotransferase; ALP=alkaline phosphatase, AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase
Preferred terms are sorted in descending frequency of all grades column, as reported for the ceritinib treatment group.
A patient with multiple adverse events was counted only in the total row.
Missing grades are included under 'All grades' column.
Source: [Study A2303-Table 14.3.1-1.4]

Events suspected to be drug-related

Overall, 95.7% of patients treated with ceritinib had AEs suspected to be study drug –related compared to 78.8% of patients treated with chemotherapy. The most frequently reported AEs (in ≥ 20% of patients) suspected as being drug-related in the ceritinib group included: diarrhea (63.5%), nausea (60.9%),

vomiting (47.8%), ALT increased (41.7%), AST increased (35.7%), and decreased appetite (33.0%). Fatigue (23.9%) was the most commonly occuring AE suspected as being drug-related in the chemotherapy group (Table 24). The AEs suspected to be related to ceritinib treatment are consistent with the known safety profile of ceritinib.

Grade 3/4 AEs suspected to be related to study treatment were reported in 52.2% and 36.3% of patients in the ceritinib group and chemotherapy group, respectively. The most frequently reported (in ≥ 10% of patients) grade 3/4 AEs suspected as being drug-related in the ceritinib included: ALT increased (20.9%), GGT increased (14.8%), and AST increased (13.0%), and in the chemotherapy group was neutropenia (13.3%) (Table 24).

Table 24: Adverse events by treatment group, suspected to be study drugrelated, by preferred term, maximum grade, and treatment group (with at least 10% incidence for all grades in either group) (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Pemetrexed N=40		Docetaxel N=73	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	**110 (95.7)**	**60 (52.2)**	**89 (78.8)**	**41 (36.3)**	**31 (77.5)**	**8 (20.0)**	**58 (79.5)**	**33 (45.2)**
Diarrhoea	73 (63.5)	2 (1.7)	15 (13.3)	1 (0.9)	1 (2.5)	0	14 (19.2)	1 (1.4)
Nausea	70 (60.9)	8 (7.0)	18 (15.9)	2 (1.8)	8 (20.0)	1 (2.5)	10 (13.7)	1 (1.4)
Vomiting	55 (47.8)	7 (6.1)	3 (2.7)	0	0	0	3 (4.1)	0
ALT increased	48 (41.7)	24 (20.9)	9 (8.0)	2 (1.8)	7 (17.5)	2 (5.0)	2 (2.7)	0
AST increased	41 (35.7)	15 (13.0)	5 (4.4)	1 (0.9)	3 (7.5)	1 (2.5)	2 (2.7)	0
Decreased appetite	38 (33.0)	1 (0.9)	17 (15.0)	1 (0.9)	4 (10.0)	0	13 (17.8)	1 (1.4)
Blood ALP increased	21 (18.3)	5 (4.3)	1 (0.9)	0	0	0	1 (1.4)	0
Weight decreased	21 (18.3)	1 (0.9)	3 (2.7)	0	0	0	3 (4.1)	0
Blood creatinine increased	20 (17.4)	0	0	0	0	0	0	0
Fatigue	20 (17.4)	3 (2.6)	27 (23.9)	4 (3.5)	12 (30.0)	2 (5.0)	15 (20.5)	2 (2.7)
GGT increased	18 (15.7)	17 (14.8)	1 (0.9)	0	0	0	1 (1.4)	0
Abdominal pain	15 (13.0)	0	2 (1.8)	0	1 (2.5)	0	1 (1.4)	0
Asthenia	15 (13.0)	4 (3.5)	13 (11.5)	2 (1.8)	4 (10.0)	1 (2.5)	9 (12.3)	1 (1.4)
Electrocardiogram QT prolonged	13 (11.3)	1 (0.9)	0	0	0	0	0	0
Alopecia	3 (2.6)	0	22 (19.5)	0	1 (2.5)	0	21 (28.8)	0
Neutropenia	3 (2.6)	0	21 (18.6)	15 (13.3)	3 (7.5)	0	18 (24.7)	15 (20.5)
Stomatitis	2 (1.7)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT= Gamma- glutamyltransferase, ALP=alkaline phosphatase.

Preferred terms are sorted in descending frequency of all grades column, as reported for the ceritinib 750 mg treatment group.

A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

A patient with multiple adverse events was counted only once in the total row.

Only AEs occurring during on-treatment period are summarized.

Missing grades are included under 'All grades' column.

MedDRA version 18.1 is used. AEs are graded according to the CTCAE V4.03.

Source:[Study A2303-Table 14.3.1-1.8]

Adverse drug reactions

The current safety pool is based on safety data from 525 patients treated with ceritinib 750 mg of the 4 clinical Studies X2101, X1101, A2201, and A2203. This pooled safety set is the basis of the current Summary of Product Characteristics with a data cut-off date of 23-Jun-2014.

In Study A2303, any terms not listed in the current reference safety information and occurring in more than 2% of patients and/or in at least 3 patients in the ceritinib group (n=115) compared to the chemotherapy group (n=113) were selected as new potential adverse drug reaction (ADR) candidates.

One new ADR and one additional term for the already existing ADR of liver laboratory test abnormalities was identified (Table 25).

Table 25: Newly identified adverse drug reactions for ceritinib treatment

Primary System Organ Class Preferred term	All grades	Frequency category
Investigations		
Liver laboratory test abnormalities[m]	~~50.5~~ **52.0**	Very common
Weight decreased	**127 (24.2)**	**Very common**

[m] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal, **blood alkaline phosphatase increased**)

Serious adverse events

Serious adverse events regardless of study drug relationship were reported in 42.6% of patients in the ceritinib group and 31.9% of patients in the chemotherapy group, with majority (39.1% vs. 30.1%) of these were grade 3/4 in both the treatment groups (Table 26).

The incidence of individual SAEs was low for both treatment groups, and commonly associated with underlying disease progression. The most frequently reported (in ≥ 2% of patients) SAEs in patients receiving ceritinib treatment were dyspnea (6.1%); nausea (5.2%); general physical health deterioration, pleural effusion, pneumonia, and vomiting (each 4.3%), pericardial effusion and pyrexia (each 3.5%), and respiratory failure (2.6%). Whereas in chemotherapy group dyspnea (4.4%) and asthenia (2.7%) were reported most frequently (Table 26).

Thirteen patients (11.3%) from the ceritinib group and 12 patients (10.6%) from the chemotherapy group experienced SAEs that were suspected by the Investigator to be related to study treatment. The most commonly reported (in ≥ 2% of patients) study drug-related SAEs in the ceritinib group were nausea (four patients, 3.5%) and vomiting (three patients, 2.6%).

Majority of these SAEs suspected to be drug-related were grade 3/4 in severity in both the treatment groups (10.4% vs. 9.7% in ceritinib vs. chemotherapy). Most of these events were single occurrences except for few of the events in the ceritinib group: nausea (three patients, 2.6%), vomiting and general health deterioration (two patients, 1.7% each).

There were no drug related SAEs with fatal outcome except one patient in the ceritinib group; this patient [A2303-1255-002] had an SAE of general status health deterioration in the context of disease progression and subsequently died. The SAE was considered to be study drug related as the Investigator could not exclude some contribution of study treatment to general status health deterioration; however the patient died due to disease progression.

The incidence of serious AESIs in the ceritinib group (irrespective of causality) in the Study A2303 included:

- Hepatotoxicity: one patient (0.9%)
- ILD/pneumonitis: two patients (1.7%)
- QT prolongation: two patients (1.7%)
- Bradycardia-related: one patient (0.9%)
- Hyperglycemia: one patient (0.9%)

- GI toxicity: eight patients (7.0%)

None of the drug-related AESIs were the primary cause of death.

Table 26: Serious adverse events regardless of study drug relationship, by treatment group, and preferred term (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Chemotherapy (N=113) Pemetrexed N=40		Chemotherapy (N=113) Docetaxel N=73	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**49 (42.6)**	**45 (39.1)**	**36 (31.9)**	**34 (30.1)**	**11 (27.5)**	**10 (25.0)**	**25 (34.2)**	**24 (32.9)**
Dyspnoea	7 (6.1)	6 (5.2)	5 (4.4)	5 (4.4)	2 (5.0)	2 (5.0)	3 (4.1)	3 (4.1)
Nausea	6 (5.2)	4 (3.5)	0	0	0	0	0	0
General physical health deterioration	5 (4.3)	5 (4.3)	2 (1.8)	2 (1.8)	1 (2.5)	1 (2.5)	1 (1.4)	1 (1.4)
Pleural effusion	5 (4.3)	5 (4.3)	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)
Pneumonia	5 (4.3)	5 (4.3)	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)
Vomiting	5 (4.3)	4 (3.5)	0	0	0	0	0	0
Pericardial effusion	4 (3.5)	3 (2.6)	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Pyrexia	4 (3.5)	2 (1.7)	2 (1.8)	0	0	0	2 (2.7)	0
Respiratory failure	3 (2.6)	3 (2.6)	0	0	0	0	0	0
Asthenia	2 (1.7)	2 (1.7)	3 (2.7)	3 (2.7)	2 (5.0)	2 (5.0)	1 (1.4)	1 (1.4)
Atrial fibrillation	2 (1.7)	1 (0.9)	1 (0.9)	1 (0.9)	1 (2.5)	1 (2.5)	0	0
Dehydration	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Diarrhoea	2 (1.7)	1 (0.9)	0	0	0	0	0	0
Epilepsy	2 (1.7)	2 (1.7)	0	0	0	0	0	0
Fatigue	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Muscular weakness	2 (1.7)	2 (1.7)	0	0	0	0	0	0
Respiratory tract infection	2 (1.7)	1 (0.9)	0	0	0	0	0	0
Seizure	1 (0.9)	0	2 (1.8)	2 (1.8)	1 (2.5)	1 (2.5)	1 (1.4)	1 (1.4)
Back pain	0	0	2 (1.8)	2 (1.8)	1 (2.5)	1 (2.5)	1 (1.4)	1 (1.4)
Neutropenic sepsis	0	0	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)
Pneumonitis	0	0	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)

Preferred terms are sorted in descending frequency of all grades column, as reported for the Ceritinib 750 mg treatment group.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple adverse events was counted only once in the total row.
Only AEs occurring during on-treatment period are summarized.
Missing grades are included under 'All grades' column.
MedDRA version 18.1 was used. AEs are graded according to the CTCAE V4.03.
Source:[Study A2303-Table 14.3.1-1.11]

Deaths

As of the data cut-off of 26-Jan-2016, 98 deaths were reported in the study. The incidence of deaths was similar in the two treatment groups, 48 patients (41.7%) and 50 patients (44.2%) died in the ceritinib and chemotherapy groups, respectively. Majority of these deaths in both the treatment groups (42/48 deaths in ceritinib and 43/50 deaths in chemotherapy group) were attributed to underlying disease. There were no deaths due to study drug-related AEs, except for one patient who died in the extension-treatment phase. This patient was initially treated with pemetrexed and crossed-over to ceritinib after disease progression in the lung. On Day 101, the patient was noted with Grade 3 hypertension and received the first dose of ceritinib on the same day. Two weeks later, the patient was hospitalized due to nausea, and was diagnosed with pulmonary embolism the next day. Due to further worsening of the clinical condition and respiratory insufficiency, palliative sedation was started, and the patient died on Day 121 due to the event (pulmonary embolism). The investigator could not exclude a possible relationship with study drug.

The on-treatment deaths were reported for 20 patients (15 patients (13.0%) and five patients (4.4%) in the ceritinib and chemotherapy treatment groups, respectively) (Table 27). Eighteen of these 20 on-treatment deaths were attributed to the underlying malignancy/or disease progression. Cause of death for the remaining two cases (both in ceritinib group) were reported as "other causes" which included

cerebrovascular accident and respiratory failure (in the context of disease progression), and were assessed as not related to ceritinib by the Investigator. Overall, the causes of death were consistent with what would be expected in a population with NSCLC and with other comorbid conditions. The slightly higher frequency of on-treatment deaths in the ceritinib could be attributed to the high rate of early disease progression in the chemotherapy group resulting short treatment exposure (6.3 weeks for chemotherapy vs. 30.3 weeks for ceritinib). In addition patients with disease progression in the chemotherapy group discontinued study treatment while more than half of the patients in the ceritinib group continued treatment with ceritinib beyond disease progression. On-treatment deaths occurred throughout the treatment period with a mean/median time from treatment start until occurrence of on-treatment death of 137/52 days and 70/28 days in the ceritin ib and chemotherapy groups, respectively; the frequency of on-treatment deaths during the first 6 weeks of study treatment was similar between the two groups.

Narratives of patients who died due to other causes in Study A2303 are presented in Table 28.

Table 27: On-treatment deaths by principal cause, primary system organ class, preferred term and treatment group (Safety Set)

Principal cause of death Primary system organ class Preferred term	Ceritinib 750 mg N=115 n (%)	Chemotherapy N=113 n (%)	Pemetrexed N=40 n (%)	Docetaxel N=73 n (%)
Total on-treatment death	15 (13.0)	5 (4.4)	2 (5.0)	3 (4.1)
Study indication	13 (11.3)	5 (4.4)	2 (5.0)	3 (4.1)
Other	2 (1.7)	0	0	0
Any primary system organ class	**15 (13.0)**	**5 (4.4)**	**2 (5.0)**	**3 (4.1)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**13 (11.3)**	**5 (4.4)**	**2 (5.0)**	**3 (4.1)**
Non-small cell lung cancer	13 (11.3)	5 (4.4)	2 (5.0)	3 (4.1)
Nervous system disorders	**1 (0.9)**	**0**	**0**	**0**
Cerebrovascular accident	1 (0.9)	0	0	0
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**0**	**0**	**0**
Respiratory failure	1 (0.9)	0	0	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported for the ceritinib 750 mg treatment group.
Only deaths during on-treatment period are summarized.
The MedDRA version 18.1 was used.
Source: [Study A2303-Table 14.3.1-1.5]

Table 28: Details of patients who died on-treatment due to "other" causes in Study A2303

Treatment Group Patient no. Age, Gender, Race Treatment duration	Cause of death System organ class Preferred term	Comments	Investigator attributed relationship to study drug
Ceritinib 750 mg [A2303-1901-001] 68-year-old, Male, Caucasian Died Day 86 Last dose received Day 85	Other Respiratory, thoracic and mediastinal disorder Respiratory failure	The patient entered the study with NSCLC metastatic to the brain, liver, lung, pleura, ascites, and mediastinal lymph nodes. No past medical history was reported. Active medical conditions included diabetes mellitus, sedation, hypertension, dyspnea (grade 2), pleural effusion (grade 3), deep vein thrombosis (grade 2), pulmonary embolism (grade 1), and fatigue. On Day 39, first post-baseline tumor evaluation showed disease progression with worsening of pleural effusion. On Day 47 of the study, ceritinib was interrupted due grade 2 creatinine increase. On Day 82, the patient was hospitalized due to disease progression. Ceritinib was restarted at a reduced dose of 600 mg the next day; however, on Day 86 the patient developed grade 4 respiratory failure and died on the same day with disease progression as contributory factor.	Not suspected
Ceritinib 750 mg [A2303-5052-001] 68-year-old, Female, Caucasian Died Day 22 Last dose received Day 9	Other Nervous system disorders Cerebrovascular accident	The patient entered the study with NSCLC metastatic to the bone, lung, lymph nodes, and thoracic spine. No past medical history was reported. Active medical conditions included hypercholesterolemia, hypothyroidism, chronic obstructive pulmonary disease, pain, vomiting (grade 1), nausea (grade 1), insomnia, and anxiety. On Day 10, the patient was hospitalized and ceritinib was interrupted due to vomiting, nausea, and diarrhea; the patient was also transfused due to anemia. ECG revealed sinus tachycardia, cardiac enzymes were normal. On Day 14, the patient was disoriented, and was diagnosed with acute stroke based on brain MRI the next day (cerebrovascular accident, grade 3). The event continued to worsen upon which it was decided to withdraw further support; on Day 22, the patient died due to the event.	Not suspected

Source: [Study A2303-Table 14.3.1-1.5], [Study A2303-Listing 14.2-1.2], [Study A2303-Listing 14.3.2-1.1], [Study A2303-Listing 16.2.7-1.1], [Study A2303-Section 14.3.3]

Adverse events leading to discontinuation

The frequency AEs leading to study drug discontinuation was similar in both the treatment groups (18 patients [15.7%] vs. 11 patients [9.7%] in ceritinib vs. chemotherapy group), and majority of these AEs were grade 3/4 in both the treatment groups (15 patients [13.0%] vs. nine patients [8.0%]).

The AEs reported (in ≥ 1% of the patients) leading to discontinuation in the ceritinib group were dyspnea (three patients, 2.6%), ALT increased, AST increased, pericardial effusion, general physical health deterioration, and pleural effusion (two patients, 1.7% each).

In the chemotherapy group, with the exception of asthenia and dyspnea which led to the discontinuation of study treatment in four and two patients, respectively, all other AEs leading to study drug discontinuation were single events.

Of the 18 patients who discontinued study treatment due to AEs in the ceritinib group, on medical review most of the AEs were related to disease progression and/or the underlying disease and were not considered causally related to study treatment as per Investigator assessment. Six patients had AEs which were considered to be drug-related by the Investigator which included transaminitis (n=2), general physical health deterioration (n=1), pericarditis (n=1), ILD (n=1), and pleural effusion (n=1). The reasons for other patients could be attributed to worsening of underlying disease and other co-morbidities.

Table 29: Adverse events leading to discontinuation by treatment group, by preferred term and maximum grade (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Chemotherapy (N=113) Pemetrexed N=40		Chemotherapy (N=113) Docetaxel N=73	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	**18 (15.7)**	**15 (13.0)**	**11 (9.7)**	**9 (8.0)**	**4 (10.0)**	**4 (10.0)**	**7 (9.6)**	**5 (6.8)**
Dyspnoea	3 (2.6)	2 (1.7)	2 (1.8)	2 (1.8)	1 (2.5)	1 (2.5)	1 (1.4)	1 (1.4)
ALT increased	2 (1.7)	2 (1.7)	0	0	0	0	0	0
AST increased	2 (1.7)	2 (1.7)	0	0	0	0	0	0
General physical health deterioration	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.9)	1 (2.5)	1 (2.5)	0	0
Pericardial effusion	2 (1.7)	2 (1.7)	0	0	0	0	0	0
Pleural effusion	2 (1.7)	2 (1.7)	0	0	0	0	0	0
Atrial flutter	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Fatigue	1 (0.9)	1 (0.9)	1 (0.9)	0	0	0	1 (1.4)	0
Interstitial lung disease	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Lung infiltration	1 (0.9)	0	0	0	0	0	0	0
Metastases to central nervous system	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Pericarditis	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Petit mal epilepsy	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Respiratory failure	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Respiratory tract infection	1 (0.9)	1 (0.9)	0	0	0	0	0	0
Vomiting	1 (0.9)	0	0	0	0	0	0	0
Asthenia	0	0	4 (3.5)	3 (2.7)	2 (5.0)	2 (5.0)	2 (2.7)	1 (1.4)
Febrile neutropenia	0	0	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Pneumonitis	0	0	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Seizure	0	0	1 (0.9)	1 (0.9)	1 (2.5)	1 (2.5)	0	0
Syncope	0	0	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)

ALT=alanine aminotransferase, AST=aspartate aminotransferase
Preferred terms are sorted in descending frequency of all grades column, as reported for the Ceritinib 750 mg treatment group.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple adverse events was counted only once in the total row.
Only AEs occurring during on-treatment period are summarized.
Missing grades are included under 'All grades' column.
MedDRA version 18.1 was used. AEs are graded according to the CTCAE V4.03.
Source:[Study A2303-Table 14.3.1-1.15]

Adverse events requiring dose adjustment or interruption

Adverse events regardless of study drug relationship requiring dose adjustment were more frequent in the ceritinib group (36.5% vs. 21.2% in chemotherapy group) (Table 30). The most frequently occurring AEs (in ≥ 2% of patients) that required dose adjustments in either treatment group included:

- Ceritinib: ALT increased (9.6%), vomiting (8.7%), nausea (7.8%), and diarrhea (5.2%), AST increased and decreased appetite (3.5% each), blood creatinine increased, fatigue, and weight decreased (2.6% each).
- Chemotherapy: neutropenia (6.2%), fatigue and neutrophil count decreased (3.5% each)

Grade 3/4 events requiring dose adjustments were reported in 9.6% patients in the ceritinib group and in 18.6% patients in the chemotherapy group. The incidence of individual grade 3/4 AEs requiring a dose adjustment was low. The most frequent AEs (in ≥ 2% of patients) requiring a dose adjustment in the ceritinib group were ALT increased and vomiting (2.6% each), and in the chemotherapy group were neutropenia (5.3%) and neutrophil count decreased (3.5%) (Table 30).

Table 30: Adverse events requiring dose change, regardless of study drug relationship, by preferred term, maximum grade, and treatment group (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Chemotherapy (N=113) Pemetrexed N=40		Chemotherapy (N=113) Docetaxel N=73	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	**42 (36.5)**	**11 (9.6)**	**24 (21.2)**	**21 (18.6)**	**6 (15.0)**	**5 (12.5)**	**18 (24.7)**	**16 (21.9)**
ALT increased	11 (9.6)	3 (2.6)	2 (1.8)	1 (0.9)	2 (5.0)	1 (2.5)	0	0
Vomiting	10 (8.7)	3 (2.6)	0	0	0	0	0	0
Nausea	9 (7.8)	1 (0.9)	0	0	0	0	0	0
Diarrhoea	6 (5.2)	0	1 (0.9)	0	0	0	1 (1.4)	0
AST increased	4 (3.5)	1 (0.9)	0	0	0	0	0	0
Decreased appetite	4 (3.5)	0	1 (0.9)	0	0	0	1 (1.4)	0
Blood creatinine increased	3 (2.6)	0	0	0	0	0	0	0
Fatigue	3 (2.6)	0	4 (3.5)	2 (1.8)	3 (7.5)	2 (5.0)	1 (1.4)	0
Weight decreased	3 (2.6)	1 (0.9)	1 (0.9)	0	0	0	1 (1.4)	0
Asthenia	2 (1.7)	0	0	0	0	0	0	0
Febrile neutropenia	0	0	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)
Leukopenia	0	0	2 (1.8)	2 (1.8)	0	0	2 (2.7)	2 (2.7)
Neutropenia	0	0	7 (6.2)	6 (5.3)	0	0	7 (9.6)	6 (8.2)
Neutrophil count decreased	0	0	4 (3.5)	4 (3.5)	0	0	4 (5.5)	4 (5.5)

ALT=alanine aminotransferase and AST=aspartate aminotransferase
Preferred terms are sorted in descending frequency of all grades column, as reported for the Ceritinib 750 mg treatment group.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple AEs was counted only once in the total row.
Only AEs occurring during on-treatment period are summarized.
Missing grades are included under 'All grades' column.
MedDRA version 18.1 was used. AEs are graded according to the CTCAE V4.03.
Source: [Study A2303-Table 14.3.1-1.16]

Adverse events regardless of study drug relationship requiring dose interruption or delay were also reported more frequently in the ceritinib group (73.0% vs. 23.9% in chemotherapy treatment group). The most frequently occurring AEs (in ≥2% of patients) requiring ceritinib dose interruption or delay in either treatment group included (Table 31):

- Ceritinib: ALT increased (28.7%), AST increased (22.6%), vomiting (14.8%), diarrhea and nausea (13.9% each), GGT increased (8.7%), blood creatinine increased and fatigue (6.1% each), asthenia, and decreased appetite (5.2% each), blood ALP increased (4.3%), abdominal pain upper, influenza, malaise, pneumonia, pyrexia, and weight decreased (2.6% each).
- Chemotherapy: leukopenia (2.7%) and fatigue (3.5%)

Grade 3/4 events requiring dose interruption or delay were reported in 50.4% of patients in the ceritinib group and 10.6% of patients in the chemotherapy group. The most frequent grade 3/4 AEs (in ≥ 2% of patients) requiring an interruption or delay in the ceritinib group were ALT increased (18.3%), AST increased (12.2%), GGT increased (8.7%), nausea (6.1%), vomiting and fatigue (4.3% each), diarrhea and asthenia (3.5% each), blood ALP increased and pneumonia (2.6% each). None of the patients in the chemotherapy group had grade 3/4 events reported in ≥ 2% of patients (Table 31).

Table 31: Adverse events requiring dose interruption or delay, regardless of study drug relationship, by preferred term and treatment group (in at least two patients in either groups) (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Chemotherapy (N=113) Pemetrexed N=40		Chemotherapy (N=113) Docetaxel N=73	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	**84 (73.0)**	**58 (50.4)**	**27 (23.9)**	**12 (10.6)**	**13 (32.5)**	**5 (12.5)**	**14 (19.2)**	**7 (9.6)**
ALT increased	33 (28.7)	21 (18.3)	1 (0.9)	1 (0.9)	1 (2.5)	1 (2.5)	0	0
AST increased	26 (22.6)	14 (12.2)	1 (0.9)	1 (0.9)	1 (2.5)	1 (2.5)	0	0
Vomiting	17 (14.8)	5 (4.3)	0	0	0	0	0	0
Diarrhoea	16 (13.9)	4 (3.5)	0	0	0	0	0	0
Nausea	16 (13.9)	7 (6.1)	0	0	0	0	0	0
GGT increased	10 (8.7)	10 (8.7)	0	0	0	0	0	0
Blood creatinine increased	7 (6.1)	0	0	0	0	0	0	0
Fatigue	7 (6.1)	5 (4.3)	4 (3.5)	0	3 (7.5)	0	1 (1.4)	0
Asthenia	6 (5.2)	4 (3.5)	0	0	0	0	0	0
Decreased appetite	6 (5.2)	1 (0.9)	1 (0.9)	1 (0.9)	0	0	1 (1.4)	1 (1.4)
Blood ALP increased	5 (4.3)	3 (2.6)	0	0	0	0	0	0
Abdominal pain upper	3 (2.6)	1 (0.9)	0	0	0	0	0	0
Influenza	3 (2.6)	0	0	0	0	0	0	0
Malaise	3 (2.6)	1 (0.9)	0	0	0	0	0	0
Pneumonia	3 (2.6)	3 (2.6)	0	0	0	0	0	0
Pyrexia	3 (2.6)	0	0	0	0	0	0	0
Weight decreased	3 (2.6)	0	0	0	0	0	0	0
Dehydration	2 (1.7)	1 (0.9)	0	0	0	0	0	0
Epilepsy	2 (1.7)	2 (1.7)	0	0	0	0	0	0
Non-cardiac chest Pain	2 (1.7)	0	0	0	0	0	0	0
Pericarditis	2 (1.7)	0	0	0	0	0	0	0
Transaminases increased	2 (1.7)	1 (0.9)	0	0	0	0	0	0
Anaemia	1 (0.9)	0	2 (1.8)	2 (1.8)	2 (5.0)	2 (5.0)	0	0
Leukopenia	1 (0.9)	0	3 (2.7)	0	2 (5.0)	0	1 (1.4)	0
Muscular weakness	1 (0.9)	1 (0.9)	2 (1.8)	0	1 (2.5)	0	1 (1.4)	0
Infusion related reaction	0	0	2 (1.8)	0	0	0	2 (2.7)	0

ALT=alanine aminotransferase, GGT=gamma- glutamyltransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase
Preferred terms are sorted in descending frequency of all grades column, as reported for the Ceritinib 750 mg treatment group.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple AEs was counted only once in the total row.
Only AEs occurring during on-treatment period are summarized.
Missing grades are included under 'All grades' column.
MedDRA version 18.1 was used. AEs are graded according to the CTCAE V4.03.
Source:[Study A2303-Table 14.3.1-1.17]

Adverse events requiring additional therapy

Adverse events requiring additional therapy (which included all non-drug therapy in addition to concomitant medications) were reported in 92.2% of patients in the ceritinib group and in 88.5% of patients in the chemotherapy group (Table 32).

The most commonly occurring AEs (in ≥ 10% of patients) that required additional therapy in the either of the treatment group included:

- Ceritinib group: nausea (52.2%), diarrhea (40.9%), vomiting (30.4%), back pain (16.5%), constipation (12.2%), headache (11.3%), and non-cardiac chest pain (10.4%)
- Chemotherapy group: nausea (17.7%), pyrexia (12.4%), cough (14.2%), and neutropenia (11.5%).

Grade 3/4 events requiring additional therapy were reported in 47.8% of patients in the ceritinib group and 49.6% of patients in the chemotherapy group. The most frequently grade 3/4 AEs (in ≥ 2% of patients) requiring additional therapy included (Table 32):

- Ceritinib group: nausea (7.8%), vomiting (7.0%), hypokalaemia (5.2%), dyspnea (4.3%), and ALT increased (2.6%)
- Chemotherapy group: neutropenia (10.6%), neutrophil count decreased (6.2%), febrile neutropenia (5.3%), anemia (3.5%), dyspnea, back pain, and arthralgia (each 2.7%).

Table 32: Adverse events requiring additional therapy, regardless of study drug relationship, by preferred term and treatment group (with a frequency cut-off of 5% in any group) (Safety set)

	Ceritinib 750 mg N=115		Chemotherapy N=113		Pemetrexed N=40		Docetaxel N=73	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	**106 (92.2)**	**55 (47.8)**	**100 (88.5)**	**56 (49.6)**	**34 (85.0)**	**13 (32.5)**	**66 (90.4)**	**43 (58.9)**
Nausea	60 (52.2)	9 (7.8)	20 (17.7)	1 (0.9)	11 (27.5)	1 (2.5)	9 (12.3)	0
Diarrhoea	47 (40.9)	2 (1.7)	10 (8.8)	1 (0.9)	0	0	10 (13.7)	1 (1.4)
Vomiting	35 (30.4)	8 (7.0)	3 (2.7)	1 (0.9)	2 (5.0)	1 (2.5)	1 (1.4)	0
Back pain	19 (16.5)	1 (0.9)	6 (5.3)	3 (2.7)	2 (5.0)	1 (2.5)	4 (5.5)	2 (2.7)
Constipation	14 (12.2)	0	8 (7.1)	0	3 (7.5)	0	5 (6.8)	0
Headache	13 (11.3)	1 (0.9)	8 (7.1)	2 (1.8)	3 (7.5)	1 (2.5)	5 (6.8)	1 (1.4)
Non-cardiac chest pain	12 (10.4)	1 (0.9)	2 (1.8)	0	2 (5.0)	0	0	0
Abdominal pain upper	11 (9.6)	1 (0.9)	5 (4.4)	0	1 (2.5)	0	4 (5.5)	0
Abdominal pain	10 (8.7)	1 (0.9)	3 (2.7)	1 (0.9)	1 (2.5)	0	2 (2.7)	1 (1.4)
Decreased appetite	10 (8.7)	0	8 (7.1)	1 (0.9)	1 (2.5)	0	7 (9.6)	1 (1.4)
Pyrexia	10 (8.7)	1 (0.9)	14 (12.4)	0	3 (7.5)	0	11 (15.1)	0
Hypokalaemia	9 (7.8)	6 (5.2)	1 (0.9)	0	1 (2.5)	0	0	0
Cough	8 (7.0)	0	16 (14.2)	1 (0.9)	5 (12.5)	0	11 (15.1)	1 (1.4)
ALT increased	8 (7.0)	3 (2.6)	1 (0.9)	0	0	0	1 (1.4)	0
Dysponea	7 (6.1)	5 (4.3)	5 (4.4)	3 (2.7)	1 (2.5)	1 (2.5)	4 (5.5)	2 (2.7)
Weight decreased	7 (6.1)	2 (1.7)	0	0	0	0	0	0
AST increased	7 (6.1)	1 (0.9)	1 (0.9)	0	0	0	1 (1.4)	0
Nasopharyngitis	7 (6.1)	0	1 (0.9)	0	1 (2.5)	0	0	0
Musculoskeletal chest pain	7 (6.1)	0	3 (2.7)	0	0	0	3 (4.1)	0
Rash	6 (5.2)	0	8 (7.1)	0	3 (7.5)	0	5 (6.8)	0
Stomatitis	5 (4.3)	0	9 (8.0)	0	3 (7.5)	0	6 (8.2)	0
Arthralgia	4 (3.5)	0	11 (9.7)	3 (2.7)	2 (5.0)	2 (5.0)	9 (12.3)	1 (1.4)
Insomnia	3 (2.6)	0	10 (8.8)	0	3 (7.5)	0	7 (9.6)	0
Myalgia	1 (0.9)	0	8 (7.1)	0	1 (2.5)	0	7 (9.6)	0
Neutropenia	0	0	13 (11.5)	12 (10.6)	0	0	13 (17.8)	12 (16.4)
Neutrophil count decreased	0	0	7 (6.2)	7 (6.2)	0	0	7 (9.6)	7 (9.6)
Febrile neutropenia	0	0	6 (5.3)	6 (5.3)	0	0	6 (8.2)	6 (8.2)
Anaemia	0	0	9 (8.0)	4 (3.5)	3 (7.5)	3 (7.5)	6 (8.2)	1 (1.4)

ALT=alanine aminotransferase, AST=aspartate aminotransferase
Source: [Study A2303-Table 14.3.1-1.19]

Adverse events of special interest

The AEs of special interest (AESI) are: hepatotoxicity, interstitial lung disease/pneumonitis, QTc prolongation, hyperglycemia, bradycardia, GI toxicity (nausea, diarrhea, vomiting) and pancreatitis.

None of the study drug-related AESIs were the primary cause of death.

Hepatotoxicity

The SMQ (narrow) 'Cholestasis and jaundice of hepatic origin', SMQ (narrow) 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions', SMQ (narrow) 'Hepatitis, non-infectious', and SMQ (narrow) 'Liver related investigations, signs and symptoms' were used to identify and define the frequency of hepatotoxicity events.

Hepatotoxicity AEs were reported in 61 patients (53.0%), with grade 3/4 hepatotoxicity AEs reported in 44 patients (38.3%). As per Investigator assessment hepatotoxicity AEs were suspected to be drug-related in 56 patients (48.7%). The hepatotoxicity AEs required dose adjustments or interruptions/delay in 42 patients (36.5%) and led to discontinuations in two patients (1.7%). The event was serious in one patient (0.9%).

The most frequent (in ≥ 20% of patients) hepatotoxicity AEs (all grades, regardless of study drug relationship) by preferred term were: ALT increased (42.6%), AST increased (36.5%), and GGT increased (22.6%).

Hepatotoxicity SAE was reported only in one patient [A2303-1250-001], who developed grade 3 jaundice on Day 668 due to biliary obstruction, and was not suspected to be drug-related, and resolved upon biliary stent.

Two patients (1.7%) discontinued ceritinib treatment due to ALT and AST increased, which were suspected to be drug-related and recovered after treatment discontinuation.

Of the 115 patients treated with ceritinib, the majority of patients (89 patients, 77.4%) had grade 0 ALT at baseline, 25 patients (21.7%) had grade 1 and one patient (0.9%) and had grade 2 elevations at baseline. Post-baseline, 93 patients (80.9%) had ALT elevation of any grade, of which 37 patients (32.2%) had grade 1, 28 patients (24.3%) had grade 2, 26 patients (22.6%) had grade 3, and two patients (1.7%) had grade 4 ALT elevations, respectively. Of the 26 patients who worsened to grade 3, 21 patients worsened from baseline grade 0 and five patients worsened from baseline grade 1. Two patients worsened from baseline grade 0 to grade 4 post-baseline.

Of the 115 patients treated with ceritinib, the majority of patients had grade 0 (93 patients, 80.9%) at baseline, and 22 patients (19.1%) grade 1 AST elevation at baseline. Post-baseline, 87 patients (75.7%) had AST elevation of any grade, 52 patients (45.2%) had grade 1, 18 patients (15.7%) had grade 2, 16 patients (13.9%) had grade 3, and one patient (0.9%) had grade 4 AST elevation, respectively. Of the 16 patients who worsened to grade 3, 13 patients worsened from baseline grade 0 and three patients worsened from baseline grade 1. One patient worsened from baseline grade 0 to grade 4 post-baseline.

Overall increases in transaminases (ALT or AST) >3 x ULN (grade 2), were seen in 48.7% of patients, with 26.1% and 1.7% of patients having an increase of >5 x ULN (grade 3) and >20 x ULN (grade 4), respectively in the ceritinib group.

The median time to first elevation of grade 2 or worse AST or ALT increase was 27.0 weeks (95% CI: 15.3, 45.9). The median time to first elevation of grade 3 or worse AST or ALT was not reached in the ceritinib group. Among the 30 patients with grade 3 or worse AST or ALT elevations, 23 patients (77%) had the elevation before 24 weeks.

All patients treated with ceritinib had grade 0 total bilirubin at baseline. Post-baseline, one patient (0.9%) had grade 3 total bilirubin (TBILI) increases. Patient [A2303-1250-001] had jaundice due to biliary obstruction, which was not considered to be study drug-related. There were no grade 4 cases.

No Hy's law case was observed in either treatment group (i.e. concurrent AT >3xULN and TBILI >2xULN and ALP <2xULN). Further there were no cases of concurrent AT >3ULN and TBILI >2xULN in the ceritinib group. One patient [A2303-1250-001] in the ceritinib group had elevation of total bilirubin >2xULN and ALT or AST >3xULN at any time during the study (not necessarily concurrently). This patient had jaundiced due to biliary obstruction (not suspected to be study drug-related) and elevated alkaline phosphate during the event. The patient recovered upon biliary stent placement.

The review of the overall safety profile of ceritinib in patients with mild hepatic impairment at baseline versus patients with normal hepatic function at baseline did not reveal any clinically relevant differences or new safety concerns, and is consistent with the known safety profile of ceritinib. No patients with moderate/severe hepatic impairment at baseline were enrolled into Study A2303.

The interpretation of the slightly higher incidence of on-treatment deaths in ceritinib treated patients with mild hepatic impairment at baseline compared to patients with normal hepatic function at baseline is limited due to the small subgroup size and limited number of patients with an event. All deaths were due to study indication.

Interstitial lung disease/pneumonitis

The SMQ (narrow) "Interstitial lung disease" and the PT 'Acute lung injury' were used to identify and define the frequency of interstitial lung disease/pneumonitis events.

Interstitial lung disease/pneumonitis AEs were reported in two patients (1.7%). The events were of grade 3 severity and serious in both the patients. One patient each had grade 3 AE of ILD (suspected to be drug-related) and lung infiltration (not suspected to be drug-related). Both the patients discontinued the treatment due to respective events. None of the patient required any dose adjustments or interruptions/delay.

QT prolongation

The SMQ (broad) "Torsade de pointes/QT prolongation" was used to identify and define the frequency of QT prolongation events.

QT prolongation AEs (primarily ECG QT prolonged) were reported in 14 patients (12.2%). Majority of these AEs were of grade 1/2 severity, and grade 3/4 events were reported in two patients (1.7%). The QT prolongation AEs in 13 patients (11.3%) were suspected to be drug-related by the Investigator. Serious events were reported in two patients (1.7%). AE requiring dose adjustments or interruptions was reported in two patients. No patient discontinued treatment due to QT prolongation AEs. No grade 4 QT prolongation or torsade de pointes case were reported; no patients with AE of QT prolongation (preferred term) had syncope/loss of consciousness.

The reported QT prolongation AEs by PT were ECG QT prolonged (13 patients; 11.3%, regardless of correction method) and loss of consciousness (one patient; 0.9%). Two patients had grade 3/4 QT prolongation AEs which were also reported as SAEs, in one of these patients the event was suspected to be study drug-related.

ECG interval abnormalities

Previous studies have shown that QTcB and QTcF did not appropriately correct QT for heart rate in ceritinib studies. Thus, QTcP correction (based on a population linear regression methodology) is considered the most appropriate correction to characterize the effect of ceritinib on the QT interval. Evaluable patients for analyses based on changes from baseline are those with a baseline ECG and at least one post-baseline ECG.

QTcP/QTcF values >480 ms and >500 ms were observed in four patients (3.5%) and one patient (0.9%), respectively (Table 33).

One patient (0.9%) had a QTcP/QTcF interval >500 ms in the ceritinib group.

Six (5.5%) patients in the ceritinib group had a decrease in the heart rate (HR) of >25% from baseline and to <50 beats per minute (Table 33).

Table 33: Number and percentage of patients with notable ECG values by treatment group (Safety set)

	Ceritinib 750 mg N=115 n/m (%)	Chemotherapy N=113 n/m (%)
QTcF (msec)		
New >450	37/113 (32.7)	11/109 (10.1)
New >480	4/114 (3.5)	1/111 (0.9)
New >500	1/114 (0.9)	0/112 (0)
Increase from baseline >30	71/114 (62.3)	7/112 (6.3)
Increase from baseline >60	7/114 (6.1)	0/112 (0)
QTcP (msec)		
New >450	35/114 (30.7)	11/110 (10.0)
New >480	4/115 (3.5)	1/111 (0.9)
New >500	1/115 (0.9)	0/112 (0)
Increase from baseline >30	66/115 (57.4)	6/112 (5.4)
Increase from baseline >60	7/115 (6.1)	0/112 (0)
HR (bpm)		
Increase >25% & to a HR >100	13/106 (12.3)	10/106 (9.4)
Decrease >25% & to a HR <50	6/110 (5.5)	1/109 (0.9)
PR (msec)		
Increase >25% & to a value >200	2/112 (1.8)	1/110 (0.9)
New PR >200 and ≤ 220	6/112 (5.4)	4/110 (3.6)
New PR >220	3/114 (2.6)	1/111 (0.9)
QRS (msec)		
Increase >25% & to a value >110	3/109 (2.8)	0/108 (0)
New QRS >110 and ≤ 120	7/109 (6.4)	2/108 (1.9)
New QRS >120	2/113 (1.8)	0/109 (0)

m: The number of patients at risk for a specific category. For new abnormality post-baseline (on treatment values), this was the number of patients with both baseline and post-baseline (on treatment), and baseline not meeting the criteria. For abnormal change from baseline, this was the number of patients with both baseline and post-baseline evaluations.
n was the number of patients meeting the criteria at least once. Unscheduled visits are included in the summary.
N: Total number of patients in the treatment arm in this analysis set.
Baseline for ECG measurement was the average of all available measurements taken prior to dosing on the date associated with the last available ECG measurement before or on the date of start of study treatment.
Change from baseline=post baseline – baseline. New=Newly occurring post baseline (on treatment) value.
Source: [Study A2303-Table 14.3-5.3]

Change in QTc versus ceritinib PK concentration

Changes from baseline in heart rate corrected QT interval were plotted against the time-matched ceritinib plasma concentrations, and the relationship was assessed using a linear mixed effects model.

Based on 86 patients, the PK/PD analysis of the QTcP data, at median steady-state Cmin (1090.0 ng/mL) suggested a concentration-dependent QTcP interval prolongation with an estimated 14.0 ms mean QTcP increase from baseline, with the upper bound of the 2-sided 90% CI for mean QTcP change from baseline <20 ms.

Bradycardia

The Novartis MedDRA query (broad) “Bradyarrhythmias and bradycardia” was used to identify and define the frequency of bradycardia events. This query includes the PT of “QT prolongation” which has also been included in the search for AESI of QT prolongation mentioned above.

Bradycardia events category were reported in 17 patients (14.8%) ceritinib group. Majority of these AEs were of grade 1/2 severity, and grade 3/4 events were reported in one patient (0.9%). These included the AE of ECG QT prolonged reported in 13 patients (11.3%) which has also been reported under QT prolongation AESI category.

Only three patients in the ceritinib group had actual AE of bradycardia, none of which was grade 3/4 or serious or led to study treatment discontinuation; two of these three cases were suspected to be study drug-related.

Based on ECG data, there were six (5.5%) patients in the ceritinib group having a decrease in the heart rate (HR) more than 25% and to less than 50 beats per minute compared to baseline.

Hyperglycaemia

The SMQ (narrow) “Hyperglycaemia/new onset diabetes mellitus” was used to identify and define the frequency of hyperglycaemia events. Additional PTs related to hyperglycaemia laboratory values were used to identify the AESI hyperglycaemia.

Hyperglycaemia AEs were reported in 10 patients (8.7%), which included events of hyperglycaemia in eight patients (7.0%) and diabetes mellitus in two patients (1.7%). Six patients (5.2%) had grade 3/4 hyperglycaemia AEs. Five of the six patients with grade 3/4 hyperglycaemia had confounding factors (concomitant medications and/or pre-existing/newly occurring disease conditions). Five patients had brain metastasis at baseline, two patients developed brain metastasis during the study, five patients had concomitant use steroids during the study and one patient [A2303-1254-003] had a single isolated increased glucose value where it is not clear if the sample was taken fasted or fed (no other AEs reported). Additionally three patients had elevated fasting plasma glucose at baseline. Additionally three patients had elevated fasting plasma glucose at baseline. No action was taken with study treatment except in one patient and five patients received anti-hyperglycaemic agents for treatment. None of the hyperglycaemia AEs were suspected to be drug-related by the Investigator. The event was considered serious in one patient (0.9%). None of the patient discontinued treatment due to hyperglycaemia AEs.

One patient (0.9%) (A2303-1201-002) in the ceritinib group had grade 3 hyperglycaemia (Day 287) which was serious. This event was not suspected to be drug-related by the Investigator, and no action was taken with study drug. The patient discontinued the study due to disease progression on Day 451, and the patient had received last dose of ceritinib at Day 441.

Blood glucose laboratory abnormalities

Based on the laboratory parameters, of the 115 patients treated with ceritinib the majority of patients (96 patients, 83.5%) had normal blood glucose at baseline (grade 0). Post-baseline, 57 patients (49.6%) had increased blood glucose, of which 40 patients (34.8%), six patients (5.2%), and 11 patients (9.6%) had grade 1, grade 2, and grade 3 hyperglycaemia respectively. Of the 11 patients who worsened to grade 3 in the ceritinib group; eight, two, and one patient worsened from baseline grade 0, 1, and 2, respectively. No patient had grade 4 increase in glucose.

In the chemotherapy group, the majority (77 patients, 68.1%) of patients had normal blood glucose at baseline. Similar to the ceritinib group, 52 patients (46.0%) had hyperglycaemia of any grade post-baseline, of which 40 patients (35.4%), five patients (4.4%), six patients (5.3%), and one patient (0.9%) had grade 1, 2, 3, 4 hyperglycaemia respectively.

Analysis of median/mean blood glucose levels at screening and during the course of the study further did not show any increase with start of ceritinib treatment or later during the study. Blood glucose levels in the ceritinib group were also not higher compared to the chemotherapy group.

Gastrointestinal toxicity

The PTs used to identify and define the frequency of GI toxicity events were ‘Diarrhoea’, ‘Nausea’, and ‘Vomiting’.

Gastrointestinal AEs were reported in 107 patients (93.0%) in the ceritinib group, with grade 3/4 AEs reported in 15 patients (13.0%). These events were suspected to be drug-related in 99 patients (86.1%). The events required dose adjustment or interruption/delay in 40 patients (34.8%), and one patient (0.9%) in the discontinued treatment due to grade 3 vomiting (not suspected to be related to ceritinib).

GI toxicity SAEs were reported in eight patients (7.0%). In six patients the GI toxicity SAEs had resolved, one patient it was not resolved at the time of the report, and one patient [A2303- 1356-001] died due to

disease progression with the event (vomiting, not related to study drug) ongoing at the time of death. In seven patients the GI toxicity SAEs were considered suspected to be study drug-related.

Pancreatitis

The Novartis MedDRA Query (broad) 'Acute pancreatitis (excl. non-specific symptoms)' was used to identify and define the frequency of pancreatitis events. This query comprises the SMQ (narrow) 'Acute Pancreatitis' and the PTs related to pancreatic enzyme abnormalities including lipase and amylase increase.

Pancreatitis AEs were reported in seven patients (6.1%) in ceritinib, with grade 3/4 AEs reported in five patients (4.3%). The AEs reported were amylase increased in all seven patients (6.1%). No AEs with PT of "pancreatitis" was reported. In four patients (3.5%) the pancreatitis AEs were suspected to be study drug-related. Two patients (1.7%) required dose adjustments or interruptions/delay. None of the pancreatitis AEs were serious or led to treatment discontinuation.

None of the seven cases in the ceritinib group are suggestive of (acute) pancreatitis based on medical review; 6/7 patients had brain metastasis at baseline of which four received brain radiotherapy around the event; in addition, 2/7 patients had grade 3 and 2/7 patients had grade 2 amylase elevation at baseline, respectively.

Pancreatitis is an important identified risk in the current risk management plan (RMP) and has been included in the Section "Special warnings and precautions for use" and in the ADR Table of the current SmPC. Patients should be monitored for lipase and amylase elevations prior to the start of the treatment with ceritinib, and periodically thereafter as clinically indicated.

Amylase/lipase laboratory abnormalities

Based on the laboratory parameters, of the 115 patients treated with ceritinib the majority of patients (98 patients, 85.2%) had normal amylase (grade 0) at baseline. Post-baseline, 43 patients (37.4%) had amylase increase of any grade, of which 29 patients (25.2%), eight patients (7.0%), three patients (2.6%) and three patients (2.6%) had grade 1, grade 2, grade 3, and 4 amylase increase, respectively. Of note, 17 patients (14.8%) had elevated amylase levels already at baseline; in particular, one out of the three grade 3 cases had grade 2 amylase increase at baseline and two had normal amylase (grade 0) at baseline, and two out of the three grade 4 cases had grade 3 amylase increase at baseline and one had normal amylase (grade 0) at baseline.

Lipase values were available for few patients only since this parameter was not routinely collected as part of the initial protocol. Of the 115 patients treated with ceritinib, majority of the patients (110 patients, 95.7%) had missing values and five patients (4.3%) had grade 0 lipase at baseline. Post-baseline, three (2.6%) patients had lipase elevations of any grade, of which two patients had grade 1 lipase elevations and one patient had grade 2 lipase elevation and no patients had grade 3 or 4 elevations.

AEs and laboratory abnormalities associated with creatinine increase and renal function

Twenty-two (19.1%) patients in the ceritinib vs. none in the chemotherapy group had creatinine elevations based on AEs. All were grade 1 or 2 in severity, none were reported as SAEs or led to study drug discontinuation, and 19/22 were considered study drug-related as per the Investigator. Most of the patients had GI toxicity (18/22 diarrhea, 9/22 vomiting) preceding and/or around the event as possible contributing factor, however, none of these patients had an AE of dehydration. Furthermore, 9/22 patients had grade 1 creatinine increase, and 1/22 patients had grade 2 creatinine increases at baseline as per laboratory data.

Based on laboratory assessments, 91 patients (79.1%) had creatinine increase of any grade post-baseline, of which 37 patients (32.2%) and 54 patients (47.0%) had grade 1 and grade 2 creatinine increase, respectively. There were no grade 3 and 4 cases of creatinine increase. In the chemotherapy group,

post-baseline 23 patients (20.3%) had creatinine increase of any grade, of which 21 patients (18.6%) had grade 1 and two patients (1.8%) had grade 2 postbaseline creatinine increase.

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. In contrast, levels of BUN did not increase.

Under the SOC of "renal and urinary disorders", AEs were reported in 10 patients (8.7%) in the ceritinib group. The AEs by preferred term included: dysuria (n=3), acute kidney injury (n=1), chromaturia (n=1), chronic kidney disease (n=1), nocturia (n=1), polyuria (n=1), renal failure (n=1), renal impairment (n=1), and urinary bladder rupture (n=1). In 2/10 patients the event was grade 3 (chronic kidney disease and urinary bladder rupture); there were no Grade 4 events. One patient [A2303-1254-003] had urinary bladder rupture on Day 389 which reported as SAE (not related to study drug). Only one patient required study drug adjustment, and three patients required study drug interruption. None of the events led to study drug discontinuation.

In addition to the 22 patients with blood creatinine increase reported under the SOC of "Investigations", creatinine renal clearance decreased was reported in three patients of which one patient had grade 3 event (A2303-1254-001; patient had grade 2 creatinine clearance decrease reported prior to start of study drug). All three events were suspected to be study drug related. None of the events were SAEs, lead to study drug discontinuation or required dose adjustment/ interruption. No patients died due to creatinine increased or renal function AEs while on ceritinib.

Renal impairment related AEs in the ceritinib treated patients showed an increased frequency of AEs with the PT of creatinine increased and hyper-creatininemia (any grade: 30.0% mild, 44.4% moderate vs 3.5% normal renal function). Elevations of creatinine were transient and reversible upon treatment discontinuation.

There were no grade 3/4 events of acute kidney injury, renal failure or renal impairment reported in the ceritinib group in Study A2303.

A slightly higher frequency of QT prolongation AEs was found among patients with mild renal impairment compared to patients with normal renal function (17.5% mild and 8.8% normal respectively). None of these events were grade 3/4, and no SAEs occurred.

Testosterone and Gonadotropin level changes

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), and was also similar between the ceritinib and chemotherapy group.

Clinical laboratory evaluations

Laboratory assessments in the Study A2303 consisted of monitoring of haematology, biochemistry (including liver laboratory tests). Data from all sources (central and local laboratories) were combined.

Haematology

The grade 3/4 haematology laboratory abnormalities were generally reported more frequently in chemotherapy-treated patients compared to ceritinib.

In the ceritinib group, the haematological abnormalities were predominantly grade 1 or 2, the grade 3/4 abnormalities were not reported in more than two patients (1.7%), except for decreased lymphocytes.

Grade 3 lymphopenia was observed in 17.4% patients in the ceritinib group vs. 23.0% in the chemotherapy group. Only one patient (0.9%) in the ceritinib group had grade 4 haematological abnormality (decreased lymphocytes) (Table 34). The following grade 3 and 4 abnormalities were observed in the ceritinib group: two patients (1.7%) had grade 3 absolute neutrophils decreased (one patient each worsened from grade 0 and grade 2), one patient (0.9%) each had grade 3 decreased haemoglobin (worsened from grade 0), thrombocytopenia (worsened from grade 0) and decreased WBCs (worsened from grade 1) during the study (no grade 4). Grade 3 absolute lymphocytes decrease was observed in 20 patients (17.4%) (eight, four, and seven patients worsened from grade 0, 1, and 2 respectively, and one patient had grade 3 abnormality at baseline), and one patient had grade 4 absolute lymphocytes decrease (worsened from grade 1).

Table 34: Haematology worst post-baseline laboratory value based on CTC grade by treatment group (Safety set)

Parameter	Worst post-baseline value											
	Ceritinib 750 mg N=115						Chemotherapy N=113					
	Any grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Any grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Absolute lymphocytes (Hyper)	1 (0.9)	0	1 (0.9)	0	0	5 (4.3)	2 (1.8)	0	2 (1.8)	0	0	8 (7.1)
Absolute lymphocytes (Hypo)	77 (67.0)	24 (20.9)	32 (27.8)	20 (17.4)	1 (0.9)	5 (4.3)	68 (60.2)	15 (13.3)	26 (23.0)	26 (23.0)	1 (0.9)	8 (7.1)
Absolute neutrophils (Hypo)	24 (20.9)	20 (17.4)	2 (1.7)	2 (1.7)	0	5 (4.3)	45 (39.9)	7 (6.2)	8 (7.1)	7 (6.2)	23 (20.4)	6 (5.3)
Hemoglobin (Hypo)	74 (64.3)	54 (47.0)	19 (16.5)	1 (0.9)	0	3 (2.6)	88 (77.9)	57 (50.4)	26 (23.0)	5 (4.4)	0	7 (6.2)
Platelet counts (Hypo)	14 (12.2)	12 (10.4)	1 (0.9)	1 (0.9)	0	3 (2.6)	14 (12.3)	11 (9.7)	0	2 (1.8)	1 (0.9)	8 (7.1)
WBC (Hyper)	0	0	0	0	0	5 (4.3)	0	0	0	0	0	6 (5.3)
WBC (Hypo)	33 (28.7)	23 (20.0)	9 (7.8)	1 (0.9)	0	5 (4.3)	48 (42.4)	14 (12.4)	13 (11.5)	15 (13.3)	6 (5.3)	6 (5.3)

WBC=While blood cells
Worst post-baseline value was for on-treatment period only.
Source: [Study A2303-Table 14.3-3.1a]

Clinical chemistry

Grade 3/4 liver parameter abnormalities (elevated ALT, AST, ALP, and GGT) were higher in the ceritinib group as compared to the chemotherapy group (Table 35); however, bilirubin increase was noted in three patients (2.6%) and there were no Hy's law cases. The frequency hyperglycaemia post-baseline, was similar in ceritinib (49.6%) and chemotherapy group (46.0%). Eleven (9.6%) vs. seven (6.2%) patients had grade 3/4 glucose increase in the ceritinib and chemotherapy group, respectively; most of these cases were confounded by concomitant medications (i.e. steroids) and/or underlying disease conditions. Post-baseline, although creatinine increase was noted in 91 patients (79.1%), none of the patient had grade 3/4 elevations, the creatinine increase was generally not associated with clinical events, and was reversible upon treatment discontinuation.

Table 35: Biochemistry shift table based on CTC grade by treatment group (Safety set)

	Worst post-baseline value											
	Ceritinib 750 mg N=115						Chemotherapy N=113					
Parameter	Any grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Any grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Albumin (Hypo)	47 (40.9)	33 (28.7)	14 (12.2)	0	0	5 (4.3)	40 (35.4)	29 (25.7)	10 (8.8)	1 (0.9)	0	7 (6.2)
SGOT (AST) (Hyper)	87 (75.6)	52 (45.2)	18 (15.7)	16 (13.9)	1 (0.9)	5 (4.3)	37 (32.7)	31 (27.4)	4 (3.5)	2 (1.8)	0	7 (6.2)
SGPT (ALT) (Hyper)	93 (80.9)	37 (32.2)	28 (24.3)	26 (22.6)	2 (1.7)	5 (4.3)	51 (45.1)	39 (34.5)	9 (8.0)	3 (2.7)	0	7 (6.2)
Total bilirubin (Hyper)	3 (2.6)	2 (1.7)	0	1 (0.9)	0	5 (4.3)	2 (1.8)	1 (0.9)	0	1 (0.9)	0	7 (6.2)
ALP (Hyper)	84 (73.0)	49 (42.6)	24 (20.9)	11 (9.6)	0	5 (4.3)	37 (32.7)	31 (27.4)	5 (4.4)	1 (0.9)	0	7 (6.2)
GGT (Hyper)	86 (74.8)	18 (15.7)	22 (19.1)	40 (34.8)	6 (5.2)	5 (4.3)	50 (44.2)	34 (30.1)	10 (8.8)	5 (4.4)	1 (0.9)	7 (6.2)
Amylase (Hyper)	43 (37.4)	29 (25.2)	8 (7.0)	3 (2.6)	3 (2.6)	5 (4.3)	30 (26.5)	22 (19.5)	2 (1.8)	5 (4.4)	1 (0.9)	7 (6.2)
Lipase (Hyper) [a]	3 (2.6)	2 (1.7)	1 (0.9)	0	0	67 (58.3)	0	0	0	0	0	101 (89.4)
Glucose (Hyper)	57 (49.6)	40 (34.8)	6 (5.2)	11 (9.6)	0	5 (4.3)	52 (46.0)	40 (35.4)	5 (4.4)	6 (5.3)	1 (0.9)	7 (6.2)
Creatinine (Hyper)	91 (79.1)	37 (32.2)	54 (47.0)	0	0	5 (4.3)	23 (20.3)	21 (18.6)	2 (1.8)	0	0	7 (6.2)
Corrected calcium (Hyper)	104 (90.4)	103 (89.6)	1 (0.9)	0	0	5 (4.3)	84 (74.3)	84 (74.3)	0	0	0	7 (6.2)
Corrected calcium (Hypo)	47 (40.9)	47 (40.9)	0	0	0	5 (4.3)	31 (27.4)	30 (26.5)	1 (0.9)	0	0	7 (6.2)
Magnesium (Hyper)	3 (2.6)	3 (2.6)	0	0	0	5 (4.3)	2 (1.8)	1 (0.9)	0	1 (0.9)	0	7 (6.2)
Phosphate (Hypo)	46 (40.0)	11 (9.6)	29 (25.2)	6 (5.2)	0	5 (4.3)	25 (22.1)	5 (4.4)	17 (15.0)	3 (2.7)	0	7 (6.2)
Potassium (Hyper)	28 (24.3)	18 (15.7)	8 (7.0)	1 (0.9)	1 (0.9)	4 (3.5)	16 (14.2)	11 (9.7)	5 (4.4)	0	0	7 (6.2)
Potassium (Hypo)	13 (11.3)	0	7 (6.1)	5 (4.3)	1 (0.9)	4 (3.5)	7 (6.2)	0	5 (4.4)	2 (1.8)	0	7 (6.2)
Sodium (Hyper)	10 (8.7)	9 (7.8)	0	1 (0.9)	0	4 (3.5)	5 (4.4)	4 (3.5)	1 (0.9)	0	0	7 (6.2)
Sodium (Hypo)	24 (20.9)	17 (14.8)	0	7 (6.1)	0	4 (3.5)	13 (11.5)	11 (9.7)	0	1 (0.9)	1 (0.9)	7 (6.2)

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, GGT=gamma- glutamyltransferase
[a] Lipase values were available for few patients only since this parameter was not routinely collected as part of the initial protocol and was included after protocol amendment 3 (25-Mar-2015).
Worst post-baseline value was for on-treatment period only.
Source: [Study A2303-Table 14.3-3.3a]

Based on laboratory data review, 12/26 (47.2%) and 15/26 (57.7%) of patients with an event of ALP and GGT increased, respectively, had an abnormal baseline value of the corresponding laboratory parameter prior to treatment start with ceritinib. The event of ALP increased resolved in 18/26 (69.2%) patients and GGT increased in 16/26 patients (61.5%). None of the AEs were SAEs, and no study drug discontinuations occurred due specifically to ALP or GGT increase, furthermore, generally do not require specific management guidelines. No association was found with bilirubin increase, and the abnormalities were reversible with no evidence for prolonged or severe cholestatic injury despite treatment continuation.

Based on a comprehensive review of the available safety information from Study A2303, “blood ALP increased” has been added as a new term to the existing ADR “Liver laboratory test abnormalities”. Furthermore, in the update SmPC, “ALP increased” has been identified as a new ADR and has been proposed to be added to Table 2 of Section 4.8 “Undesirable effects” of the SmPC under the term “Liver laboratory test abnormalities” in the system organ class (SOC) “Investigations”. “GGT increased” was already included in Table 2 of the SmPC under the same term and SOC at the time of the initial Marketing Authorization Application. Increases in ALP and GGT are managed in the context of hepatotoxicity and no additional guidance is needed in the SmPC.

Vital signs, physical findings, and other observations related to safety

Vital signs

Vital sign assessments were performed in order to characterize basic body function. The parameters collected were weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg), and respiration rate (breaths per minute).

Descriptive statistics were tabulated for baseline and change from baseline to worst post-baseline value for each vital sign measurement. Further, vital signs shift table based on clinically notable values at baseline and worst post-baseline were produced.

Changes in vital signs, weight, and physical examination findings that were considered abnormal by the Investigator were reported as AEs.

Most of the vital signs did not change notably from baseline, with the exception of weight and blood pressure.

- **Weight**: In the ceritinib group, of the 115 patients with a normal weight at baseline, 34 patients (29.6%) had a post-baseline decrease in weight of ≥ 10% compared to baseline, and six patients (5.2%) had a post-baseline increase in weight of ≥ 10%. 18.3% of patients was suspected to be related to study treatment by the Investigator and the events were resolved in 38.2% of patients. No SAEs have been described. Based on body weight measurements, the mean highest change (standard deviation [SD]) in weight post-baseline was 0.5 kg (4.1) and the mean lowest change (SD) was −5.5 kg (4.2) in the ceritinib group. More than one third of patients recovered from the initial event of weight decrease. In the chemotherapy group, of the 113 patients with a normal weight at baseline, two patients (1.8%) had a post-baseline decrease in weight of ≥ 10% compared to baseline and four patients (3.5%) had a post-baseline increase in weight of ≥ 10%.
  "Weight decreased" was included in section 4.8, Table 2 of the SmPC.
- **Sitting systolic blood pressure**: In the ceritinib group, of the 110 patients with a normal sitting systolic blood pressure (BP) at baseline, 11 patients (10.0%) had a post-baseline decrease in systolic BP to ≤ 90 mmHg and a decrease of ≥ 20 mmHg compared to baseline, and eight patients (7.3%) had a post-baseline increase in systolic BP to ≥ 160 mmHg and an increase of 20 mmHg compared to baseline. In the chemotherapy group, of the 112 patients with a normal sitting systolic BP at baseline, one patient (0.9%) had a postbaseline decrease in systolic BP to ≤ 90 mmHg and a decrease of ≥ 20 mmHg compared to baseline, and three patients (2.7%) had a post-baseline increase in systolic BP to ≥ 160 mmHg and an increase of 20 mmHg compared to baseline. The mean change (SD) in sitting systolic BP from baseline for the worst post-baseline value was 12.8 mm Hg (15.77).
- **Sitting diastolic blood pressure:** In the ceritinib group, of the 111 patients with a normal sitting diastolic BP at baseline, eight patients each (7.2%) had notable post-baseline decrease (diastolic BP of ≤ 50 mmHg and decrease of ≥ 15 mmHg compared to baseline) and increase (diastolic BP of ≥ 100 mmHg and increase of ≥ 15 mmHg compared to baseline) relative to baseline. In the chemotherapy group, of the 112 patients with a normal sitting diastolic BP at baseline, two patient (1.8%) had a post-baseline decrease in diastolic BP to ≤ 50 mmHg and decrease of ≥ 15 mmHg compared to baseline -, and five patients (4.5%) had a post-baseline increase in diastolic BP to ≥ 100 mmHg and increase of ≥ 15 mmHg compared to baseline. The mean change (SD) in sitting diastolic BP from baseline for the worst post-baseline value was 9.9 mmHg (9.27).

Electrocardiograms

The ECG data was analyzed based on central laboratory reported results.

QTcP is considered the most appropriate correction to characterize effect of ceritinib on the QT internal.

In the ceritinib group, of 114 patients (99.1%) with QTcP ≤ 450 ms at baseline, 32 patients (28.1%), three patients (2.6%), and one patient (0.9%) were noted with post-baseline QTcP value of >450-480 ms, >480-500 ms, and >500 ms, respectively. One of the three patients with >480-500 ms post-baseline already had an elevated QTcP of 463.4 ms at baseline.

In the chemotherapy group, of 111 patients with QTcP ≤ 450 ms at baseline,10 patients (9.0%) and one patient (0.9%) were noted with post-baseline QTcP values of >450-480 ms, and >480-500 ms, respectively.

Safety in special groups and situations

Analyses of AEs by region, age, gender, race, presence or absence of brain metastases, and WHO PS (0 vs. ≥ 1) showed patterns that were generally consistent with those of the overall population, and no relevant clinically meaningful differences were observed.

In Study A2303, the median age of patients randomized to the ceritinib group was 54 years (range: 30 to 77 years; n=89 <65 years, n=26 ≥ 65 years). Among the patients ≥ 65 years, two patients were ≥ 75 -84 years and none were ≥ 85 years old. In the subgroup analysis of safety by age (<65 years vs. ≥ 65 years) that was performed in Study A2303, the safety profile of patients ≥ 65 years was generally consistent with that of the overall population, and did not reveal any relevant clinically meaningful differences (≥ 10%). The incidence of most AESIs was similar between the two age groups (<65 years vs. ≥ 65 years) except for GI toxicity (96.6% vs. 80.8%) and hepatotoxicity (56.2% vs. 42.3%), where the incidence was higher in patients <65 years compared to patients ≥ 65 years.

The incidence of AESIs were generally similar across the different subgroups, with few differences (>10%) observed in the frequency of occurrence of the certain AESIs as mentioned below (Table 36). As stated above these results should be interpreted with caution due to the small size of the various subgroups and the limited number of patients with certain AESIs (e.g. bradycardia, QT prolongation).

The incidence of most AESIs was similar across regions except for bradycardia events (30.8% vs. 8.8%) and QTc prolongation (23.1% vs 7.5%), where the incidence of these events was higher in the patients from Asia pacific compared to Europe. North America region is excluded from this comparison as the sample size was very small (n=9).

Of note, bradycardia AESI also includes QT prolongation which was the most common AE in this category; the same patients are also included in the QT prolongation AESI; the number of patients with actual bradycardia was low.

The incidence of most AESIs was similar between age groups except for GI toxicity (96.6% vs 80.8%) and hepatotoxicity (56.2% vs 42.3%) where the incidence was higher in patients <65 years compared to patients ≥ 65 years of age.

The incidence of most AESIs was similar for both males and females, although differences were apparent in the incidences of bradycardia events (8.5% vs 19.1%).

Analyses of AESIs by race showed that incidences of hepatotoxicity (66.7% vs 46.9%), bradycardia (30.0% vs 8.6%), and QTc prolongation (20.0% vs 8.6%) events were higher in Asians vs. Caucasian.

There were generally no differences in the incidences of AESIs with respect to ECOG status of 0 vs. ≥ 1, except for bradycardia events (21.4% vs. 8.5%) and QTc prolongation (17.9% vs. 6.8%) which were more frequent in patients with ECOG status 0.

There was no difference in the incidence of AESIs in patients with or without brain metastasis at screening.

Table 36: AESIs in ceritinib treatment group by subgroups (Safety set)

Subgroups	N	Bradycardia		Gastrointestinal toxicity		Hepatotoxicity		Hyperglycemia		QT prolongation		ILD/Pneumonitis		Pancreatitis	
		All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Region															
North America	9	2 (22.2)	1 (11.1)	9 (100)	3 (33.3)	2 (22.2)	1 (11.1)	2 (22.2)	0	2 (22.2)	1 (11.1)	0	0	0	0
Europe	80	7 (8.8)	0	74 (92.5)	8 (10.0)	43 (53.8)	35 (43.8)	7 (8.8)	6 (7.5)	6 (7.5)	1 (1.3)	2 (2.5)	2 (2.5)	4 (5.0)	4 (5.0)
Asia Pacific	26	8 (30.8)	0	24 (92.3)	4 (15.4)	16 (61.5)	8 (30.8)	1 (3.8)	0	6 (23.1)	0	0	0	3 (11.5)	1 (3.8)
Age															
< 65 years	89	15 (16.9)	1 (1.1)	86 (96.6)	11 (12.4)	50 (56.2)	35 (39.3)	7 (7.9)	3 (3.4)	12 (13.5)	2 (2.2)	2 (2.2)	2 (2.2)	4 (4.5)	2 (2.2)
≥ 65 years	26	2 (7.7)	0	21 (80.8)	4 (15.4)	11 (42.3)	9 (34.6)	3 (11.5)	3 (11.5)	2 (7.7)	0	0	0	3 (11.5)	3 (11.5)
Gender															
Male	47	4 (8.5)	0	42 (89.4)	5 (10.6)	25 (53.2)	19 (40.4)	5 (10.6)	2 (4.3)	4 (8.5)	1 (2.1)	1 (2.1)	1 (2.1)	4 (8.5)	4 (8.5)
Female	68	13 (19.1)	1 (1.5)	65 (95.6)	10 (14.7)	36 (52.9)	25 (36.8)	5 (7.4)	4 (5.9)	10 (14.7)	1 (1.5)	1 (1.5)	1 (1.5)	3 (4.4)	1 (1.5)
Race*															
Caucasian	81	7 (8.6)	1 (1.2)	75 (92.6)	11 (13.6)	38 (46.9)	31 (38.3)	9 (11.1)	6 (7.4)	7 (8.6)	2 (2.5)	2 (2.5)	2 (2.5)	4 (4.9)	4 (4.9)
Asian	30	9 (30.0)	0	28 (93.3)	4 (13.3)	20 (66.7)	10 (33.3)	1 (3.3)	0	6 (20.0)	0	0	0	3 (10.0)	1 (3.3)
Other	2	0	0	2 (100)	0	1 (50.0)	1 (50.0)	0	0	0	0	0	0	0	0
Brain metastases at baseline															
Yes	65	9 (13.8)	0	59 (90.8)	9 (13.8)	34 (52.3)	25 (38.5)	5 (7.7)	3 (4.6)	6 (9.2)	0	2 (3.1)	2 (3.1)	6 (9.2)	4 (6.2)
No	50	8 (16.0)	1 (2.0)	48 (96.0)	6 (12.0)	27 (54.0)	19 (38.0)	5 (10.0)	3 (6.0)	8 (16.0)	2 (4.0)	0	0	1 (2.0)	1 (2.0)
ECOG status															
0	56	12 (21.4)	1 (1.8)	52 (92.9)	7 (12.5)	28 (50.0)	20 (35.7)	4 (7.1)	2 (3.6)	10 (17.9)	1 (1.8)	0	0	4 (7.1)	3 (5.4)
≥1	59	5 (8.5)	0	55 (93.2)	8 (13.6)	33 (55.9)	24 (40.7)	6 (10.2)	4 (6.8)	4 (6.8)	1 (1.7)	2 (3.4)	2 (3.4)	3 (5.1)	2 (3.4)

*The number of patients in the "Other" ethnicities was too low to make any meaningful comparisons.
AESI groups are presented alphabetically; preferred terms are sorted within the AESI group in descending frequency, as reported for the ceritinib 750 mg treatment arm.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple severity grades for an AE while on a treatment is only counted under the maximum grade.
Only AEs occurring during on-treatment period are summarized.
MedDRA version 18.1 is used. AEs are graded according to the CTCAE V4.03
Source: [Study A2303-Table 14.3.1-1.23]

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

Safety in the subgroup of patients who cross-over to ceritinib in Study A2303

Patients randomized to the chemotherapy group were allowed to cross-over to receive ceritinib therapy in the extension-treatment phase only after BIRC-confirmed RECIST- defined disease progression. Seventy-five patients from the chemotherapy group crossed over to ceritinib, and entered the extension-treatment. One of these 75 patients died before starting the first dose of ceritinib in the extension-treatment phase. At the time of the data cut-off, 28/75 patients (37.3%) in the extension-treatment phase were still ongoing. Forty-seven of the 75 patients discontinued the extension-treatment phase, and the primary reasons for discontinuation were disease progression (24 patients) (Table 1-3).

The median duration of exposure was 6.1 weeks (min-max: 3.0 to 59.9 weeks) and 28 patients (37.8%) were exposed to ceritinib 750 mg for a period of ≥ 12 weeks in the extensiontreatment phase.

In the extension-treatment phase, the pattern in incidence of the various AE categories were generally consistent with those observed during the treatment phase of the study, with numerical differences (<10%) when compared to treatment phase in all the AE categories, except for AEs requiring dose interruption/delay

which were reported higher during the treatment phase (73.0% vs. 56.8% in the extension-treatment phase) (Table 37, Table 21).

Sixteen patients died on-treatment in the extension-treatment phase. The majority of the ontreatment deaths (11/16) were attributed to disease progression, and cause of death for the remaining five deaths were reported as “other causes”, which were consistent with what would be expected in a population with NSCLC and with other comorbid conditions. The five deaths which were reported due to “other” causes were due: renal failure, intestinal perforation, hyperglycemia, pulmonary embolism, and sudden death. Of these five deaths, one death due to pulmonary embolism was suspected to be study drug-related by the Investigator.

Table 37: Overall summary of AEs (Cross-over analysis set)

Category	Ceritinib 750 mg N=74	
	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]

Overall, the pattern of AEs was also consistent with that observed in the treatment phase, although individual frequencies are slightly lower, which could be due to the shorter median duration of exposure of ceritinib in the extension-treatment phase (6.1 vs. 30.3 weeks in treatment phase).

The most frequently observed AEs (in >20% of patients) (regardless of study drug relationship) in the extension-treatment phase were: diarrhea (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%), fatigue and constipation (each 21.6%), and GGT increased (20.3%) (Table 38).

The most frequently observed grade 3/4 AEs (in >10% of patients) (regardless of study drug relationship) in the extension-treatment phase were: ALT increased (17.6%), nausea, AST increased, and GGT increased (10.8% each) (Table 38).

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

Table 38: Adverse events, regardless of study drug relationship, by preferred term (with at least 5% incidence of all grades) (Cross-over analysis set)

	Ceritinib 750 mg N=74	
Preferred term	All grades	Grade 3/4
Total	**73 (98.6)**	**55 (74.3)**
Diarrhoea	53 (71.6)	4 (5.4)
Nausea	42 (56.8)	8 (10.8)
Vomiting	35 (47.3)	7 (9.5)
ALT increased	22 (29.7)	13 (17.6)
Decreased appetite	20 (27.0)	0
AST increased	19 (25.7)	8 (10.8)
Blood creatinine increased	18 (24.3)	0
Abdominal pain	17 (23.0)	1 (1.4)
Constipation	16 (21.6)	0
Fatigue	16 (21.6)	5 (6.8)
GGTincreased	15 (20.3)	8 (10.8)
Asthenia	12 (16.2)	2 (2.7)
Dyspnoea	12 (16.2)	5 (6.8)
Pyrexia	12 (16.2)	0
Rash	12 (16.2)	0
Weight decreased	12 (16.2)	2 (2.7)
Blood alkaline phosphatase increased	11 (14.9)	2 (2.7)
Headache	10 (13.5)	1 (1.4)
Abdominal pain upper	8 (10.8)	0
Cough	8 (10.8)	0
Back pain	7 (9.5)	0
Dizziness	7 (9.5)	1 (1.4)
Hyperglycaemia	7 (9.5)	6 (8.1)
Nasopharyngitis	7 (9.5)	0
Non-Cardiac chest pain	7 (9.5)	1 (1.4)
Pleural Effusion	7 (9.5)	4 (5.4)
Pneumonia	7 (9.5)	4 (5.4)
Anaemia	6 (8.1)	1 (1.4)

Table 38: Adverse events, regardless of study drug relationship, by preferred term (with at least 5% incidence of all grades) (Cross-over analysis set) (cont.)

	Ceritinib 750 mg N=74	
Preferred term	All grades	Grade 3/4
Hypokalaemia	6 (8.1)	3 (4.1)
Musculoskeletal pain	6 (8.1)	0
Anxiety	5 (6.8)	1 (1.4)
Arthralgia	5 (6.8)	0
Dysphagia	5 (6.8)	1 (1.4)
Electrocardiogram Qt prolonged	5 (6.8)	0
Leukopenia	5 (6.8)	1 (1.4)
Malaise	5 (6.8)	0
Neutropenia	5 (6.8)	2 (2.7)
Pain	5 (6.8)	1 (1.4)
Tremor	5 (6.8)	0
Amylase increased	4 (5.4)	2 (2.7)
Dry skin	4 (5.4)	0
Hypoalbuminaemia	4 (5.4)	0
Insomnia	4 (5.4)	0
Lung infection	4 (5.4)	1 (1.4)
Muscular weakness	4 (5.4)	1 (1.4)
Pulmonary embolism	4 (5.4)	3 (4.1)
Somnolence	4 (5.4)	0
Stomatitis	4 (5.4)	0
Upper respiratory tract infection	4 (5.4)	0
Urinary tract infection	4 (5.4)	0

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma- glutamyltransferase
Preferred terms are sorted in descending frequency of all grades column.
Only AEs occurring during extension-treatment period are summarized.
Source: [Study A2303-Table 14.3.1-1.4c]

Drug interactions

Potential for drug-drug interaction is adequately reflected in the label.

Avoid co-administration of ceritinib with strong CYP3A inhibitors and inducers. If concomitant use with strong CYP3A inhibitors is unavoidable, reduce the ceritinib dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. Avoid co-administration of ceritinib with CYP3A and CYP2C9 substrates with narrow therapeutic indices. Exercise caution with concomitant use of P-gp inhibitors and inducers.Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates.

Drug-food / drink interactions

The bioavailability of ceritinib is increased in the presence of food depending on the fat content in the meal. Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken.

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

Use in pregnancy and lactation

Because of the potential risks to the human fetus, women of child-bearing potential were advised to avoid becoming pregnant and to use highly-effective contraception during treatment and up to 3 months following treatment discontinuation. In case pregnancy occurs, risk benefit evaluations must be carried out on an individual basis with careful counselling regarding potential risk to the fetus.

Mothers should avoid breast-feeding while receiving ceritinib, as it is not known whether ceritinib is excreted in milk. The potential for ceritinib to cause infertility in male and female patients is unknown.

Overdose

No new information about overdose has been generated in support of this application; recommendations are described in the approved prescribing information.

Drug abuse

No new information about abuse/dependence potential has been generated in support of this application. There is no known potential for abuse of ceritinib and no abuse studies have been performed.

Withdrawal and rebound

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

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

No studies have been performed on the effects of ceritinib on the ability to drive or operate machinery. Nevertheless, patients who receive ceritinib could experience fatigue and should drive and operate machinery with caution.

Post-marketing data

Relevant publications containing important new safety information published are regularly retrieved from the three publicly accessible, bibliographic databases Medline, Embase and Biosis Previews or by full text screenings in subscribed medical journals. The search criteria was inclusive of pregnancy outcomes (including termination) with no adverse outcomes, use in pediatric populations, compassionate supply, named patient use, lack of efficacy, asymptomatic overdose, abuse or misuse, medication error where no AEs occurred, or “near misses” and important non-clinical safety results. The search criteria used were LDK378, ceritinib, ALK inhibitor, anaplastic lymphoma kinase inhibitor, and various selective ALK inhibitors.

With the exclusion of publications describing individual case reports which have been included in PSURs, there were no new and significant safety findings published in the peerreviewed scientific literature or made available as unpublished manuscripts in PSUR 2, 3 and 4 and from 29 April 2016 to 10 August 2016.

Data from Novartis global pharmacovigilance safety database

Cumulative listings of SAE and death reports that were reported to the Novartis global pharmacovigilance database (ARGUS) from 23 ongoing Novartis-sponsored studies up to 10-Aug-2016. The evaluation of the information received until 10-Aug-2016 in 23 Novartis ongoing studies did not reveal any new safety concern or a change in frequency or severity, and does not suggest an update to the characterization of the risks is needed. It did not reveal any new relevant data impacting on the positive benefit/risk balance of Zykadia. The safety data is consistent with the known safety profile of ceritinib.

No untoward effects have been reported in ongoing trials that would materially alter the established safety profile of ceritinib.

Post-marketing surveillance

Ceritinib was granted accelerated approval in USA under the trade name of Zykadia on 29-Apr-2014 for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. In EU, Zykadia was granted conditional marketing authorization on 06-May-2015 for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. Meanwhile, it has been approved in more than 50 countries including Switzerland, Japan, and Canada.

Routine pharmacovigilance activities, including regular targeted follow-up, are continuously performed by Novartis. If new safety data emerge providing evidence of increased severity, specificity, or frequency of a safety event, Health Authorities will be notified and the Risk Management/Risk Minimization Plan reviewed and updated.

An estimate of patient exposure was based on worldwide sales volume in kilogram (kg) of active substance sold cumulatively, and on the Defined Daily Dose of 750 mg. The cumulative exposure since the International Birth Date (IBD, 29-Apr-2014) is estimated to be approximately 1214 patient-treatment-year (28-April-2016).

The post-marketing experience with ceritinib has been reviewed on an ongoing basis and the results available in Periodic Safety Update Reports (PSURs). No new information has emerged based on post-marketing usage of Zykadia that would substantially alter the known safety profile of ceritinib. The overall benefit-risk balance of ceritinib for the treatment of patients with locally advanced or metastatic ALK positive NSCLC remains positive.

4.3.3. Discussion

The MAH has submitted the confirmatory Study A2303. This was a Phase III, multi-center, randomized, open-label study of ceritinib in patients with ALK-positive metastatic NSCLC who have progressed or are intolerant to crizotinib.

The median duration of exposure to chemotherapy was 6.3 weeks compared to 30.3 weeks with ceritinib. The median duration of exposure was 14.1 weeks and 6.1 weeks for patients who took pemetrexed and docetaxel, respectively.

AEs: The most frequently reported AEs (in ≥ 20% of patients) of any grade in the ceritinib group were diarrhea (72.2%), nausea (66.1%), vomiting (52.2%), ALT increased (42.6%), decreased appetite (41.7%), AST increased (36.5%), weight decreased (29.6%), fatigue (27.0%), asthenia (22.6%), ALP increased (22.6%), GGT increased (22.6%), abdominal pain (21.7%), and back pain (21.7%). These AEs are consistent with the known safety profiles of ceritinib, and can be effectively managed dose reduction/interruption and/or use of concomitant medication.

Based on body weight measurements, the mean highest change (standard deviation [SD]) in weight post-baseline was 0.5 kg (4.1) and the mean lowest change (SD) was −5.5 kg (4.2) in the ceritinib group. More than one third of patients recovered from the initial event of weight decrease.“Weight decreased” was included in section 4.8, Table 2 of the SmPC.

AEs suspected to be drug-related: The most frequently (in ≥ 20% of patients) reported AEs of any grade suspected to be related to study drug included diarrhea (63.5%), nausea (60.9%), vomiting (47.8%), ALT increased (41.7%), AST increased (35.7%), and decreased appetite (33.0%).in the ceritinib group, and fatigue (23.9%) in the chemotherapy group.

AESI: Hepatotoxicity, ILD/pneumonitis, QT prolongation, hyperglycemia, bradycardia, GI toxicity and pancreatitis have been identified as AESIs for ceritinib, and are known to occur with other tyrosine kinase inhibitors. These were manageable with dose adjustments and/or dose interruptions (with or without use of

concomitant medication). Five patients in the ceritinib group discontinued study treatment due to AESIs. No Hy's law cases and none of the study drug-related AESIs were the primary cause of death. No deaths due to AESIs occurred in Study A2303.

Gastrointestinal toxicity AEs, although occurred the most frequently (reported in 93.0% of patients) in the ceritinib group. Majority of these events were grade 1 or 2. Grade 3/4 GI AEs were reported in 13.0% of patients. Majority of GI events were clinically managed by dose adjustment or interruption/delay, and/or concomitant medications as appropriate. Only one patient in the ceritinib group discontinued due to GI toxicity (grade 3 vomiting, not considered to be study drug-related as per Investigator assessment).

Hepatotoxicity AEs were reported in 53.0% of patients, with grade 3/4 reported in 38.3% of patient, and consisted mostly of isolated, transient and reversible increases of transaminases without clinical symptoms that were manageable with dose adjustment and/or dose interruptions. None of the patient presented with other concurrent observations related to impaired liver function. Only one patient reported a hepatotoxicity SAE (not related to study drug), and only two patients discontinued study treatment. No cases of Hy's law were reported and no patient with concurrent transaminase and bilirubin increase. Two patients in the ceritinib group discontinued treatment due to these events (increased ALT/AST). Based on biochemistry data, overall increases in AT >3 x ULN (grade 2), AT >5 x ULN (grade 3), AT >20 x ULN (grade 4) were seen in 48.7%, 26.1%, and 1.7% of patients ceritinib group. Regular monitoring of transaminase levels allows early intervention (i.e. dose adjustments or interruptions/delay) for effective management of the event.

Based on laboratory data review, 12/26 (47.2%) and 15/26 (57.7%) of patients with an event of ALP and GGT increased, respectively, had an abnormal baseline value of the corresponding laboratory parameter prior to treatment start with ceritinib. The event of ALP increased resolved in 18/26 (69.2%) patients and GGT increased in 16/26 patients (61.5%). None of the AEs were SAEs, and no study drug discontinuations occurred due specifically to ALP or GGT increase, furthermore, generally do not require specific management guidelines. No association was found with bilirubin increase, and the abnormalities were reversible with no evidence for prolonged or severe cholestatic injury despite treatment continuation.

Based on a comprehensive review of the available safety information from Study A2303, "blood ALP increased" has been added as a new term to the existing ADR "Liver laboratory test abnormalities". Furthermore, in the update SmPC, "ALP increased" has been identified as a new ADR and has been proposed to be added to Table 2 of Section 4.8 "Undesirable effects" of the SmPC under the term "Liver laboratory test abnormalities" in the system organ class (SOC) "Investigations". "GGT increased" was already included in Table 2 of the SmPC under the same term and SOC at the time of the initial Marketing Authorization Application. Increases in ALP and GGT are managed in the context of hepatotoxicity and no additional guidance is needed in the SmPC.

The review of the overall safety profile of ceritinib in patients with mild hepatic impairment at baseline versus patients with normal hepatic function at baseline did not reveal any clinically relevant differences or new safety concerns, and is consistent with the known safety profile of ceritinib. No patients with moderate/severe hepatic impairment at baseline were enrolled into Study A2303.

The interpretation of the slightly higher incidence of on-treatment deaths in ceritinib treated patients with mild hepatic impairment at baseline compared to patients with normal hepatic function at baseline is limited due to the small subgroup size and limited number of patients with an event. All deaths were due to study indication.

Ceritinib is known to have a relevant QT prolonging effect. QT prolongation suspected to be related to ceritinib was observed in 11.3% patients. Only one patient reported a grade 3 AE of QT prolongation (confounded by grade 4 hypokalemia), and only one patient had QTcP prolongation > 500 msec based on ECG, which was not reported as an SAE. There were no cases of torsade de pointes or grade 4 AEs.

No case of clinically relevant consequences has been reported. None of the QT prolongation AEs led to study

drug discontinuation. There were no grade 4 QT prolongation AEs or Torsade de points, and no patients with AE of QT prolongation (preferred term) had syncope/loss of consciousness in Study A2303. No deaths associated with QT prolongation were reported.

Bradycardia AEs were reported in 17 patients (14.8%) in ceritinib group. These included the AE of ECG QT prolonged in 11.3% of patients (same as presented in QT prolongation category). Only three patients in the ceritinib group had actual AE of bradycardia, none of which was grade 3/4 or serious or was leading to study treatment discontinuation; one of these three cases was suspected to be study drug-related.

ILD/pneumonitis AEs were low and observed in two patients in the ceritinib group; both were grade 3/4, were considered serious, and led to study treatment discontinuation. One event of ILD was suspected to be study drug-related by the Investigator. “Lung infiltration” was considered to be of infectious origin (not study drug related). No deaths were reported due to ILD/pneumonitis.

Hyperglycemia AEs were reported in 10 patients (8.7%) of which six patients (5.2%) had a grade 3/4 AE. Only one patient (0.9%) had a hyperglycemia SAE (grade 3 glucose increase in the context of brain metastasis treated with radiotherapy and dexamethasone). Five of the six patients with grade 3/4 hyperglycemia received concurrent corticosteroids and/or had other underlying disease conditions. None of the hyperglycemia AEs was suspected to be study drug related and none of the events led to study drug discontinuation. As per laboratory assessment, the frequency of hyperglycemia was similar between the ceritinib and chemotherapy groups (49.6% vs. 46.0% with worst grade ≥ 1 post baseline). In the ceritinib group, grade 3 hyperglycaemia was reported in 11 patients (9.6%), there were no grade 4 events. In the chemotherapy group, six patients (5.3%) and one patient (0.9%) had grade 3 and grade 4 hyperglycaemia respectively. Analysis of median/mean blood glucose levels at screening and during the course of the study further did not show any increase with start of ceritinib treatment or later during the study. Blood glucose levels in the ceritinib group were also not higher compared to the chemotherapy group.

Pancreatitis AEs were observed in 6.1% of patients in the ceritinib group all of which reported amylase increased as preferred term, and no AEs with PT of pancreatitis were reported. None of the events were serious and none led to treatment discontinuation. Based on medical review, none of these cases with amylase increase were suggestive of (acute) pancreatitis.

Pancreatitis is an important identified risk in the current risk management plan (RMP) and has been included in the Section “Special warnings and precautions for use” and in the ADR Table of the current SmPC. Patients should be monitored for lipase and amylase elevations prior to the start of the treatment with ceritinib, and periodically thereafter as clinically indicated.

Ninety-one patients (79%) in the ceritinib group had elevations in blood creatinine levels (all grade 1 and 2) based on laboratory assessment of which 22 (19%) were reported as AE. None of these were severe (grade 3 or 4) or serious (SAE) or lead to study drug discontinuation, and the vast majority of these patients had concurrent GI toxicity as potential contributing factor.

Renal impairment related AEs in the ceritinib treated patients showed an increased frequency of AEs with the PT of creatinine increased and hyper-creatininemia (any grade: 30.0% mild, 44.4% moderate vs 3.5% normal renal function). Elevations of creatinine were transient and reversible upon treatment discontinuation.

There were no grade 3/4 events of acute kidney injury, renal failure or renal impairment reported in the ceritinib group in Study A2303.

A slightly higher frequency of QT prolongation AEs was found among patients with mild renal impairment compared to patients with normal renal function (17.5% mild and 8.8% normal respectively). None of these events were grade 3/4, and no SAEs occurred.

In the ceritinib group, one patient each had grade 3 decreased hemoglobin, thrombocytopenia and decreased WBCs during the study (no grade 4). Grade 3 absolute lymphocytes (hypo) was reported in 17.4% of patients with only one grade 4 event. Similar rate of grade ¾ lymphopenia was reported for chemotherapy group (23.9%).

All AESIs are already reflected into de SPC (especially in the section 4.4).

SAEs: were reported more frequently in the ceritinib group (42.6% ceritinib vs. 31.9% chemotherapy) and were commonly associated with progression and/or the underlying disease condition. The frequency of study drug-related SAEs was low and similar in both groups with approximately 10% of patients.

The incidence of study-drug related SAEs was low (11.3%) and included, nausea, vomiting, general physical health deterioration, dyspnea, pleural effusion, and pneumonia. There were very few discontinuations due to AEs which were suspected to be drug-related (5.2%).

Deaths: Twenty patients died on-treatment, 15 patients (13.0%) in the ceritinib group and five patients (4.4%) in the chemotherapy group. Deaths were mostly related to the underlying disease. The higher proportion of on-treatment deaths in the ceritinib group is likely related to the longer exposure and substantial number of patients continuing beyond disease progression in the ceritinib group compared to the chemotherapy group. The frequency of on-treatment deaths during the first 6 weeks of study treatment was similar between the two groups.

There were no deaths due to study drug-related AEs in the ceritinib group.

AEs drug-discontinuation: The frequency of study drug discontinuation attributable to AEs was 15.7% vs. 9.7% in ceritinib vs. chemotherapy group. Most of these AEs in the ceritinib group were related to disease progression and were not considered causally related to study drug. Only six patients (5.2%) in the ceritinib group discontinued treatment due to AEs which were suspected to be drug-related, compared to 9 patients (8.0%) in the chemotherapy group.

Dose reductions and interruptions were primarily attributable to AEs (hepatotoxicity and GI AEs in the ceritinib group). The higher rate of dose reductions and interruptions in the ceritinib group is acceptable for a highly active daily treatment that is administered for a prolonged period of time.

Overall the frequency of AEs and AE leading to treatment interruption, dose modification, was higher in the ceritinib group. This could be attributed to the fact that exposure to study treatment in the chemotherapy group was very short potentially impacting the frequency of AEs in the chemotherapy group, and therefore, should be considered when making comparisons between the two groups. In addition, many patients with BIRC-confirmed PD in the ceritinib group continued study treatment while patients with PD in the chemotherapy group commonly crossed over to ceritinib or discontinued study treatment.

The subgroup analysis of safety by region, age, gender, race, presence or absence of brain metastases, and WHO PS (0 vs. ≥ 1) at baseline did not reveal any relevant clinically meaningful differences. Potential differences were observed in the AESIs in different subgroups, however, this should be interpreted with caution due to the small size of the various subgroups and the limited number of patients with certain AESIs (e.g. bradycardia, QT prolongation).

In Study A2303, the median age of patients randomized to the ceritinib group was 54 years (range: 30 to 77 years; n=89 <65 years, n=26 ≥ 65 years). Among the patients ≥ 65 years, two patients were ≥ 75 -84 years and none were ≥ 85 years old. In the subgroup analysis of safety by age (<65 years vs. ≥ 65 years) that was performed in Study A2303, the safety profile of patients ≥ 65 years was generally consistent with that of the overall population, and did not reveal any relevant clinically meaningful differences (≥ 10%). The incidence of most AESIs was similar between the two age groups (<65 years vs. ≥ 65 years) except for GI toxicity (96.6% vs. 80.8%) and hepatotoxicity (56.2% vs. 42.3%), where the incidence was higher in patients <65 years compared to patients ≥ 65 years.

The safety profile of patient 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.

In summary, the safety profile of ceritinib in patients with ALK-positive NSCLC has been characterized in Study A2303, and is consistent with the known safety of ceritinib in this patient population. The adverse events (AEs) are manageable and reversible within the clinical setting with dose reduction/interruption and/or use of concomitant medication; only very few patients discontinued study treatment due to ceritinib associated AEs. No new safety signals or concerns have been identified in Study A2303 except one new ADR (weight decreased) and one additional term for the already existing ADR of liver laboratory test abnormalities was identified (i.e, GGT and ALP increased). The safety profile of pemetrexed and docetaxel in this study was also in line with the expected safety profile of both drugs, however, the frequency of AEs tended to be lower, possibly related to the rapid disease progression observed in the chemotherapy group resulting in short treatment exposure.

Based on laboratory data review, 12/26 (47.2%) and 15/26 (57.7%) of patients with an event of ALP and GGT increased, respectively, had an abnormal baseline value of the corresponding laboratory parameter prior to treatment start with ceritinib. The event of ALP increased resolved in 18/26 (69.2%) patients and GGT increased in 16/26 patients (61.5%). None of the AEs were SAEs, and no study drug discontinuations occurred due specifically to ALP or GGT increase, furthermore, generally do not require specific management guidelines. No association was found with bilirubin increase, and the abnormalities were reversible with no evidence for prolonged or severe cholestatic injury despite treatment continuation.

Based on a comprehensive review of the available safety information from Study A2303, “blood ALP increased” has been added as a new term to the existing ADR “Liver laboratory test abnormalities”. Furthermore, in the update SmPC, “ALP increased” has been identified as a new ADR and has been proposed to be added to Table 2 of Section 4.8 “Undesirable effects” of the SmPC under the term “Liver laboratory test abnormalities” in the system organ class (SOC) “Investigations”. “GGT increased” was already included in Table 2 of the SmPC under the same term and SOC at the time of the initial Marketing Authorization Application. Increases in ALP and GGT are managed in the context of hepatotoxicity and no additional guidance is needed in the SmPC.

In support of this risk assessment of ceritinib, the evaluation of the information received from the MAH global pharmacovigilance safety database until 10-Aug-2016 in 22 ongoing studies did not reveal any new safety concern or a change in frequency or severity of AEs, and does not suggest an update to the characterization of the risks is needed. No new information has emerged based on post-marketing usage of ceritinib that would substantially alter the known safety profile. In conclusion, the safety data is consistent with the known safety profile of ceritinib. No untoward effects have been reported in ongoing trials and pharmacovigilance activities that would materially alter the established safety profile of ceritinib. Routine pharmacovigilance activities, including regular targeted follow-up, should be continued to be performed.

4.4. Risk management plan

The MAH submitted an updated RMP version 5.0, dated 25 October 2016 with this application.

The CHMP endorsed the Risk Management Plan version 10 with the following content:

Safety concerns

There were no changes to the safety concerns.

Table 39: Safety concerns

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

Pharmacovigilance plan

Table 40: On-going and planned studies in the post-authorisation pharmacovigilance development plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
LDK378A2110 A phase I open label multicentre 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 (Sep-2018

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 Q3-2019 (planned)

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

There were no changes to the pharmacovigilance plan which are acceptable.

Table 41: Part VI.1.3 Summary of Post authorization efficacy development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status	Date for submission of final reports
LDK378A2303, A Phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK rearranged (ALK-positive) advanced nonsmall cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib	The primary objective is to compare the antitumor activityof ceritinib versus reference chemotherapy, as measured by PFS determined by a BIRC	Confirmatory Efficacy data in adult patients with ALK-positive advanced NSCLC who have been treated previously with Chemotherapy (platinum doublet) and crizotinib. ***The primary analysis report with final PFS results confirm the beneficial effect of ceritinib over chemotherapy in patients with advanced ALK-positive NSCLC previously treated with crizotinib.***	Ongoing, ***however the MAH believes that results from this study showing benefit of ceritinib versus chemotherapy constitute comprehensive clinical data and fulfil the specific obligatio***n.	***Primary analysis report: Nov-2016*** ***Planned OS interim analysis report: 2019*** ***Final OS analysis report: 2022***

Risk minimisation measures

There are no changes to the risk minimization measures which are acceptable.

4.5. Changes to the Product Information

Please refer to Attachment which includes comments to the Product Information.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects

1. The second and final analysis of OS should be provided when available along with an update of the overall efficacy results.
2. One new ADR (weight decreased) and one additional term for the already existing ADR of liver laboratory test abnormalities were identified. Given the high incidence of GGT and ALP increased and weight decreases, more recommendations regarding management, severity and expected duration in the SmPC.
3. The Applicant should provide a more detailed assessment of AEs occurring in elderly patients, broken down in different age subgroups (Age <65 yrs, 65-74 yrs, 75-84 yrs, ⩾ 85 yrs).
4. In study 2303, 17 patients (14.8%) had elevated amylase levels already at baseline; in particular, one out of the three grade 3 cases had grade 2 amylase increase at baseline and two had normal amylase (grade 0) at baseline, and two out of the three grade 4 cases had grade 3 amylase increase at baseline and one had normal amylase (grade 0) at baseline. Post-baseline, three (2.6%) patients had lipase elevations of any grade, of which two patients had grade 1 lipase elevations and one patient had grade 2 lipase elevation and no patients had grade 3 or 4 elevations. The Applicant is requested to submit and analyze available safety results in patients with hepatic impairment. The applicant is asked to update report about pancreatitis events that occurred during the clinical study.
5. In study 2303, twenty-two (19.1%) patients in the ceritinib vs none in the chemotherapy group had creatinine elevations based on AEs. In 2/10 patients the event was grade 3 (chronic kidney disease and urinary bladder rupture). In addition to the 22 patients with blood creatinine increase reported under the SOC of “Investigations”, creatinine renal clearance decreased was reported in three patients of which one patient had grade 3 event. All three events were suspected to be study drug related. The Applicant is requested to submit and analyze available safety results in patients with renal impairment.
6. In study 2303, the number and percentage of patients with increase from baseline QTcF > 30 msec were 71/114 (62.3%) in ceritinib group vs. 7/112 (6.3%) in chemotherapy group, from baseline QTcF > 60 msec were 7/114 (6.1%) in ceritinib group vs. 0/112 (0%) in chemotherapy group and new QTcF > 450 msec were 37/113 (32.7%) vs. 11/109 (10.1%) in chemotherapy group. The number and percentage of patients with increase from baseline QTcP > 30 msec were 66/115 (57.4%) in ceritinib group vs. 6/112 (5.4%) in chemotherapy group, from baseline QTcP > 60 msec were 7/115 (6.1%) in ceritinib group vs. 0/112 (0%) in chemotherapy group. The Applicant is asked to discuss in detail these results.

6. Assessment of the responses to the request for supplementary information

Other concerns

Clinical aspects

Question 1

The second and final analysis of OS should be provided when available along with an update of the overall efficacy results.

Summary of the MAH's response

At the time of the primary progression-free survival (PFS) analysis, the first pre-planned interim OS analysis was conducted. The OS data were still immature at the time of the data cut-off (26-Jan-2016) with a total of 67 patients (58.3%) in the ceritinib arm and 66 patients (56.9%) in the chemotherapy arm censored for survival [Study A2303 CSR].

Based on the current information available, the next planned OS interim analysis (with approximately 171 OS events) is expected to be performed around December 2018. The final OS analysis (with approximately 196 OS events) is expected to be performed around May 2021. Due to the event-driven nature of these analyses, the actual timing could differ from the projections.

As specified in the protocol, no further analyses of PFS are planned as the primary PFS objective has been met. At the time of the cut-off for the primary analysis (26-Jan-2016), there were 22 patients (19.1%) in the ceritinib arm and 7 patients (6.0%) in the chemotherapy arm censored as "ongoing without an event" for PFS by BIRC [Study A2303 CSR-Section 11.4.1.1]. Hence, longer follow-up of ongoing patients for PFS is not expected to change the primary PFS analysis results substantially.

Assessment of the MAH's response

OS data were immature at the time of the primary PFS analysis. With an event rate of 42% and 43% for ceritinib and chemotherapy arm respectively, no conclusive results in terms of OS were observed (HR 1.00 95%CI 0.67, 1.49). The high cross-over rate (65% of patients had crossed over to ceritinib arm along with the subsequent therapy with ALK inhibitors) likely impacted study results, however a sensitivity analysis carried out as an attempt to correct for crossover, showed similar results (HR 0.97 95%CI 0.65, 1.45). Although these results even stressed more the need of submission of mature OS data, it does not seem possible to assess mature OS data within the current variation procedure according to the applicant´s response. The second OS interim analysis will not be available until the end of 2018 and final OS analysis is expected around May 2021. Importantly, more mature data are not expected to modify the Benefit risk balance, given the likely absence of relevant findings in survival due to the high rate of crossover. So, even further updates are recommendable, a significant effect on OS is not foreseen.

Results from the phase III trial, study A2303, showed a clinically meaningful result, both in PFS and ORR. These results are in line with data from the previous studies which were the basis of the conditional MA and appear sufficient so as to positively conclude about the benefit/risk of ceritinib, however submission of mature OS data is recommended, when available (recommendation, see section 3). The data supporting the benefit/risk of ceritinib can be considered comprehensive and supporting the switch from conditional to full MA.

Conclusion:

Issue solved

Question 2

One new ADR (weight decreased) and one additional term for the already existing ADR of liver laboratory test abnormalities were identified. Given the high incidence of GGT and ALP increased and weight decreases, more recommendations regarding management, severity and expected duration in the SmPC.

Summary of the MAH's response

Liver laboratory test abnormalities

Hepatotoxicity is a known side effect of ceritinib, and mainly characterized by asymptomatic, transient liver enzyme increases. In Study A2303, one hepatotoxicity adverse event (AE) (grade 3 jaundice) was serious [Study A2303 CSR]; this event was not suspected to be study drug-related, occurred in the context of biliary obstruction, and resolved upon biliary stent placement. In addition, 2 patients (1.7%) had hepatotoxicity AE leading to treatment discontinuation [Study A2303 CSR]. The events, alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased, of both patients resolved after treatment discontinuation. No Hy's law cases (i.e. concurrent aminotransferases >3× upper limit of normal (ULN) and total bilirubin (TIBLI) >2×ULN and ALP <2×ULN) and no concurrent aminotransferases >3×ULN and TBILI >2×ULN have been observed with ceritinib in Study A2303 [Study A2303 CSR-Section 12.3.3.4.1].

The current SmPC clearly lists AEs of liver toxicity as common side effects of ceritinib. These AEs are included in the "Special warnings and precautions for use" in Section 4.4, in the dose modification guidance in Section 4.2, and in the ADR Table in Section 4.8 ("Liver Laboratory Test Abnormalities" such as ALT increased, AST increased, GGT increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, and liver function test abnormal, and "Hepatotoxicity" including drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity). Based on a comprehensive review of the available safety information from Study A2303 using the ADR selection criteria outlined in [Study A2303 CO-Section 5.5] (i.e. event occurring in >2% of patients and/or at least 3 more patients in the ceritinib group compared to the chemotherapy group and reasonable relationship with ceritinib by medical assessment), "blood ALP increased" has been added as a new term to the existing ADR "Liver laboratory test abnormalities".

GGT/ALP together with AST/ALT and bilirubin were part of the liver panel used in Study A2303 and other certinib studies to help better characterize liver toxicity and rule out other causes (i.e. obstruction, cholestasis, bone or liver metastasis), which are common in this patient population and can be confounding factors. GGT/ALP on their own have limited clinical value and generally do not require specific management guidelines.

ALP and GGT increased

In Study A2303, of the 115 patients treated with ceritinib, 26 patients (22.6%) reported at least one AE each of blood ALP increased or GGT increased (any grade, regardless of causality) compared to 0.9% and 1.8% in the chemotherapy group, respectively [Study A2303 CSR]. Most of these (in 18.3% and 15.7% patients, respectively) were suspected to be related to study treatment [Study A2303 CSR]. None of the AEs were SAEs [Study A2303 CSR], and no study drug discontinuations occurred due specifically to ALP or GGT increase [Study A2303 CSR].

Based on AE data amongst patients who had an event of ALP increased (n=26), the median time to onset of the first ALP increase regardless of causality with study treatment was 25.5 days (range: 10 to 296 days) (Table 5-1). Most of these events were grade 1 or 2; seven patients (6.1%) reported grade 3 events; no grade 4 blood ALP increase was reported. The event resolved in 18/26 (69.2%) patients with a median time to recovery of 27.0 days (range: 17 to 123 days); in the remaining 8 patients the event was improving or

ongoing at the time of the data cut-off (6/8 patients discontinued the study due to disease progression or death, two patients were ongoing).

Amongst patients who had an event of GGT increased (n=26), the median time to onset of the first GGT increase (regardless of causality with study treatment)) was 22.0 days (range: 1 to 294 days) (Table 42). Twenty-one patients (18.3%) had grade 3 GGT increased, and 3 patients (2.6%) had a grade 4 event. As mentioned above, none of these were SAEs. The events resolved in 16/26 patients (61.5%) with a median time to recovery of 63.5 days (range: 22 to 279 days), in the remaining 10 patients the event was improving or ongoing at the time of data cut-off (8/10 patients discontinued the study due to disease progression or death, two were ongoing).

Based on laboratory data review, 12/26 (47.2%) and 15/26 (57.7%) of patients with an event of ALP and GGT increased, respectively, had an abnormal baseline value of the corresponding laboratory parameter prior to treatment start with ceritinib [CSR A2303-Listing 16.2.8-1.4], [CSR A2303-Listing 16.2.8-1.7]. In addition, most of the patients with ontreatment ALP/GGT increase had concurrent transaminitis (24/26 patients with ALP increase and 25/26 patients with GGT increase); however, there were no cases of concurrent bilirubin increase.

Table 42: Characteristics of first on-treatment adverse event "ALP increased" and "GGT increased", regardless of study drug relationship in the ceritinib group of Study A2303 (Safety set)

	ALP increased Ceritinib 750 mg N=115	GGT increased Ceritinib 750 mg N=115
First AEs - n (%)		
All AEs	26 (22.6)	26 (22.6)
Grade 1	10 (8.7)	1 (0.9)
Grade 2	9 (7.8)	1 (0.9)
Grade 3	7 (6.1)	21 (18.3)
Grade 4	0	3 (2.6)
AEs requiring dose adjustments	0	1 (0.9)
Grade 3	0	1 (0.9)
Final outcome of first AEs - n (%) [1]		
All AEs, recovered/resolved	18 (15.7)	16 (13.9)
Grade 1	6 (5.2)	1 (0.9)
Grade 2	9 (7.8)	1 (0.9)
Grade 3	3 (2.6)	14 (12.2)
All AEs, other than recovered/resolved	8 (7.0)	10 (8.7)
Grade 1	4 (3.5)	0
Grade 3	4 (3.5)	7 (6.1)
Grade 4	0	3 (2.6)
Time to onset of first AE (days) [2]		
n	26	26
Mean (SD)	48.3 (65.57)	38.5 (54.55)
Median (min-max)	25.5 (10-296)	22.0 (1-294)
Time to recovery from first AE (days) [3]		
n	18	16
Mean (SD)	40.2 (28.10)	75.4 (59.80)
Median (min-max)	27.0 (17-123)	63.5 (22-279)

AE = adverse event; SD = standard deviation

First AE is defined as a sequence of a specific event (preferred term) firstly reported in a patient.

[1] An outcome of 'Recovered/resolved with sequelae' is categorized into the 'Other than recovered/resolved'.

[2] For all first AEs, (Start date of AE) – (Start date of study drug) + 1;

[3] For first AEs recovered/resolved before data cut-off, (End date of AE recovered/resolved) - (Start date of AE) + 1.

MedDRA version 18.1 has been used for the reporting.

Source: [Study A2303 RSI Appendix 1-CHMP Table 1-1]

In summary, while common, GGT and ALP increases are transient and asymptomatic laboratory changes typically associated with transaminitis in patients treated with ceritinib (cholestatic component or mixed type injury); no association was found with bilirubin increase, and the abnormalities were reversible with no

evidence for prolonged or severe cholestatic injury despite treatment continuation. In addition, > 30% of patients with GGT and ALP increase had abnormal values at baseline. The incidence of ALP/GGT increased was consistent with the incidence observed in a more recent, larger safety pool (N=925) of ceritinib treated patients with ALK-positive NSCLC [Study A2301 SCS-Section 2.1.6.1].

“ALP increased” has been identified as a new ADR and has been proposed to be added to Table 2 of Section 4.8 “Undesirable effects” of the SmPC under the term “Liver laboratory test abnormalities” in the system organ class (SOC) “Investigations”. “GGT increased” was already included in Table 2 of the SmPC under the same term and SOC at the time of the initial Marketing Authorization Application. In addition, the current monitoring and risk management guidelines on hepatocellular injury are deemed adequate as (1) both GGT and ALP are routine parameters in hepatic laboratory test panels and (2) GGT and ALP typically present with concurrent transaminitis. Increases in these liver enzymes are therefore managed in the context of hepatotoxicity and no additional guidance is needed in the SmPC.

Weight decreased

“Weight decreased” has been identified as a new ADR based on the selection criteria outlined in [Study A2303 CO-Section 5.5].

In Study A2303, 29.6% of patients in the ceritinib group had weight decreased (any grade, regardless of causality with study treatment) compared to 6.2% in the chemotherapy group [Study A2303 CSR]. 18.3% of patients on ceritinib and 2.7% on chemotherapy had weight decreased which was suspected to be related to study treatment by the Investigator [Study A2303 CSR]. Of note, median duration of treatment exposure (6.3 weeks chemotherapy vs 30.3 weeks ceritinib) and with that the observation time was very short in the chemotherapy group compared to ceritinib [Study A2303 CSR]. Weight decrease was generally mild or moderate (grade 1 or 2); 3 patients had grade 3 weight decrease (compared to one patient in the chemotherapy group). No grade 4 weight decrease was reported, and none of the events was considered serious.

Based on body weight measurements, the mean highest change (standard deviation [SD]) in weight post-baseline was 0.5 kg (4.1) and the mean lowest change (SD) was −5.5 kg (4.2) in the ceritinib group.

The mean highest change (SD) in weight post-baseline was 0.8 kg (3.2) and the mean lowest change (SD) was −1.2 kg (2.7) in the chemotherapy group [Study A2303 CSR]. Based on AE data amongst patients who had an event of weight decreased (n=34), the median time to onset of first weight decrease regardless of causality with study treatment was 45.0 days (range: 1 to 439 days) (Table 43). The events resolved in 13/34 patients (38.2%) with a median time to recovery of 24.5 days (range: 8 to 232 days); in the remaining 21 patients the event was ongoing at the time of the data cut-off (15/21 patients discontinued the study due to disease progression or death, three patients due to subject decision, and three were ongoing; in 1/21 patients, the event had improved from grade 2 to grade 1) [Study A2303 CSR-Listing 16.2.7-1.1].

Table 43: Characteristics of first on-treatment adverse event "weight decreased", regardless of study drug relationship for ceritinib (Safety set)

	Ceritinib 750 mg N=115
First AEs - n (%)	
All AEs	34 (29.6)
Grade 1	17 (14.8)
Grade 2	14 (12.2)
Grade 3	3 (2.6)
AEs requiring dose adjustments	3 (2.6)
Grade 2	2 (1.7)
Grade 3	1 (0.9)
Final outcome of first AEs - n (%) [1]	
All AEs, recovered/resolved	13 (11.3)
Grade 1	11 (9.6)
Grade 2	2 (1.7)
All AEs, other than recovered/resolved	21 (18.3)
Grade 1	6 (5.2)
Grade 2	12 (10.4)
Grade 3	3 (2.6)
AEs requiring dose adjustment, recovered/resolved	1 (0.9)
AEs requiring dose adjustment, other than recovered/resolved	2 (1.7)
Time to onset of first AE (days) [2]	
n	34
Mean (SD)	84.3 (98.74)
Median (min-max)	45.0 (1-439)
Time to recovery from first AE (days) [3]	
n	12
Mean (SD)	62.3 (77.51)
Median (min-max)	24.5 (8-232)

AE = adverse event; SD = standard deviation

First AE is defined as a sequence of a specific event (preferred term) firstly reported in a patient.

[1] An outcome of 'Recovered/resolved with sequelae' is categorized into the 'Other than recovered/resolved'.

[2] For all first AEs, (Start date of AE) – (Start date of study drug) + 1;

[3] For first AEs recovered/resolved before data cut-off, (End date of AE recovered/resolved) - (Start date of

In summary, mild to moderate weight decrease has been observed in approximately one quarter of patients treated with ceritinib; no SAEs have been described, and 3 patients reported grade 3 weight decrease during the course of the study. Frequency and severity of weight decreased was consistent with the incidence observed in a more recent, larger safety pool (N=925) of ceritinib treated patients with ALK-positive NSCLC [Study A2301 SCS-Section 4.1.2].

Weight loss may be linked to a variety of causes including tumor cachexia-anorexia, malnutrition, comorbidities and disease progression, all of which are expected to be observed in an advanced NSCLC patient population like in Study A2303. In addition, treatment-related side effects such as asthenia, decreased appetite or gastro-intestinal toxicity (all known ADRs of ceritinib) may be (temporary) contributing factors. More than one third of patients recovered from the initial event of weight decrease. Most of the patients with an ongoing event at the time of the data cut-off, progressed and discontinued the study. The relatively low frequency of weight decrease in the chemotherapy group is likely explained by the very short treatment duration and observation time.

At this stage, Novartis is of the opinion that additional recommendations regarding management, severity or duration of weight decreased are not needed in the SmPC. Weight decreased is a common observation in the advanced oncology setting that requires individualized management depending on the underlying causes. The event has been newly listed as a very common ADR in the ceritinib SmPC. In addition, adequate guidance is provided for relevant ADRs such as gastrointestinal (GI) toxicity including dose adjustment/interruptions that should be applied for any clinically relevant ADR based on individual tolerability.

Assessment of the MAH's response

Based on laboratory data review, 12/26 (47.2%) and 15/26 (57.7%) of patients with an event of ALP and GGT increased, respectively, had an abnormal baseline value of the corresponding laboratory parameter prior to treatment start with ceritinib. The event of ALP increased resolved in 18/26 (69.2%) patients and GGT increased in 16/26 patients (61.5%). None of the AEs were SAEs, and no study drug discontinuations occurred due specifically to ALP or GGT increase, furthermore, generally do not require specific management guidelines. No association was found with bilirubin increase, and the abnormalities were reversible with no evidence for prolonged or severe cholestatic injury despite treatment continuation.

Based on a comprehensive review of the available safety information from Study A2303, "blood ALP increased" has been added as a new term to the existing ADR "Liver laboratory test abnormalities". Furthermore, in the update SmPC, "ALP increased" has been identified as a new ADR and has been proposed to be added to Table 2 of Section 4.8 "Undesirable effects" of the SmPC under the term "Liver laboratory test abnormalities" in the system organ class (SOC) "Investigations". "GGT increased" was already included in Table 2 of the SmPC under the same term and SOC at the time of the initial Marketing Authorization Application. Increases in ALP and GGT are managed in the context of hepatotoxicity and no additional guidance is needed in the SmPC.

Based on Study A2303 data, 29.6% of patients in the ceritinib group had weight decreased (any grade, regardless of causality with study treatment), 18.3% of patients was suspected to be related to study treatment by the Investigator and the events were resolved in 38.2% of patients. No SAEs have been described. Based on body weight measurements, the mean highest change (standard deviation [SD]) in weight post-baseline was 0.5 kg (4.1) and the mean lowest change (SD) was −5.5 kg (4.2) in the ceritinib group. More than one third of patients recovered from the initial event of weight decrease. Thus, additional recommendations regarding management, severity or duration of weight decreased are not needed in the SmPC, because the individualized management is required and "Weight decreased" was already included in section 4.8, Table 2 of the SmPC.

Conclusion:

Issue solved

Question 3

The Applicant should provide a more detailed assessment of AEs occurring in elderly patients, broken down in different age subgroups (Age <65 yrs, 65-74 yrs, 75-84 yrs, ⩾ 85 yrs).

Summary of the MAH's response

In Study A2303, the median age of patients randomized to the ceritinib group was 54 years (range: 30 to 77 years; n=89 <65 years, n=26 ≥ 65 years) [Study A2303 CSR]. Among the patients ≥ 65 years, two patients were ≥ 75 -84 years and none were ≥ 85 years old [Study A2303 CSR-Listing 16.2.4-1.1].

For the 2 patients ≥ 75 years age enrolled in Study A2303, a summary of key safety findings is provided below; for detailed narratives, see [Study A2303 CSR-Section 14.3.3]:

- Patient [A2303-1202-003] was a 77 year old male patient with NSCLC adenocarcinoma metastatic to bone, brain, lung and mediastinal lymph nodes at study entry; no relevant medical history was reported.
  - On Day 127, the patient reported one SAE of grade 3 hyponatremia suspected to be possibly treatment related as per the Investigator, upon which the patient was hospitalized and ceritinib temporarily interrupted. Prior to that, the patient was diagnosed with disease progression in the

brain (Day 85), however, treatment with ceritinib was continued as the Investigator judged it to be in the best interest of the patient. Between Day 105 and 116, the patient received palliative brain radiotherapy. Hyponatremia was reported to have occurred in the context of a syndrome of inappropriate diuretic hormone (SIADH) as a consequence of cerebral irradiation.
  - Grade 4 serum amylase increased was reported on Day 107. The event was not suspected to be treatment related, and recovered after 20 days with no action taken. The event was likely a consequence of the brain radiotherapy involving the salivary glands; there was no clinical evidence for (acute) pancreatitis such as vomiting or abdominal pain and lipase values were normal.
  - On Day 211, study treatment was permanently discontinued due to patient's decision.
- Patient [A2303-1254-001] was a 76 year old female patient with NSCLC adenocarcinoma metastatic to the bone lymph nodes, lung and pleura at study entry; no relevant medical history was reported. The patient had normal glucose value at baseline, and received supportive prednisolone prior/during the study; she also had grade 2 decreased creatinine clearance prior to randomization.
  - No SAEs were reported for this patient.
  - On Day 29, the patient was noted with grade 2 weight decrease, and creatinine clearance worsened to grade 3. No action was taken. The event was suspected to be related to study treatment.
  - On Day 46, a computed tomography scan revealed disease progression (worsening pleural effusion and bronchopulmonary lymph nodes, and new lesions in the brain).
  - On Day 57, the patient developed grade 3 hyperglycemia (14.2 mmol/L) which was not suspected to be treatment related as per investigator assessment; the patient had also elevated white blood cells (13.9 × 109/L) and absolute neutrophil counts (13.27 × 109/L), indicative of a possible infection. On the same day, the patient was discontinued due to disease progression and died 33 days later due to NSCLC.

In the subgroup analysis of safety by age (<65 years vs ≥ 65 years vs) that was performed in Study A2303, see clinical study report), the safety profile of patients ≥ 65 years was generally consistent with that of the overall population, and did not reveal any relevant clinically meaningful differences (≥ 10%) [Study A2303 CSR]. The incidence of most AESIs was similar between the two age groups (<65 years vs ≥ 65 years) except for GI toxicity (96.6% vs 80.8%) and hepatotoxicity (56.2% vs 42.3%), where the incidence was higher in patients <65 years compared to patients ≥ 65 years. Of note, the overall incidence of GI toxicity AESIs was high, and the subgroups relatively small [Study A2303 CSR]. In summary, the overall safety profile in the subgroup of patients <65 years is similar to the safety profile in the subgroup of patients ≥ 65 years.

A clinically meaningful and consistent PFS benefit was observed across both age categories in Study A2303 [Study A2303 CSR]. A subgroup analysis by age (i.e. ≥ 65 years vs <65 years and ≥ 70 years vs <70 years) in a more recent, larger safety pool (N=925) of ceritinib treated patients with ALK-positive NSCLC did not identify any clinically relevant differences within the subgroups [Study A2301 CSR], [Study A2301 SCS-Section 5.1.1].

This suggests that the risk/benefit profile of ceritinib is consistent in ALK-positive NSCLC patients ≥ 65 years old with that of patients <65 years.

Assessment of the MAH's response

As requested, the applicant has provided a more detailed assessment of AEs occurring in elderly patients.

In Study A2303, the median age of patients randomized to the ceritinib group was 54 years (range: 30 to 77 years; n=89 <65 years, n=26 ≥ 65 years). Among the patients ≥ 65 years, two patients were ≥ 75 -84 years and none were ≥ 85 years old.

In the subgroup analysis of safety by age (<65 years vs. ≥ 65 years) that was performed in Study A2303,

the safety profile of patients ≥ 65 years was generally consistent with that of the overall population, and did not reveal any relevant clinically meaningful differences (≥ 10%). The incidence of most AESIs was similar between the two age groups (<65 years vs. ≥ 65 years) except for GI toxicity (96.6% vs. 80.8%) and hepatotoxicity (56.2% vs. 42.3%), where the incidence was higher in patients <65 years compared to patients ≥ 65 years.

Conclusion:

Issue solved

Question 4

In study 2303, 17 patients (14.8%) had elevated amylase levels already at baseline; in particular, one out of the three grade 3 cases had grade 2 amylase increase at baseline and two had normal amylase (grade 0) at baseline, and two out of the three grade 4 cases had grade 3 amylase increase at baseline and one had normal amylase (grade 0) at baseline. Post-baseline, three (2.6%) patients had lipase elevations of any grade, of which two patients had grade 1 lipase elevations and one patient had grade 2 lipase elevation and no patients had grade 3 or 4 elevations. The Applicant is requested to submit and analyze available safety results in patients with hepatic impairment. The applicant is asked to update report about pancreatitis events that occurred during the clinical study.

Summary of the MAH's response

Safety in patients with hepatic impairment

Safety data from Study A2303 were analyzed by baseline hepatic function based on the liver function classification from the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG 2009):

- Normal hepatic function: TBILI ≤ ULN and AST ≤ ULN;
- Mild hepatic impairment: TBILI ≤ ULN and AST >ULN or TBILI >ULN and TBILI ≤ 1.5xULN and AST any value);
- Moderate hepatic impairment: TBILI >1.5xULN and TBILI ≤ 3.0×ULN and AST any value;
- Severe hepatic impairment: TBILI >3xULN and AST any value.

Of note, patients with AST/ALT >2.5xULN (except for patients with liver metastases: >5xULN) or bilirubin >1.5xULN (except Gilbert's disease: >3xULN) were excluded from the study as per protocol, hence, no patients with moderate/severe hepatic impairment at baseline were enrolled into Study A2303; 184 patients (n=92 in each treatment group) had normal liver function , and 40 patients (n=22 in the ceritinib group, n=18 in the chemotherapy group) had mild hepatic impairment at baseline.

The overall frequency of all grade AEs, grade 3/4 AEs, SAEs, AEs leading to discontinuation, and AEs requiring dose adjustments or delays was similar in patients with mild hepatic impairment at baseline compared to patients with normal hepatic function at baseline in both treatment groups in Study A2303 (Table 44). The interpretation of the slightly higher incidence of on-treatment deaths in ceritinib treated patients with mild hepatic impairment at base

line compared to patients with normal hepatic function at baseline is limited due to the small subgroup size and limited number of patients with an event, and is in line with the overall patient population. All deaths were due to study indication. The same trend was seen in the chemotherapy group [Study A2303 CSR].

A review of AEs by SOC in patients with mild hepatic impairment and normal hepatic function at baseline did not reveal any differential safety profile in the two patient populations in the ceritinib group [Study A2303 RSI Appendix 1-CHMP Table 26]. The frequency and severity of AESIs were similar in patients with mild

hepatic impairment compared to patients with normal hepatic function at baseline in the ceritinib group in Study A2303 [Study A2303 RSI Appendix 1-CHMP].

In summary, the review of the overall safety profile of ceritinib in patients with hepatic impairment at baseline versus patients with normal hepatic function at baseline did not reveal any clinically relevant differences or new safety concerns, and is consistent with the known safety profile of ceritinib.

Table 44: Overview of adverse events in patients with ALK-positive NSCLC, subgroup of hepatic impairment (Study A2303, safety set)

	Patients with normal liver function		Patients with mild hepatic impairment	
Parameter	Ceritinib 750 mg N=92	Chemotherapy N=92	Ceritinib 750 mg N=22	Chemotherapy N=18
Adverse events				
Any grade, n (%)	92 (100)	91 (98.9)	22 (100)	18 (100)
Suspected to be related to study drug, n (%)	88 (95.7)	72 (78.3)	21 (95.5)	14 (77.8)
Grade 3/4, n (%)	73 (79.3)	58 (63.0)	15 (68.2)	13 (72.2)
Suspected to be related to study drug, n (%)	51 (55.4)	31 (33.7)	8 (36.4)	9 (50.0)
On-treatment deaths				
Total, n (%)	11 (12.0)	3 (3.3)	4 (18.2)	2 (11.1)
Study indication, n (%)	9 (9.8)	3 (3.3)	4 (18.2)	2 (11.1)
Other causes, n (%) [1]	2 (2.2)	0	0	0
Serious AEs				
Any grade, n (%)	39 (42.4)	28 (30.4)	10 (45.5)	7 (38.9)
Grade 3/4, n (%)	37 (40.2)	26 (28.3)	8 (36.4)	7 (38.9)
AEs leading to study drug discontinuation				
Any grade, n (%)	14 (15.2)	9 (9.8)	4 (18.2)	2 (11.1)
Grade 3/4, n (%)	13 (14.1)	8 (8.7)	2 (9.1)	1 (5.6)
AEs req. dose adjustment or interruption/delay				
Any grade, n (%)	76 (82.6)	36 (39.1)	15 (68.2)	6 (33.3)
Grade 3/4, n (%)	51 (55.4)	21 (22.8)	10 (45.5)	6 (33.3)

AE = adverse event; req. = requiring

[1]: Other causes: Cerebrovascular accident (1 patient), respiratory failure (1 patient)

Source: [Study A2303 RSI Appendix 1-CHMP Table 2-1], [Study A2303 RSI Appendix 1-CHMP Table 2-2], [Study A2303 RSI Appendix 1-CHMP Table 2-3], [Study A2303 RSI Appendix 1-CHMP Table 2-4], [Study A2303 RSI Appendix 1-CHMP Table 2-5], [Study A2303 RSI Appendix 1-CHMP Table 2-6]

Pancreatitis

The Novartis MedDRA Query (broad) 'Acute pancreatitis (excluding non-specific symptoms)' was used to identify and define the frequency of pancreatitis events. This query comprises the standardized MedDRA query (SMQ) (narrow) 'Acute Pancreatitis' and the preferred terms (PT) related to pancreatic enzyme abnormalities including lipase and amylase increase.

In the Novartis global safety database (Argus), there have been no reports on pancreatitis related SAEs in Study A2303 from the data lock point of 26-Jan-2016 until 03-Feb-2017.

In a more recent, larger safety pool (N=925) of ceritinib treated patients with ALK-positive NSCLC, pancreatitis grouped AEs (all grades, regardless of study drug relationship) were reported in 89 patients (9.6%), with the majority of patients having laboratory test abnormalities (i.e. amylase/lipase increase) without reported evidence of pancreatitis [Study A2301 SCS Appendix 1].

In summary, the frequency and type of AEs of pancreatitis are consistent with the established safety profile of ceritinib and can be effectively managed with dose reductions/interruptions and/or use of concomitant

medication. Pancreatitis AEs mainly comprised asymptomatic increases in amylase/lipase levels. None of the pancreatitis AEs were serious or led to treatment discontinuation, and none of these were suggestive of pancreatitis. No new cases have been reported in Study A2303 since the data cut-off for the primary analysis.

Pancreatitis has been included in the Section "Special warnings and precautions for use" and in the ADR Table of the current SmPC. Patients should be monitored for lipase and amylase elevations prior to the start of the treatment with ceritinib, and periodically thereafter as clinically indicated. In addition, pancreatitis is an important identified risk in the current risk management plan (RMP).

Assessment of the MAH's response

As requested, the applicant submits and analyzes available safety results in patients with hepatic impairment. The review of the overall safety profile of ceritinib in patients with mild hepatic impairment at baseline versus patients with normal hepatic function at baseline did not reveal any clinically relevant differences or new safety concerns, and is consistent with the known safety profile of ceritinib. No patients with moderate/severe hepatic impairment at baseline were enrolled into Study A2303.

The interpretation of the slightly higher incidence of on-treatment deaths in ceritinib treated patients with mild hepatic impairment at baseline compared to patients with normal hepatic function at baseline is limited due to the small subgroup size and limited number of patients with an event. All deaths were due to study indication.

As requested, the applicant is update report about pancreatitis events that occurred during the clinical study. In a larger safety pool (N=925) of ceritinib treated patients with ALK-positive NSCLC, pancreatitis grouped AEs (all grades, regardless of study drug relationship) were reported in 89 patients (9.6%). No new cases have been reported in Study A2303 since the data cut-off for the primary analysis.

Pancreatitis is an important identified risk in the current risk management plan (RMP) and has been included in the Section "Special warnings and precautions for use" and in the ADR Table of the current SmPC. Patients should be monitored for lipase and amylase elevations prior to the start of the treatment with ceritinib, and periodically thereafter as clinically indicated.

Conclusion:

Issue solved

Question 5

In study 2303, twenty-two (19.1%) patients in the ceritinib vs. none in the chemotherapy group had creatinine elevations based on AEs. In 2/10 patients the event was grade 3 (chronic kidney disease and urinary bladder rupture). In addition to the 22 patients with blood creatinine increase reported under the SOC of "Investigations", creatinine renal clearance decreased was reported in three patients of whom one patient had grade 3 event. All three events were suspected to be study drug-related. The Applicant is requested to submit and analyze available safety results in patients with renal impairment.

Summary of the MAH's response

Safety data from Study A2303 were analyzed by baseline renal function based on the definitions from the Food and Drug Administration renal guidance (FDA PK Renal Guidance 2010):

- Normal renal function: Creatinine clearance ≥ 90 mL/min;
- Mild renal impairment: Creatinine clearance ≥ 60 and <90 mL/min;

- Moderate renal impairment: Creatinine clearance ≥ 30 and <60 mL/min;
- Severe renal impairment: Creatinine clearance <30 mL/min.

Patients with serum creatinine >1.5 g/dL and/or calculated clearance <50 mL/min were excluded from the study as per protocol.

In Study A2303, 106 patients (n=57 in the ceritinib group, n=49 in the chemotherapy group) with normal renal function were enrolled, 90 patients (n=40 in the ceritinib group, n=50 in the chemotherapy group) had mild renal impairment, and 31 patients (n=18 in the ceritinib group, n=13 in the chemotherapy group) had moderate renal impairment at baseline. One patient randomized to the chemotherapy arm had severe renal impairment at baseline. A review of the baseline patient and disease characteristics showed that patients with impaired baseline renal function were older compared to those with normal renal function (the median age for patients with moderate renal impairment was 65.5 years compared to 60.0 years for mild impairment and 48 years for patients with normal renal function) [Study A2303 RSI Appendix 1-CHMP], [Study A2303 RSI Appendix 1-CHMP].

"Renal failure", "renal impairment" and "blood creatinine increased" are listed as ADRs in the SmPC. Of note, creatinine increase is mainly considered a pharmacologic effect of ceritinib (i.e. inhibition of tubular creatinine secretion), and not due to direct nephrotoxicity (see detailed discussion in [Study A2303 CSR – Section 13]). Elevations of creatinine were transient and reversible upon treatment discontinuation. None of these events were grade 3 or 4, or serious. In addition, there were no grade 3/4 events of acute kidney injury, renal failure or renal impairment reported in the ceritinib group in Study A2303.

More details for the three grade 3 events that were specifically mentioned in Question 5 are provided below:

- Patient [A2303-1851-002] with grade 3 chronic kidney disease was a 66 year old man with a history of hypertension; baseline creatinine clearance was decreased (grade 2); creatinine clearance was fluctuating between grade 2 and 3 during the study; grade 3 chronic kidney disease was reported on Day 14 and resolved on Day 28 (suspected to be study drug related by the Investigator); the patient was ongoing at time of data cut-off (Day 608); the last creatinine value prior to discontinuation (Day 586) was normal, and creatinine clearance was back to baseline (grade 2).
- Patient [A2303-1254-003] with grade 3 iatrogenic bladder rupture (Day 389) following a urogram; the event was not related to study treatment.
- Patient [A2303-1254-001] with grade 3 creatinine renal clearance decreased was a 76 year old women with grade 2 creatinine clearance decreased at baseline; on Day 29 the event worsened to grade 3 (suspected to be study drug related by the Investigator); the patient discontinued the study on Day 57 due to disease progression (worsening of pleural effusion, pulmonary lymph nodes and new brain metastasis); the event was ongoing at time of discontinuation.

Overall, the AE pattern was similar in patients with mild and moderate renal impairment compared to patients with normal renal function at baseline in the ceritinib group in Study A2303 (Table 45). A similar trend was seen in the chemotherapy group.

Table 45: Overview of adverse events in patients with ALK-positive NSCLC, subgroup of renal impairment (Study A2303, safety set)

	Patients with normal renal function		Patients with mild renal impairment		Patients with moderate renal impairment	
Parameter	Ceritinib 750 mg N=57	Chemotherapy N=49	Ceritinib 750 mg N=40	Chemotherapy N=50	Ceritinib 750 mg N=18	Chemotherapy N=13
Adverse events						
Any grade, n (%)	57 (100)	48 (98.0)	40 (100)	50 (100)	18 (100)	13 (100)
Suspected to be related to study drug, n (%)	54 (94.7)	37 (75.5)	38 (95.0)	41 (82.0)	18 (100)	10 (76.9)
Grade 3/4, n (%)	42 (73.7)	27 (55.1)	30 (75.0)	35 (70.0)	17 (94.4)	10 (76.9)
Suspected to be related to study drug, n (%)	27 (47.4)	15 (30.6)	22 (55.0)	20 (40.0)	11 (61.1)	6 (46.2)
On-treatment deaths						
Total, n (%)	6 (10.5)	2 (4.1)	7 (17.5)	3 (6.0)	2 (11.1)	0
Study indication, n (%)	6 (10.5)	2 (4.1)	7 (17.5)	3 (6.0)	0	0
Other causes, n (%) [1]	0	0	0	0	2 (11.1)	0
Serious AEs						
Any grade, n (%)	27 (47.4)	18 (36.7)	15 (37.5)	15 (30.0)	7 (38.9)	3 (23.1)
Grade 3/4, n (%)	24 (42.1)	18 (36.7)	14 (35.0)	13 (26.0)	7 (38.9)	3 (23.1)
AEs leading to study drug discontinuation						
Any grade, n (%)	9 (15.8)	4 (8.2)	7 (17.5)	6 (12.0)	2 (11.1)	1 (7.7)
Grade 3/4, n (%)	6 (10.5)	4 (8.2)	7 (17.5)	4 (8.0)	2 (11.1)	1 (7.7)
AEs req. dose adjustment or interruption/delay						
Any grade, n (%)	42 (73.7)	18 (36.7)	34 (85.0)	18 (36.0)	16 (88.9)	7 (53.8)
Grade 3/4, n (%)	29 (50.9)	10 (20.4)	20 (50.0)	12 (24.0)	13 (72.2)	6 (46.2)

AE = adverse event; req. = requiring

[1]: Other causes: Cerebrovascular accident (1 patient), respiratory failure (1 patient)

Source: [Study A2303 RSI Appendix 1-CHMP Table 2-1], [Study A2303 RSI Appendix 1-CHMP Table 2-2], [Study A2303 RSI Appendix 1-CHMP Table 2-3], [Study A2303 RSI Appendix 1-CHMP Table 2-4], [Study A2303 RSI Appendix 1-CHMP Table 2-5], [Study A2303 RSI Appendix 1-CHMP Table 2-6]

In patients with mild and moderate renal impairment at baseline compared to patients with normal renal function, renal impairment related AEs in the ceritinib treated patients showed an increased frequency of AEs with the PT of creatinine increased and hyper-creatininemia (any grade: 30.0% mild, 44.4% moderate vs 3.5% normal renal function) [Study A2303 RSI Appendix 1-CHMP]. No grade 3/4 AEs of creatinine increase occurred in any subgroup, and there were no SAEs. This is in line with the baseline renal status of the different patient populations. In addition, single events of renal impairment, acute kidney injury, and renal failure (all grade 1/2) were reported in patients with baseline mild and moderate renal impairment, none of these events were reported as SAEs. One SAE of urinary bladder rupture was reported as an SAE in the subgroup of patients with moderate renal impairment (see above) No such events were reported from patients with baseline normal renal function (events reported only related to creatinine increased).

The frequency and severity of AESIs (hepatoxicity, gastrointestinal toxicity, QT prolongation, pneumonitis/ILD, pancreatitis, hyperglycemia, bradycardia) in patients with mild and moderate renal impairment at baseline was overall similar compared to patients with normal renal function at baseline in the ceritinib group in Study A2303 [Study A2303 RSI Appendix 1-CHMP]. A trend of higher frequency of GGT and ALP increase was seen in the mild and moderate renal impairment populations in comparison with patients with normal renal function at baseline (GGT: 12.3% normal vs 32.5% mild vs 33.3% moderate; ALP: 10.5% normal vs 30.0% mild vs 44.4% moderate [Study A2303 RSI Appendix 1-CHMP]), however, there was no major difference in the overall hepatotoxicity events [Study A2303 RSI Appendix 1-CHMP]. None of these events were reported as SAEs. Two events of study drug discontinuation were reported, one event each in a patient with normal renal function and moderate renal impairment. Both discontinuations were due to AST/ALT increase. No study drug discontinuation due to hepatotoxic events was reported in the group of patients with baseline mild renal impairment.

A slightly higher frequency of QT prolongation AEs was found among patients with mild renal impairment compared to patients with normal renal function (17.5% mild and 8.8% normal respectively, [Study A2303

RSI Appendix 1-CHMP]). One QT prolongation AE was reported in a patient (5.6%) with moderate renal impairment. None of these events were grade 3/4, and no SAEs occurred.

In summary, an examination of the overall safety profile of ceritinib in patients with renal impairment versus patients with normal renal function at baseline did not reveal any clinically relevant differences in the safety risks or any new safety concerns.

Assessment of the MAH's response

As requested, the Applicant submits and analyzes available safety results in patients with renal impairment. An examination of the overall safety profile of ceritinib in patients with renal impairment versus patients with normal renal function at baseline did not reveal any clinically relevant differences in the safety risks or any new safety concerns. No patients with serum creatinine >1.5 g/dL and/or calculated clearance <50 mL/min were enrolled into Study A2303. Creatinine increase is mainly considered a pharmacologic effect of ceritinib, and not due to direct nephrotoxicity.

In patients with mild and moderate renal impairment at baseline compared to patients with normal renal function, renal impairment related AEs in the ceritinib treated patients showed an increased frequency of AEs with the PT of creatinine increased and hyper-creatininemia (any grade: 30.0% mild, 44.4% moderate vs 3.5% normal renal function). Elevations of creatinine were transient and reversible upon treatment discontinuation. There were no grade 3/4 events of acute kidney injury, renal failure or renal impairment reported in the ceritinib group in Study A2303.

A slightly higher frequency of QT prolongation AEs was found among patients with mild renal impairment compared to patients with normal renal function (17.5% mild and 8.8% normal respectively). None of these events were grade 3/4, and no SAEs occurred.

Conclusion:

Issue solved

Question 6

In study 2303, the number and percentage of patients with increase from baseline QTcF > 30 msec were 71/114 (62.3%) in ceritinib group vs. 7/112 (6.3%) in chemotherapy group, from baseline QTcF > 60 msec were 7/114 (6.1%) in ceritinib group vs. 0/112 (0%) in chemotherapy group and new QTcF > 450 msec were 37/113 (32.7%) vs. 11/109 (10.1%) in chemotherapy group. The number and percentage of patients with increase from baseline QTcP > 30 msec were 66/115 (57.4%) in ceritinib group vs. 6/112 (5.4%) in chemotherapy group, from baseline QTcP > 60 msec were 7/115 (6.1%) in ceritinib group vs. 0/112 (0%) in chemotherapy group. The Applicant is asked to discuss in detail these results.

Summary of the MAH's response

Ceritinib is known to have a relevant QT prolonging effect, thus, a higher percentage of patients with a prolonged QTc interval is expected in the ceritinib group compared to the chemotherapy group [Study A2303 CSR].

An analysis of ECG data from 86 patients with time-matched ceritinib plasma concentrations in Study A2303 showed a concentration-dependent QTcP interval prolongation with an estimated 14.0 ms mean QTcP increase from baseline at median steady-state Cmin, with the upper bound of the 2-sided 90% confidence interval (18.1 ms) for mean QTcP change from baseline <20 ms [Study A2303 CSR-Section 12.3.3.4.3],

[Study A2303 CSR], [Study A2303 CSR]. These data are consistent with previous studies as well as the recently completed Phase III Study A2301, where a central tendency analysis at average steady-state concentrations (Cycle 2, Day 1) demonstrated that the mean QTcP change from baseline was 13.5 ms (90% CI: 11.8, 15.3) [Study A2301 SCS-Section 2.1.6.3].

Pronounced cases of QTcF or QTcP prolongation (i.e. >500 ms or >60 ms increase from baseline) were rare (see Table 46). Three (3) patients (2.6%) in the ceritinib group had a postbaseline QTcP in the interval >480 – 500 ms, and one patient (0.9%) had a post-baseline QTcP >500 ms in the ceritinib group. The latter was a 67-year-old female patient with active medical condition of left ventricular dysfunction, atherosclerosis, hypertension, and thalassemia. The patient had a QTcP interval of 436 ms at baseline; on Day 382, the ECG showed a QTcP of 502 ms which returned to 442 ms on the end-of-study (Day 430). Based on an internal cardiologist review of this patient, it was noted that the ECG tracings were of poor quality with prominent U-waves that could limit the ability to measure QTc accurately (QT offset) [Study A2303 CSR-Section 12.3.3.4.3]. In addition, one of the 3 patients with postbaseline QTcP >480 – 500 ms had already a grade 2 (>450 – 480 ms) QTcP prolongation at baseline [Study A2303 CSR].

Out of the 7 patients with QTcP increases from baseline >60 ms, all had a baseline QTcP ≤ 450 ms; one of these patients had a post-baseline increase in QTcP >500 ms (described above), two had a post-baseline increase in QTcP >480 – 500 ms, three had QTcP >450 – 480 ms, and one had QTcP <450 ms [Study A2303 CSR-Listing 16.2.9-1.2]. Similar results were observed based on QTcF (Table 46).

Table 46: Patients with notable ECG values in Study A2303 and Pooled Dataset

	Study A2303	Pooled Dataset
	Ceritinib 750 mg (n=115)	Ceritinib 750 mg (n=925)
QTcP (ms)	**n=115**	**n=919**
New >480-500	3 (2.6%)	40 (4.4%)
New >500	1 (0.9%)	12 (1.3%)
Increase from baseline >60	7 (6.1%)	58 (6.3%)
QTcF (ms)	**n=114**	**n=918**
New >480-500	3 (2.6%)	36 (3.9%)
New >500	1 (0.9%)	13 (1.4%)
Increase from baseline >60	7 (6.1%)	92 (10.0%)
Source: [Study A2303 CSR-Table 14.3-5.3] [SCS Appendix 5-Table 14.3-5.2]		

Based on AE data (SMQ broad “Torsade de pointes/QT prolongation”), grade 3 QT prolongation AEs were reported in two (1.7%) patients. None of the QT prolongation AEs led to study drug discontinuation. There were no grade 4 QT prolongation AEs or Torsade de points, and no patients with AE of QT prolongation (preferred term) had syncope/loss of consciousness. Two patients had grade 3 QT prolongation AEs which were also reported as SAEs and are described in detail in the CSR/narratives. In brief, one patient had grade 3 QT prolongation with concurrent grade 4 hypokalemia in the context of vomiting and dehydration; the event was diagnosed based on local ECG (not supported be central ECG) and resolved upon potassium substitution. The other patient had abnormal brain magnetic resonance imaging (MRI) suggestive of disease progression on Day 43, and new lesions in the liver, lung, and calvarium (with soft tissue component on brain MRI) as per RECIST; treatment was interrupted on Day 61 due to creatinine increase and upon confirmation of disease progression by BIRC. Three days later, the patient experienced grade 4 loss of consciousness and was taken to intensive care, however, he died the next day due to disease progression. The last ECG done on Day 43 was normal. The event was not suspected to be study drug related.

Pooled dataset

Frequency and type of QT prolongation AEs (SMQ broad “Torsade de pointes/QT prolongation”, all grades, regardless of study drug relationship) as well as ECG findings from a more recent, larger safety pool

(N=925) of ceritinib treated patients with ALK-positive NSCLC were consistent with those reported in study A2303 [Study A2301 SCS-Section 2.1.6.3].

Overall, post-baseline QTcP values >480 ms and >500 ms were observed in 52/919 patients (5.7%) and 12/919 patients (1.3%), respectively; 58/919 patients (6.3%) had >60 ms increase from baseline [Study A2301 SCS Appendix 5].

In conclusion, the available data in Study A2303 confirm that ceritinib has a moderate QT prolonging effect, although no case of clinically relevant consequences has been reported.

Importantly, no cases of ventricular arrhythmias (Torsade de pointes), and no patients with QT prolongation had syncope/loss of consciousness. No discontinuations due to QT prolongation, and no deaths associated with QT prolongation were reported. These results are consistent with previous experience and the larger safety pool of patients treated with ceritinib.

Assessment of the MAH's response

Ceritinib is known to have a relevant QT prolonging effect.

The available data in Study A2303 confirm that ceritinib has a QT prolonging effect, although no case of clinically relevant consequences has been reported. None of the QT prolongation AEs led to study drug discontinuation. There were no grade 4 QT prolongation AEs or Torsade de points, and no patients with AE of QT prolongation (preferred term) had syncope/loss of consciousness in Study A2303. No deaths associated with QT prolongation were reported.

Conclusion:

Issue solved.

Post-Authorisation Measures

Following the assessment of the data provided, the MAH is recommended to undertake the following:

Description
1. The second OS interim analysis report from the study A2303 should be provided in 2019
2. The final OS analysis report from the study A2303 should be submitted when available (around2022)

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance