Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 3

Extract from the Clinical Evaluation Report of Study A8081007

Proprietary Product Name: Xalkori

Sponsor: Pfizer Australia Pty Ltd

Date of report: 29 April 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

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1. Introduction

This report centres on the clinical evaluation of the data provided by the sponsor on 22 March 2013, and on 19 April 2013 in response to questions raised by the TGA, relevant to the sponsor's application to the Administrative Appeals Tribunal (AAT 2013/0179) appealing against the decision of the "Delegate of the Secretary" to reject its submission to register Xalkori for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

The evaluated data included:

- The preliminary Clinical Study Report (CSR) for Study A8081007, a Phase III study comparing
  - standard-of-care chemotherapy (pemetrexed or docetaxel) with crizotinib in previously treated
  - patients with ALK-positive non-small cell cancer (NSCLC). The sponsor stated that the final CSR for Study A8081007 will be generated following the completion of the final analysis for overall survival (OS), and anticipates that this report will be available in the first quarter of 2016. The sponsor states
  - that the preliminary CSR for Study A8081007 is considered "final for the purposes of global registration".
- A "Technical Report" providing the pre-specified sensitivity analyses of the interim OS data from Study A081007. The sponsor stated that it "chose to evaluate the impact of follow-up therapy in a separate "Technical Report" due to the complexity of the statistical methodology for these [sensitivity] analyses as well as that associated with description of the results obtained."
- The updated Risk Management Plan (RMP), Version 4.0, dated 25 February 2013. The evaluation of the RMP focused on the updated safety data.

- The sponsor's response of 19 April 2013 to questions raised by the evaluator during the evaluation of the Clinical Study Report A8081007. The relevant information from this response was taken into account by the evaluator.

2. Study A8081007 (Preliminary CSR)[1]

2.1. Pharmacokinetics

2.1.1. Overview

Study A8081007 included a pharmacokinetic (PK) evaluation of patients in the crizotinib arm of the study. The PK concentration population was defined as any patient in the safety analysis (SA) population who had at least 1 concentration of crizotinib or its metabolite PF-06260182 following crizotinib treatment at the data cut off date of 30 March 2012. The plasma pre-dose concentration population was defined as any patient in the PK concentration population who had at least 1 pre-dose concentration of crizotinib or PF-06260182, with the actual sample collection time between -1.2 to 0 hours (h) prior to the morning dose.

The steady-state mean trough plasma concentrations for crizotinib and PF-06260182 were obtained for each patient using the arithmetic mean of all available plasma pre-dose trough plasma concentrations for that patient on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1 after at least 14 consecutive days of crizotinib 250 mg twice daily (BID). In addition to the assessment of mean plasma trough concentrations of crizotinib and PF-0620182, mean PF-06260182 to crizotinib ratios were calculated.

Plasma concentrations of crizotinib and PF-06260182 were measured using validated, sensitive, and specific high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) methods

The sponsor indicates that the plasma concentration data set from Study A8081007 will be pooled with appropriate data sets from additional crizotinib studies for a population PK analysis. The results of this analysis will be presented in a separate report.

2.1.2. Results

(a) Steady-state trough plasma concentrations for crizotinib and PK-06260182

The demographics of the 152 patients in the PK concentration population were: 65 male, 87 female; 72 White, 77 Asian, 1 Black, 1 Other race; mean age 49.4 years (range: 22, 78 years); mean height 164.2 cm (range: 141, 193 cm); and mean weight 64.4 kg (range: 35.2, 160.0 kg). Of these 152 patients, 150 provided relevant data and were included in the analyses.

Crizotinib reached steady-state within the first cycle after repeated oral administration of crizotinib 250 mg BID. The geometric mean pre-dose concentrations of crizotinib were 293, 306, and 291 ng/mL on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, respectively. Similarly, the steady-state plasma concentrations of PF-0620182 achieved steady state within the first cycle. The geometric mean pre-dose concentrations of PF-06260182 following crizotinib 250 mg BID were 81.3, 85.7 and 87.1 ng/mL on Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 5 Day 1, respectively. The geometric mean pre-dose concentration ratios of PF-06260182 to crizotinib were 0.267, 0.267 and 0.291 on Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 5 Day 1, respectively.

(b) Ethnic differences – steady-state trough plasma concentrations

The demographics of the 92 patients in the PK concentration population providing relevant data were: 38 male, 54 female; 49 White, 40 Asian, 1 Black, 2 Other races; mean age 50.4 years

[1]This report includes amendments proposed by the sponsor and accepted by the TGA prior to the decision by the AAT.

(range: 22, 78 years); mean height 162.9 cm (range: 141, 189 cm); and mean weight was 63.8 kg (range: 37, 160 kg).

The geometric steady-state mean trough plasma concentrations of crizotinib and PF-06260182 were 298 (CV% = 45) ng/mL and 84.1 (CV% = 53) ng/mL, respectively. The geometric mean ratio (CV%) of PF-06260182 to crizotinib for the steady-state trough plasma concentrations was 0.272 (24%). The geometric steady-state mean trough concentration of crizotinib was higher in Asian patients than in non-Asian patients (347 [CV% = 40] versus 266 [CV% = 45] ng/mL). Similarly, the geometric steady-state mean trough plasma concentration of PF-06260182 was higher in Asian patients than in non-Asian patients (95.4 [CV% = 54] versus 75.8 [CV% = 44]). The geometric mean ratios (CV%) of PF-06260182 to crizotinib for the steady-state trough plasma concentrations were similar in Asian and non-Asian patients (0.267 [27%] versus 0.276 [21%], respectively). The results suggest that Asian patients may potentially be at an increased risk of adverse events related to Xalkori compared with non-Asian patients due to increased systemic exposure to the drug.

2.2. Pharmacodynamics

Pharmacodynamic evaluations included molecular profiling and optional biomarker analyses. The molecular profiling and biomarker analyses are ongoing and will be included in the final CSR. Concentration-QTc modelling and population PK/pharmacodynamic analysis for safety/clinical response data were planned. The sponsor states that the details and results of the population PK/pharmacodynamic analyses will be reported separately ("as appropriate").

NSCLC was determined to be ALK-positive by an investigational use only diagnostic test from Abbott Molecular. The means and median percentages of ALK-positive cells using this test were similar for the two treatment arms. Of the 173 patients tested in each of the two treatment arms, the mean (SD), median, and range of ALK positive cells (%) in the crizotinib arm were 57.4 (21.80), 58.0, and 15 to 98, respectively, and the corresponding values in the chemotherapy arm were 59.5 (20.05), 58.1, and 15 to 98.

2.3. Safety and efficacy-study methods

2.3.1. Introduction

Study A8081007. A Phase III, Randomized Open-Label Study of the Efficacy and Safety of PF-02341066 (Crizotinib) Versus Standard-of-Care Chemotherapy (Pemetrexed or Docetaxel) in patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus.

2.3.2. Objectives, design, dates, locations

(a) Objectives

The primary objective of the study was:

- to demonstrate that crizotinib (Arm A) was superior to standard-of-care chemotherapy, pemetrexed or docetaxel (Arm B), in prolonging progression-free survival (PFS) in patients with advanced non-small cell lung cancer (NSCLC) whose tumours harbor a translocation or inversion event involving the ALK gene locus and who had received only 1 prior chemotherapy regimen for advanced NSCLC (and this regimen must have been platinum-based).

The secondary objectives of the study were to:

- compare secondary measures of clinical efficacy including overall survival (OS), objective response rate (ORR), and disease control rate (DCR) between the 2 treatment arms, and to evaluate the duration of response (DR) and time-to-tumour response (TTR);

- assess the safety and tolerability of crizotinib compared to chemotherapy (pemetrexed or docetaxel);
- compare patient-reported outcomes (PRO) of health-related quality of life (HRQoL), disease/treatment-related symptoms of lung cancer, and general health status in both treatment arms;
- characterise the effects of crizotinib at therapeutic doses on QT interval (QT) in this patient population;
- determine the pharmacokinetics (PK) in this patient population using population PK (POPPK) methods and explore correlations between PK, response, and/or safety findings; to explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript; and to correlate modulation of soluble biomarkers to PK and outcome measures.

(b) Design, dates, and locations

Study A8081007 is an ongoing, Phase III, multi-national, multi-centre, randomised, open-label, efficacy and safety study of crizotinib versus standard-of-care chemotherapy (pemetrexed or docetaxel) in patients with previously treated NSCLC (with 1 prior platinum-based chemotherapy regimen) whose tumours harbor ALK fusions. The sponsor states that the study was conducted in compliance with Good Clinical Practice (GCP) guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents, including the archiving of essential documents.

The study planned to randomise 318 patients 1:1 to crizotinib (Arm A) or pemetrexed or docetaxel (Arm B). Randomisation was stratified for baseline factors of Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 versus 2), brain metastases (present versus absent) and prior epidermal growth factor receptor (EGFR) inhibitor treatment (yes versus no). Patients continued with assigned treatment until objective disease progression occurred, unacceptable toxicity occurred, or consent was withdrawn. The Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, assessed by independent radiology review (IRR), was used to determine objective disease progression. Assigned treatment could continue beyond RECIST defined disease progression (assessed by IRR) for patients considered by the investigator to be experiencing clinical benefit. For these patients, tumour assessments were no longer to be evaluated by the IRR laboratory. In addition, patients in the chemotherapy arm who had RECIST defined disease progression (assessed by IRR) were given the option to receive crizotinib in Study A8081005.

The study was initiated on 18 September 2009 (first patient visit), the data cut off date for the preliminary CSR was 30 March 2012, and the preliminary CSR was dated 02 December 2012. As of the data cut off date, 106 centres in 21 countries had enrolled patients (Australia [2 centres], Brazil [5 centres], Canada [3 centres], China [8 centres], France [6 centres], Germany [9 centres], Greece [1 centre], Hong Kong [2 centres], Hungary [2 centres], Ireland [2 centres], Italy [11 centres], Japan [10 centres], Republic of Korea [3 centres], Netherlands [1 centre], Poland [3 centres], Russian Federation [2 centres], Spain [8 centres], Sweden [1 centre], Taiwan [1 centre], United Kingdom [4 centres], and United States [22 centres]). An additional 59 centres received study drug, but did not enrol patients.

2.3.3. Inclusion and exclusion criteria

The main inclusion criteria were female or male patients, aged ≥ 18 years of age, with histologically or cytologically proven NSCLC that was locally advanced or metastatic, and positive for translocation or inversion events involving the ALK gene locus (for example, resulting in EML4-ALK fusion) as determined by an ALK break-apart FISH assay. In addition, patients were required to have progressive disease (PD) after only 1 prior platinum-based chemotherapy regimen and must have been considered appropriate candidates for additional chemotherapy with either single-agent pemetrexed or single-agent docetaxel. Patients who had

received 2 prior platinum based chemotherapy regimens were eligible if the first regimen had been given as adjuvant therapy or had been given in combination with radiation therapy for locally advanced disease. Patients who had received prior treatment with an EGFR tyrosine kinase inhibitor (TKI), such as erlotinib or gefitinib, were also eligible provided that they had also received only 1 prior platinum-based chemotherapy regimen. Tumours were required to be measurable by RECIST v1.1 criteria.

The study included pre-specified criteria for removing patients from therapy or assessment. Patients could withdraw from treatment at any time at their own request or they could be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. If a patient did not return for a scheduled visit, every effort was to be made to contact the patient. In all circumstances, every effort was to be made to document patient outcome. If a patient withdrew from the study and also withdrew consent for disclosure of future information, no further evaluations were to be performed, and no additional data were to be collected. The sponsor could retain and continue to use any data collected before withdrawal of consent.

2.3.4. Treatments

2.3.4.1. Study drugs

Patients were randomised 1:1 to receive crizotinib (Arm A) or chemotherapy (pemetrexed or docetaxel; Arm B), with each treatment cycle being 21 days. The treatments were:

- **Crizotinib 250 mg** (2 x 100 mg tablets plus 1x 50 mg tablet) was administered orally without regard to meals BID at approximately the same time each day on a continuous dosing schedule. Investigators were encouraged to employ best supportive care according to local institutional clinical practices. In addition, investigators were encouraged to employ pre-specified treatment guidance for selected adverse events (AEs) (that is, diarrhoea, bradycardia, pneumonitis, pneumonia, renal cysts), and additional safety monitoring (that is, renal imaging, urinalysis, avoidance of prolonged unprotected sun exposure or tanning). Treatment was monitored for both haematological and non-haematological toxicity and the dose could be adjusted accordingly.
- Docetaxel, 75 mg/m^2 was administered by IV infusion over 1 hour on Day 1 of a 21-day cycle or according to institutional practices. Patients were monitored for both haematological and non-haematological toxicity and the dose could be adjusted accordingly.
- Pemetrexed, 500 mg/m^2 was administered by IV infusion over 10 minutes on Day 1 of a 21-day cycle or according to institutional practices. Patients were monitored for both haematological and non-haematological toxicity and the dose could be adjusted accordingly.

Patients were not to begin a new treatment cycle with pemetrexed or docetaxel unless the following re-treatment criteria were met: absolute neutrophil count (ANC) ≥ 1500/µL; platelet count ≥ 100,000/µL; calculated creatinine clearance ≥ 45 mL/minute (pemetrexed only); total bilirubin ≤ 1 x upper limit of normal (ULN) (docetaxel only); alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) not >1.5 x ULN when alkaline phosphatase was >2.5 x ULN (docetaxel only). If these re-treatment criteria were not met (including other pre-specified AEs for each drug) on the day that a new treatment cycle was scheduled to start, then pemetrexed or docetaxel was to be delayed for a maximum of 42 days to allow sufficient time for recovery. However, if a patient had a significant toxicity from pemetrexed or docetaxel which failed to recover within 21 days or required treatment discontinuation due to the severity of the AE (investigator opinion), then chemotherapy was stopped and the patient could remain in the study with ongoing tumour assessments until RECIST defined disease progression (assessed by IRR).

Comment: The crizotinib dose of 250 mg BID was chosen because this was the maximum tolerated dose identified in Study A8081001 (previously evaluated by the TGA).

It was also the dose recommended by the sponsor in regulatory applications to approve crizotinib for the treatment of ALK-positive advanced NSCLC. Docetaxel and pemetrexed are considered to be appropriate controls as both are approved in Australia for the treatment of NSCLC at the doses used in Study A8081007. However, there are no drugs approved specifically for the treatment of ALK-positive advanced NSCLC. Docetaxel is approved for the treatment of patients with locally advanced or metastatic NSCLC, including those who have failed platinum based chemotherapy, at a dose of 75 to 100 mg/m^2 administered by intravenous (IV) infusion every three weeks. Pemetrexed is approved in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology. It is also approved as monotherapy for locally advanced or metastatic NSCLC other than predominantly squamous cell histology after prior platinum based chemotherapy. The recommended dose of pemetrexed as a single use agent is 500 mg/m^2 administered by IV infusion over 10 minutes every 21-days.

2.3.4.2. Prior and concomitant medications and procedures

Anti-cancer treatment with agents other than crizotinib, pemetrexed, or docetaxel was not allowed but medications intended solely for supportive care were permitted if considered clinically indicated by the investigator (for example, haematopoietic growth factors, colony-stimulating factors, packed red blood cell transfusion, platelet transfusion, hormone replacement therapy, and bisphosphonate therapy). Concurrent use of strong CYP3A4 inhibitors or inducers was not allowed.

In patients randomised to crizotinib, co-administration with CYP3A4 substrates was to be avoided or used with caution. In patients randomised to pemetrexed, non-steroidal anti-inflammatory drugs (NSAIDs) with long half-lives were to be discontinued at least 5 days before administration, the day of administration, and 2 days after administration. Patients who took NSAIDs concomitantly with pemetrexed were to be closely monitored for toxicity, especially myelosuppression, renal toxicity and gastrointestinal toxicity.

Palliative radiotherapy to specific disease sites was permitted if considered medically necessary by the treating physician. Crizotinib treatment was to be interrupted during palliative radiotherapy stopping 1 day before and resuming treatment 1 day after, and palliative radiotherapy was to be performed at least 1 day before or 1 day after pemetrexed or docetaxel dosing. In the event elective surgery was necessary during study participation, dosing was to be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery for all three treatments.

2.3.5. Efficacy endpoints

2.3.5.1. Primary efficacy endpoint - Progression free survival (PFS)

The primary efficacy endpoint was progression free survival (PFS) based on RECIST v1.1 (assessed by independent radiological review (IRR)). PFS was defined as the time from the date of randomisation to the date of the first documentation of objective tumour progression or death on study due to any cause, whichever occurred first.

The randomisation date was used as the baseline to calculate the date of tumour assessment. On-study tumour assessments were to be performed every 6 weeks from the date of randomisation (with the exception of bone scans) until radiographic progressive disease (PD) was documented by computed tomography (CT) or magnetic resonance imaging (MRI). CT or MRI scans were also to be performed whenever disease progression was suspected and the same imaging modality was used throughout the study to measure disease. Tumour evaluation by positron emission tomography (PET) scan or by ultrasound could not substitute for CT or MRI scans. CT or MRI scans included chest, brain, abdomen and pelvis at screening. The brain was to be included in subsequent tumour assessments if a patient had brain metastases at

screening, otherwise the brain was only evaluated when clinically indicated. A bone scan was required at screening and repeat bone scans were to be repeated every 12 weeks only if bone metastases were present at baseline, otherwise a repeat bone scan was required only if new bone metastases were suspected. A bone scan was also required at the time of determination of response for patients who had bone metastases.

All scans were sent for a blinded RECIST independent radiological review (IRR) at a central laboratory located in the USA. Tumour assessments continued every 6 weeks until RECIST-defined disease progression was confirmed by the IRR. Measurable lesions that had been previously irradiated were not to be considered target lesions unless an increase in size had been observed following completion of radiation therapy. If study drug was discontinued in the absence of confirmed RECIST-defined disease progression, patients were to remain on study until confirmation of PD was received by the IRR. When new effusions or ascites were present and represented the only potential site of disease progression, cytologic analysis was to be performed and the results, malignant or non-malignant, were to be recorded on the eCRF.

Comment: PFS is an acceptable primary endpoint (TGA adopted EMEA guideline on the clinical evaluation of anti-cancer medicines, CPMP/EWP/205/95/Rev.3/Corr[2]). Furthermore, PFS based on blinded independent radiological review of RECIST defined disease progression is consistent with the relevant EMEA/TGA guideline and mitigates the risk of bias relating to the assessment of disease progression.

2.3.5.2. Secondary and other efficacy variables

Secondary efficacy endpoints were overall survival (OS) and 6-month and 1-year OS, objective response rate (ORR), disease control rate (DCR) at 6 and 12 weeks, disease response (DR), and time-to-tumour response (TTR).

- OS was defined as the time from randomisation to the data of death from any cause.
- ORR was defined as the percent of patients with a complete response (CR) or a partial response (PR) according to RECIST v1.1 criteria as assessed by IRR.
- DR was defined as the date from the first documentation of objective tumour response (CR or DR), as assessed by IRR, to the first documentation of tumour progression assessed by the IRR, or to death due to any objective cause which ever occurred first.
- TTR was defined as the time from randomisation to first documentation of objective tumour response (CR or PR) as assessed by the IRR.
- DCR at 6 and 12 weeks was defined as the percent of patients with CR, PR, or stable disease (SD) at 6 and 12 weeks according to RECIST v1.1 as assessed by IRR. The best response of SD could be assigned if SD criteria were met at least once after randomisation at a minimum interval of 6 weeks.

Comment: All the secondary efficacy endpoints are considered to be acceptable. The selection of OS as a secondary endpoint is consistent with the relevant TGA adopted EMEA guideline relating to the clinical evaluation of anti-cancer medicines. This guideline states that OS should be reported as a secondary endpoint when PFS is reported as the primary endpoint.

Other efficacy endpoints included patient reported outcomes (PROs) using a validated lung cancer specific questionnaire, the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its corresponding module for Lung Cancer (QLQ-LC13) and the EuroQol-5D (EQ-5D) questionnaire. In addition, visual symptoms were assessed using the Visual Symptom Assessment Questionnaire-ALK (VSAQ-

[2] CPMP/EWP/205/95/Rev.3/Corr. Guideline on the evaluation of anticancer medicinal products in man

ALK). The self-administered questionnaires were to be completed at baseline, Day 1 of every cycle and at the End of Treatment or withdrawal.

2.3.6. Randomisation and blinding methods

Patients were randomised 1:1, based on a random permuted block design using a centralised interactive voice response system (IVRS), to receive either crizotinib (Arm A) or chemotherapy (Arm B). Randomisation was stratified by ECOG PS (0-1 versus 2), brain metastases (present versus absent) and previous treatment with an EGFR tyrosine kinase inhibitor (yes versus no).

For patients randomised to Arm B, the first choice was pemetrexed. This was due to docetaxel restrictive labelling (prescribing information) for liver function test (LFT) elevations and peripheral neuropathy. There were two exceptions: patients who had pemetrexed as part of their prior chemotherapy regimen and patients who had received pemetrexed as maintenance therapy. These patients were to receive docetaxel if randomised to Arm B. These patients were only allowed to enter the study if they met the LFT and peripheral neuropathy eligibility criteria before being randomised. If a patient did not meet the docetaxel eligibility criteria they had the option to enrol in Protocol A8081005. Patients who had docetaxel as part of their prior chemotherapy and had NSCLC that was predominantly squamous cell carcinoma were not eligible for this study, but had the option to receive crizotinib in Protocol A8081005.

2.3.7. Analysis populations

- The **full analysis (FA) population** included all patients who were randomised with study drug assignment designated according to initial randomisation. The FA population was the primary population for evaluation of the primary and secondary efficacy endpoints, patient characteristics, and patient disposition.
- The **safety analysis (SA) population** included all patients who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received. The SA population was the primary population for evaluating safety, and was also used for selected efficacy analyses assessing docetaxel and pemetrexed separately.
- The **PRO-evaluable population** was defined as patients from the FA population who completed a baseline and at least 1 post-baseline PRO assessment. The PRO-evaluable population was the primary population for the analysis of change from baseline scores and time-to-deterioration (TTD) in patient-reported pain in chest, dyspnoea, or cough.
- The **ECG-evaluable population** for the ECG substudy was defined as patients from the SA population who received crizotinib and who participated in the ECG substudy, and had at least one Cycle 2 Day 1 ECG measurement performed by the ECG core laboratory. The ECG substudy is being conducted at selected sites for Studies A8081007 and A8081005 and aims to enrol approximately 40 patients. Data from both studies will be analysed together. The analyses are ongoing and the final analyses are to be reported in a separate document. It is noted that this population does not include a control chemotherapy arm.

2.3.8. Sample size

(a) PFS (primary efficacy endpoint)

A total sample size of 288 patients (217 total PFS events) would provide 90% probability to demonstrate superiority of Arm A over Arm B, assuming a 1.56 fold improvement over Arm B (that is, median PFS 7 months in Arm A versus 4.5 months in Arm B; hazard ratio [HR]=0.643 based on a 1-sided log-rank test at the 2.5% level of significance). It was assumed that accrual was to be accomplished over a 20 month period and follow-up for PFS would continue until the required numbers of events were observed. Under the assumed improvement for PFS in the sample size estimation, the follow-up period would be at least 4 months after the last patient was randomised. To account for events being censored due to potential discordance between

the investigator and the IRR assessment of PFS, up to 30 extra patients were to be enrolled for a total sample size of 318 patients.

(b) OS (a secondary efficacy endpoint)

The median OS for Arm B was assumed to be 8 months. With an overall 1-sided α of 0.025 and one interim analysis (at the time of PFS analysis), the study would have 80% power to detect a 44% increase in OS when 241 deaths have occurred.

(c) Other analyses

Pre-specified sample size calculations were also undertaken for the ECG substudy of Arm A, and the MUGA/echocardiogram substudy.

2.3.9. Statistical methods

2.3.9.1. Statistical hypotheses

The main purpose of the study was to demonstrate superiority of crizotinib (Arm A) over pemetrexed or docetaxel (Arm B) in PFS. The study was designed to test the null hypothesis H_0: $\lambda = 1.0$ versus the alternative hypothesis H_A: $\lambda < 1.0$, where λ is the hazard ratio (Arm A/Arm B).

2.3.9.2. Primary endpoint analysis

The analysis of PFS included in the preliminary CSR was specified as the final analysis of this parameter. Differences in PFS between treatment arms were analysed by a 1-sided log-rank test stratified for baseline factors of ECOG PS (0-1 versus 2), brain metastases (present versus absent), and prior EGFR inhibitor treatment (yes versus no). For patients who were incorrectly stratified at the time of randomisation, either because of information available subsequent to randomisation or due to clerical error, the actual baseline value, as reported on the eCRF, for these 3 variables was used in all stratified analyses. Estimates of the PFS curves obtained from the Kaplan-Meier method were presented and displayed graphically. The median event time (and other quartiles) and corresponding 2-sided 95% CI were provided for each treatment arm. Additionally, for each treatment arm, the median PFS and a 2-sided 95% CI were provided for each level of the stratification variables and for subgroups of other relevant patient baseline characteristics. Cox regression models, adjusted for baseline stratification factors and other patient baseline characteristics, were fitted. The estimated HR and 2-sided 95% CI were provided.

PFS was also analysed using an unstratified log-rank test and following an Intent-to-Treat like approach in which PD or death were considered PFS events regardless of when they were documented (no censoring applied). In addition, PFS analysis was provided with progression of disease according to investigator assessment. Disagreement rates between PFS based on the IRR and the investigator assessment of tumour data were presented.

An analysis of PFS in the SA population was performed separately for docetaxel and pemetrexed.

2.3.10. Secondary endpoint analyses[3]

2.3.10.1. Overall Survival (OS)

The analysis of OS included in the preliminary CSR was specified as the interim analysis of this parameter. On confirmation of PD by IRR, patients in the chemotherapy arm (Arm B) had the opportunity to receive crizotinib in Study A8081005. For these patients, survival follow-up data and follow-up systemic therapies were collected in Study A8081005. Data from both study databases using the same data cut off date were used for analysis of OS and reported under Study A8081007. Differences in OS between treatment arms were analysed by the 1-sided log

[3]The Delegate noted that the analyses described did not include Duration of Response.

rank test stratified for baseline factors. Estimates of the OS curves obtained from the Kaplan-Meier method were presented. The median event time (and other quartiles) and corresponding 2-sided 95% CI for the event times were provided for each treatment arm. Treatment group comparison was also performed using the unstratified log-rank test. Cox regression models were fitted, adjusted for baseline stratification factors and other patient baseline characteristics. The estimated HR and 2-sided 95% CI were provided. Six-month and 1 year survival probabilities were estimated using the Kaplan-Meier method together with the 2-sided 95% CI. Subgroup analyses were provided for major baseline patient characteristics and for the baseline stratification factors: median OS (and other quartiles) and 2-sided 95% CI were estimated.

Since after disease progression patients in the crizotinib (Arm A) received other available treatments and patients in chemotherapy arm (Arm B) could have crossed over to crizotinib, the treatment effect on OS estimated by methods presented for the primary analysis may have been confounded. Therefore, the Statistical Analysis Plan (SAP) pre-specified that sensitivity analyses of OS based on the interim data were to be undertaken. These OS sensitivity analyses included the Rank-Preserving Structural Failure Time Model (RPSFTM) proposed by Robins and Tsiatis (1991)[1] and any applicable extensions (for example, by White et al., 1999)[2], the time-dependent Cox model and inverse probability of treatment weighting method (for example, by Robins et al., 2000)[3].

Comment: The submitted Technical Report for "Evaluating the Impact of Follow-up Systemic Therapy on Overall Survival in Study A8081007 at the Time of Interim Overall Survival Analysis" presented the results of separate OS sensitivity analyses accounting for (a) crossover and (b) post-study systemic anti-cancer therapy. The results for these sensitivity analyses and a sensitivity included in the CSR are discussed later in this CER.

2.3.10.2. Objective Response Rate (ORR)

The ORR was summarised for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F-distribution. ORR between the 2 treatment arms was compared using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified for baseline factors and an unstratified test (2-sided Pearson). An analysis of ORR in the SA population was performed separately for docetaxel and pemetrexed. Disagreement rates between ORR based on IRR and investigator assessments of tumour responses were presented.

2.3.10.3. Time-to-Tumour Response (TTR)

TTR was calculated for the subgroup of patients with objective tumour response. Descriptive statistics were provided.

2.3.10.4. Disease Control Rate (DCR)

The DCR between the 2 treatment arms was compared using a 2-sided CMH test stratified for baseline stratification factors and an unstratified test (2-sided Pearson chi-square test).

2.3.11. Adjustment for multiple comparisons

To control the family-wise Type I error for the multiple comparison between crizotinib (Arm A) and chemotherapy (Arm B), an hierarchal step-down procedure was applied to the efficacy endpoints in the following order: (1) PFS; (2) ORR; (3) OS; and (4) DCR.

2.3.12. Handling of missing efficacy endpoint data

The SAP stated that no values were to be imputed for missing data for the primary and secondary analyses. For time-to-event endpoints (OS and PFS), non-event observations were to be censored and for ORR, patients with no post-baseline or missing baseline tumour evaluations were to be counted as non-responders. Appropriate methods were provided for handling ambivalent or missing answers to the EORTC QLQ-C30, QLQ-LC13, and EQ-5D questionnaires.

2.3.13. Interim analysis

No interim analysis was planned for the primary endpoint of PFS. The final analysis of PFS was to be conducted after 217 PFS events had been documented and the results of this final PFS analysis were presented in the submitted CSR. One interim analysis of OS was performed at the time of the final PFS analysis and the results of this interim OS analysis were presented in the submitted CSR. The final analysis of OS will be provided in the final CSR.

2.3.14. Participant flow

The study planed to randomise a total of 318 patients. However, 347 patients were actually randomised as all patients who signed an informed consent form in the screening period and meeting entry criteria were randomised to study treatment. Of the 347 randomised patients, 343 (172 crizotinib and 171 chemotherapy) received study treatment, and 4 were randomised but not treated (1 randomised to chemotherapy died before dosing, 1 randomised to chemotherapy was not eligible due to a protocol violation, 1 randomised to chemotherapy received crizotinib outside the study and subsequently died and 1 was randomised to crizotinib in error but was not treated and was later enrolled in Study A8081005). Of the total number of randomised patients, 50.3% in the crizotinib and 82.2% in the chemotherapy arm permanently discontinued study treatment. The most common reasons for permanent discontinuation were global deterioration of health status and objective progression or relapse, which when combined occurred at a greater incidence in the chemotherapy arm than in the crizotinib arm. Deaths at the end of treatment were reported more frequently in the crizotinib arm than in the chemotherapy arm. Patient disposition at end of treatment is summarised below in Table 1.

Table 1: Study A8081007 - Patient disposition at end of treatment; FA.

Number (%) of Patients	Crizotinib (N=173)	Chemotherapy (N=174)	Total (N=347)
Ongoing treatment at the data cutoff date (30 March 2012)	85 (49.1)	28 (16.1)	113 (32.6)
Randomized but not treated	1 (<1.0)	3 (1.7)	4 (1.2)
Reason for discontinuation			
Adverse event	13 (7.5)	16 (9.2)	29 (8.4)
Global deterioration of health status	37 (21.4)	23 (13.2)	60 (17.3)
Lost to follow-up	0	0	0
Objective progression or relapse	21 (12.1)	85 (48.9)	106 (30.5)
Protocol violation	0	1 (<1.0)	1 (<1.0)
Study terminated by sponsor	0	0	0
Patient died	12 (6.9)	4 (2.3)	16 (4.6)
Patient no longer willing to continue treatment for reason other than AE	2 (1.2)	3 (1.7)	5 (1.4)
Other	2 (1.2)[a]	11 (6.3)[b]	13 (3.7)
Total discontinued	87 (50.3)	143 (82.2)	230 (66.3)

[a] Other reasons = investigator decision to discontinue study drug due to patient lack of cooperation (1 patient) and subjective progression (1 patient).
[b] Other reasons included = local site guidance for maximum treatment duration was 6 cycles of chemotherapy (6 patients), crossover (2 patients), patient planned to have surgery for voice hoarseness after completing 6 cycles of chemotherapy (1 patient), local radiology laboratory confirmed patient progression (2 patients).

Patient disposition at the end of treatment by study drug is summarised below in Table 2. Based on the SA population, 172 patients were treated with crizotinib, 99 patients with pemetrexed and 72 patients with docetaxel. More patients on pemetrexed (78.8%) and docetaxel (90.3%) permanently discontinued study treatment than patients on crizotinib (50.6%).

Table 2: Patient disposition at end of treatment by study drug; SA.

	Crizotinib	Pemetrexed	Docetaxel	Total
Treated, n	172	99	72	343
Completed, n (%)	0	0	0	0
Discontinued, n (%)	87 (50.6)	78 (78.8)	65 (90.3)	230 (66.3)
Ongoing at data cutoff date, n (%)	85 (49.4)	21 (21.2)	7 (9.7)	113 (32.6)

Source: Table 14.1.1.1.2
The number of patients for treated, completed, discontinued, and ongoing per the Patient Summary EOT page.
Abbreviations: n=number of patients; EOT=End of Treatment

The protocol design included long-term survival follow-up after patients discontinued from treatment. Information on the reason for discontinuation from long-term survival follow-up was collected on the "End of Study" eCRF. The most common reason for discontinuing from long-term follow-up in the crizotinib arm was death (26.6%), and "other" (61.5%) in the chemotherapy arm (most frequently due to "crossed over to Study A8081005"). The patient disposition at the end of the study (that is, end of follow-up) is summarised below in Table 3.

Table 3: Patient disposition at end of study (that is, at the end of follow-up); FA.

Number (%) of Patients	Crizotinib (N=173)	Chemotherapy (N=174)	Total (N=347)
Ongoing study at the data cutoff date (30 March 2012)	118 (68.2)	49 (28.2)	167 (48.1)
Reason for discontinuation			
Completed	0	0	0
Patient died	46 (26.6)[a]	16 (9.2)	62 (17.9)
Study terminated by sponsor	0	0	0
Lost to follow-up	1 (<1.0)	0	1 (<1.0)
Patient refused further follow-up	3 (1.7)	2 (1.1)	5 (1.4)
Other	5 (2.9)[b]	107 (61.5)[c]	112 (32.3)
Total discontinued	55 (31.8)	125 (71.8)	180 (51.9)

[a] Three additional patients died, but were listed with other as a reason for discontinuation rather than death.
[b] Other reasons: randomised by mistake, not eligible for this study; inadmissible AE; patient gave up treatment and unwilling to continue the study; confirmed progressive disease and withdrew from the study; subsequent cycle could not initiate on a planned day and need for treatment delay for more than 42 days due to AE (pneumonia).
[c] Most were "crossed over to Study A8081005".

2.3.15. Baseline data

2.3.15.1. Demographics

The baseline demographics for patients in the FA population were well balanced between the two randomised treatment arms. The mean (SD) patient age in the total FA population was 50.1 (13.0) years and ranged from 22 to 85 years, with 85.6% (n=297) of the total population being aged < 65 years and 14.4% (n=50) being aged ≥ 65 years. The total population included 153 (44.1%) males and 194 (55.9%) females. The racial grouping of the total population was White (52.2%, n=181), Asian (45.2%, n=157) and Black (1.4%, n=5). Perusal of the baseline demographics for each of the three study drugs showed that patients aged ≥ 65 years were more common in the crizotinib (15.7%, n=27) and pemetrexed (17.2%, n=17) groups than in the docetaxel group (8.3%, n=6), while patients categorised as White were marginally more common in the docetaxel group (58.3%, n=42) than in the crizotinib (51.7%, n=89) and the pemetrexed (47.5%, n=47) groups.

2.3.15.2. Disease characteristics

The baseline disease characteristics in the FA population were well balanced between the two randomised treatment arms and all patients in both treatment arms had a primary diagnosis of

NSCLC. In the total FA population, the mean duration of histopathological diagnosis until the date of randomisation was 1.2 years, with a median of 0.7 years and a range of 0.1 to 12.4 years. Measurable disease was present in 345 (99.4%) of patients, with no measurable disease being reported in 1 patient (chemotherapy arm) and status being not reported in 1 patient (crizotinib arm). Measurable disease was defined as at least 1 target lesion ≥ 2 cm or at least 1 target lesion ≥ 1 cm for spiral CT or at least 1 lymph node target lesion with shortest diameter ≥ 1.5 cm. Adequate baseline assessment was reported in 345 (99.4%) of patients, with inadequate assessment being reported in 1 patient (chemotherapy arm) and status being not reported in 1 patient (crizotinib arm). Adequate baseline assessment was defined as all evaluations, target and non-target, being within the study specific time window prior to randomisation. ECOG PS at baseline was reported as 0, 1, 2, or not reported in 137 (39.5%) patients, 179 (51.6%) patients, 30 (8.6%) patients and 1 (<1.0%) patient, respectively. The primary diagnosis, duration of disease since histopathological diagnosis to date of randomisation and ECOG PS at baseline did not markedly differ for the three study drugs.

2.3.15.3. Primary diagnosis

The primary diagnosis did not markedly differ between the two randomised treatment arms in the FA population, with 323 (93.1%) patients having adenocarcinoma. Locally advanced disease occurred more commonly in the chemotherapy arm than in the crizotinib arm (9.2% versus 4.0%, respectively), while metastatic disease was reported more commonly in the crizotinib arm than in the chemotherapy arm (95.4% versus 90.8%, respectively). The percentage of patients with a primary histological diagnosis of adenocarcinoma was similar among the three study drugs (range: 92.9% to 94.8%). Metastatic disease was reported more frequently in patients in the crizotinib and docetaxel groups (95.9%, n=165 and 93.1%, n=67), than in the pemetrexed group (88.9%, n=88).

2.3.15.4. Prior treatments for the primary diagnosis

Prior treatments for the primary diagnosis were similar in the two randomised treatment arms in the FA population. Prior surgery had occurred in 172 patients (99.4%) in the crizotinib arm and all 174 (100.0%) patients in the chemotherapy arm, with tumour resected being reported in 35 (20.3%) and 32 (18.4%) patients, respectively. Prior radiation therapy had been used in 77 (44.5%) patients in the crizotinib arm and 80 (46.0%) patients in the chemotherapy arm, while all patients in both treatment arms had received prior systemic therapies apart from 1 patient in the crizotinib arm for who this information was not collected. The best overall response profile to first line of metastatic chemotherapy was similar for the two randomised treatment arms.

2.3.15.5. Past medical history

Of the 347 randomised patients, 200 (57.6%) reported a past medical history and 331 (95.4%) reported a present medical history. Past and present medical histories were generally comparable between two randomised treatment arms. The most commonly reported present medical histories (≥ 10% of patients) and crizotinib versus chemotherapy, respectively, were: cough (41.6% versus 40.8%), dyspnea (21.4% versus 27.0%), hypertension (19.7% versus 12.6%), constipation (12.7% versus 15.5%), back pain (10.4% versus 16.1%), fatigue (13.3% versus 12.6%), insomnia (13.9% versus 10.3%), metastases to bone (9.2% versus 13.8%), and chest pain (6.4% versus 16.1%).

2.3.15.6. Prior treatments, not including treatments for primary disease

Overall, 156 (90.7%) patients on crizotinib and 166 (97.1%) patients on chemotherapy received prior drug treatment, not including treatment for their primary disease. The most commonly reported prior medications (≥ 25% of patients) in the crizotinib versus chemotherapy arms, respectively, were: folic acid (18.6% versus 46.8%); dexamethasone (13.4% versus 71.9%); cyanocobalamin (8.1% versus 26.9%).

2.3.15.7. Baseline stratification factors

Baseline stratification factors were similar between the two randomised treatment arms in the FA. The baseline stratification factors for the crizotinib versus chemotherapy arms, respectively, were: ECOG PS 0-1/PS 2 89.0% (n=154)/11.0% (n=19) versus 91.4% (n=159)/8.6% (n=15); brain metastases present/absent 34.7% (n=60)/65.3% (n=113) versus 34.5% (n=60)/65.5% (n=114); and prior EGFR TKI treatment yes/no 11.6% (n=20)/88.4% (n=153) versus 12.1% (n=21)/87.9% (n=153).

2.3.16. Major protocol deviations

There were a number of patients with major and relevant protocol deviations. The relevant study personnel warranted that "known deviations in the study do not invalidate the text in the section titled *'Ethical Conduct of Study'* regarding GCP compliance, and where, applicable, local country regulations".

Comment: It is considered unlikely that the listed protocol deviations invalidated the analysis of the efficacy and/or safety data. In general, the protocol deviations were balanced between the two treatment arms.

2.3.17. Concomitant medications

Overall, 169 (98.3%) patients in the crizotinib arm and 171 (100%) patients in the chemotherapy arm received concomitant drug treatment. The most commonly reported concomitant medications (≥ 25% of patients) and crizotinib versus chemotherapy, respectively, were: paracetamol (27.9% versus 31.0%); dexamethasone (19.8% versus 90.6%); folic acid (16.3% versus 46.2%); and cyanocobalamin (4.7% versus 25.7%). Overall, 69 (40.1%) patients in the crizotinib arm and 63 (36.8%) patients in the chemotherapy arm reported concomitant non-drug treatment.

2.4. Efficacy – Results

2.4.1. Progression free survival – primary efficacy endpoint (final analysis)

The 30 March 2012 data cut off date for the primary efficacy analysis was selected because the 217 PFS events required for the final analysis of PFS had occurred at this time-point. However, by the time of the "database snapshot" on 08 June 2012, an additional 10 PFS events had occurred within the data cut off period. Therefore, a total of 227 PFS events were included in the PFS analyses. The key results are summarised below in Table 4. The Kaplan-Meier plot of PFS is provided below in Figure 1.

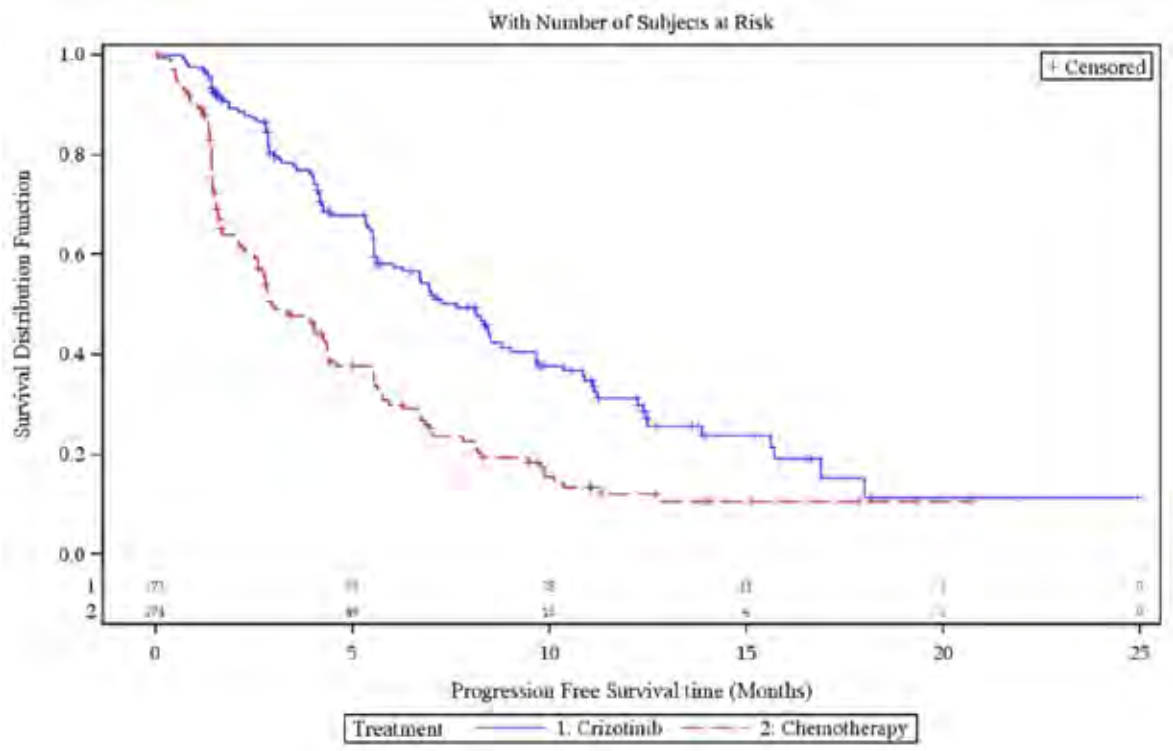
Table 4: Final progression-free survival (PFS) analysis based on IRR; FA population.

Parameter	Crizotinib (n=173)	Chemotherapy (n=174)
Number with PFS event, n (%)	100 (57.8%)	127 (73.0%)
Objective progression	84 (48.6%)	119 (68.4%)
Death without objective progression	16 (9.2%)	8 (4.6%)
Censored, n (%)	73 (42.2%)	47 (27.0%)
Median PFS, months (95% CI) [a]	7.7 (6.0, 8.8)	3.0 (2.6, 4.3)

Parameter	Crizotinib (n=173)	Chemotherapy (n=174)
Hazard Ratio (95% CI) [b]; p - value [c]	HR = 0.487 (95%CI: 0.371, 0.638); p < 0.0001	

Source: CSR, Adapted from Table 23.
[a] Median survival estimated from Kaplan-Meier curve, 95% CI based on the Brookmyer and Crowley method.
[b] Based on the Cox proportional hazards model stratified by ECOG PS score, brain metastases, and prior EGFR TKI treatment. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favour of crizotinib.
[c] 1-sided p-value from the log-rank test stratified by ECOG PS score, brain metastases, and prior EGFR TKI treatment.

Figure 1: Kaplan-Meier plot of progression-free survival (PFS) based on IRR; FA.



Median PFS was significantly longer in the crizotinib arm compared with the pemetrexed arm: 7.7 months (95% CI: 6.0, 8.8) versus 4.2 months (95% CI: 2.8, 5.7); HR = 0.589 (95% CI: 0.431, 0.804), p=0.0004. Median PFS was significantly longer in the crizotinib arm compared with the docetaxel arm: 7.7 months (95% CI: 6.0, 8.8) for versus 2.6 months (95% CI: 1.6, 4.0); HR = 0.298 (95% CI: 0.207, 0.428), p<0.0001.

When controlled for baseline stratification factors, PFS favoured crizotinib over chemotherapy (p<0.0001). As regards the stratification factors, patients with ECOG PS of 0-1 had a better PFS outcome than patients with ECOG PS of 2 (p<0.0001), and patients with no brain metastases had a better PFS outcome than patients with brain metastases (p=0.0075). There was no evidence that PFS in patients with prior EGFR-TKI treatment was better than PFS in patients without prior EGFR-TKI treatment (p=0.5016).

Subgroup analyses showed that PFS benefit with crizotinib was comparable across patients with varying baseline characteristics, including ECOG PS, brain metastases, prior EGFR inhibitor treatment group, age, gender, smoking status, histology, duration from primary diagnosis, race, and extent of disease.

The sensitivity analyses for PFS (unstratified analysis, analyses with different censoring rules for PFS, and PFS by investigator assessment) were consistent with the primary efficacy analysis for PFS. In the unstratified sensitivity analysis, the HR comparing crizotinib with chemotherapy was 0.493 (95% CI: 0.379, 0.643; p<0.0001). The results for the analyses (stratified) with different censoring rules (that is, PD or death were considered PFS events regardless of when documented), and PD based on the investigator assessment were summarised in two tables.

The overall disagreement rates (taking into account timing and occurrence of event) between PFS based on IRR assessments and investigator assessments were 35.8% (62/173) in the crizotinib arm and 30.5% (53/174) in the chemotherapy arm.

Comment: The study met its primary objective of demonstrating that crizotinib significantly prolongs PFS compared with chemotherapy. The median PFS was 7.7 months for the 173 patients randomised to crizotinib and 3.0 months for the 174 patients randomised to chemotherapy. The hazard ratio for PFS was 0.487 (95% CI: 0.371, 0.638), p < 0.0001 (1-sided stratified log-rank test), favouring crizotinib relative to chemotherapy. The observed results for PFS were consistent with the clinical assumptions used to calculate the sample size. The increased PFS seen in the crizotinib arm compared with the chemotherapy arm is considered to be clinically meaningful. The Kaplan-Meier plot showed that the curves for the crizotinib and the chemotherapy arms began to separate very soon after initiating therapy and continued to favour crizotinib over chemotherapy throughout the study period.

Of the 173 patients randomised to crizotinib, 100 (57.8%) had a PFS event and 73 (42.2%) are still in follow-up, while of the 174 patients randomised to chemotherapy, 127 (73.0%) had a PFS event and 47 (27.0%) are still in follow-up. The percentage of patients with objective progression was 1.4-fold higher in the chemotherapy arm than in the crizotinib arm (68.4%, n=119 versus 48.6%, n=84) while the percentage of patients who died without objective progression was 2.0-fold higher in the crizotinib arm than in the chemotherapy arm (9.2%, n=16 versus 4.6%, n=8). These results indicate that the difference in PFS between the two treatment arms is being driven primarily by the difference in objective disease progression.

In the subgroup analyses, PFS significantly favoured crizotinib compared with pemetrexed and crizotinib compared with docetaxel. The median PFS durations were 7.7 months, 4.2 months and 2.6 months for crizotinib, pemetrexed and docetaxel, respectively.

2.4.2. Results for the secondary efficacy endpoints

2.4.2.1. Overall survival (OS) – interim analysis

2.4.2.1.1. Primary OS analysis (interim analysis)

There was no statistically significant improvement in OS between the crizotinib arm and the chemotherapy arm, as assessed by the (interim) primary OS analysis. The key results for the primary OS analysis are summarised below in Table 5. The median duration of follow-up was similar in both the crizotinib and chemotherapy treatment arms (12.2 and 12.1 months, respectively).

Table 5: Interim overall survival analysis (stratified): FA population.

Parameter	Crizotinib (n=173)	Chemotherapy (n=174)
Number of deaths, n (%)	49 (28.3%)	47 (27.0%)
Number censored, n (%)	124 (71.7%)	127 (73.0%)

Parameter	Crizotinib (n=173)	Chemotherapy (n=174)
Median OS, months (95% CI) [a]	20.3 (18.1, NR)	22.8 (18.6, NR)
Hazard Ratio (95% CI) [b]; p -value [c]	1.021 (95% CI: 0.677, 1.540); p=0.5394	

[a] Median survival estimated from Kaplan-Meier curve, 95% CI based on the Brookmyer and Crowley method. [b] Based on the Cox proportional hazards model stratified by ECOG PS, brain metastases, and prior EGFR TKI treatment. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favour of crizotinib. [c] 1-sided p-value from the log-rank test stratified by ECOG PS, brain metastases, and prior EGFR TKI treatment.

There was no statistically significant difference in OS between the two treatment groups in either of the two pairwise comparisons. However, Kaplan-Meier estimates were not available for the median survival times in either of the two analyses due to the number of deaths being too small to calculate the parameters.

A Cox regression model of OS adjusted for baseline stratification factors and treatments showed no significant difference between the two treatment arms (p=0.9043). For the stratification factors, patients with ECOG PS of 0-1 had a better OS outcome than patients with ECOG PS of 2 (p<0.0001), patients with no brain metastases had better OS outcome than patients with brain metastases (p=0.0121) and patients who received prior EGFR TKI treatment had better OS outcome than patients with no prior EGFR TKI treatment (p=0.0189), although there were few patients in some subgroups (for example, ECOG PS score 2 [n=34]; prior EGFR TKI treatment [n=41]).

A Forest plot of OS in subgroups based on baseline characteristics was provided. No statistically significant differences were observed between crizotinib and chemotherapy in any of the subgroups.

Comment: There was no statistically significant improvement between crizotinib and chemotherapy in OS (interim primary analysis). Median overall survival was similar in the crizotinib and the chemotherapy arms (20.3 and 22.8 months, respectively), and the hazard ratio for overall survival was 1.021 (95% CI: 0.677, 1.540), p=0.5394 (1-sided stratified log-rank test). A total of 49 (28.3%) patients on crizotinib and 47 (27.0%) patients on chemotherapy were known to have died as of the data cut off date. Data for patients not known to have died were censored at the time they were last known to be alive. Overall, the number of deaths observed so far corresponds to 39.8% of the total number of deaths required for the final OS analysis (that is, 96 out of 241 deaths). The majority of patients in each treatment arm were in follow-up for survival at the data cut off date (118 [68.2%] patients on crizotinib and 120 [69.0%] patients on chemotherapy). The primary OS results are considered to be preliminary estimates due to the fact that the total number of deaths required for the final OS analysis had not been reached at the time of the data cut off date.

The primary interim OS analysis was not adjusted to account for the potentially confounding effects of crossover from chemotherapy to crizotinib. In the chemotherapy arm, 64% (112/174) of patients crossed-over to crizotinib and 12% (20/173) of patients in the crizotinib arm crossed over to chemotherapy. The CSR included a sensitivity analysis of OS censoring at the time of new anti-cancer treatment (unstratified) by treatment arm in the FA population. In this analysis, the number of deaths in the crizotinib arm was 21 (12.1%) compared with 12 (6.9%) in the chemotherapy arm. The HR was 1.362 (95% CI: 0.666, 2.785), p=0.8021, indicating a non-significant survival benefit in favour of the chemotherapy arm compared with the crizotinib

arm. The Kaplan-Meier estimates of the median duration of survival for both treatment arms had not been reached at the date of the data cut off. The total number of deaths in this analysis occurring before new anti-cancer treatment was relatively low (n=33) and accounted for 34.4% of all deaths in the primary interim OS analysis. The submission included a Technical Report that included additional pre-specified sensitivity OS analyses based on the interim OS data in Study A8081007 (see Section immediately below).

- In the crizotinib (n=172) versus pemetrexed (n=99) subgroup analysis (stratified) the HR was 1.044 (95% CI: 0.637, 1.709), p=0.5679. In this subgroup analysis, there were 48 (27.9%) deaths in the crizotinib group and 24 (25.3%) deaths in the pemetrexed group but in both groups median survival times had not been reached. In the crizotinib (n=172) versus docetaxel (n=72) subgroup analysis (stratified) the HR was 0.985 (95% CI: 0.568, 1.706), p =0.4783. In this subgroup analysis, there were 48 (27.9%) deaths in the crizotinib group and 19 (26.4%) deaths in the docetaxel group, and the Kaplan-Meier estimate of median overall survival was 18.6 month (95% CI: 18.6, -) in the docetaxel group but had not been reached in the crizotinib group.

2.4.2.1.2. Technical report - sensitivity analyses of OS

(a) OS analyses accounting for crossover status

The primary analysis of the effect of crossover on OS employed in the Technical Report was the rank preserving structural failure time models (RPSFTM) similar to the method described by Robins and Tsiatis (1999)[1]. This analysis was pre-specified in the Statistical Analysis Plan (SAP) for Study A8081007. In addition, the Technical Report also employed a Cox proportional hazards model stratified for the three baseline factors used for the primary OS analysis (that is, ECOG PS status, brain metastases, and prior EGFR TKI treatment.

The Technical Report included four OS sensitivity analyses based on the crossover status of the patients (that is, crizotinib no cross over versus chemotherapy no crossover; crizotinib no cross-over versus crizotinib to chemotherapy; chemotherapy to crizotinib versus chemotherapy to no cross-over; and chemotherapy to crizotinib versus crizotinib to chemotherapy). In each of the 4 sub-group analyses OS was compared using the HR, with 95% CI, based on a Cox proportional hazards model (stratified for the three baseline factors), with Kaplan-Meier estimates of overall survival being provided for each subgroup analysis. The HR for each of the OS sensitivity analyses was not statistically significant. In the "crizotinib no crossover" versus "chemotherapy no crossover" analysis, the HR was 0.79 (95% CI: 0.41, 1.52), indicating a non-significant survival benefit in favour of crizotinib compared with chemotherapy. In this analysis, the median overall survival in the "crizotinib no crossover group" with 153 patients was estimated to be 20.3 months (95% CI: 18.1, not reached) and in the "chemotherapy no crossover group" with 62 patients the median overall survival and the 95% CI had not been reached.

RPSFTM was employed in the Technical Report to adjust for the effect of crossover on OS and to obtain an unbiased estimate of treatment effect on OS as if the patients had not crossed over. In the RPSFTM analysis, the HR (crizotinib versus chemotherapy) was 0.83 (95% CI: O.36, 1.35) after adjusting for crossover in both directions, indicating a non-significant survival benefit in favour of crizotinib compared with chemotherapy.

The Kaplan-Meier estimated of OS after adjusting for crossover by the RPSFTM and without adjusting for crossover was provided. Without adjusting for crossover the OS curves for the two treatment arms were virtually superimposable but after adjusting for crossover the OS curves separated in favour of the crizotinib arm compared with the chemotherapy arm.

The Technical Report also included an RPSTFM analysis in the subgroup of patients treated with docetaxel as original treatment or as follow-up therapy after crossing-over from randomised crizotinib therapy. The report justifies this analysis on the basis that in some countries docetaxel may be the standard therapy for second line treatment of NSCLC. In this analysis, the HR was 0.85 [95% CI: 0.29, 1.75], indicating a non-significant overall survival benefit in favour

of the crizotinib group compared with the docetaxel group. The median OS for crizotinib treated patients in this analysis has not been reached (95% CI: 18.1 months, -), while the median OS for docetaxel treated patients was 15.8 months (95% CI: 11.0 months). However, the report states that care must be taken when interpreting these results due to the fact that the groups were not randomised and both the number of patients (n=72) and the number of deaths in the docetaxel group (n=19) were small.

No corresponding RPSFTM subgroup analysis (that is, crizotinib versus pemetrexed) was provided for patients treated with pemetrexed as original therapy or as follow-up therapy after crizotinib. However, the sponsor states that this analysis is underway and the results will be available by mid May 2013 and can be provided to the TGA on request. However, the sponsor notes that care will need to be taken when interpreting the results of this analysis due to comparison of non-randomised groups, the small number of patients treated with pemetrexed (n=99) and the limited number of OS events in pemetrexed treated patients (25 deaths).

(b) OS analysis accounting for systemic anti-cancer therapies post-disease progression

In Study A808007, patients had the option to crossover after disease progression or continue on treatment with crizotinib or chemotherapy after disease progression or switch to other systemic standard of care (SOC) follow-up anti-cancer therapies (see Table 6, below). It was expected that clinical conditions (for example, ECOG PS, changes in body weight, adverse events) would determine whether switching to follow-up systemic anti-cancer treatment occurred and which treatment was selected. These clinical conditions are potential time-dependent confounders due to the fact they are most likely risk factors for mortality while also being determinants of post-disease progression treatment.

Standard methods of OS analysis (such as time-dependent Cox model) that do not adjust for time-dependent confounders may produce biased treatment effects. Therefore, Marginal Structural Model (MSM) methodology (similar to that described by Robins[3,4]) with inverse probability of treatment weighting (IPTW) was employed to obtain valid causal inferences for the effect of randomised treatment, and for the time-dependent follow-up treatments in the presence of time-dependent confounding factors. The clinical question of interest addressed by the MSM was whether the two randomised arms would have had the same overall survival if all patients had received identical post-PD treatment (that is, after adjusting for the differential effect of post-PD treatment and time-dependent confounding factors). The MSM described in the Technical Report was pre-specified in the SAP of Study A8081007.

Patient disposition by first line post disease progression (PD) systemic anti-cancer treatment for the two randomised treatment arms is summarised below in Table 6. Differential patterns of post-PD treatments were observed between the two randomised arms. In particular, there were 157 (45% of 347) patients treated with crizotinib post-PD including 98 patients who had crossed over from chemotherapy to crizotinib and 59 patients who had continued crizotinib treatment with relatively long duration beyond PD (defined as > 21 days post-PD).

Table 6: Subject disposition by 1st line post disease progression (post-PD) treatment, systemic anti-cancer therapies post-PD excluded surgery and radiotherapy.

Randomized treatment	Subgroup by post PD treatment type	n	% (in N=347)	death (% in n)	Randomized treatment	Subgroup by post PD treatment* type	n	% (in N=347)	death (% in n)
Chemotherapy	0.No therapy	16	5%	5(31%)	Crizotinib	0.No therapy	14	4%	5(36%)
	1.Crizotinib	98	28%	31(32%)		1.Crizotinib	59	17%	14(24%)
	2.Chemotherapy	18	5%	4(22%)		2.Chemotherapy	9	3%	5(56%)
	3.SOC (other systemic therapy)	2	<1%	0(0%)		3.SOC (other systemic therapy)	13	4%	8(62%)
	4.NA (not PD)	33	10%	0(0%)		4. NA (not PD)	63	18%	2(3%)
	5.NA* (died before PD)	7	2%	7(100%)		5. NA* (died before PD)	15	4%	15(100%)

* Patients in category 5 (NA) had PFS event as death without initiation of any non-randomized systemic therapy before death.

In order to create the panel data for the analysis, the OS interim data was first partitioned into cycle (3 weeks) increments from date of randomisation to the last OS date (death or censored

data). The time-independent covariates V, time-varying covariates L(t) and post-PD treatments A(t) are summarised for each patient at each cycle increment. The V, L(t) and A(t) covariates are summarised below in Table 7.

Table 7: Covariates included in model fitting

Notation	Type of Covariate	Covariate	Definition of Covariate
V	Treatment	ITT randomized treatment	Crizotinib, Chemotherapy
	Stratification factors	ECOG Performance Status	0-1, 2
		brain metastases	present, absent
		prior EGFR TKI therapy	yes, no
	Fixed covariates	Age	years
		gender	male, female
		time since diagnosis	Duration in yrs based on histopathological diagnosis
		smoking classification	smoker/ex-smoker, never smoker
		race	Asian, non-Asian
		extent of disease	metastatic, locally advanced
		histological classification	adenocarcinoma, non-adenocarcinoma
		geographical region	US, Europe, Asia
		indicator of PD on study	0 (no),1 (yes)
		cycle since randomization	time since randomization in cycles (1cycle=3weeks)
		centered cycle^2	square of centered cycle since randomization
		centered cycle^3	cube of centered cycle since randomization
A(t)	Time-varying post-PD treatment	post PD treatment type	0=no systemic therapy 1=Crizotinib 2=Chemotherapy 3=SOC 4=not available, due to no PD on study 5=not available, due to death before PD
L(t)	Time-varying clinical status■	ECOG Performance Status	0,1,2,3-4 -99*
		occurrence of Grade 3 or 4 adverse event	0 (no),1 (yes) -99†
		body weight	% change from baseline -99§

*-99="Unknown" in LOCF by 28/56 days of last ECOG PS assessment date; †-99="Unknown" in LOCF by 28/56 days of date of discontinuation from treatment or the last date of adverse event; §-99="Unknown" in LOCF by 28/56 days of last body weight evaluation date.

If within any cycle more than one record for a patient occurred for a time dependent variable, then two methods were used to summarize the variable: “worst prognosis” or “last observation” within that cycle. The larger the values for ECOG PS, the greater the occurrences of Grade 3 or 4 AEs or the smaller the values for percentage change from baseline in body weight, the worse the prognosis. If there were gaps between last assessment dates and last OS date, three imputation methods were implemented: full last observation carried forward (LOCF), LOCF by 28 days and LOCF by 56 days. With full LOCF, no limit was applied to how long it had been since the last observation for that observation to be carried forward to impute missing values. With LOCF by 28 days or by 56 days only observations within the last 28 days or 56 days, respectively, would be carried forward to impute missing values.

Generalised estimating equation (GEE) models (the pooled logistic model) were used to estimate stabilised weights for each patient. The double inverse probability of treatment and censoring weighting (IPTWC) method was employed for the primary analyses and the inverse probability of treatment weighting IPTW method was used in a sensitivity analysis to check the robustness of the primary analyses. The IPTCW method is a double inverse weighting method constructed from the concurrent application of inverse probability of treatment weighting (IPTW) to balance the treatment-specific baseline covariates (that is, adjusts for time-dependent confounders that are affected by previous treatment) and inverse probability of censoring weighting (IPCW) overcomes dependent censoring due to time-varying factors for which no adjustment is made.[5] The IPTCW is the product of IPTW and IPCW.

The causal effects of randomised treatment were estimated using the marginal structural Cox proportional hazard model with IPTWC applied (primary model). The marginal structural Cox

proportional model with IPTW applied (sensitivity model) was used to check the robustness of the findings from the primary model. Adjusted hazard ratios of OS (with 95% CI) were calculated for randomised treatment (crizotinib versus chemotherapy) for LOCF by 28 days, LOCF by 56 days and full LOCF by the IPTCW method and the IPTW method using "worst prognosis" or "last observation" to impute missing data.

The primary analysis used the marginal structural Cox proportional hazard model with IPTWC applied and worst prognosis value within cycle and full LOCF imputation. The estimated causal hazard ratio (HR) of randomised treatment with crizotinib versus randomised treatment with chemotherapy using this model was 0.79 (95% CI: 0.47, 1.34). The HR indicates that, under the model assumptions and after accounting for baseline covariates and post-PD therapies, treatment with crizotinib appears to non-significantly improve OS outcome when compared with chemotherapy. However, no power calculations were provided for the OS sensitivity analysis but based on the total number of deaths occurring prior to disease progression (22 out of 347 patients, 6.3%) it is likely to be low. The adjusted hazards ratios for overall survival derived from the "MSMs with IPTCW" are summarised below in Table 8. The corresponding results for the "MSMs with IPTW applied" were similar to those for the "MSMs with IPTCW applied" (results not shown in the CER).

Table 8: Adjusted hazard ratios of overall survival for randomised treatment arm (crizotinib versus chemotherapy) from IPTCW marginal structural models.

MSM	LOCF by 28 days	LOCF by 56 days	Full LOCF
IPTCW – "worst prognosis"	HR = 0.79 (95% CI: 0.45, 1.40)	HR = 0.75 (95% CI: 0.45, 1.27)	**HR = 0.79 (95% CI: 0.47, 1.34)**
IPTCW – "last observation"	HR = 1.18 (95% CI: 0.66, 2.03)	HR = 0.64 (95% CI: 0.33, 1.24)	HR = 0.82 (95% CI: 0.48, 1.40)

Comment: The primary RPSTFM and MSM (IPTCW) OS sensitivity analyses both showed a non-significant trend towards greater survival benefit in the crizotinib arm compared with the chemotherapy arm. However, the predictive power of the OS sensitivity analyses is limited by the relatively small number of patients available for the analyses, the immaturity of the OS data (that is, only approximately 40% of the total number of deaths required for the final analysis have occurred), the relatively high proportion of patients in the chemotherapy arm crossing over to crizotinib, and the very small number of deaths occurring prior to disease progression in patients in the chemotherapy arm not subsequently exposed to crizotinib.

No predicted median OS times were provided for the crizotinib or chemotherapy arms in the MSM analyses. The sponsor states that the MSM analyses aim to adjust for potentially confounding effects of post-progression systemic anti-cancer therapies as time-varying covariates, as well as other potential confounders such as baseline patient characteristics. Therefore, there are other covariates besides treatment group in the model to predict OS (that is, baseline characteristics, disease progression time, type of post-progression systemic anti-cancer therapies, and other time-varying covariates). Predicted median OS for the crizotinib and chemotherapy arms could be provided for an individual population with specific levels for the combination of covariates in the MSM. However, the sponsor considers that each of these predicted medians would be very specific and would not be able to be generalized to the study population.

2.4.2.2. Objective response rate

The study demonstrated a statistically significant greater ORR in the crizotinib arm compared with the chemotherapy arm. The ORR by IRR (CR+PR) was 65.3% (95% C1: 57.7, 72.4) in the crizotinib arm and 19.5% (95% C1: 13.9, 26.2) in the chemotherapy arm. The difference in the ORR between the two treatment arms was 45.8% (95% CI: 36.6, 55.0); p <0.0001, Pearson chi-square test. Of the 113 patients in the crizotinib arm with an objective response, 1 (<1.0%) had a complete response (CR) and 112 (64.7%) had a partial response. Of the 34 patients in the chemotherapy arm with an objective response, no patients had a CR and all 34 (19.5%) patients had a PR.

The ORR for crizotinib was significantly greater than for pemetrexed (65.7% [95% CI: 58.1, 72.8] versus 29.3% [95% CI: 20.6, 39.3]; p<0.0001, stratified CMH). The ORR for crizotinib was significantly greater than for docetaxel (65.7% [95% CI: 58.1, 72.8] versus 6.9% [95% CI: 2.3, 15.5]; p<0.0001, stratified CMH). Best overall response for the two pairwise comparisons is summarised in Table 51, page 91.

2.4.2.3. Disease control rate (DCR)

The DCR at both Week 6 and Week 12 was significantly higher for crizotinib compared with chemotherapy. At Week 6, the DCR for crizotinib was 81.5% (95% CI: 74.9, 87.0) compared with 55.2% (95% CI: 47.5, 62.7) for chemotherapy, p<0.0001 (Pearson Chi-square test). At Week 12, the DCR for crizotinib was 64.2% (95% CI: 56.5, 71.3) compared with 38.5% (95% CI: 31.2, 46.2) for chemotherapy, p < 0.0001 (Pearson Chi-square test). However, the statistically significant results for the comparisons between the two treatment arms should be considered to be nominal rather than confirmatory as the analysis of OS (the endpoint preceding DCR in the hierarchal order of testing) was not statistically significant.

2.4.2.4. Time to tumour response

In the 113 patients randomised to crizotinib who had objective tumour response, the mean (SD) TTR was 8.6 (6.2) weeks, and the median TTR was 6.3 weeks (range: 4.4, 48.4 weeks). In the 34 patients randomised to chemotherapy who had objective tumour response, the mean (standard deviation (SD)) TTR was 16.9 (10.1) weeks and the median TTR was 12.6 weeks (range: 5.0, 37.1 weeks). The results were presented descriptively with no statistical analysis of the pairwise comparison being undertaken.

2.4.2.5. Duration of response (DR)

Objective response (CR or PR) was achieved by 113 (65.3%) patients in the crizotinib arm and 34 (19.59%) patients in the chemotherapy arm. Of these patients, subsequent objective disease progression or death occurred in 61 (54%) patients in the crizotinib arm and 20 (58.8%) patients in the chemotherapy arm. In the crizotinib arm (n=173), the mean (SD) DR was 25.4 (16.4) weeks, and the median DR was 19 weeks (range: 2.1, 72.4 weeks). In the chemotherapy arm (n=174), the mean (SD) DR was 17.3 (10.9) weeks, and the median DR was 14.2 weeks (range: 3.0, 43.6 weeks). The median DR estimate, using the Kaplan-Meier method, was 32.1 weeks (95% CI: 26.4, 42.3) in the crizotinib arm and 24.4 weeks (95% CI: 15.0, 36.0) in the chemotherapy arm. The results for DR were updated with information provided by the sponsor to the TGA.

2.4.3. Results for other efficacy endpoints

The study included a number of patient reported outcomes (PROs) assessed in the PRO evaluable population consisting of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm. The results of the PRO outcomes were summarised in a series of Forest plots: global quality of life and function domains assessed by the EORTC QLQ-C30; EORTC QLQ-C30 symptoms; and EORTC QLC-LC13 symptoms. In general, all PROs significantly favoured the crizotinib arm compared with the chemotherapy arm.

The time to deterioration (TTD) was analysed for the symptoms of pain in the chest, cough and dyspnoea based on the EORTC QLQ-LC13 questionnaire. Patients were censored in the TTD analyses if they had not shown deterioration at the last visit date prior to the data cut off date. The median TTD in pain in chest, dyspnea or cough as a composite endpoint was 5.6 months (95% CI: 3.4, 11.0 months) in the crizotinib arm compared with 1.4 months (95% CI: 1.0, 1.8 months) in the chemotherapy arm. The percentage of patients with deterioration of symptom was 56.2% (91/162) in the crizotinib arm and 73.5% (111/151) in the chemotherapy arm and the respective probabilities of being symptom free at 6 months were 48.5% (95% CI: 40.1, 56.4) and 22.9% (95% CI: 15.9, 30.7).-The HR (crizotinib versus chemotherapy) was 0.535 (95% CI: 0.404, 0.709), p<0.0001 (2-sided Hochberg adjusted unstratified log-rank test), indicating that the probability of being symptom free at 6 months significantly favoured crizotinib relative to chemotherapy.

2.5. Safety – Results

2.5.1. Exposure

2.5.1.1. Duration of study treatment

The duration of study treatment was longer in the crizotinib arm than in the chemotherapy arm (duration of treatment was defined as total number of dosing days from date of first to last dose [or data cut off date, whichever was earlier] + 1 counting gaps for crizotinib and including 21 days for last cycle for chemotherapy). The median duration of treatment in the crizotinib arm was 31.0 weeks (range: 1.3, 110.1 weeks) and 12.3 weeks (range: 3.0, 90.0 weeks) in the chemotherapy arm (see Table 9, below). In the chemotherapy arm, the median duration of treatment in the pemetrexed arm (n=99) was 18 weeks (range: 3, 90 weeks) and 9.1 weeks (range: 3, 66 weeks) in the docetaxel arm (n=72).

Table 9: Duration of treatment; SA population.

	Crizotinib (N=172)	Chemotherapy (N=171)
Mean (SD) duration (weeks)	36.5 (25.9)	18.6 (17.9)
Median (range)	31.0 (1.3, 110.1)	12.3 (3.0, 90.1)
≤ 4 weeks	10 (5.8%)	25 (14.6%)
> 4 to ≤ 12 week	30 (17.4%)	57 (33.3%)
> 12 to ≤ 24 weeks	23 (13.4%)	51 (29.8%)
> 24 to ≤ 52 weeks	63 (36.6%)	26 (15.2%)
> 52 to ≤ 104 week	45 (26.2%)	12 (7.0%)
> 104 weeks	1 (0.6%)	0

Comment: The longer duration of treatment in the crizotinib arm compared with the chemotherapy arm is likely to be related to investigators electing to keep patients on crizotinib following objective disease progression due to either clinical benefits being present or to uncertainty relating to the effectiveness of alternative treatments. In contrast, the shorter duration of treatment in the chemotherapy arm compared with the crizotinib arm is likely to be related to investigators electing to switch patients on chemotherapy to crizotinib following

objective disease progression. There were no data on whether patients continuing treatment with crizotinib following objective disease progression benefited from continued treatment, or on the optimal duration of continued treatment following objective disease progression.

2.5.1.2. Dose administration

The total number of cycles started and the median number of cycles started was greater in the crizotinib arm (2097 total started, 10.5 median number started [range: 1, 37]) than in both the pemetrexed arm (740 total started, 6 median number started [range: 1, 60]) and the docetaxel arm (285 total started, 3 median number started [range: 1, 22]). The percentage of subjects completing ≥ 10 cycles was notably greater in the crizotinib arm (57.0%; 98/172) than in both the pemetrexed arm (25.3%; 25/99) and the docetaxel arm (5.6%; 4/72).

2.5.1.3. Dose intensity

The mean and median relative dose intensities were similar for crizotinib (92.0%, 98.5%, respectively), pemetrexed (98.6%, 99.7%, respectively) and docetaxel (92.6%, 97.8%, respectively). The mean intended dose intensities were 500 mg/day, 166.7 mg/day, and 25 mg/day for crizotinib (n=172), pemetrexed (n=99) and docetaxel (n=72), respectively. The corresponding mean (SD) actual dose intensities were 459.8 (66.4) mg/day (range: 201.7, 500.0), 164.4 (6.8) mg/day (range: 128.7, 182.8) and 23.2 (3.5) mg/day (range: 0.2, 25.7) for crizotinib (n=172), pemetrexed (n=99) and docetaxel (n=72), respectively.

2.5.1.4. Dosing interruptions (crizotinib arm)

In the **crizotinib arm**, 46.5% (80/172) of patients had at least one dose interruption (that is, any missed dose for more than 1 day in a cycle). Maximum dosing interruptions were reported in the following percentage of patients: 11.0% for < 1 week; 12.8% for 1 to < 2 weeks; 12.8% for 2 to < 3 weeks; 5.2% to 3 to < 4 weeks and 4.7% for ≥ 4 weeks.

2.5.1.5. Dose reductions

In the **crizotinib arm**, 20.3% (35/172) of patients required at least one dose reduction defined as any reduction below 500 mg/day lasting more than 1 day. In the 35 patients with at least one dose reduction, the mean duration of the dose reduction was 176.4 days, ranging from 2 to 635 days.

In the **pemetrexed arm**, 3.0% (3/99) of patients required at least one dose reduction defined as any reduction below the protocol starting dose. In the 3 patients with at least one dose reduction, the mean duration of the dose reduction was 5.3 days, ranging from 1 to 14 days.

In the **docetaxel arm**, 27.8% (20/72) of patients had a least one dose reduction defined as any reduction below the starting dose. In the 20 patients with at least one dose reduction, the mean duration of dose reduction was 4.1 days, ranging from 1 to 19 days. Of the 20 patients requiring a dose reduction, 19 required dose reductions ≤ 2 weeks and 1 required a dose reduction of 2 to ≤ 4 weeks.

2.5.1.6. Chemotherapy infusion interruptions and cycle delays

In the **pemetrexed arm** (n=99), 1 (1.0%) patient had at least 1 infusion interruption with the reason being other than adverse events, and 15 (15.2%) patients had a least 1 cycle delay. The duration of the cycle delay and the number of patients (n) experiencing the delay were: > 1-2 weeks, n=5; > 2-3 weeks, n=8; > 3-4 weeks; n=2.

In the **docetaxel arm** (n=72), 8 (11.1%) patients had a least 1 infusion interruption (all due to adverse events) and 5 (5.1%) patients had at least 1 cycle delay. The duration of the cycle delay and the number of patients (n) experiencing the delay were: > 1-2 weeks; n=2; > 2-3 weeks, n=1; > 3-4 weeks, n=1; and > 4-5 weeks, n=1.

2.5.2. Adverse events

2.5.2.1. Summary of treatment-emergent adverse events (TEAEs)

Treatment-emergent adverse events (TEAE) and treatment-related adverse events (TRAEs) are summarised below in Table 10. The events were not adjusted for longer treatment duration in the crizotinib arm compared with the chemotherapy arm.

Table 10: Treatment-emergent adverse events (all causality and treatment-related); SA

	Crizotinib (n=172)		Chemotherapy (n=171)	
	All Causality	Treatment-related	All Causality	Treatment-related
Number of AEs	2085	1235	1358	815
Patients with AEs	172 (100.0)	164 (95.3)	168 (98.2)	151 (88.3)
Patients with SAEs	64 (37.2)	20 (11.6)	40 (23.4)	24 (14.0)
Patients with Grade 3 or 4 AEs	97 (56.4)	57 (33.1)	78 (45.6)	54 (31.6)
Patients with Grade 5 AEs	25 (14.5)	4 (2.3)	7 (4.1)	1 (0.6)
Patients discontinued due to AEs	30 (17.4)	11 (6.4)	23 (13.5)	17 (9.9)
Patients with dose reduced due to AEs	28 (16.3)	26 (15.1)	25 (14.6)	24 (14.0)
Patients with temporary discontinuation due to AEs	67 (39.0)	54 (31.4)	27 (15.8)	14 (8.2)

Note: Except for the number of AEs, patients were counted only once per treatment in each row. Serious adverse events (SAEs) according to investigator assessment. MedDRA (v15.0) coding dictionary applied.

The investigator obtained and recorded on the case report form (CRF) all observed or volunteered AEs. AEs were classified by type, incidence, severity (graded by the NCI CTCAE v4.0), timing, seriousness, and relationship to treatment. AEs included adverse drug reactions, illnesses with onset during the study and exacerbation of previous illnesses. Additionally, the investigator recorded any clinically significant changes in physical examination findings and abnormal objective test findings as AEs (for example, electrocardiogram (ECG), laboratory tests). Baseline tumour-related signs and symptoms were to be recorded as AEs during the study if they worsened in severity or increased in frequency. Adverse events (serious and non-serious) were to be recorded on the CRF from the time the subject had taken at least one dose of study treatment through to the last visit. For all AEs, the investigator attempted to obtain information allowing determination of both the outcome of the AE and whether it met the criteria for classification as a serious adverse event (SAE). If the AE or its sequelae persisted, follow-up was required until resolution or stabilisation acceptable to the investigator and sponsor occurred.

2.5.2.2. Commonly occurring all causality treatment-emergent adverse events

All causality treatment-emergent adverse events (TEAEs) were reported in 100.0% (n=172) of patients in the crizotinib arm and 98.2% (n=168) of patients in the chemotherapy arm. TEAEs by MedDRA preferred term reported with an incidence of ≥ 5% in the crizotinib arm by decreasing order of frequency compared with the chemotherapy arm were tabulated. The most commonly occurring TEAEs reported with a frequency of ≥ 20 % in the crizotinib arm (versus chemotherapy) were diarrhoea (59.9% versus 19.3%), nausea (54.7% versus 37.4%), visual impairment (47.1% versus 5.3%), vomiting (46.5% versus 17.5%), constipation (42.4% versus 22.8%), alanine aminotransferase (ALT) increased (36.0% versus 11.7%), decreased appetite (27.3% versus 26.3%), fatigue (26.7% versus 33.3%), aspartate aminotransferase (AST) increased (26.2% versus 9.4%), dysgeusia (25.6% versus 9.4%), peripheral oedema (25.6% versus 8.2%), and neutropenia (21.5% versus 10.5%).

The sponsor considered that meaningfully different TEAEs were those reported with an incidence of ≥ 10% of patients across all cycles in either treatment arm, and with a ≥ 5% absolute difference between treatment arms (see Table 11, below). The TEAES identified in upper case in Table 11 (for example, VISION DISORDERS) represent adverse event clustered terms (that is, clustered MedDRA preferred terms) and the lower case terms are MedDRA preferred terms. In this CER, clustered term adverse events are identified by upper case and MedDRA preferred term adverse events are identified by lower case. This identification convention follows that adopted in the CSR.

Table 11:Most common (≥ 10% patients) treatment-emergent all-causality AEs with a ≥ 5% absolute difference between treatments, unshaded terms occurred at a higher frequency on crizotinib than chemotherapy and shaded terms occurred at a higher frequency on chemotherapy than crizotinib; SA

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
Diarrhoea	103 (59.9)	33 (19.3)
VISION DISORDER	103 (59.9)	16 (9.4)
Nausea	94 (54.7)	64 (37.4)
Vomiting	80 (46.5)	30 (17.5)
Constipation	73 (42.4)	39 (22.8)
ELEVATED TRANSAMINASES	66 (38.4)	25 (14.6)
EDEMA	54 (31.4)	27 (15.8)
Dysgeusia	44 (25.6)	16 (9.4)
UPPER RESPIRATORY INFECTION	44 (25.6)	22 (12.9)
DIZZINESS	37 (21.5)	14 (8.2)
Fatigue	46 (26.7)	57 (33.3)
Alopecia	14 (8.1)	35 (20.5)

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
DYSPNEA	23 (13.4)	32 (18.7)
Rash	15 (8.7)	29 (17.0)
Arthralgia	11 (6.4)	20 (11.7)
Myalgia	3 (1.7)	18 (10.5)

MedDRA (v15.0) coding dictionary applied.

Crizotinib (n=172) versus pemetrexed (n=99): All causality treatment-emergent adverse events (MedDRA preferred terms) were reported in 100.0% (n=172) of patients in the crizotinib arm and 97.0% (n=96) of patients in the pemetrexed arm. Diarrhoea, VISION DISORDER, nausea, vomiting, constipation, ELEVATED TRANSAMINASES, EDEMA, NEUTROPENIA, dysgeusia, UPPER RESPIRATORY INFECTION, DIZZINESS, NEUROPATHY and ABDOMINAL PAIN were all reported with a meaningfully higher frequency in the crizotinib arm than in the pemetrexed arm. On the other hand, fatigue, COUGH, and rash were reported with a meaningfully higher frequency in the pemetrexed arm than in the crizotinib arm.

Crizotinib (n=172) versus docetaxel (n=72): All causality treatment-emergent adverse events (MedDRA preferred terms) were reported in 100.0% (n=172) of patients in the crizotinib arm and 100.0% (n=72) of patients in the docetaxel arm. VISION DISORDER, diarrhoea, nausea, vomiting, constipation, ELEVATED TRANSAMINASES, EDEMA, UPPER RESPIRATORY INFECTION, dysgeusia, DIZZINESS, and back pain were all reported with a meaningfully higher frequency in the crizotinib arm than in the docetaxel arm. On the other hand, alopecia, NEUTROPENIA, NEUROPATHY, STOMATITIS, myalgia, DYSPNEA, white blood cell count decreased, and arthralgia were reported with a meaningfully higher frequency in the docetaxel arm than in the crizotinib arm.

2.5.2.3. Commonly occurring treatment-related treatment-emergent adverse events

Treatment-related, treatment-emergent adverse events (TRAEs) were reported in 95.3% (n=164) of patients in the crizotinib arm and 88.3% (n=151) of patients in the chemotherapy arm. The most commonly occurring TRAEs by MedDRA preferred term reported with a frequency of ≥ 20 % in the crizotinib arm (versus chemotherapy) were diarrhoea (52.9% versus 16.4%), nausea (52.3% versus 34.5%), visual impairment (47.1% versus 1.8%), vomiting (43.6% versus 12.9%), ALT increased (34.9% versus 10.5%), constipation (31.4% versus 19.3%), AST increased (25.6% versus 7.6%), dysgeusia (25.0% versus 9.4%), peripheral oedema (21.5% versus 4.1%) and neutropenia (20.3% versus 9.4%). The most commonly reported TRAEs (≥ 10% of patients) by clustered or MedDRA preferred terms across all treatment cycles in the crizotinib and chemotherapy arms are summarised below in Table 12.

Table 12: Most common (≥ 10% patients) treatment-emergent treatment-related adverse events with a ≥ 5% absolute difference between treatment, unshaded terms occurred at a higher frequency on crizotinib than chemotherapy and shaded terms occurred at a higher frequency on chemotherapy than crizotinib; SA

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
VISION DISORDER	101 (58.7)	8 (4.7)
Diarrhoea	91 (52.9)	28 (16.4)

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
Nausea	90 (52.3)	59 (34.5)
Vomiting	75 (43.6)	22 (12.9)
ELEVATED TRANSAMINASES	62 (36.0)	23 (13.5)
Constipation	54 (31.4)	33 (19.3)
EDEMA	46 (26.7)	15 (8.8)
NEUTROPENIA	44 (25.6)	37 (21.6)
Dysgeusia	43 (25.0)	16 (9.4)
DIZZINESS	21 (12.2)	8 (4.7)
ABDOMINAL PAIN	19 (11.0)	9 (5.3)
Fatigue	30 (17.4)	50 (29.2)
Decreased appetite	31 (18.0)	32 (20.5)
Alopecia	4 (2.3)	34 (19.9)
Rash	14 (8.1)	28 (16.4)
ANEMIA	19 (11.0)	26 (15.2)
STOMATITIS	15 (8.7)	22 (12.9)
Asthenia	13 (7.6)	22 (12.9)
NEUROPATHY	14 (8.1)	19 (11.9)
Pyrexia	7 (4.1)	19 (11.9)

MedDRA (v15.0) coding dictionary applied.

2.5.2.4. All causality Grade 3/4/5 adverse events

All causality maximum Grade 3/4/5 TEAEs (MedDRA preferred terms) were reported in 58.7 % (101/172) of patients in the crizotinib arm (G3 = 35.5% [n=61]; G4 = 8.7% [n=15]; G5 = 14.5% [n=25]) and in 46.2% (79/171) of patients in the chemotherapy arm (G3 = 28.7% [n=49]; G4 = 13.5% [n=23]; G5 = 4.1% [n=7]).

All causality maximum Grade 3/4 TEAEs (MedDRA preferred terms) in ≥ 2% of patients in the crizotinib arm versus the chemotherapy arm were: any (44.2% versus 42.1%); ALT increased (12.8% versus 2.3%), neutropenia (9.9% versus 8.2%), AST increased (5.2% versus 0.6%), pulmonary embolism (4.7% versus 1.8%), dyspnoea (4.1% versus 2.9%); pneumonia (3.5% versus 1.8%); electrocardiogram QT prolonged (3.5% versus 0%); hypokalaemia (3.5% versus 0%); neutrophil count decreased (3.5% versus 4.1%); syncope (2.9% versus 0%); anaemia

(2.3% versus 4.7%); constipation (2.3% versus 0%); decreased appetite (2.3% versus 1.8%); fatigue (2.3% versus 4.1%) and hypophosphataemia (2.3% versus 1.8%).

The sponsor considered meaningfully different Grade 3/4 TEAEs (clustered or MedDRA preferred terms) to be events reported with an incidence of ≥ 2% of patients across all cycles in either treatment arm and with at least a 2 fold difference between treatment arms (see Table 13, below).

Table 13: Most common (≥ 2% of patients) treatment-emergent all causality Grade 3/4 adverse events with at least a 2 fold difference between treatments, unshaded terms occurred at a higher frequency on crizotinib than chemotherapy and shaded terms occurred at a higher frequency on chemotherapy than on crizotinib; SA

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
ELEVATED TRANSAMINASES	27 (15.7)	4 (2.3)
Electrocardiogram QT prolonged	6 (3.5)	0 *
Hypokalaemia	6 (3.5)	0
Syncope	5 (2.9)	0
Constipation	4 (2.3)	0
White blood count decreases	2 (1.2)	8 (4.7)
STOMATITIS	0	5 (2.9)

* = No scheduled on-treatment ECG assessments for the chemotherapy arm. MedDRA (v15.0) coding dictionary applied.

Crizotinib (n=172) versus pemetrexed (n=99): All causality maximum Grade 3/4 adverse events (MedDRA preferred terms) were reported in 44.2% (n=76) of patients in the crizotinib arm and 24.3% (n=24) of patients in the pemetrexed arm. Grade 3/4 TEAEs reported with a meaningfully higher frequency in the crizotinib arm versus the pemetrexed arm were ELEVATED TRANSAMINASES (15.7%, n=27 versus 4.0%, n=4), NEUTROPENIA (13.4%, n=23 versus 4.0%, n=4), DYSPNEA (4.1%, n=7 versus 1.0%, n=1), electrocardiogram QT prolonged (3.5%, n=6 versus 0), hypokalaemia (3.5%, n=6 versus 0), pneumonia (3.5%, n=6 versus 1.0%, n=1), syncope (2.9%, n=5 versus 0) and constipation (2.3%, n=4 versus 0). Pericardial effusion was the only Grade 3/4 adverse event reported with a meaningfully higher frequency in the pemetrexed arm than in the crizotinib arm (2.0%, n=2 versus 0.6%, n=1).

Crizotinib (n=172) versus docetaxel (n=72): All causality maximum Grade 3/4 adverse events (MedDRA preferred terms) were reported in 44.2% (n=76) of patients in the crizotinib arm and 66.6% (n=48) of patients in the docetaxel arm. Grade 3/4 TEAEs reported with a meaningfully higher frequency in the crizotinib arm versus the docetaxel arm were ELEVATED TRANSAMINASES (15.7%, n=27 versus 0), PULMONARY EMBOLISM (5.2%, n=9 versus 1.4%, n=1), electrocardiogram QT prolonged (3.5%, n=6 versus 0), hypokalaemia (3.5%, n=6 versus 0), syncope (2.9%, n=5 versus 0), constipation (2.3%, n=4 versus 0). Grade 3/4 TEAEs reported with a meaningfully higher frequency in the docetaxel arm versus the crizotinib arm were NEUTROPENIA (40.3%, n=29 versus 13.4%, n=23), white blood cell count decreased (8.3%, n=6 versus 1.2%, n=2), fatigue (6.9%, n=5 versus 2.3%, n=4), leukopenia (5.6%, n=4 versus 1.7%,

n=3), STOMATITIS (5.6%, n=4 versus 0), pleural effusion (4.2%, n=3 versus 1.2%, n=2), and NEUROPATHY (2.8%, n=2 versus 0.6%, n=1).

2.5.2.5. Treatment-related Grade 3/4 adverse events

Treatment-related maximum Grade 3/4 adverse events (MedDRA preferred terms) were reported in 31.4% (n=54) of patients in the crizotinib arm and 31.6% (n=53) of patients in the chemotherapy arm. The most common (≥ 2% of patients) Grade 3/4 TRAEs across all cycles in the crizotinib and chemotherapy arms are summarised below in Table 14.

Table 14: Most common (≥ 2% of patients) treatment-emergent treatment-related Grade 3/4 adverse events, unshaded terms occurred at a higher frequency on crizotinib than chemotherapy and shaded terms occurred at a higher frequency on chemotherapy than crizotinib; SA

Events	Crizotinib (n=172); n (%)	Chemotherapy (n=171); n (%)
ELEVATED TRANSAMINASES	21 (12.2)	4 (2.3)
Electrocardiogram QT prolonged	4 (2.3)	0 *
NEUTROPENIA	21 (12.2)	31 (18.1%)
White blood count decreases	0	8 (4.7%)
Fatigue	2 (1.2)	6 (3.5%)
ANEMIA	0	6 (3.5%)
STOMATITIS	0	5 (2.9%)
Leukopenia	3 (3.7%)	4 (2.3%)

* = No scheduled on-treatment ECG assessments for the chemotherapy arm. MedDRA (v15.0) coding dictionary applied.

2.5.2.6. Adverse events – prespecified tiers (1, 2 and 3)

(a) Tier-1 adverse events

Tier-1 adverse events were prespecified MedDRA preferred term or clustered term events of clinical importance listed in the sponsor's product Safety Review Plan. Tier-1 TEAEs (all causality) that occurred statistically significantly more frequently in the crizotinib arm than in the chemotherapy arm were constipation, diarrhoea, ELEVATED TRANSAMINASES and HEPATOTOXICITY, NAUSEA and VOMITING, pneumonitis and QTc prolongation (see Table 15, below). No Tier-1 TEAEs (all causality) of special interest occurred statistically significantly more frequently in the chemotherapy arm than in the crizotinib arm. Tier-1 TEAEs (all causality) for which no statistically significant differences between the two treatment arms were reported were fatigue (p=0.248) and LEUKOPENIA (p=0.535).

Table 15: Tier-1 statistically significant all causality, all grades, treatment-emergent adverse events of special interest by MedDRA term or Cluster; SA.

Events	CZT n=172	CHM n=171	Risk Δ	95% CI	p value

Events	CZT n=172	CHM n=171	Risk Δ	95% CI	p value
Constipation	73 (42.4%)	39 (22.8%)	19.635	9.149, 29.433	< 0.001
Diarrhoea	103 (59.9%)	33 (19.3%)	40.585	30.485, 49.787	< 0.001
ELEVATED TRANSAMINASES and HEPATOTOXICITY	69 (40.1%)	26 (14.2%)	24.912	15.111, 34.015	< 0.001
NAUSEA and VOMITING	111 (64.5%)	70 (40.9%)	23.599	12.161, 33.800	< 0.001
PNEUMONITIS	7 (4.1%)	1 (0.6%)	3.485	0.216, 7.690	0.036
QTc prolongation	8 (4.7%)	0	4.651	1.848, 8.959	0.005

Note: P-values and confidence intervals (CIs) are not adjusted for multiplicity and should be used for screening purpose only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference (Risk Δ) is computed as Crizotinib (CZT) versus Chemotherapy (CHM).

Tier-1 Grade 3/4/5 TEAEs (all causality) of special interest that occurred statistically significantly more frequently in the crizotinib arm than in the chemotherapy arm were constipation, ELEVATED TRANSAMINASES and HEPATOTOXICITY, PNEUMONITIS, and QTc prolongation (see Table 16, below). No Tier-1 Grade 3/4/5 TEAES (all causality) of special interest occurred statistically significantly more frequently in the chemotherapy arm than in the crizotinib arm.

Table 16: Tier-1 statistically significant all causality, Grades 3/4/5, treatment-emergent adverse events of special interest by MedDRA term or Cluster; SA.

Events	CZT n=172	CHM n=171	Risk Δ	95% CI	p value
Constipation	4 (2.3%)	0	2.326	0.028, 5.913	0.048
ELEVATED TRANSAMINASES and HEPATOTOXICITY	28 (16.3%)	4 (2.3%)	13.940	7.719, 20.557	< 0.001
PNEUMONITIS	4 (2.3%)	0	2.326	0.028, 5.913	0.048
QT_C prolongation	6 (3.5%)	0	3.488	0.947, 7.484	0.014

Note: P-values and confidence intervals (CIs) are not adjusted for multiplicity and should be used for screening purpose only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference (Risk Δ) is computed as Crizotinib (CZT) versus Chemotherapy (CHM).

Tier-1 treatment-related AEs of special interest that occurred statistically significantly more frequently in the crizotinib arm than in the chemotherapy arm were constipation, diarrhoea, ELEVATED TRANSAMINASES and HEPATOTOXICITY, NAUSEA and VOMITING and QTc prolongation. Fatigue was the only Tier-1 TREAE of special interest that occurred statistically significantly more frequently in the chemotherapy arm than in the crizotinib arm.

Tier-1 Grade 3/4/5 treatment-related AEs of special interest that occurred statistically significantly more frequently in the crizotinib arm than in the chemotherapy arm were ELEVATED TRANSAMINASES and HEPATOTOXICITY and QTc prolongation. LEUKOPENIA was the only Tier 1 TRAE of special interest that occurred statistically significantly more frequently in the chemotherapy arm than in the crizotinib arm.

(b) Tier-2 adverse events

Tier-2 events were events that were not Tier-1 but were "common". A Tier-2 event was defined as an adverse event occurring in least 10% of patients for all grades in any treatment group. Tier-2 TEAEs (all causality) of special interest occurring in ≥10% of patients in any treatment group by preferred term and reported statistically significantly more commonly in patients in the crizotinib arm versus the chemotherapy arm were visual impairment (47.1% versus 5.3%), peripheral oedema (25.6% versus 8.2%), dysgeusia (25.6% versus 9.4%), dizziness (16.3% versus 7.0%) and nasopharyngitis (14.0% versus 3.5%). Tier-2 TEAEs (all causality) of special interest occurring in ≥10% of patients in any treatment group by preferred term and reported statistically significantly more commonly in patients in the chemotherapy arm versus the crizotinib arm were alopecia (20.5% versus 8.1%), rash (17.0% versus 8.7%) and myalgia (10.5% versus 1.7%). Tier-2 TEAEs (all causality) of special interest occurring in ≥10% of patients in any treatment group by MedDRA system organ class and preferred term were provided in a table.

Tier-2 treatment-related AEs of special interest occurring in ≥10% of patients in any treatment group by preferred term and reported statistically significantly more commonly in patients in the crizotinib arm versus the chemotherapy arm were visual impairment (47.1% versus 1.8%), dysgeusia (25.0% versus 9.4%) and peripheral oedema (21.5% versus 4.1%). Tier-2 TRAEs of special interest occurring in ≥10% of patients in any treatment group by preferred term and reported statistically significantly more commonly in patients in the chemotherapy arm versus the crizotinib arm were alopecia (19.9% versus 2.3%), rash (16.4% versus 8.1%) and pyrexia (11.1% versus 4.1%). Tier-2 TRAEs of special interest occurring in ≥10% of patients in any treatment group by MedDRA system organ class and preferred term were provided in a table.

For Grade 3/4/5 TEAEs (combined), a Tier-2 event was defined as an event occurring in at least 5% of patients in any treatment group. The only statistically significant Tier-2 Grade 3/4/5 TEAE (all causality) of special interest occurring in ≥ 5% of patients in any treatment group was disease progression, which occurred in 7.6% (13/172) of patients in the crizotinib arm and 1.8% (3/171) of patients in the chemotherapy arm.

(c) Tier-3 events

Tier-3 events were events that were not Tier-1 or Tier-2 events.

2.5.3. Selected adverse events of special interest (time to onset and duration)

The sponsor reviewed selected **treatment-related, TEAEs** of special interest (MedDRA preferred term and clustered terms) for prevalence, time to first onset and duration. The time to first onset (days) of treatment-related, TEAEs of special interest in the randomised treatment arms, the duration and the prevalence of the events by cycle were tabulated. Relevant outcomes from the analyses are summarised later in this CER.

2.5.4. Deaths and serious adverse events (SAEs)

2.5.4.1. Deaths

Deaths occurring while on study treatment or within 28 days of the last dose of study drug were reported in a total of 23 (13.4%) patients on crizotinib and 6 (9.2%) patients on chemotherapy (without cross-over). A total of 25 patients on crizotinib and 38 patients on chemotherapy (9 who did not cross-over to receive crizotinib in Study A8081005 plus 29 who did cross over to receive crizotinib in Study A8081005) died more than 28 days after last dose of study drug. The most common cause of death was disease under study (40 [23.3%] patients on crizotinib and 39 [22.8%] patients on chemotherapy, including 25 patients who crossed over to receive crizotinib in Study A8081005). The summary of deaths is provided below in Table 17.

Table 17: Summary of deaths; SA

Summary of Deaths	Crizotinib N=172 n (%)	Chemotherapy (Without Crossover) N=65 n (%)	Chemotherapy (Crossover to 1005) N=106 n (%)	Total N=343 n (%)
Deaths from all causes	48 (27.9)	15 (23.1)	29 (27.4)	92 (26.8)
Within 28 days of last dose of study drug	23 (13.4)	6 (9.2)	0	29 (8.5)
More than 28 days after last dose of study drug	25 (14.5)	9 (13.9)	29 (27.4)	63 (18.4)
Death within 30 days of first dose of study drug	3 (1.7)	3 (4.6)	0	6 (1.8)
Death within 60 days of first dose of study drug	10 (5.8)	7 (10.8)	2 (1.9)	19 (5.5)
Cause of death[a]				
Disease under study	40 (23.3)	14 (21.5)	25 (23.6)	79 (23.0)
Study treatment toxicity[b]	1 (0.6)	0	2 (1.9)	3 (0.9)
Unknown[c]	1 (0.6)	0	0	1 (0.3)
Other	6 (3.5)	1 (1.5)	2 (1.9)	9 (2.6)

Summary of Death data was based on 'Notice of Death' eCRF page. Abbreviations: N/n=number of patients; eCRF=electronic case report form. [a]More than 1 cause of death may be reported. [b]Details of study treatment toxicity are provided in separate table, [c] One patient with death of "unknown" cause was subsequently modified to "disease under study".

There were 32 Grade 5 AEs (that is, deaths) in the treatment phase of the study, 25 (14.5%) in the crizotinib arm and 7 (4.1%) in the chemotherapy arm. Included in these 32 deaths were 2 patients on crizotinib and 1 patient on chemotherapy who had non-treatment related Grade 5 AEs reported > 28 days after the last day of the study drug. Death related to disease progression was the most commonly reported Grade 5 AE during the treatment phase (14/25 [56.0%] deaths in the crizotinib arm and 3/7 [42.9%] deaths in the chemotherapy arm). Death related to individual reports of pulmonary disease occurred notably more commonly in the crizotinib arm than in the chemotherapy arm (that is, ILD, pneumonitis, acute respiratory distress syndrome, pneumonia).

There were 6 deaths considered by the investigator and/or the sponsor to be related to or at least possibly related to study treatment (5 [2.9%] in the crizotinib arm and 1 [0.6%] in the chemotherapy arm [pemetrexed]). The 5 treatment-related deaths in the crizotinib treatment arm were ILD (1 death), pneumonitis (1 death), arrhythmia which appears to have been due to bradycardia (1 death), sudden death probable heart failure (1 death) and unknown cause (1 death). The (1) treatment-related death in the chemotherapy arm (pemetrexed) was due to sepsis. In addition to the 5 treatment-related deaths in the crizotinib treatment reported at the data cut off date, there was 1 reported death due to liver failure in a patient meeting Hy's law criteria for potential drug induced liver injury after the data cut off date.

2.5.4.2. Serious adverse events (including Grade 5 events)

SAEs (including Grade 5 events) were reported more commonly in the crizotinib arm than in the chemotherapy arm (37.2% [64/172] versus 23.4% [40/171]). Tabulations of SAEs (all causality) reported in ≥ 1% of patients in the crizotinib arm versus chemotherapy were provided.

SAEs reported with an incidence of ≥ 1% in the crizotinib arm and more commonly than in the chemotherapy arm were, in decreasing order of frequency, disease progression (7.6 % versus 1.8%), pneumonia (4.1% versus 1.8%), pulmonary embolism (2.9% versus 1.8%), dyspnoea (2.3% versus 1.8%), interstitial lung disease (1.7% versus 0%), ALT increased (1.2% versus 0%), AST increased (1.2% versus 0%), convulsion (1.2% versus 0.6%), hypoglycaemia (1.2% versus 0.6%), lung abscess (1.2% versus 0%), lung infection (1.2% versus 0.6%) and vomiting (1.2% versus 0%).

SAEs occurring with an incidence of ≥ 1% in the chemotherapy arm and more commonly than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (7.0% versus 0.6%), anaemia (1.2% versus 0.6%) and deep vein thrombosis (1.2% versus 0.6%).

Grade 3 and 4 SAEs occurred in 17.4% (n=30) and 2.3% (n=4) of patients, respectively, in the crizotinib arm, compared with 12.3% (n=21) and 4.7% (n=8) of patients, respectively, in the chemotherapy arm. Of the SAEs (all grades), 53.1% (34/64) were Grade 3 or 4 events in the crizotinib arm compared with 72.5% (29/40) in the chemotherapy arm.

Treatment-related SAEs were reported in 11.6% (20/172) of patients in the crizotinib arm and 14.0% (24/171) of patients in the chemotherapy arm. The only treatment-related SAE reported in ≥ 2% of patients in either treatment arm was febrile neutropenia (0.6% [1/172] crizotinib versus 7.0% [12/171], chemotherapy).

2.5.5. Discontinuations, dose interruptions, dose discontinuations

2.5.5.1. Permanent discontinuations due to adverse events

TEAEs (all causality) resulting in permanent treatment discontinuation were reported in 17.4% (30/172) of patients in the crizotinib arm and 13.5% (23/171) of patients in the chemotherapy arm.

TEAEs (MedDRA preferred term) resulting in ≥ 1% of patients permanently discontinuing from treatment in the crizotinib arm and occurring more frequently than in the chemotherapy arm were, in decreasing order of frequency, disease progression (2.9% versus 0%), interstitial lung disease (1.7% versus 0%), pulmonary embolism (1.2% versus 0%), ALT increased (1.2% versus 0%), AST increased (1.2% versus 0%), and dyspnoea (1.2% versus 0%).

TEAEs (MedDRA preferred term) resulting in ≥ 1% of patients permanently discontinuing from treatment in the chemotherapy arm and occurring more frequently than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (1.8% versus 0%), asthenia (1.2% versus 0%), pericardial effusion (1.2% versus 0%), and pleural effusion (1.2% versus 0%).

TREAs were reported in 6.4% (11/171) of patients in the crizotinib arm and 9.9% (17/171) of patients in the chemotherapy arm.

2.5.5.2. Temporary discontinuations due to adverse events

Temporary treatment discontinuations due to TEAEs (all causality) were reported in 39.0% (67/172) of patients in the crizotinib arm and 15.8% (27/171) of patients in the chemotherapy arm.

TEAEs (MedDRA preferred term) resulting in temporary treatment discontinuations in ≥ 1% of patients in the crizotinib arm and reported more commonly than in the chemotherapy arm were, in decreasing order of frequency, neutropenia (8.1% versus 0%), ALT increased (6.4% versus 0%), nausea (4.7% versus 0%), AST increased (3.5% versus 0.6%), vomiting (3.5%

versus 0%), pneumonia (2.9% versus 0.6%), neutrophil count decreased (2.3% versus 0%), upper abdominal pain (2.3% versus 0%), leukopenia (1.7% versus 0%), peripheral oedema (1.7% versus 0%), constipation (1.2% versus 0%), pyrexia (1.2% versus 0%), gastroenteritis (1.2% versus 0%), lung infection (1.2% versus 0%), sinus bradycardia (1.2% versus 0%), ECG QT prolonged (1.2% versus 0%), transaminases increased (1.2% versus 0%), decreased appetite (1.2% versus 0%) and brain oedema (1.2% versus 0%).

The only TEAE (MedDRA preferred term) resulting in temporary treatment discontinuation in ≥ 1% of patients in the chemotherapy arm and reported more commonly than in the crizotinib arm was dizziness (1.2% versus 0.6%).

2.5.5.3. Dose reductions due to adverse events

Dose reductions due to TEAEs were reported in 16.3% (28/172) of patients in the crizotinib arm and 14.6% (25/171) of patients in the chemotherapy arm.

TEAEs (MedDRA preferred term) resulting in dose reductions in ≥ 1% of patients in the crizotinib arm and more commonly than in the chemotherapy arm were, in decreasing order of frequency, ALT increased (7.6% versus 0%), ECG QT prolonged (2.9% versus 0%), AST increased (2.3% versus 0%), neutropenia (2.3% versus 1.2%) and neutrophil count decreased (1.2% versus 0%).

TEAEs (MedDRA preferred term) resulting in dose reductions in ≥ 1% of patients in the chemotherapy arm and reported more commonly than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (7.0% versus 0%), fatigue (1.2% versus 0%) and mucosal inflammation (1.2% versus 0%).

2.5.6. Clinical laboratory

2.5.6.1. Introduction

Haematology and blood chemistry results were graded according to NCI CTCAE v4.0. Summaries of relevant shifts of baseline grade by maximum post baseline CTCAE grade were presented. Patients who developed toxicities of Grade ≥ 3 were also listed. An evaluation of drug-induced serious hepatotoxicity (e-DISH) was performed and an e-DISH scatter plot of maximum ALT versus maximum total bilirubin on study was presented. Clinical laboratory values deemed to be clinically significant by investigators were reported as adverse events.

2.5.6.2. Haematology

(a) Crizotinib versus chemotherapy

In the crizotinib arm (versus chemotherapy), the most common shifts from Grade ≤ 2 to Grade 3 events occurring in ≥ 2% of patients were absolute neutrophils (10.6% versus 4.2%), lymphopenia (8.2% versus 23.0%) and white blood cells (5.3% versus 5.5%), and the most common shifts from Grade ≤ 2 to Grade 4 occurring in ≥ 1% of patients were absolute neutrophils (2.4% versus 7.9%). In the chemotherapy arm (versus crizotinib), the most common shifts from Grade ≤ 2 to Grade 3 events occurring in ≥ 2% of patients were lymphopenia (23.0% versus 8.2%), white blood cells (5.5% versus 5.3%) and absolute neutrophils (4.2% versus 10.6%), and the most common shifts from Grade ≤ 2 to Grade 4 events occurring in ≥ 1% of patients were absolute neutrophils (7.9% versus 2.4%), platelets (1.2% versus 0%) and white blood cells (1.2% versus 0%).

(b) Crizotinib, pemetrexed and docetaxel

The most common shifts from Grade ≤ 2 at baseline to Grade 3 events were lymphopenia (27.4% versus 8.2% [crizotinib]) in the pemetrexed group, and lymphopenia (17.1% versus 8.2% [crizotinib]) in the docetaxel group. The most common shifts from Grade ≤ 2 at baseline to Grade 4 events were platelets (2.1% versus 0% [crizotinib]) in the pemetrexed group, and

absolute neutrophils (18.6% versus 2.4% [crizotinib]) and white blood cells (2.9% versus 0% [crizotinib]) in the docetaxel group.

2.5.6.3. Chemistry

(a) Crizotinib versus chemotherapy

The most common shifts from baseline Grade ≤ 2 to post baseline Grade 3 events occurring in ≥ 2% of patients in the crizotinib arm (versus chemotherapy) were ALT (12.9% versus 4.2%), AST (8.8% versus 0%), hypophosphataemia (4.7% versus 7.5%), hypokalaemia (4.1% versus 0%) and hyperglycaemia (3.5% versus 3.0%). Few Grade 4 chemistry laboratory results were observed in the crizotinib arm and the only shift from baseline CTCAE Grade ≤ 2 CTCAE to post baseline Grade 4 events was ALT (4.1%, crizotinib versus 0%, chemotherapy). There were no shifts in creatinine from baseline Grade ≤ 2 to post baseline Grade ≥ 3 events in either of the two treatment arms.

The most common shifts from baseline Grade ≤ 2 to post-baseline Grade 3 events occurring in ≥ 2% of patients in the chemotherapy arm (versus crizotinib) were hypophosphataemia (7.5% versus 4.7%), ALT (4.2% versus 12.9%), hyperglycaemia (3.0% versus 3.5%) and alkaline phosphatase (2.4% versus 1.8%). Few Grade 4 chemistry laboratory results were observed in the chemotherapy arm, and no individual chemistry laboratory shift from baseline Grade ≤ 2 to post baseline Grade 4 events occurred in ≥ 1% of patients in the chemotherapy arm.

(b) Crizotinib, pemetrexed and docetaxel

The most common shifts from Grade ≤ 2 at baseline to Grade 3 events post-baseline occurring in ≥ 2% of patients in the pemetrexed group (versus crizotinib) were hypophosphataemia (7.5% versus 4.7%), ALT (6.3% versus 12.9%), alkaline phosphatase (3.2% versus 1.8%), hyperglycaemia (2.1% versus 3.5%), hypermagnesaemia (2.1% versus 1.2%). Few Grade 4 chemistry laboratory results were observed in the pemetrexed group. Shifts from Grade ≤ 2 at baseline to Grade 4 events post baseline occurring in ≥ 1% of patients in the pemetrexed group (versus crizotinib) were total bilirubin (1.1% versus 0%), hypercalcaemia (1.1% versus 0.6%) and hyperglycaemia (1.1% versus 0%).

The most common shifts from Grade ≤ 2 at baseline to Grade 3 event post-baseline occurring in ≥ 2% of patients in the docetaxel group (versus crizotinib) were hypophosphataemia (7.4% versus 4.7%), hyperglycaemia (4.3% versus 3.5%) and hyponatraemia (4.3% versus 0%). Few Grade 4 chemistry laboratory results were observed in the docetaxel group. The only shift from Grade ≤ 2 at baseline to Grade 4 post-baseline occurring in ≥ 1% of patients in the docetaxel group (versus crizotinib) was hypokalaemia (1.4% versus 0%).

2.5.7. Other safety assessments

2.5.7.1. Vital signs

(a) Pulse rate

Minimum and maximum change from baseline in vital signs (blood pressure and pulse rate) and body weight were summarised in the CSR. Maximum on study pulse rates of > 120 beats per minute (bpm) were reported in 0.6% (1/170) of patients in the crizotinib arm and 8.4% (14/171) of patients in the chemotherapy arm and the corresponding TEAE of tachycardia was reported in 0.6% (1/172) and 1.2% (2/171) of patients, respectively. Minimum on study pulse rates of < 50 bpm were reported in 11.2% (19/170) of patients in the crizotinib arm and 0.6% (1/167) of patients in the chemotherapy arm. In the crizotinib and chemotherapy arms, maximum decreases from baseline of ≥ 30 bpm were reported in 40.8% (69/169) and 4.8% (8/171) of patients, respectively. The TEAE of bradycardia was reported in 4 (2.3%) patients in the crizotinib arm and no patients in the chemotherapy arm. The clustered term of BRADYCARDIA was reported in 8 (4.7%) patients in the crizotinib arm and no patients in the chemotherapy arm.

(b) Blood pressure

In the crizotinib arm, 3.0% (5/168) of patients had an increase in systolic blood pressure of ≥ 40 mmHg and 7.7% (13/168) of patients had an increase in diastolic blood pressure of ≥ 20 mmHg, with the corresponding results in the chemotherapy arm being 1.8% (3/166) and 12.7% (21/166), respectively. The TEAE of hypertension was reported in 3.5% (6/172) of patients in the crizotinib arm and 0.6% (1/171) of patients in the chemotherapy arm.

In the crizotinib arm, 8.9% (15/172) of patients had a maximum decrease in systolic blood pressure from baseline of ≥ 40 mmHg and 36.9% (62/168) had a maximum decrease in diastolic blood pressure from baseline of ≥ 20 mmHg, with the corresponding results in the chemotherapy arm being 3.0% (5/171) and 15.7% (26/166) respectively. No patients in either treatment arm had a maximum reduction in systolic blood pressure from baseline of ≥ 60 mmHg, while only 1 patient in the crizotinib arm and 2 patients in the chemotherapy arm had maximum reductions in diastolic blood pressures from baseline of ≥ 40 mmHg. The TEAE of hypotension was reported in 2.3% (4/172) of patients in the crizotinib arm and 1.8% (3/171) of patients in the chemotherapy arm.

(c) Body weight

Maximum increases in body weight from baseline of ≥ 10% were reported in 14.4% (23/160) of patients in the crizotinib arm and 8.5% (14/165) in the chemotherapy arm and the corresponding results for maximum decrease in body weight from baseline of ≥ 10% were reported in 8.1% (13/169) and 3.0% (5/165) of patients in the crizotinib and chemotherapy arms, respectively.

2.5.7.2. Electrocardiogram

ECGs were obtained from all patients in the crizotinib arm during the study and a group of approximately 21 patients participated in substudy involving additional data. The ECG substudy is ongoing and the sponsor indicates that it will be reported separately. No data were presented on patients in the chemotherapy arm. In the crizotinib arm, maximum post dose QTcF of < 450 ms was reported in 89.8% (132/147) of patients, 450 to < 480 ms in 6.1% (9/147) of patients, 480 to < 500 ms in 0.7% (1.147) of patients, and ≥ 500 ms in 3.4% (5/147) of patients. In the crizotinib arm, maximum QTcF changes from baseline of < 30 ms were reported in 81.9% (118/144) of patients, ≥ 30 to < 60 ms in 11.8% (17/144) of patients and ≥ 60 ms in 6.3% (9/144) of patients.

The central tendency analysis for patients in the crizotinib arm included summary statistics with 90% CIs of changes from baseline for both QTcB and QTcF. The mean changes from baseline for QTcB and QTcF ranged from -7.4 to 1.9 ms and 3.4 to 8.3 msec, respectively, at time points on Cycle 1 Day 1 and Cycle 2 Day 1. The highest upper bounds of the 2-sided 90% CIs for QTcB and QTcF were 4.4 ms and 13.1 msec, respectively. Overall, the ECG results suggest that crizotinib has the potential to prolong the QTc interval.

2.5.7.3. MUGA/ECHO

Of 31 patients evaluated for changes in the left ventricular ejection fraction (LVEF) (17 crizotinib and 14 chemotherapy), no crizotinib and 1 (7.1%) chemotherapy patient had a maximum relative decrease from baseline in LVEF of > 20% (but not below the lower limit of the reference range).

2.5.7.4. ECOG performance status (PS)

All patients had ECOG PS of 0, 1, or 2 at baseline. A total of 11 (6.4%) patients on crizotinib and 14 (8.0%) patients on chemotherapy had a shift from ECOG PS of 0, 1, or 2 at baseline to a worst ECOG PS of 3, 4, or 5 on study.

2.5.7.5. Ophthalmic evaluations

Most patients had biomicroscopy examinations at baseline and most of these results were normal. There were 77 patients in the crizotinib arm and 8 patients in the chemotherapy arm with follow-up on-treatment biomicroscopy examinations. Only a few patients had new findings or worsening findings at follow-up, while 72 to 77 patients in the crizotinib arm and 7 to 8 patients in the chemotherapy arm had no changes in biomicroscopy from baseline depending on the assessed parameter.

Most patients had fundoscopy examinations at baseline and most of these results were normal. There were 77 patients in the crizotinib arm and 8 patients in the chemotherapy arm with follow-up on-treatment fundoscopy examinations. Only a few patients had new findings or worsening findings at follow-up, while 70 to 77 patients in the crizotinib arm and 4 to 8 patients in the chemotherapy had no changes in fundoscopy from baseline depending on the assessed parameter.

Most patients had visual acuity and distance examinations at baseline. A total of 68 patients in the crizotinib arm and 7 patients in the chemotherapy arm had follow-up visual acuity and distance examinations. There was a 2 line decrease in best corrected visual acuity (BCVA) in both eyes in 8.8% (6/68) patients in the crizotinib arm while no patients had a decrease of ≥ 3 lines. The decrease in BCVA in the crizotinib arm was attributable to worsening of cataracts in 4 patients and to retinal metastases in 2 patients. In the chemotherapy arm, there was a 2 line decrease in the left eye in 16.7% (1/6) of patients, and a ≥ 3 line decrease in the right eye in 14.3% (1/7) of patients.

2.5.8. Safety in special groups

2.5.8.1. Age

The TEAE profiles (all causality, all cycles) for patients aged < 65 years and patients aged ≥ 65 years are summarised below in Table 18. In patients aged < 65, the profiles for Grade 1/2 and Grade 3/4 TEAEs were similar for the crizotinib and chemotherapy groups but Grade 5 TEAEs occurred more commonly in the crizotinib group than in the chemotherapy group. In patients aged ≥ 65 years, Grade 3/4 and Grade 5 events occurred notably more commonly in the crizotinib group compared with the chemotherapy group. The main difference between patients in the two crizotinib groups was the higher incidence of Grade 3/4 events and particularly Grade 5 events in patients aged ≥ 65 years compared with patients aged < 65 years. However, the observed differences between patients aged < 65 years and ≥ 65 years should be interpreted cautiously due to the marked imbalance in patient numbers between the two age groups.

Table 18: Treatment emergent adverse events (all causality, all cycles) in patients aged < 65 years and ≥ 65 years, n (%); SA

	Patients aged < 65 years		Patients aged ≥ 65 years	
	Crizotinib (n=144)	Chemo (n=148)	Crizotinib (n=27)	Chemo (n=23)
Patients with TEAEs	145 (100.0)	146 (98.6)	27 (100.0)	22 (95.7)
Patients with Grade 1/2 TEAEs	66 (45.5)	75 (50.7)	5 (18.5)	14 (60.9)
Patients with Grade 3/4 TEAEs	62 (42.8)	65 (43.9)	14 (51.8)	7 (30.4)
Patients with Grade	17 (11.7)	6 (4.1)	8 (29.6)	1 (4.3)

	Patients aged < 65 years		Patients aged ≥ 65 years	
5				

2.5.8.2. Sex

The TEAE profiles (all causality, all cycles) by sex are summarised below in Table 19. In both males and females, the main difference between the two treatment groups was the notably higher incidence of Grade 5 events in the crizotinib group compared with the chemotherapy group. In the crizotinib group, the main difference between the sexes was the notably higher incidence of Grade 3/4 events in females compared with males.

Table 19: Treatment emergent adverse events (all causality, all cycles) by sex, n (%); SA

	Male		Female	
	Crizotinib (n=75)	Chemo (n=77)	Crizotinib (n=97)	Chemo (n=94)
Patients with TEAEs	75 (100.0)	75 (97.4)	97 (100)	93 (98.9)
Patients with Grade 1/2 TEAEs	35 (46.6)	44 (57.2)	36 (37.1)	45 (47.8)
Patients with Grade 3/4 TEAEs	28 (37.3)	26 (33.8)	48 (49.5)	46 (48.9)
Patients with Grade 5	12 (16.0)	5 (6.5)	13 (13.4)	2 (2.1)

2.5.8.3. Race

The TEAE profiles (all causality, all cycles) by race (White and Asian) are summarised below in Table 20. In White patients, the main difference between the two treatment groups was the lower incidence of Grade 1/2 events and the higher incidence of Grade 5 events in the crizotinib group compared with the chemotherapy group. In Asian patients, the overall safety profile was notably worse in the crizotinib group compared with the chemotherapy group. In the crizotinib group, the main difference between the two racial groups was the notably higher incidence of Grade 3/4 events in Asian patients compared with White patients.

Table 20: Treatment emergent adverse events (all causality, all cycles) by race n (%); SA

	White		Asian	
	Crizotinib (n=89)	Chemo (n=89)	Crizotinib (n=79)	Chemo (n=77)
Patients with TEAEs	89 (100.0)	87 (97.8)	79 (100.0)	76 (98.7)
Patients with Grade 1/2 TEAEs	39 (43.8)	46 (51.7)	31 (39.2)	41 (53.3)
Patients with Grade 3/4 TEAEs	36 (40.5)	39 (43.8)	37 (46.8)	30 (39.0)

	White		Asian	
Patients with Grade 5	14 (15.7)	2 (2.2)	11 (13.9)	5 (6.5)

2.6. Evaluator's comments on benefits of treatment with crizotinib based on Study A8081007

Overall, it is considered that the results of Study A8081007 show that the benefits of crizotinib are greater than those of standard of care chemotherapy (pemetrexed or docetaxel) for the treatment of previously treated ALK-positive NSCLC. However, the interim analysis of Overall Survival (OS) showed no statistically significant difference between crizotinib and chemotherapy. It should be noted that in the preliminary Company Study Report (CSR) the analysis of Progression Free Survival (PFS) was the final analysis of this parameter as the prespecified number of events had been reached at the date of the data cut off, while the analysis of the OS was an interim analysis of this parameter as the specified number of events had not been reached at the date of data cut off.

The primary objective of the study was to show that crizotinib was superior to standard-of-care chemotherapy (pemetrexed or docetaxel) in prolonging the duration of PFS (objective tumour progression or death, whichever occurred first). The primary analysis of the PFS was based on Independent Radiology Review Response Evaluation Criteria in Solid Tumours (IRR RECIST) criteria in patients randomised to open-label treatment stratified by baseline ECOG PS [4] (0-1 versus 2), brain metastases (yes versus no) and previous treatment with an epidermal growth factor tyrosine kinase inhibitor (EGFR TKI) (yes versus no). The study met the primary objective and demonstrated that the median time to PFS was 4.7 months longer in the crizotinib arm compared with the chemotherapy arm and that this increase was statistically significant. At the time of the data cut off, 57.8% (100/173) of patients in the crizotinib arm had experienced a PFS event compared with 73.0% (127/119) of patients in the chemotherapy arm, with a median PFS of 7.7 months (95% CI: 6.0, 8.8 months) and 3.0 months (2.6, 4.3 months), respectively. The hazard ratio (HR) for PFS was 0.487 (95% CI: 0.371, 0.638), p<0.0001 (1-sided log rank test), indicating a significantly lower risk of experiencing a PFS event in the crizotinib arm compared with the chemotherapy arm.

The secondary efficacy endpoints of Objective response rate (ORR), Time to tumour response (TTR), Duration of response (DR) and Disease control rate (DCR) but not OS support the primary PFS outcome. In the interim OS analysis there was no statistically significant difference in overall survival between the two treatment arms. The median duration of overall survival was similar in the crizotinib and chemotherapy treatment arms (20.3 months [95% CI: 18.1, not reached] versus 22.8 months [95% CI: 18.6, not reached]) and the HR (crizotinib versus chemotherapy) was 1.021 (95%: CI 0.677, 1.540). At the time of the interim OS analysis, 49 (28.3%) deaths had occurred in the 173 patients in the crizotinib arm and 47 (27.0%) deaths had occurred in the 174 patients in the chemotherapy arm. However, the number of deaths

[4] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

reported at the time of the interim analysis (that is, 96 deaths) corresponds to only 39.8% of the total number of deaths (that is, 241 deaths) required for the final OS analysis. The interim OS analysis is underpowered to demonstrate a meaningful statistically significant difference between the two treatment arms. Furthermore, the interim OS analysis is potentially confounded by patients who crossed over from one-treatment arm to the other following objective disease progression and by the use of post disease progression anti-cancer systemic therapies. Pre-specified sensitivity analyses of the interim OS data provided in the Technical Report failed to demonstrate a statistically significant difference between crizotinib and chemotherapy arms as regards overall survival. Overall, it is considered that the interim OS data should be considered to be exploratory rather than confirmatory.

The ORR (complete response (CR) + partial response (PR)), a secondary efficacy endpoint, was statistically significantly greater in the crizotinib arm compared with the chemotherapy arm (65.3% [95% CI: 57.7, 72.4] versus 19.5% [95% CI: 13.9, 26.2], respectively). The absolute ORR difference between the two treatment arms was 45.8% (95% CI: 36.5, 55.0); p<0.001, Pearson chi-square test. Of the 113 patients with an ORR in the crizotinib arm, 1 (<1.0%) had a complete response (CR) and 112 (64.7%) had a partial response. Of the 34 patients in the chemotherapy arm with a complete response, no patients had a CR and all 34 (19.5%) patients had a PR. Descriptive results for the two other secondary efficacy endpoints or TTR and DR based on patients achieving an objective response both favoured crizotinib compared with chemotherapy.

The secondary efficacy endpoints of DCR (Complete response (CR)+Partial response (PR)+ Stable disease (SD)) at Week 6 and Week 12 both statistically significantly (p<0.0001) favoured the crizotinib arm compared with the chemotherapy arm (81.5% [95% CI: 74.9, 87.0] versus 55.2% (95% CI: 47.5, 62.7), respectively, at Week 6 and 64.2% [95% CI: 56.5, 71.3] versus 38.5% (95% CI: 31.2, 46.2), respectively, at Week 12.). However, the statistically significant results are considered to be nominal rather than confirmatory due to the pre-specified hierarchal order of testing to control for multiple efficacy comparisons (that is, PFS then ORR then OS then DCR), and the failure of the OS analysis preceding DCR to show a statistically significant difference between the two treatment arms.

Other efficacy endpoints based on improvement from baseline in PROs relating to quality of life and symptoms consistently favoured crizotinib compared with chemotherapy. In the ETORC QLC-30 core questionnaire[5], changes from baseline in estimates of global quality of life, physical functioning, role functioning, emotional functioning, and social functioning all significantly favoured crizotinib compared with chemotherapy, with no significant difference between the treatment arms for cognitive functioning. In the EORTC QLQ-30 symptom questionnaire, changes from baseline in estimates of fatigue, pain, dyspnoea, insomnia, and appetite loss all significantly favoured crizotinib compared with chemotherapy. In this questionnaire, changes from baseline in estimates of constipation and diarrhoea significantly favoured chemotherapy compared with crizotinib, while changes from baseline in estimates of nausea and vomiting were similar in both treatment arms. In the EORTC QLC-LC13 lung cancer symptom questionnaire, changes from baseline in estimates of dyspnoea, coughing, haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm and shoulder and pain in other parts all significantly favoured crizotinib compared with chemotherapy. However, it should be noted that the PROs were not specified as either primary or secondary efficacy endpoints but were referred to as "other" efficacy endpoints. Furthermore, no adjustments of statistical significance levels were made to account for multiplicity of testing. Overall, it is considered that the PROs should be considered to be exploratory rather than confirmatory.

The median Time to deterioration (TTD) in pain in chest, dyspnea, or cough determined from the EORTC QCQ-LC13 questionnaire as a composite endpoint was 5.6 months (95% CI: 3.4, 11.0

[5] The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients.

months) in the crizotinib arm compared with 1.4 months (95% CI: 1.0, 1.8 months) in the chemotherapy arm. The HR (crizotinib versus chemotherapy) was 0.535 (95% CI: 0.404, 0.709), p<0.0001 (2-sided Hochberg adjusted unstratified log-rank test), indicating that the risk of experiencing the composite endpoint was significantly lower in the crizotinib arm compared with the chemotherapy arm.

2.7. Evaluator's comments on risks of treatment with crizotinib based on study A8081007

Treatment emergent adverse events (TEAEs) were reported both as all causality events and treatment-related events (that is, events judged by the investigator to be at least possibly related to the study drug). It is considered that comparison between the crizotinib and chemotherapy treatment arms based on treatment-related TEAEs is subject to potential bias due to the open-label design of the study. Consequently, the conclusions relating to risks of treatment focuses primarily on all causality TEAEs and TEAEs referred to in the following summary are all causality unless otherwise stated.

Overall, it is considered that the safety profile of crizotinib is inferior to that of standard of care chemotherapy (pemetrexed or docetaxel) for the treatment of previously treated ALK-positive NSCLC. While the frequency of TEAEs (all grades) was similar in patients in the crizotinib and chemotherapy arms (100% versus 98.2%), the incidence of serious adverse events (SAEs) was greater in the crizotinib arm than in the chemotherapy arm (37.2% versus 23.4%), as were Grade 3 or 4 AEs (56.4% versus 45.6%), Grade 5 AEs (14.5% versus 4.1%), permanent discontinuations due to AEs (17.4% versus 13.5%), dose reductions due to AEs (16.3% versus 14.6%), and temporary discontinuations due to AEs (39.0% versus 15.8%).

TEAEs were reported in 100.0% (172/172) of patients in the crizotinib arm (2085 events) and 98.2% (168/171) of patients in the chemotherapy arm (1358 events). The maximum severity categories for the TEAEs in the crizotinib versus chemotherapy treatment arms were Grade 1 (12.2% versus 16.4%), Grade 2 (29.1% versus 35.7%), Grade 3 (35.5% versus 28.7%), Grade 4 (8.7% versus 13.4%), and Grade 5 (14.5% versus 4.1%).

The median duration of treatment in the crizotinib arm was longer than in the crizotinib arm (31 weeks) compared with the chemotherapy arm (12 weeks) and the safety data were not adjusted for different durations of exposure. Nevertheless, it can be reasonably concluded from the safety data reported in the preliminary CSR that there is a clinically meaningful increased risk in the crizotinib arm compared with the chemotherapy arm, in decreasing order of frequency, of diarrhoea (59.9% versus 19.3%), VISION DISORDER (59.9% versus 9.4%), nausea (54.7% versus 37.4%), vomiting (46.5% versus 17.5%), constipation (42.4% versus 22.8%), ELEVATED TRANSAMINASES (38.4% versus 14.6%), EDEMA (31.4% versus 15.8%), dysgeusia (25.6% versus 9.4%), UPPER RESPIRATORY INFECTION (25.6% versus 12.9%), and DIZZINESS (21.5% versus 8.2%). On the other hand, it can be reasonably concluded that there is a clinically meaningful increased risk in the chemotherapy arm compared with the crizotinib arm, in decreasing order of frequency, of fatigue (33.3% versus 26.7%), alopecia (20.5% versus 8.1%), DYSPNOEA (18.7% versus 13.4%), rash (17.0% versus 8.7%), arthralgia (11.7% versus 6.4%), and myalgia (10.5% versus 1.7%).

SAEs (including Grade 5 events) were reported more commonly in the crizotinib arm than in the chemotherapy arm (37.2% [64/172] versus 23.4%, [40/171]). SAEs reported with an incidence of ≥ 1% in the crizotinib arm and reported more commonly than in the chemotherapy arm were, in decreasing order of frequency, disease progression (7.6 % versus 1.8%), pneumonia (4.1% versus 1.8%), pulmonary embolism (2.9% versus 1.8%), dyspnoea (2.3% versus 1.8%), interstitial lung disease (1.7% versus 0%), alanine aminotransferase (ALT) increased (1.2% versus 0%), aspartate aminotransferase (AST) increased (1.2% versus 0%), convulsion (1.2% versus 0.6%), hypoglycaemia (1.2% versus 0.6%), lung abscess (1.2% versus 0%), lung

infection (1.2% versus 0.6%), and vomiting (1.2% versus 0%).SAEs occurring with an incidence of ≥ 1% in the chemotherapy arm and reported more commonly than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (7.0% versus 0.6%), anaemia (1.2% versus 0%) and deep vein thrombosis (1.2% versus 0%).

The incidence of deaths from all causes in the crizotinib arm was 27.9% (48/172) compared with 23.1% (15/65) in the chemotherapy arm without cross-over. The majority of deaths in both the crizotinib and chemotherapy arms without cross-over were considered to be due to NSCLC (that is, the disease under study). The incidence of death within 28 days of the last dose of the study drug was higher in the crizotinib arm than in the chemotherapy arm without cross-over (13.4% [23/172] versus 9.2% [6/65]), while the incidence of death more than 28 days after the last dose of study drug was similar in the two treatment arms (14.5% [25/172] versus 13.9% [9/65], respectively). However, the incidence of death within 30 days of the first dose of study drug was higher in chemotherapy arm without cross-over than in the crizotinib arm (4.6% [3/65] versus 1.7% [3/172]), as was the incidence of death within 60 days of first dose of study drug (10.8% [7/65] versus 5.8% [10/172]).

During the treatment phase of the study there were 32 Grade 5 TEAEs (that is, deaths), 25 (14.5%) in the crizotinib arm and 7 (4.1%) in the chemotherapy arm. Included in these 32 deaths were 2 patients on crizotinib and 1 patient on chemotherapy who had non-treatment related Grade 5 TEAEs reported > 28 days after the last day of the study drug. Death related to disease progression was the most commonly reported Grade 5 TEAE in the treatment phase (14/25 [56.0%] in the crizotinib arm versus 3/7 [42.9%] in the chemotherapy arm). Death related to pulmonary disease occurred notably more commonly in the crizotinib arm than in the chemotherapy arm (that is, ILD, pneumonitis, acute respiratory distress syndrome, pneumonia).

There were 6 deaths considered by the investigator and/or the sponsor to be at least possibly related to study treatment (5 [2.9%] in the crizotinib arm versus 1 [0.6%] in the chemotherapy arm [pemetrexed]). The 5 treatment-related deaths in the crizotinib treatment arm were Interstitial lung disease (ILD) (1 death), pneumonitis (1 death), arrhythmia which appears to have been due to bradycardia (1 death), sudden death probably due to heart failure (1 death), and unknown cause (1 death). The (1) treatment-related death in the chemotherapy arm (pemetrexed) was due to sepsis. In addition to the 5 treatment-related deaths in the crizotinib treatment reported at the data cut off date, there was 1 reported death due to liver failure in a patient meeting Hy's law criteria for potential drug induced liver injury occurring after the data cut-off date.

Permanent treatment discontinuations were reported more frequently in the crizotinib arm than in the chemotherapy arm (17.4% [30/172] versus 13.5% [23/171]), respectively. TEAEs resulting in ≥ 1% of patients permanently discontinuing from treatment in the crizotinib arm and occurring more frequently than in the chemotherapy arm were, in decreasing order of frequency, disease progression (2.9% versus 0%), interstitial lung disease (1.7% versus 0%), pulmonary embolism (1.2% versus 0%), ALT increased (1.2% versus 0%), AST increased (1.2% versus 0%), and dyspnoea (1.2% versus 0%). TEAEs resulting in ≥ 1% of patients permanently discontinuing from treatment in the chemotherapy arm and occurring more frequently than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (1.8% versus 0%), asthenia (1.2% versus 0%), pericardial effusion (1.2% versus 0%) and pleural effusion (1.2% versus 0%).

Temporary treatment discontinuations due to TEAEs were reported notably more frequently in the crizotinib arm than in the chemotherapy arm (39.0% [67/172] versus 15.8% [27/171]). TEAEs resulting in temporary treatment discontinuations in ≥ 1% of patients in the crizotinib arm and reported more commonly than in the chemotherapy arm were, in decreasing order of frequency, neutropenia (8.1% versus 0%), ALT increased (6.4% versus 0%), nausea (4.7% versus 0%), AST increased (3.5% versus 0.6%), vomiting (3.5% versus 0%), pneumonia (2.9% versus 0.6%), neutrophil count decreased (2.3% versus 0%), upper abdominal pain (2.3%

versus 0%), leukopenia (1.7% versus 0%), peripheral oedema (1.7% versus 0%), constipation (1.2% versus 0%), pyrexia (1.2% versus 0%), gastroenteritis (1.2% versus 0%), lung infection (1.2% versus 0%), sinus bradycardia (1.2% versus 0%), ECG QT prolonged (1.2% versus 0%), transaminases increased (1.2% versus 0%), decreased appetite (1.2% versus 0%) and brain oedema (1.2% versus 0%). The only TEAE resulting in temporary treatment discontinuation in ≥ 1% of patients in the chemotherapy arm and reported more commonly than in the crizotinib arm was dizziness (1.2% versus 0.6%).

Dose reductions due to TEAEs were reported in 16.3% (28/172) of patients in the crizotinib arm and 14.6% (25/171) of patients in the chemotherapy arm. TEAEs resulting in dose reductions in ≥ 1% of patients in the crizotinib arm and reported more commonly than in the chemotherapy arm were, in decreasing order of frequency, ALT increased (7.6% versus 0%), ECG QT prolonged (2.9% versus 0%), AST increased (2.3% versus 0%), neutropenia (2.3% versus 1.2%) and neutrophil count decreased (1.2% versus 0%). TEAEs resulting in dose reductions in ≥ 1% of patients in the chemotherapy arm and reported more commonly than in the crizotinib arm were, in decreasing order of frequency, febrile neutropenia (7.0% versus 0%), fatigue (1.2% versus 0%), and mucosal inflammation (1.2% versus 0%).

TEAEs of particular interest associated with crizotinib are discussed below:

2.7.1. Hepatotoxicity

The primary safety concern relating to treatment with crizotinib is considered to be the potential for drug induced liver injury (DILI). There was 1 patient in the crizotinib arm meeting Hy's law criteria for potential DILI who died due to liver failure. This patient was an Asian woman aged 73 years who developed hepatic failure on Day 33 of treatment with crizotinib 250 mg twice a day (BID). The patient permanently discontinued treatment on Day 33 and died on Day 140 due to hepatic failure.

Increased ALT (all Grades) was reported in 36.0% (n=62) of patients in the crizotinib compared with 11.7% (n=20) of patients in the chemotherapy arm, while increased ALT (Grade 3 or 4) was reported in 12.8% (n=22) and 2.3% (n=4) of patients, respectively. Increased AST (all Grades) was reported in 26.2% (n=45) of patients in the crizotinib arm compared with 9.4% (n=16) of patients in the chemotherapy arm, while increased AST (Grade 3 or 4) was reported in 5.3% (n=9) and 0.6% (n=1) of patients, respectively.

In general, increased ALT and increased AST events observed in the crizotinib arm were manageable by temporary treatment discontinuation or dose reduction rather than permanent treatment discontinuation. In the crizotinib arm, increased ALT resulted in 1.2% (n=2) of patients permanently discontinuing (both Grade 3 events), while increased AST resulted in 1.2% (n=2) of patients permanently discontinuing (both Grade 3 events). No patients in the chemotherapy arm permanently discontinued treatment due to increases in ALT or AST events. Temporary treatment discontinuation due to increased ALT was reported in 6.4% (n=11) patients in the crizotinib arm compared with no patients in the chemotherapy arm and the corresponding results for increased AST were 3.5% (n=6) and 0.6% (n=1), respectively. In the crizotinib arm, dose reductions due to increased ALT were reported in 7.6% (n=13) of patients and dose reductions due to increased AST were reported in 2.3% (n=4) of patients. No dose reductions were reported in the chemotherapy arm for increased ALT or AST.

In the crizotinib arm, the median time to first onset for treatment-related ELEVATED TRANSAMINASES was 23 days (range: 3, 716) and the median duration was 85 days (95% CI: 51, 144), while in the chemotherapy arm the median time to first onset was 22 days (range: 3, 150 days) and the median duration was 64 days (95% CI: 24, 98). Treatment-related ELEVATED TRANSAMINASES occurred in 13.4% of patients in the first cycle in the crizotinib arm and increased in the next 5 cycles with levels ranging from 13.6% to 21.2%. Treatment-related ELEVATED TRANSAMINASES occurred in 6.4% of patients in Cycle 1 in the chemotherapy arm and increased in the next 5 cycles with levels ranging from 4.1% to 12.8%.

HEPATOTOXICITY (all causalities, all grades) was reported in 5 (2.9%) patients in the crizotinib arm (n=3 [Grade 1/2] and n=2 [Grade 3]) compared with 1 (0.6%) patient in the chemotherapy arm (n=1 [Grade 2], pemetrexed group). In the crizotinib arm, hepatobiliary disorders (System Organ Class (SOC)) were reported in 7.0% (n=12) of patients, with preferred term events of cytolytic hepatitis, hepatic function abnormal, hyperbilirubinaemia and liver injury each being reported in 2 patients. In the chemotherapy arm, hepatobiliary disorders (SOC) were reported in 4.7% (n=8) of patients, with preferred term events of hyperbilirubinaemia being reported in 3 patients and hepatic function abnormal in 2 patients.

2.7.2. Diarrhoea

Diarrhoea (all grades) was reported more commonly in the crizotinib arm than in the chemotherapy arm (59.9%, n=103 versus 19.3%, n=33, respectively). All reports of diarrhoea in both treatment arms were Grade 1 or 2 in severity, apart from one Grade 3 event in the chemotherapy arm. There were no permanent treatment discontinuations due to diarrhoea in either treatment arm, while temporary treatment discontinuations due to diarrhoea were reported in 1 (0.6%) patient in the chemotherapy arm and no patients in the crizotinib arm. Dose reductions due to diarrhoea were reported in 1 (0.6%) patient in the crizotinib arm and no patients in the chemotherapy arm.

Diarrhoea in both treatment arms rarely required treatment modification in either the crizotinib or chemotherapy arms and appears to have been primarily managed symptomatically. The use of loperamide preparations during treatment was notably more common in the crizotinib arm than in the chemotherapy arm (24.4%, n=42 versus 5.3%, n=9). The greater use of loperamide in the crizotinib arm compared with the chemotherapy arm was consistent with both the increased frequency of clinically meaningful diarrhoea in the crizotinib arm compared with the chemotherapy arm and the significantly greater increase from baseline in the EORTC QLQ-C30 symptom score for this event in the crizotinib arm compared with the chemotherapy arm.

In the crizotinib arm, the median time to first onset of treatment-related diarrhoea was 6 days (range: 1, 397) and the median duration of the event was 72 days (95% CI: 27, 135), while in the chemotherapy arm the median time to onset was 8.5 days (range: 1, 310) and the mean duration of the event was 8.5 days (95% CI: 4, 30). Treatment-related diarrhoea occurred in 36.6% of patients in the first cycle in the crizotinib arm, and remained at consistently high over the next 5 cycles with levels ranging from 24.3% to 29.6%. Treatment-related diarrhoea occurred in 11.1% of patients in the first cycle in the chemotherapy arm and fell over the next 5 cycles with levels ranging from 2.6% to 7.5%.

2.7.3. Nausea and vomiting

Vomiting (all grades) was reported more commonly in the crizotinib arm than in the chemotherapy arm (46.5%, n=80 versus 17.5%, n=30) and vomiting (Grade 3 or 4) was reported only in the crizotinib arm (1.2%, n=2). There were no permanent treatment discontinuations due to vomiting in either treatment arm but temporary treatment discontinuations and dose reductions due to vomiting were reported in 6 (3.5%) and 1 (0.6%) patients in the crizotinib arm, respectively, compared with no patients in the chemotherapy arm.

In the crizotinib arm, the median time to first onset of treatment-related vomiting was 2 days (range: 1, 439) and the median duration this event was 13 days (95% CI: 9, 22). In the chemotherapy arm the median time to first onset of treatment-related vomiting was 14.5 days (range: 2, 459) and the duration of the event was 3 days (95% CI: 2, 21). Treatment-related vomiting occurred in 36.6% of patients in the first cycle in the crizotinib arm after and fell over the next 5 cycles with levels ranging from 6.2% to 9.6%. Treatment-related vomiting occurred in 8.2% of patients in the first cycle after in the chemotherapy arm and fell over the next 5 cycles with levels ranging from 1.8% to 6.4%.

Nausea (all grades) was reported more commonly in the crizotinib arm than in the chemotherapy arm (54.7%, n=94 versus 37.4%, n=64) and there were 2 patients (1.2%) with Grade 3 events and 1 patient (0.6%) with a Grade 5 event in the crizotinib arm compared with 1 (0.6%) patient with a Grade 3 event in the chemotherapy arm. The Grade 5 TEAE of nausea in the crizotinib arm was incorrectly listed and was corrected after the data cut off date (the patient had a Grade 1 event of nausea and a Grade 5 event or pulmonary embolism). Permanent treatment discontinuations due to nausea were reported in 1 (0.6%) patient in the crizotinib arm and no patients in the chemotherapy arm. Temporary treatment discontinuations were reported in 8 (4.7%) patients in the crizotinib arm and no patients in the chemotherapy arm. Dose reductions were reported in 1 (0.6%) patient in the crizotinib arm and no patients in the chemotherapy arm.

In the crizotinib arm, the median time to first onset of treatment-related nausea was 2 days (range: 1, 247 days) and the median duration of the event was 42 days (95% CI: 22, 71), while in the chemotherapy arm the median time to first onset of treatment-related nausea was 4 days (range: 1, 424) and the median duration of the event was 17 days (95%CI: 8, 35). Treatment-related nausea occurred in 43.6% of patients in the first cycle in the crizotinib arm and fell over the next 5 cycles with levels ranging from 15.2% to 20.1%. Treatment-related nausea occurred in 24.6% of patients in the first cycle in the chemotherapy arm and fell over the next 5 cycles with levels ranging from 11.3% to 18.5%.

Concomitant use of anti-emetics and anti-nauseants during the study were reported more commonly in the chemotherapy arm (67.3%, n=115) than in the crizotinib arm (20.3%, n=35), despite nausea and vomiting occurring more often in the crizotinib arm than in the chemotherapy arm. There were no significant differences between the two treatment arms in the change from baseline in the EORTC QLQ-C30 symptom score for “nausea and vomiting”.

2.7.4. Constipation

Constipation (all grades) was reported more commonly in the crizotinib arm than in the chemotherapy arm (42.4%, n=73 versus 22.8%, n=39). All events in both treatment arms were Grade 1 or 2 in severity apart from 4 (2.3%) patients with Grade 3 events in the crizotinib arm. There were no permanent treatment discontinuations or dose reductions due to constipation in either treatment arm. Temporary treatment discontinuations due to constipation were reported in 2 (1.2%) patients in the crizotinib arm and no patients in the chemotherapy arm.

2.7.5. Eye disorders

Eye disorders (all grades) were reported in 64.5% (n=111) of patients in the crizotinib arm and 19.9% (n=34) of patients in the chemotherapy arm and nearly all disorders were Grade 1 events (59.3%, n=102 versus 17.0%, n=29, respectively) with the remainder being Grade 2 events (5.2%, n=9 versus 2.9%, n=5). The most commonly reported eye disorders in the crizotinib arm occurring in ≥ 5% of patients were visual impairment (47.1%, n=81) followed by photopsia (9.9%, n=17) and blurred vision (8.1%, n=14). All other visual TEAEs occurred in ≤ 5 patients (that is, ≤ 3.0% of patients). In the chemotherapy arm, the only eye disorder reported in ≥ 5% of patients was visual impairment (5.3%, n=9), and the only other eye disorder reported in ≥ 3% of patients was lacrimation increased (4.7%, n=8).

Permanent treatment discontinuations due to eye disorders were reported in no patients in either treatment arm, while temporary treatment discontinuations were reported in 1 (0.6%) patient in the chemotherapy arm (diplopia) and no patients in the crizotinib arm. Dose reductions due to eye disorders were reported in 3 (1.8%) patients in the crizotinib arm (1 each photopsia, vision blurred, and vitreous floaters) and no patients in the chemotherapy arm. These results suggest that patients in both treatment arms continued without requiring treatment adjustments.

In the crizotinib arm, the median time to first onset of treatment-related VISION DISORDER was 5 days (range: 1, 213) and the median duration of the disorders was 247 days (95% CI: 168,

460), while in the chemotherapy arm the median time to first onset was 12.5 days (range: 2, 6 days) and the median duration was not reached. Treatment-related VISION DISORDERS occurred in 51.2% of patients in the first cycle in the crizotinib arm and remained high in the following 5 cycles ranging from 44.2% to 50.8%. Treatment-related VISION DISORDERS occurred in 3.5% of patients in the first cycle in the chemotherapy arm and remained low in the following 5 cycles ranging from 2.6% to 3.1%.

Based on the Visual Symptom Assessment Questionnaire (VSAQ), visual disturbances during the first 18 treatment cycles was reported by 42% to 62% of patients in the crizotinib arm compared with 0% to 20% of patients in the chemotherapy arm. The majority of patients in the crizotinib arm reporting visual disturbance in the first 18 treatment cycles reported > 1 event per day and these events occurred more frequently in the evening than in the morning. In both treatment arms most patients reported events lasting ≤ 1 minute. The most commonly experienced visual disturbances in the crizotinib arm were shimmering, flashing or trailing lights, streamers, strings or floaters and overlapping shadows or after images. The most commonly experienced visual disturbances in the chemotherapy arm were hazy or blurry vision. Among patients reporting visual disturbances in each cycle in the crizotinib arm, most (61% to 92%) reported that visual effects were not at all or a little bothersome and most (70% to 93%) indicated no or minimal impact on daily activities at each cycle. Of the 77 patients in the crizotinib arm with baseline and post-treatment ophthalmic evaluations only a few had new findings detected following treatment.

2.7.6. Oedema

The most notable difference in "General disorders and administration site conditions" (SOC) relating to oedema (face, generalised, oedema peripheral, or oedema) occurred for peripheral oedema. Peripheral oedema was reported in 25.6% (n=44) of patients in the crizotinib arm (all Grade 1 or 2 events) and 8.2% of patients in the chemotherapy arm (all Grade 1 events). There no reports of permanent treatment discontinuations or dose reductions due to peripheral oedema, while temporary treatment discontinuations due to this event were reported in 3 (1.7%) patients in the crizotinib arm and no patients in the chemotherapy.

In the crizotinib arm, the median time to first onset of treatment related EDEMA was 49 days (range: 3, 599) and the median duration of the event was 170 days (95% CI: 104, 365), while in the chemotherapy arm the median time to first onset was 126 days (range: 10, 505) and the median duration was 127 days (95% CI: 13, 207). Treatment-related EDEMA occurred in 5.2% of patients in the first cycles in the crizotinib arm and increased in the following 5 cycles ranging from 8.4% to 16.8%. Treatment-related EDEMA occurred in 2.1% of patients in the first cycle in the chemotherapy arm and was marginally higher in the following 5 cycles ranging from 0.9% to 4.2%.

2.7.7. Neutropenia

Neutropenia was reported in 21.5% (n=37) of patients in the crizotinib arm (Grade 3 or 4, 9.9% [n=17]) compared with 10.5% (n=18) of patients in the chemotherapy arm (Grade 3 or 4, 8.2% [n=14]). No permanent treatment discontinuations due to neutropenia were reported in either treatment arm, while temporary treatment discontinuations were reported in 8.1% (n=14) of patients in the crizotinib arm and no patients in the chemotherapy arm. Dose reduction due to neutropenia was reported in 2.3% (n=4) of patients in the crizotinib arm and in 1.2% (n=2) of patients in the chemotherapy arm.

In the crizotinib arm, the median time to first onset of treatment-related NEUTROPENIA was 43 days (range: 12, 568) and the median duration was 72 days (95% CI: 31, 173), while in the chemotherapy arm the median time to first onset was 10 days (range: 6, 76) and the median duration was 9 days (95% CI: 6, 11). Treatment-related NEUTROPENIA occurred in 8.7% of patients in the first cycle in the crizotinib arm and remained relatively constant over the following 5 cycles ranging from 7.8% to 8.5%. Treatment-related NEUTROPENIA occurred in

17.0% of patients in the first cycle in the chemotherapy arm and notably declined over the following 5 cycles ranging from 2.1% to 7.5%.

2.7.8. Febrile neutropenia

Febrile neutropenia was reported in 0.6% (n=1) patients in the crizotinib arm compared with 9.4% (n=16) patients in the chemotherapy arm. Permanent treatment discontinuation due to febrile neutropenia was reported in 1.8% (n=3) of patients in the chemotherapy arm and no patients in the crizotinib arm, while temporary treatment discontinuation was reported in 0.6% (n=1) of patients in both treatment arms. Dose reduction due to febrile neutropenia was reported in 7.0% (n=12) of patients in the chemotherapy arm and no patients in the crizotinib arm.

2.7.9. Leukopenia

Leukopenia was reported in 8.7% (n=15) patients in the crizotinib arm (Grade 3 or 4, 1.7% [n=3]), and in 5.3% (n=9) of patients in the chemotherapy arm (Grade 3 or 4, 2.3% [n=4]). No permanent treatment discontinuations due to leukopenia were reported in either treatment arm, while temporary treatment discontinuations were reported in 3 (1.7%) patients in the crizotinib and no patients in the chemotherapy arm. Dose reductions due to leukopenia were reported in 1 (0.6%) patient in both treatment arms.

2.7.10. Neuropathy

In "Nervous System disorders" (SOC), the most commonly occurring "neuropathy" MedDRA preferred event in the crizotinib arm was peripheral sensory neuropathy reported in 4.1% (n=7) of patients (all Grade 1 or 2), while in the chemotherapy arm this event was reported in 3.5% (n=60 of patients (all Grade 1 or 2). Peripheral neuropathy was reported in 2.3% (n=4) of patients in the crizotinib arm (all Grade 1 events) and 5.3% (n=9) of patients in the chemotherapy arm (8 Grade 1 events and 1 Grade 3 event). Polyneuropathy was reported in 1 (0.6%) patient in the chemotherapy arm (Grade 1 event) and no patients in the crizotinib arm.

NEUROPATHY (all causality) was reported in 19.2% (n=33) of patients in the crizotinib arm and 10.7% (n=29) of patients in the chemotherapy arm. Permanent treatment discontinuations resulting from NEUROPATHY (all causality) was reported in 2 (1.2%) patients in the chemotherapy arm (paraesthesia and peripheral sensory neuropathy, 1 patient each) and no patients in the crizotinib arm.

In the treatment sub-group analysis, NEUROPATHY (all causality) was reported in 19.2% (n=33) of patients in the crizotinib group, 10.1% (n=10) of patients in the pemetrexed group, and 26.4% (n=19) of patients in the docetaxel group.

NEUROPATHY (treatment-related) was reported in 14 (8.1%) patients in the crizotinib arm and 19 (11.1%) patients in the chemotherapy arm. The median time to onset was 43.5 days (range: 2, 355) in the crizotinib arm and 45.0 days (range: 1, 171) in the chemotherapy arm, while the median duration of the event was 85 days (95% CI: 45, not reached) and 161 days (95% CI: 20, not reached), respectively. In the crizotinib arm, NEUROPATHY (treatment-related) was reported in 3.5% of patients in the first cycle and remained relatively constant over the following 5 cycles ranging from 2.4% to 4.6%. In the chemotherapy arm NEUROPATHY (treatment-related) was reported in 4.1% of patients in the first cycle and remained relatively constant over the following 5 cycles ranging from 3.6% to 7.0%.

2.7.11. Dizziness

Dizziness (all grades) was reported in 16.3% (n=28) of patients in the crizotinib arm and 7.0% (n=12) of patients in the chemotherapy arm. In both the arms, dizziness was reported as Grade 1 or 2 events in all patients, apart from 1 (0.6%) patient with a Grade 3 event in the crizotinib arm. Postural dizziness was reported in 4.7% (n=8) of patients in the crizotinib arm (all Grade 1 events) and 1.2% (n=2) of patients in the chemotherapy arm (both Grade 1 events).

There were no permanent treatment discontinuations due to dizziness or postural dizziness reported in either treatment arm. Temporary treatment discontinuations due to dizziness were reported in 1 (0.6%) patient in the crizotinib arm and 2 (1.2%) patients in the chemotherapy arm, while postural dizziness was not reported as leading to temporary treatment discontinuation in either treatment arm. There were no dose reductions due to dizziness or postural dizziness in either treatment arm.

2.7.12. Cardiac disorders

Cardiac disorders (SOC) were reported in 12.8% (n=22) patients in the crizotinib arm and 5.3% (n=9) patients in the chemotherapy arm. In the crizotinib arm, there were 3 (1.7%) reports of bradycardia and 5 (2.9%) reports of sinus bradycardia, 1 report of arrhythmia and 1 report of cardiac arrest. In the chemotherapy arm, the only cardiac disorders occurring in more than 1 patient were pericardial effusion (3 patients, 1.8%) and tachycardia (2 patients, 1.2%). There were no reports of arrhythmia in the chemotherapy arm but 1 report of ventricular tachycardia. There were no reports of bradycardia or cardiac arrest in the chemotherapy arm.

Cardiac disorders resulted in 1 (0.6%) permanent treatment discontinuation in the crizotinib arm (arrhythmia Grade 5) compared with 4 (2.3%) permanent treatment discontinuations in the chemotherapy arm (cardiomyopathy Grade 2, left ventricular dysfunction Grade 2, and pericardial effusion Grades 4 and 5). Cardiac disorders resulted in 5 (2.9%) temporary treatment discontinuations in the crizotinib arm (2 for sinus bradycardia and 1 each for arrhythmia, cardiac arrest, ventricular dilatation) compared with no patients in the chemotherapy arm. No patients in either treatment arm had dose reductions due to cardiac disorders.

2.7.13. Electrocardiogram QT prolonged

ECG QT prolonged ("investigations" [SOC]) was reported in 4.7% (n=8) of patients in the crizotinib arm (6 Grade 3 events, 1 each Grade 1 and 2 events) and no patients in the chemotherapy arm.[6] (No permanent treatment discontinuations were reported for ECG QT prolonged in the crizotinib arm, while 2 (1.2%) temporary treatment discontinuations and 5 (2.9%) dose reductions were reported.

2.7.14. Interstitial lung disease (ILD) and pneumonitis

ILD was reported in 3 (1.7%) patients in the crizotinib arm (1 each for Grades 1, 3 and 5) and in no patients in the chemotherapy arm. Permanent treatment discontinuation occurred for each of the 3 cases of ILD.

Pneumonitis was reported in 3 (1.7%) patients in the crizotinib arm (1 each for Grades 1, 2, and 5) and in 1 (0.6%) patient in the chemotherapy arm (Grade 1 event). Permanent treatment discontinuation due to pneumonitis (Grade 5) was reported in 1 (0.6%) patient in the crizotinib arm and no patients in the chemotherapy arm. Temporary treatment discontinuations were reported in 1 (0.6%) patient in the crizotinib arm and no patients in the chemotherapy arm and no dose reductions due to pneumonitis were reported in either treatment arm.

The median time to first onset of treatment-related INTERSTITIAL LUNG DISEAES in the crizotinib arm (n=5, 2.9%) was 66 days (range: 9, 335) and there were no data on median duration, while in the chemotherapy arm there was one report of this condition with time to first onset of 203 days and duration of 50 days.

2.8. Risk-benefit balance based on Study A8081007

It is considered that the benefits of crizotinib are greater than those for standard of care chemotherapy (pemetrexed or docetaxel) for the treatment of patients with previously treated

[6] Sponsor correction: The protocol did not require on-treatment ECGs for the chemotherapy arm.

ALK-positive NSCLC. The primary benefit of crizotinib compared with chemotherapy relates to the clinically meaningful median improvement of 4.7 months in PFS, supported by improvements in the ORR, DCR at Week 6 and 12 and PRO quality of life and symptom outcomes. However, there was no overall survival benefit (or detriment) in the crizotinib arm compared with the chemotherapy arm based on the interim OS analysis.

It is considered that risks of crizotinib are greater than those for standard of care chemotherapy (pemetrexed or docetaxel) for the treatment of patients with previously treated ALK-positive NSCLC. However, most of the commonly occurring risks associated with crizotinib were generally manageable by temporary treatment discontinuation, dose reductions and/or symptomatic treatment rather than by permanent treatment discontinuation. Of concern, there were small but potentially fatal risks of DILI and ILD related to treatment with crizotinib. While regular liver function monitoring may assist early recognition and appropriate management of elevated hepatic transaminase levels associated with crizotinib, such monitoring is unlikely to prevent drug induced liver injury due to the idiosyncratic and unpredictable nature of the condition. There are no known monitoring methods to prevent ILD due to crizotinib.

The risk-benefit assessment for crizotinib compared with standard of care chemotherapy (pemetrexed or docetaxel) for the treatment of patients with previously treated ALK-positive NSCLC is considered to be finally balanced. The risk-benefit balance hinges on whether the clinically meaningful PFS benefit, in the absence of an OS benefit, observed with crizotinib compared with chemotherapy outweighs the inferior safety profile of crizotinib, including the potentially fatal risks of DILI and ILD, compared with chemotherapy. On balance, it is considered that the benefits of treatment with crizotinib compared with standard of care chemotherapy (pemetrexed or docetaxel) for previously treated ALK-positive NSCLC outweighs the risks.

2.9. Relevant safety data from the RMP V4.0 dated 25 February 2013

2.9.1. Exposure

The data lock for Risk Management Plan (RMP) version 4.0 (V4.0) was 31 December 2012 and the date of final sign off was 25 February 2013. The RMP included safety data on 1106 patients treated for "ALK-positive advanced NSCLC" with crizotinib 250 mg BID from Studies A8081005 (#5) and A8081007 (#7) (see Table 21, below).Of the 1106 patients in the safety analysis population, 934 were from Study #5 with a data cut off date of 15 February 2012 and 172 were from Study #7 with a data cut off date of 30 March 2012. It should be noted that the patient number and data cut off date for study #7 (30 March 2012) are identical to those provided in the preliminary CSR for this study. Consequently, the safety data for crizotinib from Study #7 in the RMP is the same as that in the preliminary CSR for study #7 evaluated above. Overall mean relative dose intensity was > 90% for all time intervals in both Study #5 and Study #7, apart from ≤ 4 weeks in Study #7 where it was 89.76%.

Table 21: RMP – Duration of exposure in patients treated with crizotinib 250 mg bd from studies #1005 and #1007.

Duration	Persons	Person-time (months)
1 dose	1106	36.3
At least 1 month	1008	1243.9
At least 3 months	768	2710.9
At least 6 months	501	3827.0

Duration	Persons	Person-time (months)
At least 12 months	171	2401.9
At least 18 months	38	764.1
At least 24 months	1	24.9
Total	**1106**	**7254.3**

Pooled serious adverse event (SAE) data from the Pfizer (Argus) Safety Database provided in the RMP originated from 1,600 ALK-positive NSCLC patients treated with crizotinib in clinical trials with a starting dose of 250 mg BID as of the data cut off date of 31 December 2012. The contribution of individual clinical trials to the total number of patients in the database is: 153 patients from Study A8081001 (#1); 1050 patients from Study #5; 172 patients from Study #7; 32 patients from Study A8081013 (#13); 140 patients randomised and treated from Study A8081014 (#14); and 53 patients who crossed over from chemotherapy to crizotinib from Study #14. Multiple SAEs may have been reported from individual patients.

Worldwide exposure to crizotinib based on audited sales and prescription data from International Marketing Services (IMS) Health from the first worldwide approval in the US on 26 August 2011 through third quarter of 2012 (402 days) is 473,200 standard units (394,000 from the USA). The total worldwide exposure corresponds to approximately 588 patient-years of exposure.

2.9.2. Demographics

Of the 1106 patients in Studies #1005 and #1007, 476 were males (406 aged < 65 years; 70 aged > 65 years) and 630 were females (521 aged < 65 years; 109 aged ≥ 65 years). The mean (SD) age of the 1106 patients was 51.1 (12.4) years, the median age was 52 years and the range was 19 to 83 years. The racial background of the 1106 patients was 576 (52.1%) White, 488 (44.1%) Asian, 20 (1.8%) Black, and 22 (2.0%) Other. Of the 1106 patients, 293 (26.5%) were aged < 44 years, 241 (21.8%) were aged between 44 and < 52 years, 250 (22.6%) were aged between 52 and < 60 years, and 322 (29.1%) were aged ≥ 60 years.

2.9.3. Important identified risks

2.9.3.1. Introduction

The RMP specified the following events as "important identified risks": hepatotoxicity; pneumonitis/interstitial lung disease; QTc prolongation; bradycardia; vision disorder; renal cyst; oedema; leukopenia; and neuropathy. The RMP specified the following events as "important potential risks": reproductive toxicity; and photosensitivity. The RMP included tabulated lists of all causality AEs and treatment-related AEs (based on investigator assessment) coded by MedDRA (V15.1) preferred terms and graded by CTCAE (V4). The all causality AEs were also categorised as recovered or not recovered (including missing outcome and unknown outcome).

In addition, the RMP also included similar tabulated lists of SAEs categorised by outcome (hospitalised, recovered, not recovered and fatal). Each important identified and potential risk included AEs/SAEs terms that were compatible with the risk. The following description of important identified risks and important potential risks relates to all causality events unless otherwise specified.

2.9.3.2. Hepatotoxicity

a) All causality AEs (Studies #5 and #7)

There were 313 (28.3%) patients with AEs identified as being compatible with hepatotoxicity. These AEs were ALT increased (n=249, 22.5%), ascites (n=3, 0.3%), AST increased (n=181, 16.4%), blood bilirubin increased (n=8, 0.7%), cytolytic hepatitis (n=5, 0.5%), GGT increased (n=10, 0.9%), hepatic encephalopathy (n=1, 0.1%), hepatic enzyme increased (n=1, 0.1%), hepatic failure (n=2, 0.2%), hepatic function abnormal (n=8, 0.7%), hepatic lesion (n=3, 0.3%), hepatic pain (n=2, 0.2%), hepatic steatosis (n=1, 0.1%), hepatitis (n=1, 0.1%), hepatomegaly (n=1, 0.1%), hepatotoxicity (n=4, 0.4%), hyperbilirubinaemia (n=3, 0.3%), cholestatic jaundice (n=1, 0.1%), liver disorder (n=6, 0.5%), liver function test abnormal (n=2, 0.2%), liver injury (n=3, 0.3%), perihepatic discomfort (n=1, 0.1%) and transaminases increased (n=11, 1.0%).

Of the 313 patients with hepatotoxicity, 195 (17.6%) were reported as recovered and 118 (10.7%) were reported as not recovered. Grade 5 events were reported in 2 (0.2%) patients (1 x hepatic failure and 1 x liver injury). No specific risk groups or risk factors for hepatotoxicity have been identified.

There were three AEs considered to be compatible with possible hepatotoxicity occurring in ≥ 1% of patients (ALT increased, AST increased, and transaminases increased). ***Increased ALT*** occurred in 22.5% (n=249) of patients, with the majority of events (15.6%, n=172) being Grade 1 (11.8%, n=130) or Grade 2 (3.8%, n=42) and the remainder (7.0%, n=77) being Grade 3 (5.6%, n=62) or Grade 4 (1.4%, n=15). ***Increased AST*** occurred in 16.4% (n=181) of patients, with the majority of events (13.5%, n=149) being Grade 1 (11.1%, n=123) or Grade 2 (2.4%, n=26) and the remainder (2.9%, n=32) being Grade 3 (2.5%, n=28) or Grade 4 (0.4%, n=4). ***Transaminases increased*** occurred in 1.0% (n=11) of patients, with 0.5% (n=5) of events being Grade1 (0.4%, n=4) or Grade 2 (0.1%, n=1), and 0.6% (n=6) of events being Grade 3 (0.5%, n=5) or Grade 4 (0.1%, n=1).

The frequency ***of treatment-related AEs*** compatible with possible hepatotoxicity is very common at 26.4% (95% CI 23.8, 29.1); 292/1106 patients.

In its letter of 22 March 2013 (response to Question 3), the sponsor states that increases to Grade 3 or 4 ALT were observed in 17% of patients in StudyA8081007, 4% of patients in Study A8081001 and 8% of patients in Study A8081005. The sponsor goes on to state that Grade 3 and 4 changes were generally asymptomatic and reversible on dosing interruption. Patients usually resumed treatment at a lower dose of crizotinib without recurrence. However, the sponsor noted that 2 (1%) patients from Study A8081007, 1 (<1%) patient from Study A081001 and 6 (<1%) patients from Study A8081005 required permanent treatment discontinuation. The sponsor commented that transaminase elevations generally occurred within the first 2 months of treatment.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 34 (2.1%) SAEs (all causality) compatible with possible hepatotoxicity in the pooled SAE database (n=1,600) – 10 reports of ALT increased (4 hospitalised, 10 recovered); 6 reports of AST increased (3 hospitalised, 6 recovered); 3 reports of DILI (2 hospitalised, 2 recovered, 1 not recovered); 2 reports of ascites (2 hospitalised, 2 recovered); 2 reports of blood bilirubin increased (1 hospitalised, 1 recovered, 1 not recovered); 2 reports of hepatic failure (1 hospitalised, 2 fatal); 2 reports of hepatitis (2 hospitalised, 2 recovered); 2 reports of hepatotoxicity (2 recovered); 1 report of hepatic enzyme increased (hospitalised and recovered); 1 report of hepatocellular injury (hospitalised and recovered); 1 report of liver function test abnormal (hospitalised and recovered); 1 report of liver injury (hospitalised and fatal); and 1 report of transaminases increased (recovered). There were three SAE reports (all causality) of death associated with crizotinib: 2 x hepatic failure and 1 report of liver injury.

(c) Drug induced liver injury (DILI)

Cases of fatal drug induced hepatotoxicity have occurred in < 1% of patients in clinical trials. Concurrent elevations in ALT > 3 x ULN and total bilirubin > 2 x ULN without elevated alkaline phosphatase have occurred in < 1% of patients in clinical trials.

(d) Preventability

It is not known which patients may be at increased risk of developing hepatotoxicity during treatment with crizotinib. The European Union Summary of Product Characteristics (SmPC) specifies that all patients should have monthly transaminases and total bilirubin levels measured, with more frequent testing if clinically indicated. The SmPC describes dose interruptions, dose reductions and discontinuations based on specified increases in ALT or AST levels (in association with specified total bilirubin levels).

2.9.3.3. Pneumonitis / interstitial lung disease

a) All causality AEs (Studies #5 and #7)

There were 34 patients (3.1%) with AEs identified as being compatible with pneumonitis/interstitial lung disease. These AEs were acute respiratory syndrome (n=2, 0.2%), bronchiolitis (n=1, 0.1%), interstitial lung disease (n=6, 0.5%), lung infiltration (n=1, 0.1%), pneumonitis (n=21, 1.9%), pulmonary fibrosis (n=1, 0.1%) and radiation pneumonitis (n=3, 0.3%). Of the 34 patients with pneumonitis/interstitial lung disease, 23 (2.1%) were reported as recovered and 11 (1.0%) were reported as not recovered. There were 5 (0.5%) Grade 5 events, 3 (0.3%) associated with interstitial lung disease, 2 (0.2%) associated with pneumonitis and 1 (0.1%) associated with acute respiratory distress syndrome.

Of the 34 patients with pneumonitis/interstitial lung disease, 23 (2.1%) were reported as recovered and 11 (1.0%) were reported as not recovered (that is, includes missing outcomes and unknown outcomes). Grade 5 AEs were reported in 6 (0.5%) patients (3 x interstitial lung disease, 2 x pneumonitis and 1 x acute respiratory distress syndrome).

AEs reported in ≥ 2 patients were pneumonitis (n=21, 1.9%), interstitial lung disease (n=6, 0.5%), radiation pneumonitis (n=3, 0.3%) and acute respiratory syndrome (n=2, 0.2%). Of the 21 patients with ***pneumonitis*****,** there 2 (0.2%) patients with Grade 5 events, 12 (1.1%) patients with Grade 1 or 2 events and 7 (0.7%) patients with Grade 3 or 4 events. Of the 6 patients with ***interstitial lung disease***, there were 3 (0.3%) patients with Grade 5 events, 2 (0.2%) patients with Grade 1 events and 1 (0.1%) patient with a Grade 3 event. Of the 2 patients with ***acute respiratory distress syndrome***, there was 1 (0.1%) patient with a Grade 5 event and 1 (0.1%) patient with a Grade 3 event.

The frequency of ***treatment-related AEs*** compatible with possible pneumonitis/interstitial lung disease is common at 1.8% (95% CI: 1.1, 2.8); 20/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 30 (1.9%) SAEs (all causality) compatible with pneumonitis/interstitial lung disease in the pooled SAE database (n=1,600) – 18 reports of pneumonitis (15 hospitalised, 7 recovered, 5 not recovered, 6 fatal); 8 reports of interstitial lung disease (6 hospitalised, 3 recovered, 1 not recovered, 4 fatal); 2 reports of acute respiratory distress syndrome (both fatal); 1 report of alveolitis (hospitalised, not recovered); and 1 report of radiation pneumonitis (hospitalised, not recovered).

(c) Preventability

There are no known preventive measures to reduce the incidence or decrease the severity of crizotinib related pneumonitis/interstitial lung disease.

2.9.3.4. QTc Prolongation

(a) All causality AEs (studies #5 and #7)

There were 58 (5.2%) patients with AEs (all causality) identified as being potentially compatible with QTc prolongation. These AEs were cardiac arrest (n=2, 0.2%), ECG QT prolonged (n=33, 3.0%), loss of consciousness (n=1, 0.1%), sudden death (n=1, 0.1%) and syncope (n=22, 2.0%). Of the 58 patients with QTc prolongation, 53 (4.8%) were reported as recovered and 5 (0.5%) were reported as not recovered. There were 2 (0.2%) Grade 5 events, 1 (0.1%) associated with cardiac arrest and 1 (0.1%) sudden death.

There were two AEs considered to be potentially compatible with QTc prolongation occurring in ≥ 2% of patients (ECG QT prolongation and syncope). ***ECG QT prolongation*** occurred in 33 (3.0%) patients, including 16 (1.5%) patients with Grade 1 or 2 events and 17 (1.5%) patients with Grade 3 or 4 events. ***Syncope*** occurred in 22 (2.0%) patients and all events were Grade 3.

The frequency of ***treatment-related AEs*** compatible with possible QT prolongation is common at 3.5% (95% CI: 2.5, 4.8); 39/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 20 (1.3%) SAEs considered to be potentially compatible with QTc prolongation in the pooled SAE database (n=1,600) – 12 events of syncope (11 hospitalised, 10 recovered, 2 not recovered); 4 events of ECG QT prolonged (2 hospitalised, 4 recovered); 2 events of cardiac arrest (1 hospitalised, 1 not recovered, 1 fatal); 1 event of cardio-respiratory arrest (fatal); 1 sudden death.

(c) Preventability

It is not known which patients may be at increased risk of developing symptomatic QTc prolongation during treatment with crizotinib. There are no known specific preventive measures to reduce the incidence or decrease the severity of QTc prolongation in individual patients. However, dose reduction may be appropriate once the QTc prolongation has been identified. The sponsor proposes periodic on-treatment ECG and electrolyte monitoring and specifies particular actions to be undertaken if Grade 3 QTc prolongation occurs.

2.9.3.5. Bradycardia

(a) All causality AEs (Studies #5 and #7)

There were 65 (5.9%) patients with AEs identified as compatible with bradycardia. These AEs (MedDRA preferred terms) were bradycardia (n=29, 2.6%), heart rate decreased (n=1, 0.1%) and sinus bradycardia (n=35, 3.2%). Of the 65 patients with bradycardia, 42 (3.8%) were reported as recovered and 23 (2.1%) were reported as not recovered (includes missing outcomes and unknown outcomes). There were no Grade 4 or 5 AEs.

There were two AEs considered to be compatible with bradycardia occurring in ≥ 2% of patients (bradycardia and sinus bradycardia). ***Bradycardia (MedDRA preferred term)*** occurred in 29 (2.6%) patients, including 28 (2.6%) with Grade 1 or 2 events and 1 (0.1%) with a Grade 3 event. **Sinus bradycardia (MedDRA preferred term)** occurred in 35 (3.2%) patients, including 34 (3.1%) with Grade 1 or 2 events and 1 (0.1%) with a Grade 3 event.

The frequency of ***treatment-related AEs*** compatible with possible bradycardia is common at 5.1% (95% CI: 3.9, 6.5); 56/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 2 (0.1%) SAEs (all causality) considered to be potentially compatible with bradycardia in the pooled SAE database (n=1,600) - 2 bradycardia (2 hospitalised and 2 recovered).

(c) Preventability

It is not known which patients may be at increased risk of developing bradycardia during treatment with crizotinib. There are no known preventive measures to reduce the incidence or severity of these disorders.

2.9.3.6. Vision disorder

(a) All causality AEs (Studies #5 and #7)

There were 634 (57.3%) patients with AEs compatible with vision disorder. Of the 634 patients with AEs compatible with vision disorder, 301 (27.2%) were reported as recovered and 333 (30.1%) were reported as not recovered. Nearly all vision disorders were Grade 1 or 2 in severity (n=627, 98.9%), with 5 (0.5%) events being Grade 3 and 2 (0.2%) event being Grade 4. There were no Grade 5 AEs.

There were four AEs considered to be compatible with vision disorders occurring in ≥ 2% of patients (visual impairment, photopsia, vision blurred, and vitreous floaters). ***Visual impairment*** occurred in 458 (41.4%) patients including 442 (40.0%) with Grade 1 events, 13 (1.2%) with Grade 2 events, and 3 (0.3%) with Grade 3 events. ***Photopsia*** occurred in 97 (8.8%) patients including 94 (8.5%) with Grade 1 events and 3 (0.3%) with Grade 2 events. ***Vision blurred*** occurred in 62 (5.6%) patients including 50 (4.5%) with Grade 1 events, 11 (1.0%) with Grade 2 events, and 1 (0.1%) with a Grade 3 event. ***Vitreous floaters*** occurred in 38 (3.4%) of patients and all were Grade 1 events.

The frequency of ***possible treatment-related vision disorder*** is very common at 55.2% (95% CI: 52.17, 58.11); 610/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 4 (0.3%) SAEs (all causality) considered to be compatible with vision disorder in the pooled SAE database (n=1,600) – 1 retinal detachment (hospitalised and recovered); 1 blurred vision (hospitalised, not recovered); 1 visual acuity reduced (hospitalised, recovered); and 1 vitreous haemorrhage (hospitalised, recovered).

(c) Preventability

It is not known which patients may be at increased risk of developing vision disorders during treatment with crizotinib. There are no known preventive measures to reduce the incidence of severity of these disorders.

2.9.3.7. Renal cyst

(a) All causality AEs (Studies #5 and #7)

There were 19 (1.7%) patients with AEs compatible with renal cyst, including 15 (1.4%) with Grade 1 events; 3 (0.3%) with Grade 2 events; and 1 (0.1%) with a Grade 3 event. There were no Grade 5 AEs. Of the 19 patients with AEs compatible with renal cyst, 3 (0.3%) were reported as recovered and 16 (1.5%) were reported as not recovered. The frequency of ***treatment-related*** AEs compatible with possible renal cyst is common at 1.6% (95% CI: 0.97, 2.56); 18/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 17 (1.1%) SAEs in the pooled SAE database (n=1,600) – 15 renal cyst (5 hospitalised, 2 recovered, 13 not recovered); 1 renal abscess (hospitalised, recovered); and 1 renal haematoma (hospitalised, recovered).

(c) Preventability

It is not known how the development of renal cysts in patients treated with crizotinib can be prevented.

2.9.3.8. Oedema

(a) All causality AEs (Studies #5 and #7)

There were 433 (39.2%) patients with AEs compatible with oedema. The majority of AEs (MedDRA preferred terms) compatible with oedema were peripheral oedema (n=350, 31.6%). The only other AEs occurring in ≥ 2% of patients were oedema (n=69, 6.2%) and face oedema (n=27, 2.4%). Of the 433 patients with oedema, 182 (16.5%) were reported as recovered and 251 (22.7%) were reported as not recovered. There were no Grade 5 or Grade 4 AEs.

The details of the three AEs compatible with oedema and occurring in ≥ 2% of patients are summarised as follows. ***Peripheral oedema*** occurred in 350 (31.6%) patients including 341 (30.8%) with Grade 1 or 2 events and 8 (0.7%) with Grade 3 events. ***Oedema MedDRA preferred term*** occurred in 69 (6.2%) patients including 67 (6.1%) with Grade 1 or 2 events and 2 (0.2%) with Grade 3 events. ***Face oedema*** occurred in 27 (2.4%) patients and all were Grade 1 or 2 events.

The frequency of ***treatment-related AEs*** compatible with possible oedema is very common at 28.6% (95% CI: 95% CI: 25.9, 31.3).

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 13 (0.8%) SAEs in the pooled SAE database (n=1,600) - 6 reports of peripheral oedema (6 hospitalized, 4 recovered, 2 not recovered); 4 reports of generalized oedema (3 hospitalized, 1 recovered, 3 not recovered); 2 reports of oedema MedDRA preferred term (2 hospitalized, 2 recovered); and 1 report of chronic obstructive airways disease (hospitalized, not recovered).

(c) Preventability

It is not known how the development of oedema in patients treated with crizotinib can be prevented.

2.9.3.9. Leukopenia

(a) All causality AEs (Studies #5 and #7)

There were 228 (20.6%) patients with AEs compatible with leukopenia. The AEs were febrile neutropenia (n=5, 0.5%, granulocytopenia (n=1, 0.1%), neutropenia (n=142, 12.8%), leukopenia (n=73, 6.6%), lymphopenia (n=37, 3.3%), monocyte count decreased (n=1, 0.1%), lymphocyte count decreased (n=17, 1.5%), and neutrophil count decreased (n=38, 34%).Of the 228 patients with leukopenia, 140 (12.7%) were reported as recovered and 88 (8.0%) were reported as not recovered. There were no Grade 5 events.

The details of the four AEs occurring in ≥ 2% of patients are summarised as follows. ***Neutropenia*** occurred in 142 (12.8%) patients, including 28 (2.5%) with Grade 1 events, 37 (3.3%) with Grade 2 events, 62 (5.6%) with Grade 3 events and 15 (1.4%) with Grade 4 events. ***Leukopenia*** occurred in 73 (6.6%) patients including 38 (3.4%) with Grade 1 events, 18 (1.6%) with Grade 2 events and 17 (1.5%) with Grade 3 events. ***Neutrophil count decreased*** occurred in 38 (3.4%) patients, including 9 (0.8%) with Grade 1 events, 11 (1.0%) with Grade 2 events, 17 (1.5%) with Grade 3 events and 1 (0.1%) with a Grade 4 event. ***Lymphopenia*** occurred in 37 (3.3%) of patients, including 3 (0.3%) with Grade 1 events, 8 (0.7%) with Grade 2 events, 21 (1.9%) with Grade 3 events and 5 (0.5%) with Grade 4 events.

The frequency of ***treatment-related AEs*** compatible with leukopenia was very common at 17.7% (95% CI: 95% CI: 15.5, 20.1).

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 9 (0.6%) SAEs (all causality) compatible with leukopenia in the pooled SAE database (n=1,600) – 7 reports of febrile neutropenia (6 hospitalised, 6 recovered, 1 not recovered); and 2 reports of neutropenia (2 recovered).

(c) Preventability

It is not known which patients may be at increased risk of developing leukopenia during treatment with crizotinib. The optimal frequency of monitoring has not been determined. The sponsor proposes dosing interruptions, dosing reductions or dosing discontinuation and appropriate management for patients developing Grade 3 or 4 leukopenia while on crizotinib treatment.

2.9.3.10. Neuropathy

(a) All causality AEs (Studies #5 and #7)

There were 211 (19.1%) patients with AEs compatible with neuropathy. AEs occurring in ≥ 2% of patients were – paraesthesia 62 (5.6%) patients (n=56, [5.1%] with Grade 1 events; 6 [0.5%] with Grade 2 events); hypoaesthesia 35 (3.2%) patients (n=32 [2.9%] with Grade 1 events; 1 [0.1%] with a Grade 2 event; and 2 [0.2%] with a Grade 3 event); peripheral neuropathy 34 (3.1%) patients (n=28 [2.5%] with Grade 1 events; n=6 [0.5%] with Grade 2 events); peripheral sensory neuropathy 33 (3.0%) patients (n=26 [2.4%] with Grade 1 events; n=6 [0.5%] with Grade 2 events); n=1 [0.1%] with a Grade 3 event); and muscular weakness 28 (2.5%) patients (n=13 [1.2%] with Grade 1 events; n=10 [0.9%] with Grade 2 events; 4 [0.4%] with Grade 3 events; 1 [0.1%] with a Grade 4 event). Of the 211 patients with AEs compatible with leukopenia, 113 (10.2%) were reported as recovered and 98 (8.9%) were reported as not recovered (includes missing outcomes and unknown outcomes). There were no Grade 5 AEs.

The frequency of **treatment-related AEs** compatible with neuropathy was common at 9.9% (95% CI: 95% CI: 8.2, 11.8); 109/1106 patients.

(b) All causality SAEs (Studies #1, #5, #7, #13, and #14)

There were 8 (0.5%) SAEs (all causality) compatible with neuropathy in the pooled SAE database (n=1,600) - 4 reports of muscular weakness (4 hospitalized, 2 recovered, 2 not recovered); 1 paraesthesia (hospitalized, recovered); 1 peripheral motor neuropathy (hospitalised, not recovered); 1 peripheral sensorimotor neuropathy (hospitalised, recovered); and 1 peripheral sensory neuropathy (hospitalised, not recovered).

(c) Preventability

It is not known which patients may be at increased risk of developing leukopenia during treatment with crizotinib. There are no known preventive measures.

2.9.4. Important potential risks

The RMP identified two important potential risks, reproductive toxicity and photosensitivity.

Reproductive toxicity (all causality) was reported in 8 (07%) patients - 4 (0.2%) with hypogonadism (2 [0.2%] with Grade 1 events; 2 [0.2%] with Grade 2 events); and 4 (0.4%) with irregular menstruation (all Grade 1 events). Of the 8 patients with AEs compatible with reproductive toxicity, 2 (0.2%) were reported to have recovered and 6 (0.5%) were reported not to have recovered. There were no Grade 3, 4 or 5 AEs. There were no SAEs. The frequency of ***treatment-related AEs*** compatible with possible reproductive toxicity is uncommon at 0.5% (95% CI: 0.15, 1.1); 5/1106 patients.

Photosensitivity (all causality) was reported in 5 (0.5%) patients – 4 with photosensitivity reaction (n=3, 0.3%, with Grade 1 events; n=1, 0.1%, with a Grade 2 event); and 1 (0.1%) with sunburn (Grade 1 event). Of the 5 patients with AEs compatible with photosensitivity, 3 (0.3%)

were reported to have recovered and 2 (0.2%) were reported not to have recovered. There were no Grade 3, 4 or 5 AEs. There were no SAEs. The frequency of ***treatment-related AEs*** compatible with possible photosensitivity is low at 0.3% (95% CI: 0.06, 0.79); 3/1106 patients.

2.9.5. Important missing information

The RMP lists the following important missing information: (a) patients with severe hepatic impairment; (b) patients with severe renal impairment; (c) paediatric patients; (d) pregnant and lactating women; (e) drug interaction with strong CYP3A inhibitors, strong CYP3A4 inducers, CYPA3A4 substrates with narrow therapeutic indices, P-glycoprotein substrates, proton-pump inhibitors or H2 antagonists; and (f) patients undergoing long-term treatment.

2.9.6. Patient and prescriber education/information brochures

The patient and prescribe education/information brochures included in the RMP are considered to be satisfactory.

2.9.7. Clinical evaluator's conclusion on the safety data in the RMP

The safety data in the RMP is consistent with the safety data from Study A8081007. The safety data are also consistent with the safety data submitted by the sponsor in its original application to register Xalkori.

3. References

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