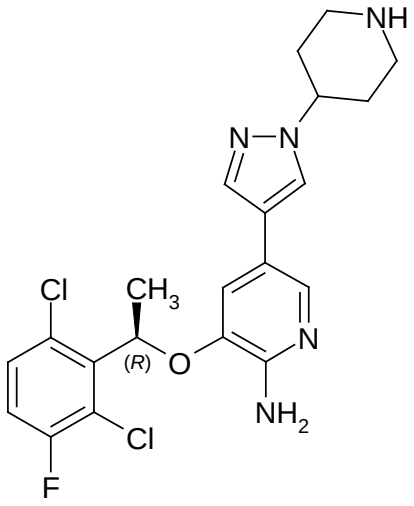
PRODUCT INFORMATION

XALKORI® (crizotinib)

NAME OF THE MEDICINE

Australian Approved Name (AAN): Crizotinib

Chemical Structure:



Chemical Name: (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

Molecular Formula: $C_{21}H_{22}Cl_2FN_5O$

Molecular Weight: 450.34 Daltons

CAS Registry Number: 877399-52-5

DESCRIPTION

Crizotinib is a white to pale yellow powder with a pKa of 9.4 (piperidinium cation) and 5.6 (pyridinium cation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

XALKORI is supplied as hard gelatin capsules containing 200 mg or 250 mg of crizotinib and the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycollate, magnesium stearate and colloidal anhydrous silica.

The capsules are differentiated by size, colour and printing. The capsule shells for the 200 mg strength consist of a pink opaque cap and white opaque body and the capsule shells for the 250 mg strength consist of a pink opaque cap and body. The pink opaque capsule shell components contain gelatin, titanium dioxide and iron oxide red. The white opaque capsule shell components contain gelatin and titanium dioxide. The capsule shells are printed with black printing ink.

PHARMACOLOGY

Pharmacodynamics

Crizotinib is an inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events). Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros) and Recepteur d'Origine Nantais (RON) RTKs. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1 and c-Met in biochemical assays and inhibited phosphorylation and modulated kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrated growth inhibitory activity and induced apoptosis in tumour cell lines exhibiting ALK fusion events (including echinoderm microtubule-associated protein-like 4 [EML4]-ALK and nucleophosmin [NPM]-ALK) or ROS1 fusion events.

Crizotinib demonstrated antitumour activity in mice bearing tumour xenografts that expressed ALK fusion proteins. The antitumour efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumours *in vivo*. Crizotinib also produced marked, dose-dependent regression of tumours in athymic mice with NIH-3T3 cell implants expressing human oncogenic ROS fusion proteins, and the antitumour efficacy of crizotinib was correlated with inhibition of ROS1 phosphorylation.

Pharmacokinetics

Absorption

Following oral single dose administration in the fasted state, crizotinib is absorbed with median time to achieve peak concentrations of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable with a median accumulation ratio of 4.8. The absolute bioavailability of crizotinib was determined to be 43% (range 32% to 66%) following the administration of a single 250 mg oral dose.

A high-fat meal reduced crizotinib area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) by approximately 14% when a 250 mg single dose was given to healthy volunteers. Crizotinib can be administered with or without food.

Distribution

The geometric mean volume of distribution (Vss) of crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins *in vitro* is 91%; in the *in vitro* study, there was variability in the fraction of unbound crizotinib at a clinically relevant concentration. *In vitro* studies suggest that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism

In vitro studies demonstrated that CYP3A4/5 were the major enzymes involved in the metabolic clearance of crizotinib. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-dealkylated metabolites.

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP2B6 and CYP3A.

Excretion

Following single doses of crizotinib, the apparent plasma terminal half-life of crizotinib was 42 hours in patients.

Following the administration of a single 250 mg radiolabelled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in faeces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in faeces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/hr) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Pharmacokinetics in Special Patient Groups

Hepatic Impairment

As crizotinib is extensively metabolised in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Clinical studies relevant to the indications excluded patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x ULN or, if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN. Study 1012 was an open-label, non-randomised clinical study of patients with advanced cancer (including mostly patients with hepatic and colon cancer in groups with hepatic impairment). Based on National Cancer Institute (NCI) classification, patients had either mild (either AST >Upper Limit of Normal (ULN) and total bilirubin ≤ULN or any AST and total bilirubin >ULN but £1.5×ULN), moderate (any AST and total bilirubin >1.5×ULN and £3×ULN) or severe (any AST and total bilirubin >3×ULN) hepatic impairment. Patients with advanced cancer with normal (AST and total bilirubin ≤ULN) hepatic function were matched controls for mild or moderate hepatic impairment.

Following crizotinib 250 mg twice daily dosing, patients with mild hepatic impairment (N=10) showed similar systemic crizotinib exposure at steady state compared to patients with normal hepatic function (N=8), with geometric mean ratios for area under the plasma concentration-time curve as daily exposure at steady state (AUC_{daily}) and C_{max} of 91.1% (90% CI: 56.6%, 146.8 %) and 91.2% (90% CI: 57.5%, 144.7%), respectively.

Following crizotinib 200 mg twice daily dosing, patients with moderate hepatic impairment (N=8) showed higher systemic crizotinib exposure compared to patients with normal hepatic function (N=9) at the same dose level, with geometric mean ratios for AUC_{daily} and C_{max} of 150% (90% CI: 91.8%, 243.5 %) and 144% (90% CI: 89.1%, 232.1%), respectively. However, the systemic crizotinib exposure in patients with moderate hepatic impairment at the dose of 200 mg twice daily was comparable to that observed from patients with normal hepatic function at a dose of 250 mg twice daily, with geometric mean ratios for AUC_{daily} and C_{max} of 114% (90% CI: 73.6 %, 176.9%) and 109% (90% CI: 70.1%, 169 %), respectively.

The systemic crizotinib exposure parameters AUC_{daily} and C_{max} in patients with severe hepatic impairment (N=6) receiving a crizotinib dose of 250 mg once daily were approximately 64.7% (90% CI: 39.5%, 105.9%) and 72.6% (90% CI: 49.1 %, 107.5%), respectively, of those from patients with normal hepatic function receiving a dose of 250 mg twice daily (see DOSAGE AND ADMINISTRATION – Dose Modification – *Hepatic Impairment* and PRECAUTIONS - Hepatotoxicity).

Renal Impairment

Patients with mild (creatinine clearance [CLcr] 60 to <90 mL/min) and moderate (CLcr 30 to <60 mL/min) renal impairment were enrolled in single-arm Studies 1001 and 1005. The effect of renal function, as measured by baseline CLcr on observed crizotinib steady-state trough concentrations ($C_{trough, ss}$) was evaluated. In Study 1001, the adjusted geometric mean of plasma $C_{trough, ss}$ in mild (N=35) and moderate (N=8) renal impairment patients were 5.1% and 11% higher, respectively, than those in patients with normal renal function. In Study 1005, the adjusted geometric mean $C_{trough, ss}$ of crizotinib in mild (N=191) and moderate (N=65) renal impairment groups were 9.1% and 15% higher, respectively, than those in patients with normal renal function. In addition, the population pharmacokinetic analysis from Studies 1001, 1005 and 1007 indicated CLcr did not have a clinically meaningful effect on the pharmacokinetics of crizotinib. Due to the small size of the increases in crizotinib exposure (5%-15%), no starting dose adjustment is recommended for patients with mild or moderate renal impairment.

After a single 250 mg dose in subjects with severe renal impairment (CLcr <30 mL/min) not requiring peritoneal dialysis or haemodialysis, crizotinib AUC_{inf} and C_{max} increased by 79% and 34%, respectively, compared to those with normal renal function. An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis (see DOSAGE AND ADMINISTRATION – Dose Modification – *Renal Impairment*).

Age

Based on the population pharmacokinetic analyses from Studies 1001, 1005 and 1007, age has no effect on crizotinib pharmacokinetics (see CLINICAL TRIALS - Elderly and DOSAGE AND ADMINISTRATION – Dose Modification – *Elderly*).

Body weight and gender

Based on the population pharmacokinetic analyses form Studies 1001, 1005 and 1007, there was no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics. No starting dose adjustment is required.

Ethnicity

Based on the population pharmacokinetic analyses form Studies 1001, 1005 and 1007, the predicted area under the plasma concentration-time curve at steady-state (AUC_{ss}) (95% CI) was 23%-37% higher in Asian patients (n=523) than in non-Asian patients (n=691).

Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in patients with either ALK-positive or ROS1-positive NSCLC who received crizotinib 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Thirty four of 1619 patients (2.1%) with at least 1 post-baseline ECG assessment were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec and 79 of 1585 patients (5.0%) with a baseline and at least 1 post-baseline ECG assessment had an increase from baseline QTcF ≥60 msec by automated machine-read evaluation of ECG (see PRECAUTIONS - QT Interval Prolongation).

An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. A central tendency analysis indicated that a QTc effect ≥20 msec can be excluded. A pharmacokinetic/ pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see PRECAUTIONS - QT Interval Prolongation).

CLINICAL TRIALS

Previously Untreated ALK-Positive Advanced NSCLC – Randomised Phase 3 Study 1014

The use of single-agent crizotinib for the first-line treatment of ALK-positive advanced NSCLC in patients with or without brain metastases was investigated in a multicentre, multinational, randomised, open-label Phase 3 Study 1014. The primary objective of this study was to demonstrate that crizotinib was superior to first-line standard-of-care platinum-based chemotherapy (pemetrexed-cisplatin or pemetrexed-carboplatin) in prolonging Progression-Free Survival (PFS) as assessed by independent radiology review (IRR) in patients with ALK-positive advanced NSCLC who had not received previous systemic treatment for advanced disease. Secondary objectives were to compare measures of clinical efficacy including Objective Response Rate (ORR) as assessed by IRR, Duration of Response (DR), Overall Survival (OS), Intracranial Time to Progression (IC-TTP) as assessed by IRR and Patient-Reported Outcomes (PRO).

The full analysis population for Study 1014 included 343 patients with ALK-positive advanced NSCLC as identified by Fluorescence In Situ Hybridisation (FISH) prior to randomisation. One hundred seventy-two (172) patients were randomised to the crizotinib arm (171 patients received crizotinib 250 mg orally twice daily) and 171 patients were randomised to the chemotherapy arm (169 patients received chemotherapy; 91 patients were treated with pemetrexed/cisplatin and 78 patients were treated with pemetrexed/carboplatin). Chemotherapy consisted of pemetrexed 500 mg/m^2 in combination with cisplatin 75 mg/m^2 or carboplatin at a dose calculated to produce an AUC of 5 or 6 mg • min/mL. Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles. The median duration of study treatment was 47 weeks in the crizotinib arm and 18 weeks in the chemotherapy arm. Patients could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Patients in the chemotherapy arm who completed 6 cycles were to continue in the study without further treatment, but have ongoing tumour assessments until RECIST-defined disease progression as determined by IRR. Patients in the chemotherapy arm who had RECIST-defined progression of disease as assessed by IRR had the option to receive crizotinib. One hundred twenty (70%) patients received

crizotinib after the randomisation phase (109 patients through the crossover process and 11 patients as follow-up therapy).

Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2), race (Asian vs non-Asian), and brain metastases (present vs absent).

Baseline demographic and disease characteristics were similar between the crizotinib and chemotherapy treatment arms with regard to gender (female: 61% vs 63% for crizotinib vs chemotherapy, respectively), median age (52 years vs 54 years), race (White: 53% vs 50%, and Asian: 45% vs 47%); smoking status (current smokers: 6% vs 3%, former smokers: 33% vs 32%, and never smokers: 62% vs 65%), metastatic disease (98% in both treatment arms), tumour histology (adenocarcinoma: 92% vs 93%), performance status (ECOG 0 or 1: 94% vs 95%, and ECOG 2: 6% vs 5%) and brain metastases (present 26% vs 28%).

Crizotinib significantly prolonged PFS compared to chemotherapy as assessed by IRR. OS data were not mature at the time of the PFS analysis. Efficacy data from Study 1014 are summarised in Table 1 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 1. Efficacy Results from Randomised Phase 3 Study 1014 (Full Analysis Population) in Patients with Previously Untreated ALK-Positive Advanced NSCLC

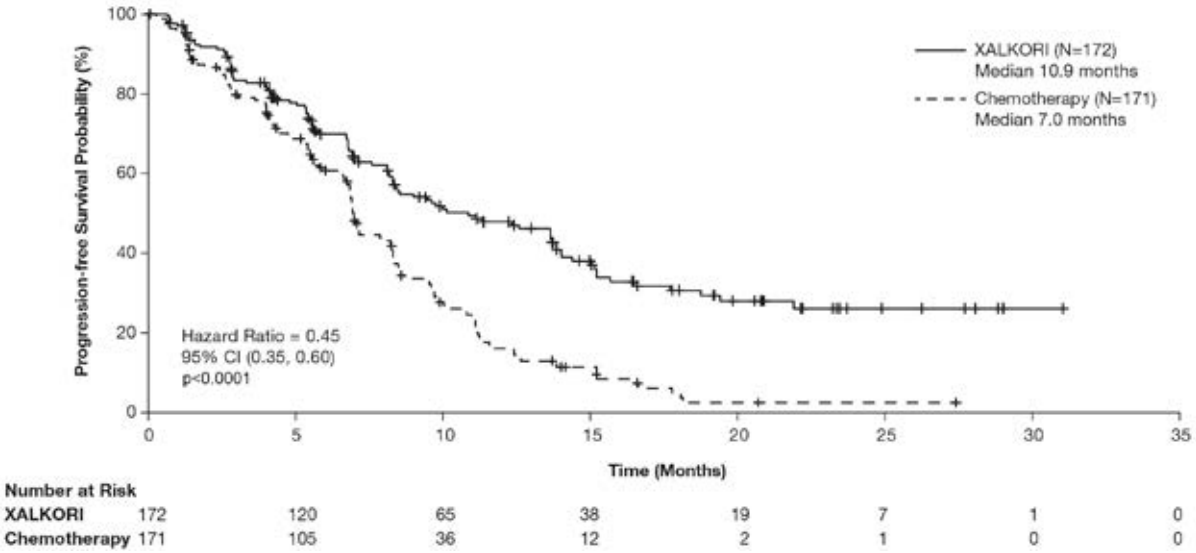
Response Parameter	**Crizotinib (N=172)**	**Chemotherapy (N=171)**
Progression-Free Survival (Based on IRR)		
Number with event, n (%)	100 (58%)	137 (80%)
Median PFS in months (95% CI)	10.9 (8.3, 13.9)	7.0[a] (6.8, 8.2)
HR (95% CI)[b]	0.45 (0.35, 0.60)	
p-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	44 (26%)	46 (27%)
Median OS in months (95% CI)	NR	NR
HR (95% CI)[b]	0.82 (0.54, 1.26)	
p-value[c]	0.1804	
12-Month survival probability[d] % (95% CI)	83.5 (76.7, 88.5)	78.6 (71.3, 84.2)
18-Month survival probability[d] % (95% CI)	68.6 (59.5, 76.1)	67.3 (58.1, 74.9)
Objective Response Rate (based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45%[e] (37, 53)
p-value[f]	<0.0001	
Duration of Response		
Months[g] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

Abbreviations: N/n=number of patients; CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; NR=not reached; PFS=progression-free survival; OS=overall survival.

a. Median PFS times were 6.9 months (95% CI: 6.6, 8.3) for pemetrexed/cisplatin (HR=0.49; p-value <0.0001 for crizotinib compared with pemetrexed/cisplatin) and 7.0 months (95% CI: 5.9, 8.3) for pemetrexed/carboplatin (HR=0.45; p-value <0.0001 for crizotinib compared with pemetrexed/carboplatin).
b. Based on the Cox proportional hazards stratified analysis.
c. Based on the stratified log-rank test (1-sided).
d. OS analysis was not adjusted for the potentially confounding effects of crossover.

e. ORRs were 47% (95% CI: 37, 58) for pemetrexed/cisplatin (p-value <0.0001 compared with crizotinib) and 44% (95% CI: 32, 55) for pemetrexed/carboplatin (p-value <0.0001 compared with crizotinib).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 1. Kaplan-Meier Curves for Progression-Free Survival (Based on IRR) by Treatment Arm in Study 1014 (Full Analysis Population) in Patients with Previously Untreated ALK-Positive Advanced NSCLC

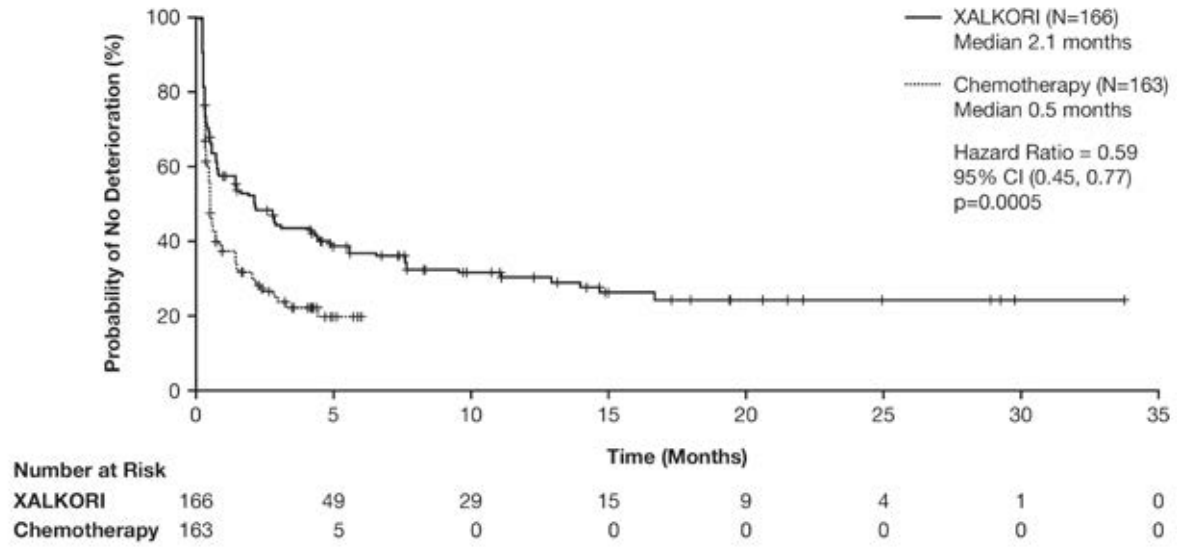


Based on IRR assessment, a total of 9 (23.1%) of the 39 patients in the crizotinib arm and 12 (30.0%) of the 40 patients in the chemotherapy arm with previously treated baseline brain metastases experienced progression of intracranial lesions or developed new intracranial lesions. For patients with previously treated baseline brain metastases, the median intracranial TTP (IC-TTP) was 15.7 months in the crizotinib arm and 12.5 months in the chemotherapy arm (HR=0.45 [95% CI: 0.19, 1.07]; 1-sided p-value=0.0315). A total of 16 (12.1%) of the 132 patients in the crizotinib arm and 14 (10.7%) of the 131 patients in the chemotherapy arm without baseline brain metastases developed new intracranial lesions. For patients without baseline brain metastases, the median IC-TTP was not reached in either the crizotinib or the chemotherapy arms (HR=0.69 [95% CI: 0.33, 1.45]; 1-sided p-value=0.1617).

Patient-reported symptoms and global QOL was collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1), Day 7 and Day 15 of Cycle 1, and Day 1 of each subsequent treatment cycle. A total of 166 patients in the crizotinib arm and 163 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC-13 questionnaires at baseline and at least 1 post-baseline visit.

Time to Deterioration (TTD) was pre-specified as the time from randomisation to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough) or dyspnoea (EORTC QLQ-LC13 dyspnoea). The median TTD in patient-reported pain in chest, dyspnoea or cough as a composite endpoint was 2.1 months (95% CI: 0.8 months, 4.2 months) in the crizotinib arm compared to 0.5 months (95% CI: 0.4 months, 0.7 months) in the chemotherapy arm. Treatment with crizotinib was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnoea or cough compared to chemotherapy (hazard ratio 0.59; 95% CI: 0.45, 0.77; Hochberg-adjusted log-rank 2-sided p-value=0.0005).

Figure 2. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnoea or Cough (Composite Endpoint) by Treatment Arm (Patient-Reported Outcome Evaluable Population) in Patients with Previously Untreated ALK-Positive Advanced NSCLC



The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 13.8; p-value <0.0001).

Previously Treated ALK-Positive Advanced NSCLC – Randomised Phase 3 Study 1007

The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in a multicentre, multinational, randomised, open-label Phase 3 study (Study 1007). The primary objective of this study was to demonstrate that crizotinib 250 mg orally twice daily was superior to standard-of-care chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) intravenously (IV) every 21 days in prolonging Progression-Free Survival (PFS) in patients with ALK-positive advanced NSCLC who had received one prior chemotherapy regimen. Patients were required to have ALK-positive NSCLC as identified by FISH prior to randomisation. Patients randomised to chemotherapy could cross over to receive crizotinib in Study 1005 upon RECIST-defined disease progression confirmed by independent radiology review (IRR). The primary efficacy endpoint was PFS with disease progression events determined by IRR. Secondary endpoints included ORR as determined by IRR, DR, OS and PRO.

The full analysis population for Study 1007 included 347 patients with ALK-positive advanced NSCLC. One hundred seventy-three (173) patients were randomised to the crizotinib arm (172 patients received crizotinib) and 174 patients were randomised to the chemotherapy arm, (99 [58%] patients received pemetrexed and 72 [42%] patients received docetaxel). Randomisation was stratified by ECOG performance status (PS) (0-1, 2), brain metastases (present, absent) and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The median duration of study treatment was 31 weeks in the crizotinib arm as compared to 12 weeks in the chemotherapy arm.

Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Fifty eight of 84 (69%) patients treated with crizotinib and 17 of 119 (14%) patients treated with chemotherapy continued treatment for at least 3 weeks after objective disease progression.

Baseline demographic and disease characteristics for patients in this study were similar between the crizotinib and chemotherapy arms with regard to gender (female: 57% vs 55% for crizotinib vs chemotherapy, respectively), median age (51 years vs 49 years), race (White: 52% in both treatment arms, and Asian: 46% vs 45%), smoking status (current smokers: 3% vs 5%, former smokers: 34% vs 31%, and never smokers: 62% vs 64%), metastatic disease (95% vs 91%), tumour histology (adenocarcinoma: 94% vs 92%), performance status (ECOG 0 or 1: 89% vs 91%, ECOG 2: 11% vs 9%) and brain metastases (present: 35% in both treatment arms).

Crizotinib significantly prolonged PFS compared to chemotherapy as assessed by IRR. Efficacy data from Study 1007 are summarised in Table 2 and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 2. Efficacy Results from Randomised Phase 3 Study 1007 (Full Analysis Population) in Patients with Previously Treated ALK-Positive Advanced NSCLC*

Response Parameter	Crizotinib (N=173)	Chemotherapy (N=174)
Progression-Free Survival (Based on IRR)		
Number with event, n (%)	100 (58%)	127 (73%)
Median PFS in months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37, 0.64)	
p-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	116 (67%)	126 (72%)
Median OS in months (95% CI)	21.7 (18.9, 30.5)	21.9 (16.8, 26.0)
HR (95% CI)[b]	0.85 (0.66, 1.10)	
p-value[c]	0.1145	
Objective Response Rate (based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20%[e] (14, 26)
p-value[f]	<0.0001	
Duration of Response		
Median[g], months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

Abbreviations: N/n=number of patients; CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; PFS=progression-free survival; OS=overall survival.

* PFS, ORR and DR are based on the data cutoff date of 30 March 2012; OS is based on the data cutoff date of 31 August 2015.

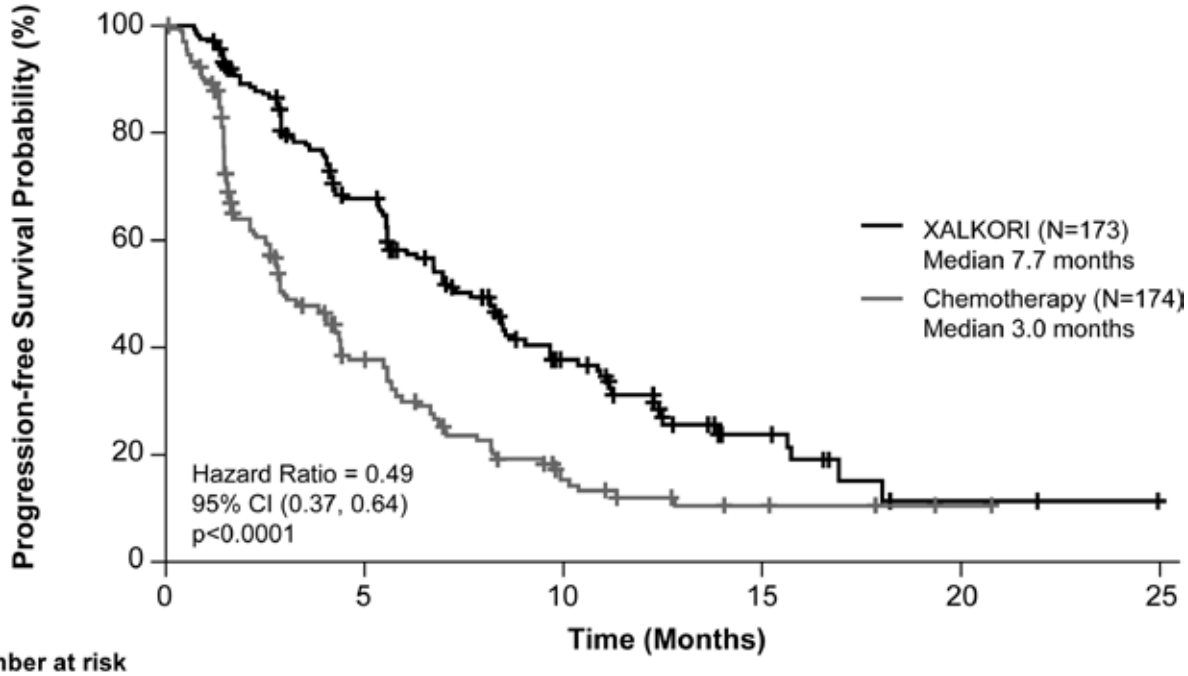
a. Median PFS times were 4.2 months (95% CI: 2.8, 5.7) for pemetrexed (HR=0.59; p-value=0.0004 for crizotinib compared with pemetrexed) and 2.6 months (95% CI: 1.6, 4.0) for docetaxel (HR=0.30; p-value <0.0001 for crizotinib compared with docetaxel).

b. Based on the Cox proportional hazards stratified analysis.

c. Based on the stratified log-rank test (1-sided).

d. Based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of crossover.
e. ORRs were 29% (95% CI: 21, 39) for pemetrexed (p-value <0.0001 compared with crizotinib) and 7% (95% CI: 2, 16) for docetaxel (p-value <0.0001 compared with crizotinib).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 3. Kaplan-Meier Curves for Progression-Free Survival (Based on IRR) by Treatment Arm in Randomised Phase 3 Study 1007 (Full Analysis Population) in Patients with Previously Treated ALK-Positive Advanced NSCLC



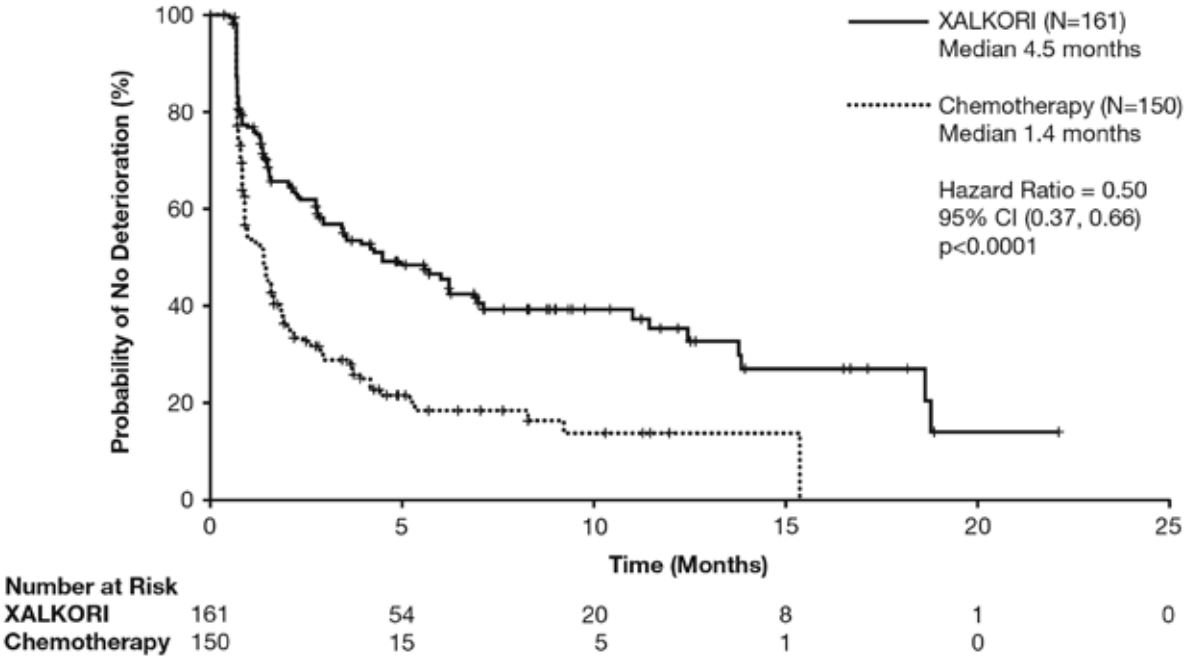
Number at risk						
XALKORI	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Patient reported symptoms and global QOL were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1 Cycle 1) and Day 1 of each subsequent treatment cycle. A total of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 post-baseline visit.

TTD was pre-specified as the time from randomisation to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough) or dyspnoea (EORTC QLQ-LC13 dyspnoea). The median TTD in patient-reported pain in chest, dyspnoea or cough as a composite endpoint was 4.5 months (95% CI: 3.0 months, 6.9 months) in the crizotinib arm compared to 1.4 months (95% CI: 1.0 months, 1.6 months) in the chemotherapy arm. Treatment with crizotinib was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnoea or cough compared to chemotherapy (hazard ratio 0.50; 95% CI: 0.37, 0.66; Hochberg-adjusted log-rank p-value <0.0001). The Kaplan-Meier Plot of TTD in pain in chest, dyspnoea or cough as a composite endpoint by arm for the patient-reported outcome evaluable population is shown in Figure 4.

The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 9.84; p-value <0.0001).

Figure 4. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnoea or Cough (Composite Endpoint) by Treatment Arm (Patient-Reported Outcome Evaluable Population) in Patients with Previously Treated ALK-Positive Advanced NSCLC



Single-Arm Studies in ALK-Positive Advanced NSCLC

The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in two multicentre, multinational, single-arm studies (Studies 1001 and 1005). Patients enrolled into these studies had received prior systemic therapy, with the exception of 22 patients in Study 1001 and 3 patients in Study 1005 who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was ORR according to RECIST. Secondary endpoints included Time to Tumour Response (TTR), DR, Disease Control Rate (DCR), PFS and OS. Patients received 250 mg of crizotinib orally twice daily.

In Study 1001 (N=149), the demographic characteristics were 49% female; median age 52 years; baseline ECOG performance status of 0 or 1 (88%) and 2 or 3 (12%), 64% White and 28% Asian; <1% current smokers, 28% former-smokers and 71% never smokers. The disease characteristics were 94% metastatic, 97% adenocarcinoma histology and 15% with no prior systemic therapy for metastatic disease.

In Study 1005 (N=934), the demographic characteristics were 57% female; median age 53 years; baseline ECOG performance status of 0/1 (82%) or 2/3 (18%), 52% White and 44% Asian; and 4% current smokers, 30% former smokers and 66% never smokers. The disease characteristics were 92% metastatic, 94% adenocarcinoma histology.

In Study 1001, patients with advanced NSCLC were required to have ALK-positive tumours prior to entering the clinical trial. ALK-positive NSCLC was identified using a number of local clinical trial assays. One hundred forty-nine patients with ALK-positive advanced NSCLC were enrolled into Study 1001 at the time of data cutoff for the PFS and ORR analyses. The median duration of treatment was 43 weeks. There were 3 complete responses and 85 partial responses for an ORR of 62%. The median response duration was 49.1 weeks. There were an additional 30 patients who had stable disease for a DCR at 8 weeks of 83%. Fifty-one percent of objective tumour responses were achieved during the first 8 weeks of treatment. Study 1001 OS data were updated based on 154 ALK-positive advanced NSCLC patients. The median OS at the time of data cutoff was 28.9 months (95% CI: 21.1, 40.1).

In Study 1005, patients with advanced NSCLC were required to have ALK-positive tumours prior to entering the clinical trial. For most patients, ALK-positive NSCLC was identified by FISH. Nine hundred thirty-four patients with ALK-positive advanced NSCLC were treated with crizotinib in Study 1005 at the time of data cutoff for the PFS and ORR analyses. The median duration of treatment for these patients was 23 weeks. Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression at the discretion of the investigator if the benefit/risk assessment justified continuation of treatment. Seventy-seven of 106 patients (73%) continued crizotinib treatment for at least 3 weeks after objective disease progression.

Seven hundred sixty-five patients with ALK-positive advanced NSCLC from Study 1005 were both evaluable for response and identified by the same FISH assay used in randomised Phase 3 Study 1007. There were 8 complete responses and 357 partial responses for an ORR of 48% The median DR was 47 weeks. Eighty-three percent of objective tumour responses were achieved within the first 12 weeks of treatment. Study 1005 OS data were updated based on 905 ALK-positive advanced NSCLC patients identified by the same FISH assay used in randomised Phase 3 Study 1007. The median OS at the time of data cutoff was 21.5 months (95% CI: 19.3, 23.6).

Efficacy data from Studies 1001 and 1005 are provided in Table 3.

Table 3. ALK-Positive Advanced NSCLC Efficacy Results from Studies 1001 and 1005

Efficacy Parameter	**Study 1001**	**Study 1005**
	N=149[a]	**N=765**[a]
ORR[b] [% (95% CI)]	62 (53, 70)	48 (44, 51)
TTR [median (range)] weeks	7.9 (2.1, 57.3)	6.1 (3, 49)
DR[c] [median (95% CI)] weeks	49.1 (39.3, 89.3)	47.3 (36, 54)
PFS[c] [median (95% CI)] months	9.9 (7.7, 13.4)	7.8 (6.9, 9.5)[d]
	N=154[e]	**N=905**[e]
Number of deaths, n (%)	83 (54%)	504 (56%)
OS[c] [median (95% CI)] months	28.9 (21.1, 40.1)	21.5 (19.3, 23.6)

Abbreviations: N/n=number of patients; CI=confidence interval: ORR=objective response rate; TTR=time to tumour response; DR=duration of response; PFS=progression-free survival; OS=overall survival.

a, Per data cutoff dates 1 June 2011 (Study 1001) and 15 February 2012 (Study 1005).

b. 6 patients were not evaluable for response in Study 1001 and42 patients were not evaluable for response in Study 1005.

c. Estimated using the Kaplan-Meier method.

d. PFS data from Study 1005 included 807 patients in the safety analysis population who were identified by the FISH assay (per data cutoff date 15 February 2012).

e. Per data cutoff date 30 November 2013.

ROS1-Positive Advanced NSCLC

The use of single-agent crizotinib in the treatment of ROS1-positive advanced NSCLC was investigated in multicentre, multinational, single-arm Study 1001. A total of 53 ROS1-positive advanced NSCLC patients were enrolled in the study at the time of data cutoff, including 46 patients with previously treated ROS1-positive advanced NSCLC and 7 patients who had no prior systemic treatment. The primary efficacy endpoint was ORR according to RECIST as assessed by investigator. Secondary endpoints included ORR as assessed by IRR, TTR, DR, PFS and OS. Patients received crizotinib 250 mg orally twice daily.

The demographic characteristics were 57% female; median age 55 years; baseline ECOG performance status of 0 or 1 (98%) or 2 (2%), 57% White and 40% Asian; 25% former smokers, and 75% never smokers. The disease characteristics were 91% metastatic, 96% adenocarcinoma histology and 13% with no prior systemic therapy for metastatic disease.

In Study 1001, patients were required to have ROS1-positive advanced NSCLC prior to entering the clinical trial. For most patients, ROS1-positive NSCLC was identified by FISH. The median duration of treatment was 101 weeks. There were 5 complete responses and 32 partial responses for an ORR of 70% (95% CI: 56%, 82%). The median DR was not reached (95% CI: 15.2 months, NR). Fifty-one percent of objective tumour responses were achieved during the first 8 weeks of treatment. The median PFS at the time of data cutoff was 19.3 months (95% CI: 14.8, NR). Overall survival data were not mature at the time of data cutoff. Efficacy data from ROS1-positive advanced NSCLC patients from Study 1001 are provided in Table 4.

Table 4. ROS1-Positive Advanced NSCLC Efficacy Results from Study 1001

Efficacy Parameter[a]	**Study 1001**
	N=53[b]
ORR [% (95% CI)]	70 (56, 82)
ORR[c] [% (95% CI)] (Independent Radiology Review)	66 (51, 79)
TTR [median (range)] weeks	8 (4, 32)
DR[d] [median (95% CI)] months	NR (15.2, NR)
PFS[d] [median (95% CI)] months	19.3 (14.8, NR)

Abbreviations: N=number of patients; CI=confidence interval: ORR=objective response rate; NR=not reached; TTR=time to tumour response; DR=duration of response; PFS=progression-free survival.

a. All efficacy analyses dependent on disease assessments were based on the derived investigator assessment of tumour data except where otherwise indicated.
b. Per data cutoff date 30 November 2014.
c. Based on N=50.
d. Estimated using the Kaplan-Meier method.

Elderly

Of 171 ALK-positive NSCLC patients treated with crizotinib in randomised Phase 3 Study 1014, 22 (13%) were 65 years or older, and of 109 ALK-positive patients treated with crizotinib who crossed over from the chemotherapy arm, 26 (24%) were 65 years or older. Of 172 ALK-positive patients treated with crizotinib in Phase 3 Study 1007, 27 (16%) were 65 years or older. Of 154 and 1063 ALK-positive NSCLC patients in single arm studies 1001 and 1005, 22 (14%) and 173 (16%) were 65 years or older, respectively. In ALK-positive

NSCLC patients, the frequency of adverse reactions was generally similar for patients <65 years of age and patients ³ 65 years of age with the exception of oedema and constipation, which were reported with greater frequency in Study 1014 among patients treated with crizotinib ³ 65 years of age. No overall differences in safety or efficacy were observed in comparison with younger patients. Of the 53 ROS1-positive NSCLC patients in single arm Study 1001, 15 (28%) were 65 years or older.

INDICATIONS

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

XALKORI is indicated for the treatment of patients with ROS1-positive advanced non-small cell lung cancer (NSCLC).

CONTRAINDICATIONS

Use of XALKORI is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients.

PRECAUTIONS

Assessment of ALK and ROS1 status

When assessing either ALK or ROS1 status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of 1722 patients treated with crizotinib across clinical trials. Concurrent elevations in ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN without significant elevations of alkaline phosphatase (≤2×ULN) have been observed in less than 1% patients treated with crizotinib.

Transaminase elevations generally occurred within the first 2 months of treatment. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC, median time to onset of increased Grade 1 or 2 transaminases was 23 days. Median time to onset of increased Grade 3 or 4 transaminases was 43 days. Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of patients, respectively.

Grade 3 and 4 transaminase elevations were generally reversible upon dosing interruption. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), dose reductions associated with transaminase elevations occurred in 76 (4%) patients. Seventeen (1%) patients required permanent discontinuation from treatment associated with elevated transaminases, suggesting that these events were generally manageable by dosing modifications as defined in Table 9 (see DOSAGE AND ADMINISTRATION – Dose Modification).

Liver function tests including ALT, AST and total bilirubin should be monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevations. For patients with hepatic impairment at commencement, monitoring once a week is recommended for the first 4 weeks, every 2 weeks for the next 4 weeks and then monthly, with appropriate dose interruptions or modifications (see DOSAGE AND ADMINISTRATION - Dose Modification). For patients who develop transaminase elevations, see DOSAGE AND ADMINISTRATION - Dose Modification.

Interstitial Lung Disease (Pneumonitis)

Crizotinib has been associated with severe, life-threatening or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials with a frequency of 26 (2%) of 1722 patients treated with crizotinib. These cases generally occurred within 90 days (range 5 days to 790 days) after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of pneumonitis should be excluded. Crizotinib should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see DOSAGE AND ADMINISTRATION - Dose Modification).

QT Interval Prolongation

Automated machine-read QTc prolongation without accompanying arrhythmia has been observed (see PHARMACOLOGY - *Cardiac Electrophysiology*). Crizotinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation or who are taking medications that are known to prolong the QT interval. When using crizotinib in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered. For patients who develop QTc prolongation, see DOSAGE AND ADMINISTRATION - Dose Modification.

Bradycardia

Bradycardia has been reported in clinical studies and it was usually asymptomatic. The full effect of crizotinib on pulse rate may not develop until several weeks after start of treatment. Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Monthly monitoring of pulse rate and blood pressure is recommended. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia, crizotinib should be withheld and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see DOSAGE AND ADMINISTRATION - Dose Modification and ADVERSE EFFECTS).

Cardiac Failure

In clinical studies with crizotinib and during post-marketing surveillance, severe, life-threatening or fatal adverse events of cardiac failure were reported (see ADVERSE EFFECTS).

Patients with or without pre-existing cardiac disorders receiving crizotinib should be monitored for signs and symptoms of heart failure. Dosing interruption, dose reduction or discontinuation should be considered as appropriate if such symptoms are observed.

Leucopenia

Crizotinib has been associated with neutropenia and, less commonly, febrile neutropenia. Dosing interruption is recommended in patients with Grade 3-4 neutropenia (see DOSAGE AND ADMINISTRATION - Dose Modification). Onset of neutropenia may occur after many months of exposure to crizotinib. Lymphopenia has also been observed. Monitor white blood cell count (including differential count) monthly and additionally as clinically indicated (e.g., if Grade 3-4 abnormalities are observed, or if fever or infection occurs).

Gastrointestinal Perforation

Crizotinib should be used with caution in patients at risk for gastrointestinal perforation (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medications with a recognised risk of gastrointestinal perforation).

Crizotinib should be discontinued in patients who develop gastrointestinal perforation. Patients should be informed of the signs of gastrointestinal perforation and be advised to consult their doctor immediately if these signs are experienced.

Visual Effects

In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss.

In patients with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), crizotinib treatment should be discontinued. Ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss should be performed. There is insufficient information to characterise the risks of resumption of crizotinib in patients with a severe visual loss. A decision to resume crizotinib should consider the potential benefit to the patient.

Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity.

Effects on Fertility

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given ≥50 mg/kg/day for 28 days (approximately 2-fold human clinical exposure based on AUC). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day for 3 days. Exposure at the no effect level for male reproductive organ effects was less than the clinical AUC and 4 times the clinical AUC for female reproductive organ effects.

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with crizotinib.

Use in Pregnancy (Category D)

Crizotinib may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using crizotinib. Crizotinib was not shown to be teratogenic in pregnant rats or rabbits, but the maximum doses (200 and 60 mg/kg/day, respectively) were low, resulting in maximum exposures of only 3 and 2 times the human clinical exposure based on AUC in rats and rabbits, respectively. Reduced fetal body weights were observed in both species at 200 and 60 mg/kg/day in the rat and rabbit, respectively and were considered adverse effects. Exposure at the no effect level was similar to or below the human clinical exposure based on AUC.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving crizotinib. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

Female patients taking crizotinib during pregnancy or who become pregnant while taking crizotinib should be apprised of the potential hazard to a fetus. Male patients taking crizotinib should also be apprised of the potential hazard to a fetus if their partner is or should become pregnant.

Use in Lactation

It is not known whether crizotinib and its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from exposure to crizotinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

The safety and efficacy of XALKORI in paediatric patients have not been established.

Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 5 times human clinical exposure based on AUC in adult patients). Exposure at the no effect level was approximately 2 times the AUC in adult patients at the recommended human dose. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

Use in the Elderly

No overall differences in safety or efficacy were observed in comparison with younger patients, and no starting dose adjustment is required (see PHARMACOLOGY - *Pharmacokinetics in Special Patient Groups – Age,* CLINICAL TRIALS – Elderly and DOSAGE AND ADMINISTRATION – Dose Modification – *Elderly*).

Use in Hepatic Impairment

Crizotinib should be used with caution in patients with hepatic impairment (see PHARMACOLOGY - *Pharmacokinetics in Special Patient Groups – Hepatic Impairment* and DOSAGE AND ADMINISTRATION – Dose Modification – *Hepatic Impairment*).

Use in Renal Impairment

No starting dose adjustment is needed for patients with mild or moderate renal impairment, since the population pharmacokinetic analysis indicated no clinically meaningful changes in steady-state crizotinib exposure in these patients (see PHARMACOLOGY - *Pharmacokinetics in Special Patient Groups – Renal Impairment*). If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of crizotinib should be adjusted (see DOSAGE AND ADMINISTRATION – Dose Modification – *Renal Impairment*).

Genotoxicity

Crizotinib was genotoxic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cells, in an *in vitro* human lymphocyte chromosome aberration assay and in an *in vivo* rat bone marrow micronucleus assay. Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity studies with crizotinib have not been performed.

In vitro Phototoxicity

The results of an *in vitro* phototoxicity study demonstrated that crizotinib may have phototoxic potential.

Effects on Ability to Drive and Use of Machines

No studies on the effect of crizotinib on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness or fatigue while taking XALKORI.

INTERACTIONS WITH OTHER MEDICINES

Crizotinib is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A. *In vitro* studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

Agents that may increase crizotinib plasma concentrations - Coadministration of Crizotinib and CYP3A Inhibitors

Coadministration of crizotinib with strong CYP3A inhibitors may increase crizotinib plasma concentrations. Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, of those seen when crizotinib was administered alone. Coadministration of crizotinib (250 mg once daily) with itraconazole (200 mg once daily), a strong CYP3A inhibitor, resulted in 57% and 33% increases in crizotinib steady-state area under the plasma concentration-time curve from 0 hour to time tau, the dosing interval (AUC_{tau}) and C_{max}, respectively, compared to when crizotinib was given alone.

Therefore, the concomitant use of strong CYP3A inhibitors (certain protease inhibitors such as atazanavir, indinavir, ritonavir and saquinavir, certain azole antifungals such as itraconazole, ketoconazole and voriconazole, certain macrolides such as clarithromycin and troleandomycin) should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided.

Agents that may decrease crizotinib plasma concentrations - Coadministration of Crizotinib and CYP3A Inducers

Coadministration of crizotinib (250 mg twice daily) with rifampicin (600 mg once daily), a strong CYP3A4 inducer, resulted in 84% and 79% decreases in crizotinib steady-state AUC_{tau} and C_{max}, respectively, compared to when crizotinib was given alone. Coadministration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's wort, should be avoided.

Agents whose plasma concentrations may be altered by crizotinib

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Caution should be exercised in administering crizotinib in combination with drugs that are predominantly metabolised by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, fentanyl, sirolimus and tacrolimus.

Coadministration of crizotinib should be avoided with CYP3A substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias, including but not limited to ergotamine.

Coadministration of Crizotinib and CYP3A Substrates

Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC_{inf} was 3.7-fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Coadministration with other CYP Substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

Crizotinib is an inhibitor of CYP2B6 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are predominantly metabolised by CYP2B6. *In vitro* studies in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A.

Coadministration with UGT Substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for uridine diphosphate glucuronosyltransferase (UGT)1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Coadministration with Drugs that are Substrates of Transporters

Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are substrates of P-gp.

Crizotinib is an inhibitor of hepatic uptake transporter, organic cation transporter 1 (OCT1) and renal uptake transporter, organic cation transporter 2 (OCT2) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered drugs that are substrates of OCT1 or OCT2.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins organic anion transporting polypeptide (OATP)1B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT)1 or OAT3 at clinically relevant concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic or renal uptake of drugs that are substrates for these transporters.

Effect on Other Transport Proteins

In vitro, crizotinib is not an inhibitor of hepatic efflux bile salt export pump transporter (BSEP) at clinically relevant concentrations.

Coadministration of Crizotinib with Agents that Increase Gastric pH

The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Administration of a single 250 mg crizotinib dose following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 10% decrease in crizotinib total exposure (AUC_{inf}) and no change in peak exposure (C_{max}); the extent of the change in total exposure was not clinically meaningful. Therefore, starting dose adjustment is not required when crizotinib is coadministered with agents that increase gastric pH (such as proton-pump inhibitors, H_2 blockers or antacids).

ADVERSE EFFECTS

Summary of Safety Profile

The data described below reflect exposure to crizotinib in 1669 patients with ALK-positive advanced NSCLC who participated in randomised Phase 3 Studies 1007 and 1014 or in single-arm Studies 1001 and 1005 with the data cutoff date of 30 November 2013, and in 53 patients with ROS1-positive advanced NSCLC who participated in single-arm Study 1001 with the data cutoff date of 30 November 2014, for a total of 1722 patients (see CLINICAL TRIALS). These patients received a starting oral dose of 250 mg taken twice daily continuously. In Study 1014, the median duration of study treatment was 47 weeks for patients in the crizotinib arm (N=171); the median duration of treatment was 23 weeks for patients who crossed over from the chemotherapy arm to receive crizotinib treatment (N=109). In Study 1007, the median duration of treatment was 48 weeks for patients in the crizotinib arm (N=172). For ALK-positive NSCLC patients in Studies 1001 (N=154) and 1005 (N=1063), the median duration of treatment was 57 and 45 weeks, respectively. For ROS1-positive NSCLC patients in Study 1001 (N=53), the median duration of treatment was 101 weeks.

Clinical Trials Experience

The most serious adverse reactions in 1722 patients with either ALK-positive or ROS1-positive advanced NSCLC were hepatotoxicity, ILD/pneumonitis and QT interval prolongation (see PRECAUTIONS). The most common adverse reactions (≥25%) in patients with either ALK-positive or ROS1-positive NSCLC were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness and neuropathy.

In 1722 patients with either ALK-positive or ROS1-positive NSCLC treated with crizotinib, all-causality adverse events associated with dosing interruptions or dose reductions occurred in 763 (44%) and 259 (15%) patients, respectively. All-causality adverse events associated with permanent treatment discontinuation occurred in 302 (18%) patients.

ADR Frequency and Category Overview Table

Table 5 presents adverse drug reactions experienced by ALK-positive NSCLC patients who participated in randomised Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001 or 1005 (N=1669) and in ROS1-positive NSCLC patients who participated in single-arm Study 1001 (N=53) for a total dataset of 1722 patients (see CLINICAL TRIALS).

Note: The adverse drug reactions are listed by System Organ Class (SOC) and frequency categories, defined using the following conventions: very common (³ 1/10), common (³ 1/100 to <1/10), uncommon (³ 1/1000 to <1/100), rare (³ 1/10,000 to <1/1,000), and very rare (<1/10,000). The adverse drug reactions are listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

Table 5. Adverse Drug Reactions for Crizotinib*

System Organ Class	Frequency Category	Adverse Drug Reaction	Frequency (%)
Blood and Lymphatic System Disorders	Very common	Neutropenia[a]	22
		Leucopenia[b]	15
Metabolism and Nutrition Disorders	Very common	Decreased appetite	30
Nervous System Disorders	Very common	Neuropathy[c]	25
		Dizziness[d]	26
		Dysgeusia	21
Eye Disorders	Very common	Vision disorder[e]	63
Cardiac Disorders	Very common	Bradycardia[f]	13
	Common	Cardiac failure[g]	1
		Prolonged electrocardiogram QT	4
		Syncope	3

System Organ Class	Frequency Category	Adverse Drug Reaction	Frequency (%)
Respiratory, Thoracic and Mediastinal Disorders	Common	Interstitial lung disease[h]	3
Gastrointestinal Disorders	Very common	Vomiting	51
		Diarrhoea	54
		Nausea	57
		Constipation	43
	Common	Oesophagitis[i]	2
		Dyspepsia	8
Hepatobiliary Disorders	Very common	Elevated transaminases[j]	32
	Common	Increased blood alkaline phosphatase	7
	Uncommon	Hepatic failure	<1
Skin and Subcutaneous Tissue Disorders	Very common	Rash	13
Renal and Urinary Disorders	Common	Renal Cyst[k]	3
		Increased blood creatinine[l]	8
General Disorders and Administration Site Conditions	Very common	Oedema[m]	47
		Fatigue	30
Investigations	Common	Decreased blood testosterone[n]	2

* The percentages of adverse drug reactions were based on the data cutoff date of 30 November 2013 for patients with ALK-positive NSCLC and based on the data cutoff date of 30 November 2014 for patients with ROS1-positive NSCLC.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

a. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased).
b. Leucopenia (Leucopenia, White blood cell count decreased).
c. Neuropathy (Burning sensation, Dysaesthesia, Formication, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Polyneuropathy, Sensory disturbance, Skin burning sensation).
d. Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope).
e. Vision disorder (Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Visual perseveration, Vitreous floaters).
f. Bradycardia (Bradycardia, Heart rate decreased, Sinus bradycardia).
g. Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema). Across clinical studies (n=1722), 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.
h. Interstitial lung disease (Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis).
i. Oesophagitis (Oesophagitis, Oesophageal ulcer).
j. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased).
k. Renal cyst (Renal abscess, Renal cyst, Renal cyst haemorrhage, Renal cyst infection).
l. Increased blood creatinine (Blood creatinine increased, Creatinine renal clearance decreased).
m. Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).
n. Decreased blood testosterone (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Previously Untreated ALK-Positive Advanced NSCLC - Randomised Phase 3 Study 1014

The safety analysis population in randomised Phase 3 Study 1014 included 171 patients who received crizotinib and 169 patients who received chemotherapy (91 pemetrexed in combination with cisplatin, 78 pemetrexed in combination with carboplatin). The median duration of study treatment was 47 weeks for patients on crizotinib and 18 weeks for patients on chemotherapy for which a maximum of 6 cycles was permitted.

All-causality adverse events associated with dosing interruptions occurred in 70 (41%) patients on crizotinib and 58 (34%) patients on chemotherapy. All-causality adverse events associated with dose reductions occurred in 11 (6%) patients on crizotinib and 14 (8%) patients on chemotherapy. All-causality adverse events associated with permanent discontinuation from treatment occurred in 21 (12%) patients on crizotinib and 24 (14%) patients on chemotherapy.

Table 6 presents adverse drug reactions experienced by patients in both the crizotinib and chemotherapy arms of randomised Phase 3 Study 1014. The conventions for adverse reactions listed by SOC and frequency categories are defined above. The adverse drug reactions are listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

Table 6. Adverse Drug Reactions Reported in Patients Who Received Crizotinib or Chemotherapy in Randomised Phase 3 Study 1014

Adverse Drug Reaction	Frequency category	Crizotinib (N=171)		Chemotherapy (N=169)	
		All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Blood and Lymphatic System Disorders					
Neutropenia[a]	Very common	36 (21)	19 (11)	51 (30)	26 (15)
Leucopenia[b]	Common	12 (7)	3 (2)	26 (15)	9 (5)
Metabolism and Nutrition Disorders					
Decreased appetite	Very common	51 (30)	4 (2)	57 (34)	1 (<1)
Nervous System Disorders					
Neuropathy[c]	Very common	35 (21)	2 (1)	38 (23)	0 (0)
Dizziness[d]	Very common	31 (18)	0 (0)	17 (10)	2 (1)
Dysgeusia	Very common	45 (26)	0 (0)	9 (5)	0 (0)
Eye Disorders					
Vision disorder[e]	Very common	122 (71)	1 (<1)	16 (10)	0 (0)
Cardiac Disorders					
Bradycardia[f]	Very common	23 (14)	2 (1)	1 (<1)	0 (0)
Cardiac failure[g]	Common	4 (2)	1 (<1)	1 (<1)	0 (0)
Prolonged electrocardiogram QT	Common	10 (6)	4 (2)	3 (2)	0 (0)
Syncope	Uncommon	1 (<1)	1 (<1)	2 (1)	2 (1)
Respiratory, Thoracic and Mediastinal Disorders					
Interstitial lung disease[h]	Common	2 (1)	1 (<1)	1 (<1)	0 (0)
Gastrointestinal Disorders					
Vomiting	Very common	78 (46)	3 (2)	60 (36)	5 (3)
Diarrhoea	Very common	105 (61)	4 (2)	22 (13)	1 (<1)
Nausea	Very common	95 (56)	2 (1)	99 (59)	3 (2)
Constipation	Very common	74 (43)	3 (2)	51 (30)	0 (0)
Dyspepsia	Very common	23 (14)	0 (0)	4 (2)	0 (0)

Adverse Drug Reaction	Frequency category	Crizotinib (N=171)		Chemotherapy (N=169)	
		All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Oesophagitis[i]	Common	10 (6)	3 (2)	1 (<1)	0 (0)
Hepatobiliary Disorders[j]					
Elevated transaminases[k]	Very common	61 (36)	24 (14)	22 (13)	4 (2)
Increased blood alkaline phosphatase	Common	4 (2)	0 (0)	2 (1)	0 (0)
Skin and Subcutaneous Tissue Disorders					
Rash	Very common	18 (11)	0 (0)	19 (11)	0 (0)
Renal and Urinary Disorders					
Renal cyst[l]	Common	8 (5)	0 (0)	1 (<1)	0 (0)
Increased blood creatinine[m]	Common	8 (5)	0 (0)	5 (3)	0 (0)
General Disorders and Administration Site Conditions					
Fatigue	Very common	49 (29)	5 (3)	65 (39)	4 (2)
Oedema[n]	Very common	83 (49)	1 (<1)	21 (12)	1 (<1)
Investigations					
Decreased blood testosterone[o]	Uncommon	1 (<1)	0 (0)	0 (0)	0 (0)

Abbreviations: N=total number of patients; n=number of patients meeting prespecified criteria.

* The percentages of adverse drug reactions were based on the data cutoff date of 30 November 2013, with the exception of Increased blood creatinine, for which frequency was based on the data cutoff date of 15 July 2014.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the study up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

a. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased).
b. Leucopenia (Leucopenia, White blood cell count decreased).
c. Neuropathy (Dysaesthesia, Gait disturbance, Hypoaesthesia, Muscular weakness, Neuralgia, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral sensory neuropathy, Polyneuropathy, Sensory disturbance).
d. Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope).
e Vision disorder (Diplopia, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual field defect, Visual impairment, Vitreous floaters).
f. Bradycardia (Bradycardia, Sinus bradycardia).
g. Cardiac failure (Cardiac failure, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema)
h. Interstitial lung disease (Interstitial lung disease, Pneumonitis).
i. Oesophagitis (Oesophagitis, Oesophageal ulcer).
j. There were no cases of hepatic failure in Study 1014.
k. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic function abnormal, Transaminases increased).
l. Renal cyst (Renal cyst).
m. Increased blood creatinine (Blood creatinine increased).
n. Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).
o. Decreased blood testosterone (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Previously Treated ALK-Positive Advanced NSCLC - Randomised Phase 3 Study 1007

The safety analysis population in Study 1007 included 172 patients who received crizotinib and 171 patients who received chemotherapy (99 pemetrexed, 72 docetaxel). The median duration of study treatment was 48 weeks for patients on crizotinib and 13 weeks for patients on chemotherapy.

All-causality adverse events associated with dosing interruptions occurred in 76 (44%) patients on crizotinib and 28 (16%) patients on chemotherapy. All-causality adverse events associated with dose reductions occurred in 30 (17%) patients on crizotinib and 25 (15%) patients on chemotherapy. All-causality adverse events associated with permanent discontinuation from treatment occurred in 34 (20%) patients on crizotinib and 34 (20%) patients on chemotherapy.

Table 7 presents adverse drug reactions experienced by patients in both the crizotinib and chemotherapy arms of Study 1007. The conventions for adverse reactions listed by SOC and frequency categories are defined above. The adverse drug reactions are listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

Table 7. Adverse Drug Reactions Reported in Patients Who Received Crizotinib or Chemotherapy in Randomised Phase 3 Study 1007

Adverse Drug Reaction	Frequency Category	Crizotinib (N=172)		Chemotherapy (N=171)	
		All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Blood and Lymphatic System Disorders					
Neutropenia[a]	Very common	54 (31)	24 (14)	40 (23)	33 (19)
Leucopenia[b]	Very common	38 (22)	7 (4)	23 (14)	12 (7)
Metabolism and Nutrition Disorders					
Decreased appetite	Very common	55 (32)	5 (3)	47 (28)	3 (2)
Nervous System Disorders					
Neuropathy[c]	Very common	41 (24)	1 (<1)	30 (18)	2 (1)
Dizziness[d]	Very common	44 (26)	1 (<1)	15 (9)	0 (0)
Dysgeusia	Very common	44 (26)	0 (0)	17 (10)	0 (0)
Eye Disorders					
Vision disorder[e]	Very common	108 (63)	0 (0)	15 (9)	0 (0)
Cardiac Disorders[f]					
Prolonged electrocardiogram QT	Common	9 (5)	6 (4)	0 (0)	0 (0)
Bradycardia[g]	Common	14 (8)	0 (0)	0 (0)	0 (0)
Syncope	Common	6 (4)	6 (4)	0 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders					
Interstitial lung disease[h]	Common	7 (4)	1 (<1)	1 (<1)	0 (0)
Gastrointestinal Disorders					
Vomiting	Very common	90 (52)	4 (2)	32 (19)	0 (0)
Diarrhoea	Very common	108 (63)	1 (<1)	34 (20)	1(<1)
Nausea	Very common	100 (58)	3 (2)	64 (37)	1 (<1)
Constipation	Very common	82 (48)	4 (2)	39 (23)	0 (0)
Oesophagitis[i]	Common	4 (2)	0 (0)	0 (0)	0 (0)
Dyspepsia	Common	5 (9)	0 (0)	6 (4)	0 (0)
Hepatobiliary Disorders					
Elevated transaminases[j]	Very common	74 (43)	31 (18)	25 (15)	4 (2)
Increased blood alkaline phosphatase	Very common	17 (10)	1 (<1)	6 (4)	0 (0)
Hepatic failure	Uncommon	1 (<1)	1 (<1)	0 (0)	0 (0)
Skin and Subcutaneous Tissue Disorders					
Rash	Very common	21 (12)	0 (0)	30 (18)	0 (0)

Adverse Drug Reaction	Frequency Category	Crizotinib (N=172)		Chemotherapy (N=171)	
		All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Renal and Urinary Disorders					
Renal cyst[k]	Common	8 (5)	0 (0)	1 (<1)	0 (0)
Increased blood creatinine[l]	Common	13 (8)	0 (0)	3 (2)	0 (0)
General Disorders and Administration Site Conditions					
Fatigue	Very common	52 (30)	4 (2)	60 (35)	8 (5)
Oedema[m]	Very common	74 (43)	0 (0)	28 (16)	0 (0)
Investigations					
Decreased blood testosterone[n]	Uncommon	1 (<1)	0 (0)	0 (0)	0 (0)

Abbreviations: N=total number of patients; n=number of patients meeting prespecified criteria.

* The percentages of adverse drug reactions were based on the data cutoff date of 30 November 2013, with the exception of Increased blood creatinine, for which frequency was based on the data cutoff date of 15 July 2014.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the study up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

a. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased).
b. Leucopenia (Leucopenia, White blood cell count decreased).
c. Neuropathy (Dysaesthesia, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Muscular weakness, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy, Polyneuropathy, Skin burning sensation).
d. Dizziness (Balance disorder, Dizziness, Dizziness postural).
e. Vision disorder (Diplopia, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual impairment, Vitreous floaters).
f. There were no cases of cardiac failure in the crizotinib arm and one case in the chemotherapy arm in Study 1007.
g. Bradycardia (Bradycardia, Sinus bradycardia).
h. Interstitial lung disease (Acute respiratory distress syndrome, Interstitial lung disease, Pneumonitis).
i. Oesophagitis (Oesophagitis, Oesophageal ulcer).
j. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic function abnormal, Transaminases increased).
k. Renal cyst (Renal cyst).
l. Increased blood creatinine (Blood creatinine increased).
m. Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).
n. Decreased blood testosterone (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Single-Arm Studies in ALK-Positive Advanced NSCLC

The safety analysis population in Study 1005 included 1063 patients who received crizotinib. The median duration of treatment was 45 weeks. All-causality adverse events associated with dosing interruptions and dose reductions occurred in 476 (45%) patients and 192 (18%) patients in Study 1005, respectively. All-causality adverse events associated with permanent discontinuation from treatment occurred in 202 (19%) patients in Study 1005. The most common adverse reactions (≥25%) in Study 1005 were vision disorder, nausea, vomiting, diarrhoea, oedema, constipation elevated transaminases, decreased appetite, fatigue and neuropathy. The most common Grade 3 or 4 adverse reactions (≥3%) in Study 1005 were neutropenia, elevated transaminases, fatigue and leucopenia.

The safety analysis population in Study 1001 included 154 patients who received crizotinib. The median duration of treatment was 57 weeks. All-causality adverse events associated with dosing interruptions and dose reductions occurred in 73 (47%) patients and 18 (12%) patients in Study 1001, respectively. All-causality adverse events associated with permanent

discontinuation occurred in 24 (16%) patients in Study 1001. The most common adverse reactions (≥25%) in Study 1001 were consistent with those in randomised Phase 3 Study 1007 and single-arm Study 1005 and were vision disorder, nausea, diarrhoea, oedema, vomiting, constipation, dizziness, fatigue, neuropathy, decreased appetite and rash. The most common Grade 3 or 4 adverse reactions (≥3%) in Study 1001 were elevated transaminases, neutropenia, syncope, nausea, vomiting, oedema, fatigue and neuropathy.

Single-Arm Study of ROS1-Positive Advanced NSCLC

The safety analysis population in Study 1001 included 53 patients with ROS1-positive NSCLC who received crizotinib. The median duration of treatment was 101 weeks. All-causality adverse events associated with dosing interruptions and dose reductions occurred in 24 (45%) patients and 6 (11%) patients, respectively. All-causality adverse events associated with permanent discontinuation from treatment occurred in 4 (8%) patients in Study 1001.

The most common adverse reactions (≥10%) in Study 1001 were consistent with those seen in patients with ALK-positive advanced NSCLC and were vision disorder (87%), nausea (58%), oedema (55%), vomiting (51%), diarrhoea (45%), constipation (43%), dizziness (40%), elevated transaminases (36%), fatigue (32%), neuropathy (30%), bradycardia (26%), rash (26%), decreased appetite (25%), dysgeusia (23%), neutropenia (17%) and increased blood creatinine (11%). The most common Grade 3 adverse reactions (≥2%) were neutropenia (9%), syncope (6%), vomiting (6%), elevated transaminases (4%) and prolonged electrocardiogram QT (4%). No Grade 4 adverse reactions were reported. There were 9 (17.0%) patient deaths within 28 days after the last dose of crizotinib, all of which were due to disease progression.

Description of Selected Adverse Effects

Visual Effects

In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality vision disorder, most commonly visual impairment, photopsia, blurred vision and vitreous floaters, was experienced by 1084 (63%) of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% had events that were mild in severity. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1722 patients treated with crizotinib.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with crizotinib in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally occurred within 8 days (range 1 day to 984 days) after the initiation of treatment. The majority of patients in the crizotinib arms in Study 1007 and Study 1014 (>50%) reported visual disturbances, which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire.

Gastrointestinal Effects

Nausea (57%), diarrhoea (54%), vomiting (51%) and constipation (43%) were the most commonly reported gastrointestinal events. Most events were mild to moderate in severity. The median time to onset for nausea or vomiting was 3 days and these events declined in frequency

after 3 weeks of treatment. Supportive care should include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Median times to onset for diarrhoea and constipation were 13 and 17 days, respectively. Supportive care for diarrhoea and constipation should include the use of standard antidiarrhoeal and laxative medications, respectively.

Nervous System Effects

All-causality neuropathy as defined in Table 5 was experienced by 435 (25%) of 1722 patients treated with crizotinib and was primarily Grade 1 or 2 in severity. Dizziness and dysgeusia were also very commonly reported and were primarily Grade 1 in severity.

Bradycardia

In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality bradycardia was experienced by 219 (13%) of 1722 patients treated with crizotinib. Most events were mild in severity. A total of 259 (16%) of 1666 patients with at least 1 post-baseline vital sign assessment had a pulse rate <50 bpm. The use of concomitant medications associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in the PRECAUTIONS and DOSAGE AND ADMINISTRATION - Dose Modification sections.

Renal Cyst

All-causality complex renal cysts were experienced by 52 (3%) of 1722 patients treated with crizotinib. There were no reports of clinically relevant abnormal urinalyses or renal impairment in these cases, although local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Laboratory Abnormalities/Testing

Haematological Laboratory Abnormalities

In clinical studies of crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leucocytes and neutrophils were observed in 64 (4%) and 226 (13%) patients, respectively. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. In patients who develop haematologic laboratory abnormalities, see DOSAGE AND ADMINISTRATION - Dose Modification.

Hepatic Laboratory Abnormalities

In clinical studies of crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 ALT, AST, and alkaline phosphatase were observed in 187 (11%), 95 (6%) and 33 (2%) patients, respectively. Patients should be monitored for hepatotoxicity and managed as recommended (see PRECAUTIONS – Hepatotoxicity and DOSAGE AND ADMINISTRATION – Dose Modification).

Renal Laboratory Abnormalities

In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, the estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m^2 (n=1681) to a median of 80.23 mL/min/1.73 m^2 at 2 weeks of treatment (n=1499). Median eGFR appeared to be relatively stable from 12 weeks of treatment (78.06 mL/min/1.73 m^2, n=1338) through 104 weeks of treatment (75.45 mL/min/1.73 m^2, n=315) and increased to 83.02 mL/min/1.73 m^2 at 28 days after the last dose of crizotinib (n=123).

Shifts to eGFR Grade 4 (15 to <30 mL/min/1.73 m^2) or to eGFR Grade 5 (<15 mL/min/1.73 m^2) were observed in 3% and <1% of patients, respectively.

DOSAGE AND ADMINISTRATION

ALK and ROS1 Testing

An accurate and validated assay for either ALK or ROS1 is necessary for the selection of patients for treatment with XALKORI. Either ALK-positive or ROS1-positive NSCLC status needs to be established to select patients for treatment with crizotinib because these are the only patients for whom benefit has been shown (see CLINICAL TRIALS).

Assessment for either ALK-positive or ROS1-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. Improper assay performance can lead to unreliable test results.

Recommended Dosing

The recommended dose schedule of XALKORI is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy.

XALKORI may be taken with or without food (see PHARMACOLOGY – Pharmacokinetics *Absorption*). Capsules should be swallowed whole.

Missed Dose

If a dose of XALKORI is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose Modification

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken orally twice daily and, if further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily. Dose reduction guidelines for haematologic and non-haematologic toxicities are provided in Tables 8 and 9.

Table 8. XALKORI Dose Modification – Haematologic Toxicities[a]

CTCAE[b] Grade	XALKORI Dosing
Grade 3	Withhold until recovery to Grade ≤2, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤2, then

	resume at 200 mg twice daily[c]

a Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
b (NCI Common Terminology Criteria for Adverse Events (CTCAE).
c In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 4 recurrence.

Table 9. XALKORI Dose Modification – Non-Haematologic Toxicities

CTCAE[a] Grade	XALKORI Dosing
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade £1 or baseline, then resume at 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any Grade interstitial lung disease/ pneumonitis[c]	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily[b]
Grade 4 QTc prolongation	Permanently discontinue
Grade 2, 3 Bradycardia[d] (symptomatic, may be severe and medically significant; medical intervention indicated)	Withhold until recovery to Grade ≤ 1 or to heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above
Grade 4 Bradycardia[d,e] (life-threatening consequences; urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate of 60 bpm or above, with frequent monitoring.
Grade 4 Ocular Disorder (Visual Loss)	Discontinue during evaluation of severe vision loss.

a NCI Common Terminology Criteria for Adverse Events.
b In case of recurrence, withhold until recovery to Grade £1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade ≥3 recurrence.
c Not attributable to NSCLC progression, other pulmonary disease, infection or radiation effect.
d Heart rate less than 60 beats per minute (bpm).
e Permanently discontinue for recurrence.

Hepatic impairment

As crizotinib is extensively metabolised in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Crizotinib should be used with caution if treatment is contemplated in patients with hepatic impairment. Patients should be closely monitored for liver function and adverse events (see PHARMACOLOGY - Pharmacokinetics in Special Patient Groups – Hepatic Impairment and PRECAUTIONS - Hepatotoxicity). For patients who develop transaminase elevations, see Table 9 XALKORI Dose Modification – Non-Haematologic Toxicities.

A clinical study was conducted in patients with advanced cancer and varying degrees of hepatic impairment, based on NCI classification, who received multiple doses of crizotinib to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib (see PHARMACOLOGY - Pharmacokinetics in Special Patient Groups – Hepatic Impairment). The pharmacokinetic data from this study suggest that dosage adjustment might not be needed in mild hepatic impairment (either AST >ULN and total bilirubin ≤ULN or any AST and total bilirubin >ULN but £1.5×ULN).

For patients with moderate hepatic impairment (any AST and total bilirubin >1.5×ULN and £3×ULN), the pharmacokinetic data suggest the use of a reduced starting dose of 200 mg twice daily should be considered, because the systemic crizotinib exposure increased compared to that from patients with normal hepatic function receiving the same dose of 200 mg twice daily, but was comparable to that from patients with normal hepatic function receiving 250 mg twice daily.

The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin >3×ULN) should not be greater than 250 mg once daily, as crizotinib doses greater than 250 mg once daily have not been studied in patients with severe hepatic impairment and may result in increases of systemic crizotinib exposure to supra-therapeutic levels.

Renal impairment

No starting dose adjustment is needed for patients with mild (CLcr 60 to < 90 mL/min) or moderate (CLcr 30 to < 60 mL/min) renal impairment. The crizotinib dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment (see PHARMACOLOGY - *Pharmacokinetics in Special Patient Groups – Renal Impairment*).

Elderly

No starting dose adjustment is required (see PHARMACOLOGY - *Pharmacokinetics in Special Patient Groups – Age* and CLINICAL TRIALS - Elderly).

OVERDOSAGE

There have been no known cases of crizotinib overdose. Treatment of overdose with crizotinib should consist of general supportive measures. There is no antidote for crizotinib.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

200 mg strength: hard gelatin capsule with white opaque body and pink opaque cap containing a white to pale yellow powder, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body. Bottles or blister packs contain 60 capsules.

250 mg strength: hard gelatin capsule with pink opaque cap and body containing a white to pale yellow powder, printed with black ink "Pfizer" on the cap, "CRZ 250" on the body. Bottles or blister packs contain 60 capsules.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

27 September 2013

DATE OF MOST RECENT AMENDMENT

13 December 2017

® Registered trademark