# Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer

ESMO Open Cancer Horizons

# Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer

Fiona Blackhall,[1] D Ross Camidge,[2] Alice T Shaw,[3] Jean-Charles Soria,[4] Benjamin J Solomon,[5] Tony Mok,[6] Vera Hirsh,[7] Pasi A Jänne,[8] Yuankai Shi,[9] Pan-Chyr Yang,[10] Tommaso De Pas,[11] Toyoaki Hida,[12] Javier De Castro Carpeño,[13] Silvana Lanzalone,[14] Anna Polli,[14] Shrividya Iyer,[15] Arlene Reisman,[16] Keith D Wilner,[17] Dong-Wan Kim[18]

**To cite:** Blackhall F, Ross Camidge D, Shaw AT, *et al*. Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer. *ESMO Open* 2017;**2**:e000219. doi:10.1136/esmoopen-2017-000219

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2017-000219).

Received 18 May 2017
Accepted 29 May 2017

For numbered affiliations see end of article.

**Correspondence to**
Dr Dong-Wan Kim; kimdw@snu.ac.kr

## ABSTRACT

**Purpose** Crizotinib is a potent, orally administered tyrosine kinase inhibitor approved for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC). We report final results from PROFILE 1005, the largest clinical trial to date for an ALK inhibitor in ALK-positive NSCLC.

**Patients and methods** PROFILE 1005 (NCT00932451) was a multicenter, single-arm phase 2 trial of the efficacy, safety and tolerability of crizotinib (250 mg twice daily; 3 week continuous treatment cycles) in patients with ALK-positive NSCLC after failure of ≥1 lines of systemic treatment for locally advanced/metastatic disease. Patients' tumour ALK status was initially determined by a central laboratory until a protocol amendment permitted enrolment of patients based on locally determined ALK status. Co-primary endpoints were objective response rate (ORR), evaluated using Response Evaluation Criteria in Solid Tumours V.1.1 and adverse events (AEs). Cancer-specific patient-reported outcomes (PROs) were also assessed using the European Organisation for the Research and Treatment of Cancer QLQ-C30 and its lung cancer module QLQ-LC13.

**Results** 1069 patients were enrolled; 1066 received crizotinib. The as-treated population comprised 908 and 158 patients, in whom tumour positive ALK-status was determined centrally (± locally) or locally only, respectively. At baseline, a majority of patients were <65 years (84%), 66% were never smokers and 46% were Asian. Derived investigator-assessed ORR was 54% (95% CI 51 to 57) and 41% (95% CI 33 to 49) in the central-testing and local-testing subgroups, respectively. The most common treatment-related AEs in the overall population (any grade) were vision disorder (58%), nausea (51%), diarrhoea (47%) and vomiting (47%). PRO scores demonstrated clinically meaningful improvement in lung cancer symptoms and global quality of life.

**Conclusion** The efficacy, safety and PRO profiles of crizotinib in this cohort of 1066 patients with ALK-positive NSCLC are consistent with previous reports.

**Trial registration number** Phase 2 trial (NCT00932451); Results.

## Key questions

### What is already known about this subject?

► Crizotinib is a first-in-class, oral, potent, small molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1 and c-MET, approved in several countries for the treatment of ALK-positive metastatic non-small-cell lung cancer (NSCLC).

### What does this study adds?

► PROFILE 1005 is the largest study to date for any ALK inhibitor in ALK-positive advanced NSCLC and provides further data from over 1000 patients supporting the clinical efficacy and safety profile of crizotinib in patients with previously treated ALK-positive NSCLC.

### How might this impact on clinical practice?

► The results of this study strengthen the evidence base for crizotinib as the standard of care for ALK-positive NSCLC.

## INTRODUCTION

The first-in-class anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, is a potent, orally administered inhibitor of ALK, MET and ROS1 tyrosine kinases.[1] The single-arm phase 1 trial of crizotinib (PROFILE 1001) showed an objective response rate (ORR) of 61% in 143 patients with advanced ALK-positive

NSCLC.[2] Based on the results from the first 136 patients enrolled in the present study where an ORR of 51% was observed, crizotinib received accelerated approval in 2011 by the US Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic NSCLC that is ALK positive,[3] as detected by a FDA-approved test. A conditional approval in the EU for the treatment of adults with previously treated ALK-positive NSCLC was also received.[4] The results of the randomised phase 3 PROFILE 1007 study demonstrating superiority of crizotinib to standard-of-care single-agent chemotherapy, in patients with previously treated ALK-positive NSCLC, supported conversion to full approval in the USA and the EU.[5]

The most common adverse events (AEs) associated with crizotinib in PROFILE 1007 included vision disorders (most commonly visual impairment, photopsia or blurred vision), gastrointestinal effects (most commonly diarrhoea, nausea, vomiting or constipation) and elevated liver aminotransferases.[5] Subsequently, in the first-line setting, significantly prolonged progression-free survival (PFS) was demonstrated for crizotinib compared with standard pemetrexed-plus-platinum chemotherapy in the PROFILE 1014 study in patients with previously untreated advanced ALK-positive NSCLC, with a similar safety profile observed to that seen in PROFILE 1007.[6]

Here, we report the final results of PROFILE 1005 that enrolled 1066 patients treated with crizotinib. This large study expands knowledge of the incidence of toxicities noted previously (eg, bradycardia, renal cysts) and permits improved characterisation of crizotinib.

## METHODS

### Patients

In the original protocol, the study sample size was set at 250 patients and considered to be adequate to estimate ORR and its 95% CI, in case the true ORR ranged from 30% to 50%. Based on enrolment rate and the closure of PROFILE 1007 to enrollment in some countries, the sample size was initially increased to 400 patients, which was also considered adequate to detect AEs of low frequency. Subsequently, the sample size was further increased to 800 patients in order to better understand possible genetic associations with specific renal and hepatic AEs. The sample size was revised again to allow continued enrolment of patients from the chemotherapy arm of PROFILE 1007 and to allow enrolment of up to an additional 250 patients to meet country-specific regulatory requirements, giving a projected enrolment in the order of 1100 patients.

Eligible patients were aged ≥18 years with locally advanced or metastatic ALK-positive NSCLC that had progressed after one or more systemic treatment regimens. Initially, the ALK status of all tumours was determined by a central laboratory using break-apart fluorescence in situ hybridisation (FISH) (Abbott Molecular, Des Plaines, Illinois, USA). In January 2011 (at which point 233 patients had been recruited), the protocol was amended to allow enrolment of patients whose tumours were determined to be ALK-positive at a local laboratory, with no requirement as to the specific test used and the cut-off defining ALK-positivity. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0–3, adequate bone marrow and organ function and resolution of all acute toxic effects of prior therapy or surgical procedures to grade ≤1 (except for alopecia). Patients with brain metastases were eligible if asymptomatic or if treated, neurologically stable for ≥2 weeks. All patients provided written informed consent prior to screening.

Patients in the chemotherapy arm of PROFILE 1007 were permitted to enrol in this study in order to receive crizotinib following independent radiology laboratory-defined disease progression.

### Study design and treatment

This was an open-label, multinational, phase 2 clinical trial performed at 143 centres in 22 countries. The institutional review board or independent ethics committee at each participating centre approved the protocol, which complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki and local laws. The study began in January 2010 and the cut-off date for the final analysis reported here was 16 March 2015.

Patients were to receive open-label crizotinib orally at a starting dose of 250 mg twice daily given on a continuous daily dosing schedule until disease progression, clinical deterioration, unacceptable toxicity, withdrawal of patient consent or protocol non-compliance. Patients with progressive disease (PD) could continue treatment if the investigator considered them to be deriving clinical benefit. A treatment cycle was defined as 3 weeks.

### Study assessments and conduct

Radiographic tumour assessments were performed at screening, every 6 weeks for the first 10 cycles and thereafter, every 12 weeks. Antitumour efficacy was evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1. Brain and bone scans were performed at screening and, if necessary, at intervals of 6 (for brain) or 12 (for bone) weeks. Safety assessments included monitoring AEs, vital signs, physical examinations, 12 lead ECGs, ophthalmological examinations and clinical laboratory evaluations. AEs were reported and graded using National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0. Patient reported outcomes (PROs) of global quality of life (QOL), disease/treatment-related symptoms of lung cancer and general health status were assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC13 and the EuroQol-5D (EQ-5D) questionnaire. These PROs were scored according to the EORTC QLQ-C30 scoring manual and the EQ-5D

**Table 1** Patient demographics and baseline disease characteristics (as-treated population)

| | Central ALK-testing subgroup (n=908) | Local ALK-testing subgroup (n=158) | All patients (n=1066) |
|---|---|---|---|
| Sex | | | |
| Male | 393 (43) | 72 (46) | 465 (44) |
| Female | 515 (57) | 86 (54) | 601 (56) |
| Age (years), n (%) | | | |
| <65 years | 777 (86) | 117 (74) | 894 (84) |
| ≥65 years | 131 (14) | 41 (26) | 172 (16) |
| Median (range) | 52.0 (19–84) | 53.0 (21–84) | 52.0 (19–84) |
| Race n (%) | | | |
| White | 434 (48) | 98 (62) | 532 (50) |
| Black | 16 (2) | 4 (3) | 20 (2) |
| Asian | 442 (49) | 53 (34) | 495 (46) |
| Japanese | 67 (7) | 14 (9) | 81 (8) |
| Korean | 138 (15) | 6 (4) | 144 (14) |
| Chinese | 224 (25) | 28 (18) | 252 (24) |
| Other Asian | 13 (1) | 5 (3) | 18 (2) |
| Other | 16 (2) | 3 (2) | 19 (2) |
| Smoking classification, n (%) | | | |
| Never | 612 (67) | 90 (57) | 702 (66) |
| Former | 259 (29) | 62 (39) | 321 (30) |
| Current | 37 (4) | 6 (4) | 43 (4) |
| Duration since histopathological diagnosis (years) | | | |
| Mean (range) | 2.1 (0.0–13.7)* | 1.8 (0.1–9.5) | 2.1 (0.0–13.7) |
| Extent of disease, n (%) | | | |
| Locally advanced | 77 (9) | 9 (6) | 86 (8) |
| Metastatic | 831 (92) | 149 (94) | 980 (92) |
| Histological classification, n (%) | | | |
| Adenocarcinoma | 859 (95) | 147 (93) | 1006 (94) |
| Squamous-cell carcinoma | 22 (2) | 4 (3) | 26 (2) |
| Large-cell carcinoma | 7 (<1) | 2 (1) | 9 (<1) |
| Other† | 20 (2) | 5 (3) | 25 (2) |
| ECOG performance status, n (%) | | | |
| 0 | 214 (24) | 38 (24) | 252 (24) |
| 1 | 541 (60) | 94 (60) | 635 (60) |
| 2 | 125 (14) | 18 (11) | 143 (13) |
| 3 | 28 (3) | 8 (5) | 36 (3) |
| Number of prior therapies for metastatic disease | | | |
| 0 | 2 (<1) | 0 | 2 (<1) |
| 1 | 231 (25) | 67 (42) | 298 (28) |
| 2 | 335 (37) | 49 (31) | 384 (36) |
| ≥3 | 340 (37) | 42 (27) | 382 (36) |

Data are n (%) unless otherwise indicated.
*Disease duration was not specified for one patient.
†Other classification includes adenosquamous carcinoma, sarcomatoid, mucoepidermoid, epidermoid, hepatoid carcinoma and other.
ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

user guide. Visual symptoms were assessed on the Visual Symptom Assessment Questionnaire-ALK (VSAQ-ALK).

### Analyses

The as-treated population included all enrolled patients treated with ≥1 dose of crizotinib. The response-evaluable population comprised all patients in the as-treated population who had adequate baseline tumour assessments. The primary efficacy endpoint was ORR (percentage of patients with a confirmed complete or partial response) as per RECIST V.1.1, derived based on investigator assessment, in the response-evaluable population. The derived best overall response (BOR) was based on the target lesion measurements, non-target lesion assessments and new lesion records provided by the investigator. Other efficacy endpoints included duration of tumour response and time to first tumour response (both assessed in the response-evaluable population), PFS and overall survival (OS; both assessed in the as-treated population). Efficacy data were summarised both for patients in whom tumour ALK status was determined centrally (± locally) and those determined locally only ('central' and 'local' subgroups, respectively), although the study was not designed to compare efficacy in the two subgroups. ORRs in each subgroup were also summarised by baseline characteristics. For each calculated ORR, two-sided 95% exact CIs were provided. Time-to-event endpoints were analysed using the Kaplan-Meier method; two-sided 95% CIs were provided for median PFS and OS. Safety data were summarised in the as-treated population and in subsets (gender, ≥65 vs <65 years, Asian vs non-Asian ethnicity). Based on previous experience with crizotinib, the following AEs of special interest were also summarised (including the following clustered terms, footnote #2 in table 3): elevated transaminases, hepatotoxicity, interstitial lung disease (ILD, encompassing pneumonitis), ECG QT prolonged and renal cysts. Additional analyses of AEs of special interest also included time to first onset and duration of the adverse event. PRO endpoints were analysed in the PRO-evaluable population (all patients in the as-treated population who completed a baseline PRO assessment and one or more postbaseline PRO assessments). For the change from baseline analyses of PRO scores, the change was considered statistically significantly different from 0 (at $p<0.05$) if the 95% CIs excluded 0. There were no adjustments for multiplicity testing.

## RESULTS

Between January 2010 and September 2014, 1069 patients were enrolled, 1066 received crizotinib, 908 had ALK-positive status determined centrally (± locally) and 158 determined solely by local-testing (see table 1 in the online Supplementary file 1). In the local only subgroup, methods used to determine ALK status were FISH (n=124), PCR (n=26) or immunohistochemistry (IHC) (n=8). All treated patients had adequate baseline tumour assessment, and therefore the response-evaluable population was the same as the as-treated population.

At baseline, patients' median (range) age was 52.0 years (19–84), a majority of patients (84%) were <65 years old, 50% of patients were White, 46% were Asian and 66% were never smokers (table 1). The median duration of treatment was 45.6 weeks (95% CI 42.1 to 50.1). A total of 122 (11%) patients across both subgroups were still receiving crizotinib at the time of data cut-off. The reasons for permanent treatment discontinuation are shown in table 2 in the online Supplementary file 1. The most common reasons for permanent discontinuation were disease progression (31%) and deterioration of health status (27%). In the central and local only testing subgroups, 63% and 52% of patients with RECIST-defined PD continued crizotinib beyond PD (median duration, 21.9 and 19.8 weeks, respectively).

### Efficacy

The ORR in the central-testing subgroup was 54% (95% CI 51 to 57) (table 2). ORR results by patient demographic and disease characteristics are also summarised in table 2. The ORR was 41% (95% CI 33 to 49), in the subgroup of 158 patients with positive local ALK testing only. For the 163 patients whose tumour samples had positive ALK status obtained locally and confirmed centrally, the ORR was 57% (95% CI 49 to 65), in line with the centrally tested group (ORR of 54%). The median PFS in the central-testing and local-testing subgroups was 8.4 months (95% CI 7.1 to 9.7) and 6.9 months (95% CI 5.6 to 9.4), respectively (figure 1A, table 2) and the median OS was 21.8 months (95% CI 19.4 to 24.0) and 16.9 months (95% CI 13.4 to 21.5), respectively (figure 1B, table 2). The PFS and OS by number of prior therapies are shown in table 3 in the online Supplementary file 1).

### Safety and tolerability

Treatment-related adverse events (TRAEs) occurred in 96% of patients (table 3). The most common TRAEs (any grade) were vision disorder (58%), nausea (51%), diarrhoea (47%) and vomiting (47%). Other common events (in ≥30% patients) were oedema (38%), constipation (35%) and elevated transaminases (30%). The most common grade 3 or 4 TRAEs were neutropenia (13%) and elevated transaminases (8%).

TRAEs reported at a higher frequency (≥10 percentage points higher) in female patients than male patients were vision disorder, nausea, vomiting, oedema, neutropenia and dysgeusia. Oedema occurred at a higher frequency in patients aged ≥65 than <65 years. Constipation, neutropenia, elevated transaminases, leucopenia and decreased appetite were reported at a higher frequency among those of Asian than non-Asian ethnicity.

When looking at the TRAEs characterising the safety profile of crizotinib, the most frequently reported was vision disorder (58%; which includes visual impairment, photopsia, vision blurred, vitreous floaters, photophobia and diplopia). This was mild or moderate in the majority

**Table 2** Efficacy results (as-treated population*)

| Parameter | Central ALK-testing (n=908) Result | 95% CI | Local ALK-testing (n=158) Result | 95% CI |
|---|---|---|---|---|
| BOR, n (%) | | | | |
| CR | 11 (1) | – | 1 (<1) | – |
| PR | 480 (53) | – | 63 (40) | – |
| ORR, n (%) | 491 (54) | 51 to 57† | 64 (41) | 33 to 49† |
| Median DR, months | 11.8 | 10.4 to 12.8‡ | 9.5 | 6.9 to 15.2‡ |
| DCR, n (%) | | | | |
| At 6 weeks | 742 (82) | 79 to 84† | 110 (70) | 62 to 77† |
| At 12 weeks | 643 (71) | 68 to 74† | 97 (61) | 53 to 69† |
| Median time to first tumour response, weeks | 6.1 | 2.7 to 164§ | 6.3 | 4.7 to 65.9§ |
| Median PFS, months | 8.4 | 7.1 to 9.7‡ | 6.9 | 5.6 to 9.4‡ |
| Survival probability, % | | | | |
| At 6 months | 82 | 79 to 84¶ | 78 | 70 to 8§¶ |
| At 12 months | 67 | 63 to 70¶ | 62 | 54 to 60¶ |
| Median OS, months | 21.8 | 19.4 to 24.0‡ | 16.9 | 13.4 to 21.5‡ |

**ORR by patient characteristics***

| | Central ALK-testing (n=908) | | | Local ALK-testing (n=158) | | |
|---|---|---|---|---|---|---|
| | n/N** | % | 95% CI† | n/N** | % | 95% CI† |
| Overall | 491/908 | 54 | 51 to 57 | 64/158 | 41 | 33 to 49 |
| Number of prior therapies for metastatic disease | | | | | | |
| 0 | 2/2†† | 100 | 16 to 100 | 0 | – | – |
| 1 | 126/231 | 55 | 48 to 67 | 27/67 | 40 | 29 to 53 |
| 2 | 166/335 | 50 | 44 to 55 | 20/49 | 41 | 27 to 56 |
| ≥3 | 197/340 | 58 | 53 to 63 | 17/42 | 41 | 26 to 57 |
| Sex | | | | | | |
| Male | 211/393 | 54 | 49 to 59 | 27/72 | 38 | 26 to 50 |
| Female | 280/515 | 54 | 50 to 59 | 37/86 | 43 | 32 to 54 |
| Age‡‡ | | | | | | |
| <65 years | 424/777 | 55 | 51 to 58 | 49/117 | 42 | 33 to 51 |
| ≥65 years | 67/131 | 51 | 42 to 60 | 15/41 | 37 | 22 to 53 |
| Race | | | | | | |
| Non-Asian | | | | | | |
| White | 215/434 | 50 | 45 to 54 | 36/98 | 37 | 27 to 47 |
| Black | 9/16 | 56 | 30 to 80 | 1/4 | 25 | 0.6 to 81 |
| Asian | | | | | | |
| Japanese | 37/67 | 55 | 43 to 67 | 9/14 | 64 | 35 to 87 |
| Korean | 105/138 | 76 | 68 to 83 | 3/6 | 50 | 12 to 88 |
| Chinese | 111/224 | 50 | 43 to 56 | 9/28 | 32 | 16 to 52 |
| Other Asian | 7/13 | 54 | 25 to 81 | 5/5 | 100 | 48 to 100 |
| Other | 7/16 | 44 | 20 to 70 | 1/3 | 33 | 0.8 to 91 |
| ECOG PS§ | | | | | | |
| 0 | 127/214 | 59 | 52 to 66 | 15/38 | 40 | 24 to 57 |

Continued

Table 2 Continued

| ORR by patient characteristics* | Central ALK-testing (n=908) | | | Local ALK-testing (n=158) | | |
|---|---|---|---|---|---|---|
| | n/N** | % | 95% CI† | n/N** | % | 95% CI† |
| 1 | 304/541 | 56 | 52 to 60 | 35/94 | 37 | 28 to 48 |
| 2 | 52/125 | 42 | 33 to 51 | 11/18 | 61 | 36 to 83 |
| 3 | 8/28 | 29 | 13 to 49 | 3/8 | 38 | 9 to 76 |
| Smoking status | | | | | | |
| Never | 334/612 | 55 | 51 to 59 | 44/90 | 49 | 38 to 60 |
| Current | 22/37 | 60 | 42 to 75 | 1/6 | 17 | 0.4 to 64 |
| Former | 135/259 | 52 | 46 to 58 | 19/62 | 31 | 20 to 44 |

*ORR, DCR, duration of response and time to first response were analyzed in the response1evaluable population (central1testing subgroup) and in the response1evaluablepopulation (local1testing subgroup) (note: numbers of patients in these subgroups were the same as in the as1treated population).
†Calculated using the exact method based on the F distribution.
‡Based onBrookmeyer and Crowley method.
§Range.
¶Calculated using the normal approximation to the log transformed cumulative hazard rate .
**Number with response/total number with patient characteristic.
††Two patients received only adjuvant treatment, but had disease progression within 6 months after adjuvant treatment and were considered eligible for the study.
‡‡At baseline.
ALK, anaplastic lymphoma kinase; CI,confidence interval;DCR, disease-control rate (% complete response+partial response+stable disease); ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

of patients (grade ≤2: 58%), with a median (range) time to first onset of 7 (1–1363) days after commencing treatment. Most (≥65%) of the patients who reported experiencing a visual symptom in the first 30 cycles, assessed on the VSAQ-ALK, indicated that they had no or minimal impact (scores 0–3 of 10) on daily activities. A treatment-related grade 4 optic atrophy event was reported in one patient.[7] Nausea, diarrhoea and vomiting were predominantly mild to moderate in severity (table 3), with a median (range) time to first onset of 3 (1–1022), 13 (1–1383) and 2 (1–1055) days, respectively.

Treatment-related elevated transaminases of any grade occurred in 30% of patients, with a median time to first onset of 23 (1–1331) days. A total of 286/1066 (27%) patients had elevations in alanine aminotransferase (ALT) and 4/1066 (0.4%) had elevations in total bilirubin levels. Drug-induced liver injury meeting Hy's law criteria (elevated transaminases and total bilirubin levels without evidence of cholestasis) developed in eight patients, including two cases of hepatotoxicity events with a fatal outcome. Twenty-five patients (2%) experienced treatment-related ILD, with a median time to onset of 78 (6–1028) days; 10 patients (1%) had treatment-related ILD of grade 3 severity or worse. Thirteen cases of treatment-related ILD, three of which were fatal, were associated with treatment discontinuation.

ECG QT prolongation was reported as a TRAE in 37 patients (4%); 12 patients had events of grade 3 severity. Fifteen of 999 patients (2%) had corrected QT (QTc) using Fridericia's correction (QTcF) of ≥500 ms and a maximum QTcF change from baseline of ≥60 ms was observed in 47/981 patients (5%). Seven patients (0.7%) had treatment-related syncope but whether associated with a change in QTc is not known. No patients permanently discontinued crizotinib due to QT prolongation, although six and eight underwent dosing interruptions and dose reductions, respectively. Bradycardia was reported as a TRAE for 11% of patients (mostly grade 1 or 2 in severity). In 13% of patients, a pulse rate <50 beats/min on treatment was noted.

Renal cysts considered treatment-related were reported for 30 patients (3%). Most cases were grade 1 or 2 although 9 were grade 3. These cysts were occasionally symptomatic, in some cases associated with invasion into adjacent tissues, and developed between 36 and 910 days (median 230 days) after starting crizotinib. Renal cysts were not associated with clinically relevant changes in renal function.

Shifts in clinical laboratory test values from grade 2 or less at baseline to grade 3 or 4 postbaseline are shown in table 4 in the online Supplementary file 1). Among haematological laboratory tests, the most frequent of these shifts were lymphopenia (20%) and neutropenia (15%). Among clinical laboratory chemistries, the most frequent were hypophosphatemia (12%) and increased ALT (10%).

Permanent discontinuation of crizotinib due to TRAE occurred in 60 patients (6%); the most frequent TRAE associated with permanent treatment discontinuation was ILD (n=13; see table 5 in the online Supplementary

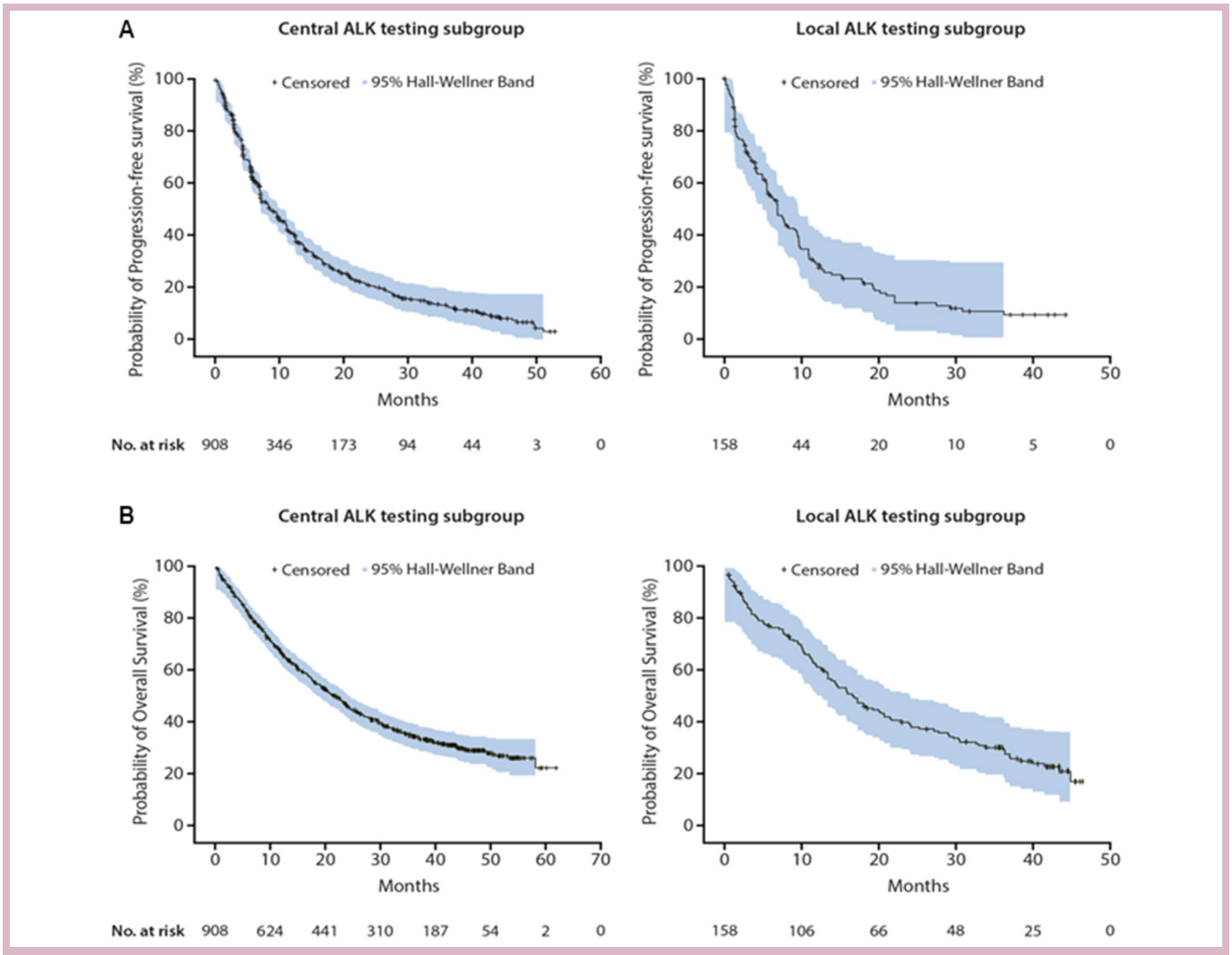


**Figure 1** Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival (as-treated population). ALK=anaplastic lymphoma kinase.

file 1). TRAEs most commonly associated with dose reductions were elevated transaminases (5%), neutropenia (4%) and fatigue (2%). The most frequent TRAEs associated with dosing interruptions were neutropenia (11%), elevated transaminases (5%), vomiting (4%) and nausea (4%). A total of 119 patients (11%) experienced treatment-related serious adverse events, each of which occurred in less than 2% of patients (see table 6 in the online Supplementary file 1). At data cut-off, 709 patients (67%) had died (any causality) during the study, of which 235 patients died ≤28 days after the last dose of crizotinib; disease progression (n=640) was the most common cause of death. Fifteen patients died due to TRAEs: ILD in four patients, pneumonia and death in three patients each, hepatotoxicity in two patients and dyspnoea, pulmonary embolism and lung infection in one patient each (see table 7 in the online Supplementary file 1).

### Patient-reported outcomes

In the PRO-evaluable population (n=976), mean change from baseline in patient-reported EORTC QLQ-C30 global QOL scores showed a statistically significant (95% CI excluded 0) and clinically meaningful improvement (≥10 point)[8] over Cycles 3–14 (figure 2), maintained through Cycles 2 and 15–30. The majority of patients had improved (43%) or stable (39%) scores in global QOL over the course of treatment (see table 8 in the online Supplementary file 1). Of the symptoms included on the QLQ-C30 scale, those for which the highest proportion (≥40%) of patients experienced an improvement from baseline were pain (48%), fatigue (46%), insomnia (43%) and dyspnoea (42%); constipation (44%) and diarrhoea (44%) were the symptoms for which the highest proportion (≥40%) of patients experienced worsening from baseline (see table 8 in the online Supplementary file 1). Symptoms included on the QLQ-LC13 scale that had the highest proportion (≥40%) of patients improved from baseline were coughing (51%), dyspnoea (41%) and pain in other parts (41%; see table 8 in the online Supplementary file 1). A statistically significant improvement in health status, as measured by EQ-5D visual analogue

**Table 3** Treatment-related adverse events (as-treated population, n=1066)

| | | Maximum CTCAE | |
|---|---|---|---|
| **Event, n (%)** | **Any grade** | **Grade 3** | **Grade 4** |
| Any AE | 1022 (96) | 345 (32) | 68 (6) |
| Adverse events in≥10% of patients | | | |
| Vision disorder† | 615 (58) | 1 (0.1) | 0 |
| Nausea | 547 (51) | 17 (2) | 0 |
| Diarrhoea | 499 (47) | 12 (1) | 0 |
| Vomiting | 496 (47) | 11 (1) | 0 |
| Oedema | 409 (38) | 15 (1) | 0 |
| Constipation | 369 (35) | 2 (0.2) | 0 |
| Elevated transaminases† | 321 (30) | 69 (7) | 13 (1) |
| Neutropenia† | 226 (21) | 109 (10) | 28 (3) |
| Fatigue | 225 (21) | 27 (3) | 0 |
| Decreased appetite | 224 (21) | 6 (0.6) | 1 (0.1) |
| Dysgeusia | 206 (19) | 0 | 0 |
| Leucopenia† | 165 (16) | 32 (3) | 1 (0.1) |
| Dizziness† | 161 (15) | 2 (0.2) | 0 |
| Neuropathy† | 137 (13) | 5 (0.5) | 0 |
| Abdominal pain† | 134 (13) | 2 (0.2) | 0 |
| Bradycardia† | 112 (11) | 3 (0.3) | 0 |
| Other adverse events of special interest<10% frequency* | | | |
| QT prolongation | 37 (4) | 12 (1) | 0 |
| Renal cysts† | 30 (3) | 9 (0.8) | 0 |
| Interstitial lung disease† | 25 (2) | 4 (0.4) | 2 (0.2) |
| Hepatotoxicity† | 21 (2) | 6 (0.6) | 4 (0.4) |

*AEs of special interest for crizotinib were predefined based on their clinical significance or frequency of observation in previous clinical studies and potential attribution to treatment with crizotinib.
†Certain preferred terms were in aggregate using clustered terms, because the frequency of certain medical concepts or conditions may have been underestimated by reliance on single Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. MedDRA Preferred Terms within each clustered term that were actually reported are marked with an asterisk: Abdominal pain (Abdominal discomfort* or Abdominal pain* or Abdominal pain lower* or Abdominal pain upper* or Abdominal tenderness*); Bradycardia (or Bradycardia* or Heart rate decreased* or Sinus arrest or Sinus bradycardia*); Dizziness (Balance disorder* or Dizziness* or Dizziness exertional or Dizziness postural* or Presyncope*); Elevated transaminases (Alanine aminotransferase or Alanine aminotransferase abnormal* or Alanine aminotransferase increased* or Aspartate aminotransferase or Aspartate aminotransferase abnormal* or Aspartate aminotransferase increased* or Gamma-glutamyltransferase abnormal or Gamma-glutamyltransferase increased* or Hepatic enzyme abnormal or Hepatic enzyme increased* or Hepatic function abnormal* or Hypertransaminasemia or Liver function test abnormal or Transaminases or Transaminases abnormal or Transaminases increased*); Hepatotoxicity (Acute hepatic failure or Cholestatic liver injury or Coma hepatic or Drug-induced liver injury* or Hepatic encephalopathy or Hepatic failure* or Hepatic necrosis or Hepatic steatosis* or Hepatitis fulminant or Hepatocellular injury* or Hepatorenal failure or Hepatorenal syndrome or Hepatotoxicity* or Liver disorder* or Liver injury* or Mixed liver injury or Subacute hepatic failure); Interstitial lung disease (Acute interstitial pneumonitis or Acute lung injury or Acute respiratory distress syndrome* or Alveolitis* or Alveolitis allergic or Alveolitis necrotising or Diffuse alveolar damage or Eosinophilic pneumonia or Eosinophilic pneumonia acute or Idiopathic pulmonary fibrosis or Interstitial lung disease* or Pneumonitis* or Pulmonary toxicity); (* or White blood cell count decreased*); Neuropathy (Acute polyneuropathy or Amyotrophy or Areflexia or Autoimmune neuropathy or Autonomic failure syndrome or Autonomic neuropathy or Axonal neuropathy or Biopsy peripheral nerve abnormal or Burning feet syndrome or Burning sensation* or Decreased vibratory sense or Demyelinating polyneuropathy or Dysaesthesia* or Electromyogram abnormal or Formication* or Gait disturbance* or Genital hypoaesthesia or Guillain-Barre syndrome or Hyperaesthesia* or Hypoaesthesia* or Hyporeflexia or Hypotonia* or Ischaemic neuropathy or Loss of proprioception or Miller Fisher syndrome or Mononeuritis or Mononeuropathy or Mononeuropathy multiplex or Motor dysfunction* or Multifocal motor neuropathy or Muscle atrophy* or Muscular weakness* or Myelopathy or Nerve conduction studies abnormal or Nerve degeneration or Neuralgia* or Neuritis* or Neuromuscular toxicity or Neuromyopathy or Neuropathy peripheral* or Neuropathy vitamin B6 deficiency or Neurotoxicity* or Paraesthesia* or Peripheral motor neuropathy* or Peripheral nerve lesion or Peripheral nerve palsy or Peripheral nervous system function test abnormal or Peripheral sensorimotor neuropathy* or Peripheral sensory neuropathy* or Peroneal muscular atrophy or Peroneal nerve palsy* or Phrenic nerve paralysis or Polyneuropathy* or Polyneuropathy chronic or Polyneuropathy idiopathic progressive or Radiation neuropathy or Sensorimotor disorder or Sensory disturbance* or Sensory loss or Skin burning sensation* or Temperature perception test decreased or Tinel's sign or Toxic neuropathy* or Ulnar neuritis); Neutropenia (Febrile neutropenia* or Neutropenia* or Neutrophil count decreased*); Renal cyst (Renal abscess* or Renal cyst* or Renal cyst excision or Renal cyst * or Renal cyst infection* or Renal cyst ruptured); Vision disorder (Chromatopsia or Diplopia* or Halo vision* or Photophobia* or Photopsia* or Vision blurred* or Visual acuity reduced* or Visual brightness or Visual impairment* or Visual perseveration* or Vitreous floaters*).
CTCAE, common terminology criteria for adverse events.

scale scores, was observed from Cycle 2 and maintained through Cycle 30.

## DISCUSSION

The results of PROFILE 1005 are consistent with previous reports for the clinical benefit of crizotinib with an ORR of 54% demonstrated in a large population of patients with previously treated advanced ALK-positive NSCLC determined by break-apart FISH in a central laboratory. This ORR is largely in line with that in the single-arm PROFILE 1001 trial (61%) and the crizotinib arm of the phase 3 PROFILE 1007 trial in previously treated patients (65%)

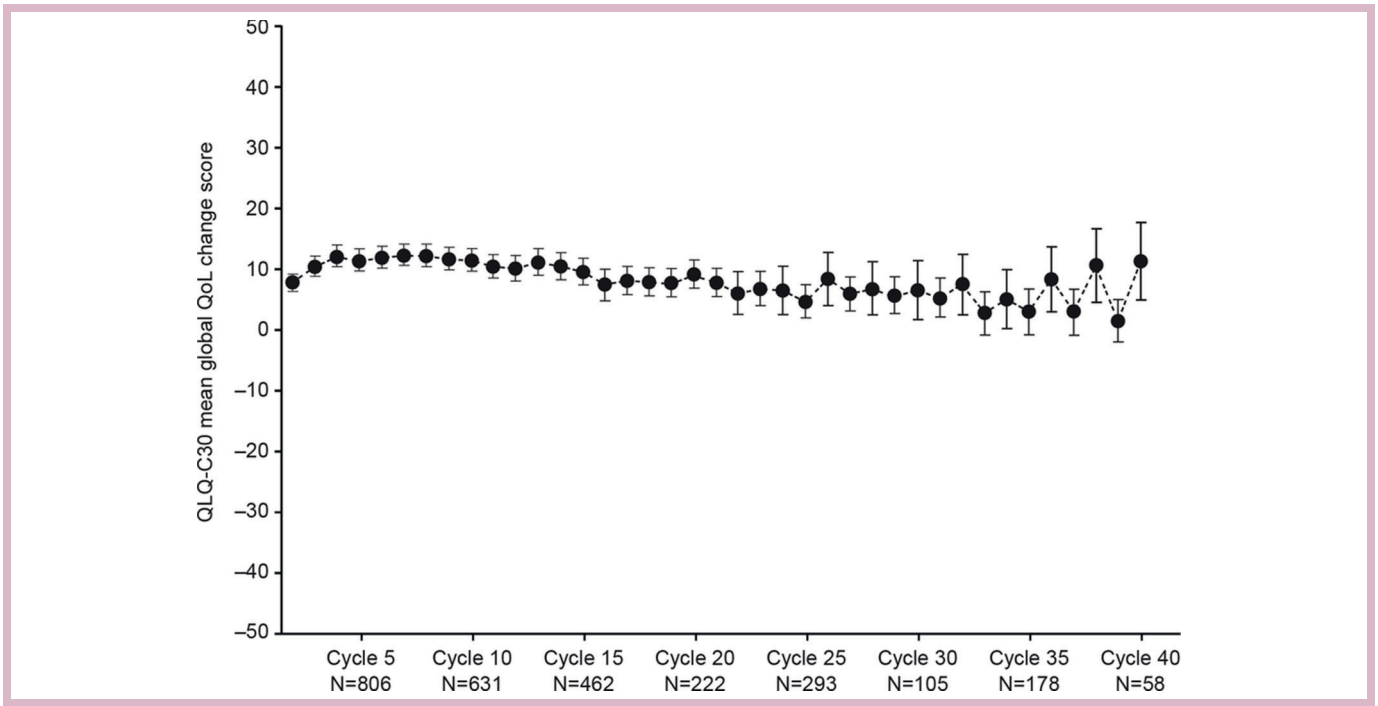


**Figure 2** Mean change from baseline in patient-reported European Organisation for the Research and Treatment of Cancer QLQ-C30 global quality of life (patient-reported outcome-evaluable population).

but, as would be expected, less than in the crizotinib arm of the first-line PROFILE 1014 trial (74%).[2 5 6] In the present study, patients were heavily pretreated, with 72% having received ≥2 prior lines of treatment for metastatic disease, and responses were required to be confirmed, while the designs of the randomised PROFILE 1007 and 1014 studies did not require confirmation of tumour response. Tumour responses in the central-testing subgroup were rapid (median time to response, 6.1 weeks), consistent with the time of the first scheduled postbaseline tumour assessment and durable (median duration of response, 11.8 months).[2 5] Median PFS was 8.4 months, consistent with previous reports.[2 5]

The local ALK testing subgroup (n=158; ORR 41%, 95% CI 33 to 49) included patients with ALK-positive tumours by local testing only and excluded concordant cases also ALK positive by central testing (see table 1 in the online Supplementary file 1). The higher response rate obtained in patients with ALK-positive tumours by two independent tests, local and central (n=163; ORR 57%, 95% CI 49 to 65), may possibly be attributed to a lower false positive rate as compared with patients with ALK positive tumours by a single local test.

Crizotinib had a side effect profile with AEs that were generally tolerable and manageable by dosing interruption, dose reduction and/or standard medical therapy as there was a low frequency of permanent treatment discontinuations associated with TRAEs. Most TRAEs were mild or moderate in severity. The most common TRAEs were visual and gastrointestinal in nature consistent with previous reports.[2 5 6] Patient-reported visual events were transient, with minimal impact on daily activities, also as previously reported.[2 5 9]

The frequencies of hepatotoxicity, ILD and QTc prolongation were in line with previous reports[5 6]: treatment-related ILD of ≥grade 3 occurred in 1.0% of patients, no grade 4 ECG QTc prolongation was reported and bradycardia, mainly ≤grade 2, occurred in ~10% of patients in this study. Although renal imaging was not mandatory, renal cyst development[10] was reported in 3% of patients and was not associated with clinically relevant changes in renal function.

While the large cohort of patients in PROFILE 1005 enables more precise characterisation of the incidence of clinically important AEs identified in prior studies and in case reports,[5 6 10] the TRAEs observed were similar to those seen in the preliminary results on which the initial approval of crizotinib was based, showing that smaller number of patients allowed the safety profile of crizotinib to be well characterised.

Symptom burden in patients with advanced lung cancer is usually high with a negative impact on QOL.[11 12] The PRO data reported herein demonstrated clinically meaningful improvements in key lung cancer symptoms and global QOL.

In conclusion, this study, the largest to date for any ALK inhibitor, supports the clinical efficacy and safety profile of crizotinib in patients with previously treated ALK-positive NSCLC. No new safety concerns were identified and AE frequencies were similar to, and consistent with, those reported in previous trials.

The results of this study strengthen the evidence base for crizotinib as the standard of care for ALK-positive NSCLC.

**Author affiliations**
[1]Institute of Cancer Sciences, Manchester University and Christie Hospital NHS Foundation Trust, Manchester, UK
[2]Division of Oncology, University of Colorado Comprehensive Cancer Center, Aurora, Colorado, USA
[3]Department of Hematology/Oncology, Massachusetts General Hospital, Boston, , Massachusetts, USA
[4]Department of Medical Oncology, Institut Gustave Roussy, Paris, France
[5]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[6]State Key Laboratory of South China, Hong Kong Cancer Institute and The Chinese University of Hong Kong, Shatin, China
[7]Division of Medical Oncology, McGill University Health Centre, Montreal, Canada
[8]Lowe Center for Thoracic Oncology, The Belfer Institute for Applied Cancer Science, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA
[9]Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[10]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[11]Department of Oncology, European Institute of Oncology, Milan, Italy
[12]Department of Thoracic Oncology, Aichi Cancer Center Central Hospital, Nagoya, Japan
[13]Medical Oncology Service, Hospital Universitario La Paz, Madrid, Spain
[14]Pfizer Oncology, Milan, Italy
[15]Pfizer Oncology, New York, New York, USA
[16]Pfizer Global Innovative Pharma Business, New York, New York, USA
[17]Pfizer Oncology, La Jolla, California, USA
[18]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

**Acknowledgements** We thank the patients, families and the teams of investigators, research nurses, study coordinators and operations staff who made this work possible. We are also grateful to Dr Filippo De Marinis for the care of patients initially enrolled by Dr De Pas at the IEO, Milan, Italy. Medical writing support was provided by Wendy Sacks and Kayleigh Bassiri at ACUMED (New York, USA and Tytherington, UK), Clair Clowes and Simon Lancaster at inScience Communications (Chester, UK) and was funded by Pfizer.

**Contributors** We confirm that all authors made substantial contributions to the concept and design or analysis and interpretation of data and to the drafting of the manuscript or revising it critically for important intellectual content. Editorial support was provided by Wendy Sacks and Kayleigh Bassiri at ACUMED (New York, New York, USA), an Ashfield Company, part of UDG Healthcare and by Claire Clowes and Simon Lancaster at inScience Communications (Chester, UK) and was funded by Pfizer. This article has not been published elsewhere, nor is it under consideration for publication by another journal.

**Funding** Pfizer, Inc

**Competing interests** We have already uploaded ICMJE form of each authors when Ann Oncol submission

**Patient consent** Obtained.

**Ethics approval** The institutional review board or independent ethics committee at each participating centre approved the protocol, which complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki and local laws.

**Provenance and peer review** Not commissioned; internally peer reviewed.



## REFERENCES

1. Christensen JG, Zou HY, Arango ME, *et al*. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. *Mol Cancer Ther* 2007;6:3314–22.
2. Camidge DR, Bang YJ, Kwak EL, *et al*. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011–9.
3 Kim DW, Ahn M-J, Shi Y, *et al*, 2012. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell Lung Cancer (NSCLC) (Poster), American Society of clinical oncology (ASCO) 48th Annual Meeting, Chicago. Abstract 7533.
4. Ou SH, Bartlett CH, Mino-Kenudson M, *et al*. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. *Oncologist* 2012;17:1351–75.
5. Shaw AT, Kim DW, Nakagawa K, *et al*. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368:2385–94.
6. Solomon BJ, Mok T, Kim DW, *et al*. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167–77.
7. Chun SG, Iyengar P, Gerber DE, *et al*. Optic neuropathy and blindness associated with crizotinib for non-small-cell lung cancer with EML4-ALK translocation. *J Clin Oncol* 2015;33:e25–e26.
8. Osoba D, Rodrigues G, Myles J, *et al*. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–44.
9. Salgia R, Solomon BJ, Shaw AT, *et al*. Visual effects in anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) patients treated with crizotinib. *ASCO Meeting Abstracts* 2012;30:7596.
10. Schnell P, Bartlett CH, Solomon BJ, *et al*. Complex renal cysts associated with crizotinib treatment. *Cancer Med* 2015;4:887–96.
11. Iyer S, Roughley A, Rider A, *et al*. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. *Support Care Cancer* 2014;22:181–7.
12. LeBlanc TW, Nickolich M, Rushing CN, *et al*. What bothers lung cancer patients the most? A prospective, longitudinal electronic patient-reported outcomes study in advanced non-small cell lung cancer. *Support Care Cancer* 2015;23:3455–63.