Non-small-cell lung cancer (NSCLC) is associated with a poor prognosis and low survival rates, providing a strong rationale for the development of new treatment options. The discovery of ALK gene rearrangements in a subset of NSCLC specimens and the identification and development of the first-in-class ALK inhibitor crizotinib provided a personalised treatment option for patients with advanced ALK-positive NSCLC. Crizotinib demonstrated rapid and durable responses in advanced ALK-positive NSCLC patients in phase I and II studies, leading to accelerated FDA approval. Subsequent evaluation in phase III studies showed that crizotinib improved progression-free survival compared with platinum-based doublet chemotherapy in previously untreated patients and compared with pemetrexed or docetaxel in previously treated patients. Crizotinib was shown to have an acceptable safety profile and also to improve quality of life and symptom scores. Overall, crizotinib has been shown to provide a valuable first- and second-line treatment option and is now the first-line standard of care for patients with advanced ALK-positive NSCLC.

**Key words:** anaplastic lymphoma kinase, crizotinib, non-small-cell lung cancer

**introduction**

Non-small-cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for up to 85% of cases [1], and is associated with a 5-year survival rate of only 22% [2]. NSCLC is usually advanced by the time of diagnosis, and systemic therapies are the primary treatment modality [3, 4], with standard chemotherapy for advanced NSCLC resulting in relatively poor survival rates [4]. For example, one study of platinum-based chemotherapy regimens for advanced NSCLC patients resulted in a median survival of 7.9 months and 1- and 2-year survival rates of 33% and 11%, respectively [5]. As a result, there is an unmet clinical need in advanced NSCLC, with potential to improve outcomes by identifying distinct molecular subtypes of patients who may respond to specific targeted therapies.

Several genomic alterations have been shown to play important roles in NSCLC, including mutations in epidermal growth factor receptor (EGFR), KRAS, BRAF and MET, and rearrangements in anaplastic lymphoma kinase (ALK) and ROS1 [6]. The EGFR gene is mutated in ~10% of patients with NSCLC [7] and was the first actionable biomarker in NSCLC, with patients bearing EGFR-mutant tumours demonstrating responses to the EGFR inhibitors erlotinib, gefitinib and afatinib [8–10].

In 2007, fusions between the ALK and echinoderm microtubule-associated protein-like 4 (EML4) genes were discovered in NSCLC specimens [7, 11]. Rearrangements of the ALK gene are present in ~3%–5% of patients with NSCLC, providing an oncogenic driver in these patients’ tumours [12]. The role and detection of ALK in NSCLC are discussed in more detail by Hallberg and Palmer and Kerr and López-Ríos in this issue.

Crizotinib is a first-in-class, small-molecule inhibitor of ALK [13] that has been approved in the USA for the treatment of ALK-positive metastatic NSCLC [14]. In Europe, crizotinib is indicated for use in patients with both previously untreated and previously treated ALK-positive NSCLC [15]. Here, we discuss the discovery and development of crizotinib and review its efficacy, safety and impact on quality of life (QoL) in patients with advanced ALK-positive NSCLC.

**crizotinib in patients with NSCLC**

**characterisation and early development**

Crizotinib is an orally bioavailable small-molecule inhibitor of the receptor tyrosine kinases c-MET, ALK and ROS1 [16–18] that was initially identified in 2005 [19] and developed to target c-MET [16]. However, 1 year after the start of clinical trials, ALK was recognised as a molecular target in NSCLC [7, 11, 16] and shortly afterwards a diagnostic assay was developed to screen for ALK-positive patients [16], allowing crizotinib to be evaluated in this population. The first patient with advanced ALK-positive NSCLC was treated with crizotinib in December 2007, resulting in rapid improvement in symptoms and prompting large-scale screening efforts and the recruitment of additional ALK-positive patients into a phase I study [16].

**efficacy**

**phase I and II studies.** To evaluate the potential efficacy of crizotinib, tumour samples from ~1500 patients with advanced NSCLC were screened, resulting in the identification of 82
ALK-positive patients, most of whom had received previous treatment [20]. These patients were enrolled into an expanded cohort of an ongoing phase I study (PROFILE 1001) and received crizotinib 250 mg twice daily in 28-day cycles, a dose which was established in the dose-escalation phase of the study. Of the 82 ALK-positive patients, 46 had a confirmed partial response (PR) and one had a complete response (CR) according to Response Evaluation Criteria in Solid Tumors (RECIST), giving an objective response rate of 57%. In addition, 27 patients (33%) had stable disease, including five with unconfirmed PRs. At the first restaging scans, six patients (7%) had disease progression [20].

An updated analysis of patients enrolled in the PROFILE 1001 study provided further evidence of the benefits of crizotinib in patients with ALK-positive stage III or IV NSCLC [21]. Additional enrolment provided a population of 143 evaluable patients who received crizotinib, 87 (61%) of whom had an objective response, including three CRs and 84 PRs. Best tumour responses in patients with measurable disease are shown in Figure 1. Median time to first documented objective response was 7.9 weeks, with a median duration of response of 49.1 weeks. Median progression-free survival (PFS) was 9.7 months, and estimated overall survival was 88% at 6 months and 75% at 12 months [21]. The PROFILE 1001 study is still ongoing, with crizotinib being studied in molecularly defined cohorts of patients with MET gene amplification [22], MET exon 14 alteration [23] and ROS1 gene rearrangement [24]. Of note, the activity seen in the ROSI cohort [24] led to the FDA approval of crizotinib for patients with ROS1-positive advanced NSCLC in March 2016.

To further evaluate the efficacy of crizotinib in ALK-positive NSCLC, a multicentre, single-arm phase II study (PROFILE 1005) enrolled 901 patients with ALK-positive advanced NSCLC and measurable lesions [25]. Patients received crizotinib 250 mg twice daily in 21-day cycles until progression or intolerable adverse events. Data are available from 261 patients enrolled and treated up to February 2011, 259 of whom were evaluable for response. In this population, 155 patients (60%) had an objective response (4 CRs and 151 PRs), 69 had stable disease and 19 had objective progression. Median duration of response was 45.6 weeks, and median time to response was 6.1 weeks. Estimated median PFS was 8.1 months [25].

### phase III studies

On the basis of the rapid and durable responses seen in the phase I and II studies [20, 21, 25], crizotinib received accelerated approval from the FDA in 2011; the time between the discovery of ALK fusions in NSCLC (2007) and the approval of crizotinib (2011) represented an unprecedented timeframe in the development of a novel anti-cancer agent. The results from the phase I and II studies of crizotinib also led to the initiation of phase III crizotinib studies, and data are available from two phase III studies that evaluated crizotinib as treatment for previously treated (PROFILE 1007 [26]) and previously untreated (PROFILE 1014 [27]) patients with advanced ALK-positive NSCLC.

**previously treated advanced NSCLC**: PROFILE 1007 was an open-label, phase III study that compared crizotinib with chemotherapy in 347 patients with locally advanced or metastatic ALK-positive NSCLC whose disease had progressed after one previous platinum-based chemotherapy regimen [26]. Patients were randomised to crizotinib 250 mg twice daily in a 3-week cycle or intravenous chemotherapy (pemetrexed 500 mg/m² or docetaxel 75 mg/m²) every 3 weeks. Patients receiving chemotherapy were permitted to cross over to crizotinib after disease progression as part of the PROFILE 1005 study.

At the time of the primary analysis of PROFILE 1007, the intention-to-treat (ITT) population comprised 173 patients randomised to crizotinib and 174 to chemotherapy who had been followed up for a median of 12.2 and 12.1 months, respectively [26]. Median PFS was significantly higher in the crizotinib group (7.7 months) than in the chemotherapy group (3.0 months), with a hazard ratio (HR) for progression or death of 0.49 (95% confidence interval [CI]: 0.37, 0.64; P < 0.001) (Figure 2A); the PFS

![Figure 1](image-url). Waterfall plot of best percentage change in tumour lesions from baseline in patients with measurable disease in the phase I PROFILE 1001 study (n = 133). Reprinted from [21], with permission from Elsevier.
benefit with crizotinib was consistent across all patient subgroups analysed. Subgroup analysis by type of chemotherapy showed that median PFS was significantly higher with crizotinib than with either pemetrexed (HR: 0.59; 95% CI: 0.43, 0.80; \( P < 0.001 \)) or docetaxel (HR: 0.30; 95% CI: 0.21, 0.43; \( P < 0.001 \)). Interestingly, patients in the pemetrexed group achieved greater PFS than those in the docetaxel group, consistent with previous studies demonstrating a greater sensitivity to pemetrexed in patients with ALK-positive versus wild-type tumours [28, 29]. A potential rationale for this observation is that ALK-positive tumours may express lower levels of thymidylate synthase than ALK-negative tumours [30]. In PROFILE 1007, the objective response rate was significantly higher in patients receiving crizotinib compared with those receiving chemotherapy (65% versus 20%; \( P < 0.001 \)), and median duration of response with crizotinib was longer (32 versus 24 weeks; Table 1) [26]. There was no significant difference in overall survival between treatment groups (HR for death with crizotinib: 1.02; 95% CI: 0.68, 1.54; \( P = 0.54 \)) [26]. This lack of difference probably reflects the low number of overall survival events that had occurred (40% of the total number of events required for the analysis) and the large proportion of patients (64%) in the chemotherapy group that crossed over to crizotinib following progression.

Previously untreated advanced NSCLC: PROFILE 1014 was an open-label, phase III study that compared crizotinib with chemotherapy in 343 patients with advanced ALK-positive NSCLC who had not previously been treated with systemic therapy [27]. Patients were randomised to either oral crizotinib 250 mg twice daily in a 3-week cycle or intravenous chemotherapy (pemetrexed 500 mg/m², plus either cisplatin 75 mg/m² or carboplatin at a target area under the curve of 5–6 mg/ml/min) every 3 weeks for up to six cycles. Patients receiving chemotherapy were permitted to cross over to crizotinib after progression.

The ITT population in PROFILE 1014 comprised 172 patients randomised to crizotinib and 171 to chemotherapy who at the time of the primary analysis had been followed up for a median of 17.4 and 16.7 months, respectively [27]. Median PFS was significantly higher with crizotinib (10.9 months) than with chemotherapy (7.0 months), with a HR for progression or
inhibitors such as ceritinib, alectinib, brigatinib and lorlatinib, within the CNS, including evaluation of second-generation ALK research is required to optimise the management of progression was significant in the crizotinib group than in the chemotherapy group (74% versus 45%; P < 0.001), and median duration of response was longer (49 versus 23 weeks; Table 1) [27]. As in the PROFILE 1007 study, there was no difference in overall survival between treatment groups (HR for death with crizotinib: 0.82; 95% CI: 0.54, 1.26), likely as a consequence of the relatively low all-cause death rate (26%) and the high rate of crossover (70%) from chemotherapy to crizotinib.

**intracranial activity.** The CNS is one of the principal sites of disease progression for patients receiving crizotinib therapy [31]. The PFS benefit of crizotinib over chemotherapy in the PROFILE 1007 and PROFILE 1014 studies was similar for patients with and without brain metastases at baseline [26, 27]. In a retrospective joint analysis of the PROFILE 1005 and PROFILE 1007 studies, the 12-week intracranial disease control rate with crizotinib was 62% and 56% in patients with previously treated and previously untreated brain metastases, respectively; however, systemic objective response rates were higher than intracranial objective response rates: 46% versus 33% and 53% versus 18% for previously treated and previously untreated brain metastases, respectively; however, systemic objective response rates were higher than intracranial objective response rates: 46% versus 33% and 53% versus 18% for previously treated and previously untreated brain metastases [31]. The intracranial activity of crizotinib was confirmed prospectively in the PROFILE 1014 study, where the 12-week intracranial disease control rate in patients with previously treated brain metastases at baseline was significantly higher in the crizotinib group than in the chemotherapy group (85% versus 45%; P < 0.001) [32]. Further research is required to optimise the management of progression within the CNS, including evaluation of second-generation ALK inhibitors such as ceritinib, alectinib, brigatinib and lorlatinib, which have demonstrated intracranial activity [33].

## safety

**safety profile in phase III studies.** Crizotinib was generally well tolerated in clinical studies of patients with advanced ALK-positive NSCLC, and the safety profile was similar in the phase III studies PROFILE 1014 [27] and PROFILE 1007 [26]. Adverse events that occurred with a frequency at least 5 percentage points greater in the crizotinib group compared with the chemotherapy group in both studies were vision disorder, diarrhoea, oedema, vomiting, constipation, elevated liver transaminases, upper respiratory tract infection, dysgeusia and dizziness (Table 2). In addition, crizotinib-treated patients had higher frequencies of abdominal pain, headache, pyrexia and pain in extremity in PROFILE 1014 and of nausea in PROFILE 1007, compared with chemotherapy (Table 2). Adverse events that were more frequent with chemotherapy than with crizotinib included fatigue (both studies); neutropenia, stomatitis, asthenia, anaemia, leucopenia and thrombocytopenia (PROFILE 1014); and dyspnoea, rash and alopecia (PROFILE 1007). When comparing adverse event rates between treatment groups, it should be noted that patients in the crizotinib groups had longer study treatment exposures than those in the chemotherapy groups.

In both phase III studies, most adverse events were of grade 1 or 2 severity [26, 27]. Grade 3 or 4 aminotransferase elevations occurred in 14% and 16% of crizotinib-treated patients in PROFILE 1014 and PROFILE 1007, respectively, compared with 2% of chemotherapy recipients in both studies. Aminotransferase elevations were managed primarily by dose interruption or dose reduction. The upcoming final analysis from the PROFILE 1005 phase II study will provide further safety data from ~1000 crizotinib-treated patients.

**safety and tolerability considerations during clinical use of crizotinib.** Visual disturbances associated with crizotinib were generally transient and had little or no impact on activities of daily life of 0.45 (95% CI: 0.35, 0.60; P < 0.001) (Figure 2B); this improvement in PFS was consistent across patient subgroups. Objective response rate was significantly higher in the crizotinib group than in the chemotherapy group (74% versus 45%; P < 0.001), and median duration of response was longer (49 versus 23 weeks; Table 1) [27]. As in the PROFILE 1007 study, there was no difference in overall survival between treatment groups (HR for death with crizotinib: 0.82; 95% CI: 0.54, 1.26), likely as a consequence of the relatively low all-cause death rate (26%) and the high rate of crossover (70%) from chemotherapy to crizotinib.

### Table 1. Response to treatment in the intention-to-treat population in the phase III PROFILE 1014 and PROFILE 1007 studies [26, 27]

<table>
<thead>
<tr>
<th>Response</th>
<th>Previously untreated patients (PROFILE 1014)</th>
<th>Previously treated patients (PROFILE 1007)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crizotinib (N = 172)</td>
<td>Chemotherapy (N = 171)</td>
</tr>
<tr>
<td>Type of response, a n (%)</td>
<td>Complete response</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>125 (73)</td>
</tr>
<tr>
<td></td>
<td>Stable disease</td>
<td>29 (17)</td>
</tr>
<tr>
<td></td>
<td>Progressive disease</td>
<td>8 (5)</td>
</tr>
<tr>
<td></td>
<td>Could not be evaluated b</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Objective response rate, % (95% CI) c</td>
<td>74 (67–81)</td>
<td>45 (37–53)</td>
</tr>
<tr>
<td>Median time to response (range), d weeks</td>
<td>6.1 (2.6–41.3) f</td>
<td>12.2 (5.2–36.9) f</td>
</tr>
<tr>
<td>Median duration of response (range), e weeks</td>
<td>49.1 (35.2–60.0) f</td>
<td>23.0 (17.8–25.2) f</td>
</tr>
</tbody>
</table>

a Tumour responses were assessed using Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, and were confirmed by independent radiologic review.

b Responses could not be evaluated in four patients in each group because of early death.

c P < 0.001 for comparison between treatment groups (95% CI calculated using the exact method based on the F distribution).

d Time to tumour response calculated from date of randomisation to date of the first documentation of partial or complete response as determined by independent radiologic review.

e Duration of response calculated from date of the first documentation of a PR or CR to date of RECIST-defined progression or death using Kaplan–Meier method.

f Original data converted from months to weeks by multiplying by 4.345.
However, ophthalmologic or neurologic evaluation may be necessary for patients whose visual disturbances persist or worsen during treatment. Before beginning crizotinib, patients should be warned that visual disturbances may occur and that they might affect activities such as driving in the dark [34].

Gastrointestinal adverse events were common in crizotinib studies but were generally mild or moderate and could usually be managed with supportive care rather than dose reduction or interruption [34].

Crizotinib was associated with QTc prolongation in a small proportion of patients (2%–4%) in the phase III studies [26, 27] and with bradycardia in 5%–10% [15]. Although the clinical significance and long-term effects of bradycardia and QTc prolongation in patients receiving crizotinib are unclear, caution should be taken for patients with a history of or predisposition for QTc prolongation [34]. Physicians should also be aware that QTc prolongation may be more likely to occur in individuals with electrolyte disturbances secondary to vomiting, diarrhoea or impaired renal function. Electrocardiographic monitoring should be considered for patients with a history of cardiac disease and in those taking medications associated with QTc prolongation. Use of medications associated with bradycardia, such as β-blockers, should be carefully evaluated before and during crizotinib treatment [34].

The occurrence of grade 3 or 4 aminotransferase elevations in 14%–16% of crizotinib-treated patients in phase III studies [26, 27] has led to concern regarding a risk of hepatic adverse effects [34]. Crizotinib should not be used in patients with severe hepatic impairment (bilirubin >3 × upper limit of normal), and all patients should be monitored for liver enzymes and total bilirubin every week for the first 2 months of therapy (with monthly monitoring and as clinically indicated thereafter) [34]. Patients should also be educated about signs and symptoms of drug-induced liver injury and hepatic failure [34].

Although crizotinib was associated with potentially fatal pneumonitis or interstitial lung disease (ILD) in a few number of patients [26, 27], such events may be related to NSCLC or previous treatment (such as radiotherapy) rather than to crizotinib [34]. Decisions to withdraw crizotinib should be made on a case-by-case basis. Crizotinib should, however, be discontinued if treatment-related pneumonitis occurs and standard treatments for ILD should be considered [34].

### Table 2. Adverse events in the phase III PROFILE 1014 and PROFILE 1007 studies [26, 27]

<table>
<thead>
<tr>
<th>Response</th>
<th>Previously untreated patients (PROFILE 1014)</th>
<th>Previously treated patients (PROFILE 1007)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crizotinib (N = 171)</td>
<td>Chemotherapy (N = 169)</td>
</tr>
<tr>
<td>Adverse events that were ≥5% more frequent with crizotinib, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>122 (71)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>105 (61)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Oedema</td>
<td>83 (49)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>78 (46)</td>
<td>60 (36)</td>
</tr>
<tr>
<td>Constipation</td>
<td>74 (43)</td>
<td>51 (30)</td>
</tr>
<tr>
<td>Elevated liver transaminases</td>
<td>61 (36)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>55 (32)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>45 (26)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>45 (26)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>37 (22)</td>
<td>25 (15)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32 (19)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>31 (18)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>27 (16)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Adverse events that were ≥5% more frequent with chemotherapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49 (29)</td>
<td>65 (38)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36 (21)</td>
<td>51 (30)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>24 (14)</td>
<td>34 (20)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 (13)</td>
<td>41 (24)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>15 (9)</td>
<td>54 (32)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>12 (7)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1)</td>
<td>31 (18)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rash</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alopecia</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

No adjustments have been made to account for differences in the duration of treatment exposure between groups. Adverse events are listed here if they were reported in 15% or more of patients in either treatment group and if there was at least a 5% difference between the two groups. NR, not reported (i.e. adverse event occurred in <15% of patients or with <5% difference between groups and was not reported in the published articles).
Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30) and module for lung cancer (QLC-LC13), compared with chemotherapy [27]. Crizotinib-treated patients also had significant improvements in individual domains (physical, social, emotional and role functioning) compared with chemotherapy. As well as improving QoL scores, crizotinib also significantly improved pain, dyspnoea and insomnia (QLQ-C30); and dyspnoea, cough, chest pain, arm or shoulder pain and pain in other parts (QLQ-LC13) [27]. Patients receiving crizotinib also had a significantly longer time to worsening of lung cancer symptoms (cough, dyspnoea or chest pain) compared with chemotherapy (HR: 0.62; 95% CI: 0.47, 0.80; \( P = 0.002 \)).

In the phase III PROFILE 1007 study, second-line crizotinib resulted in significantly greater improvements, compared with chemotherapy, in overall and individual domain scores on the QLC-C30 and QLC-LC13 and a significantly delay in time to worsening of symptoms (HR: 0.54; 95% CI: 0.40, 0.71; \( P < 0.001 \)) [26]. In addition, post hoc analyses showed that general health status (measured using the EuroQol-5D instrument) was significantly better in crizotinib-treated patients (score 0.82) than among those receiving chemotherapy (score 0.73; \( P < 0.05 \)) [35]. Crizotinib was also found to result in greater improvements compared with docetaxel for global QoL and all individual domains and compared with pemetrexed for global QoL and physical functioning [35].

### progression on crizotinib therapy

Despite significantly improved PFS with crizotinib [26, 27], advanced ALK-positive NSCLC patients will inevitably develop progressive disease. There is evidence that some patients can continue to derive benefit from crizotinib therapy beyond RECIST-defined progression. In the PROFILE 1001 study, 39 of 69 patients (56%) with disease progression continued to receive crizotinib for over 2 weeks (and 12 patients for ≥6 months) at the investigator’s decision due to ongoing clinical benefit [21]. Similarly, in the PROFILE 1014 study, 74 of 89 patients (83%) with progressive disease continued to receive crizotinib for a median of 3.0 months [27]. In a joint analysis of 194 patients with RECIST-defined disease progression in the PROFILE 1005 and PROFILE 1007 studies, 120 continued to receive crizotinib [36]. These patients had significantly longer overall survival from the time of progression (median 16.4 versus 3.9 months; HR: 0.27, 95% CI: 0.17, 0.42; \( P < 0.0001 \)) than those who discontinued crizotinib [36].

While they can continue to derive benefit from crizotinib beyond progression, patients will ultimately develop resistance and require a switch in therapy. The second-generation ALK inhibitors alectinib and ceritinib have been shown to be effective in crizotinib-resistant patients [37, 38], and when used sequentially with crizotinib, have resulted in long-term survival [39]. Furthermore, recently presented data from a phase III study in Japanese patients suggest that first-line alectinib may also be a future treatment option for patients with ALK-positive NSCLC [40]. ALK inhibitors vary in their potency against different ALK kinase domain mutations [41–44]; therefore, re-biopsy at the time of disease progression may provide valuable information about the most effective inhibitor for sequential treatment. This is illustrated by a recent report of sequential ALK inhibitor therapy that demonstrates the utility of re-biopsy in providing patients with a personalised treatment sequence [45].

### summary

NSCLC is a common cancer and has a very poor prognosis. The identification of novel targets for treatment has led to the development of new options that can improve outcomes in selected patients. Patients whose tumours express ALK fusion proteins are eligible for treatment with ALK inhibitors, the first of which was crizotinib.

In phase I and II studies, crizotinib resulted in rapid and durable treatment responses in patients with ALK-positive NSCLC, and these studies led to rapid regulatory approval. In subsequent phase III studies, crizotinib was shown to be generally well tolerated and associated with significant improvements in efficacy and QoL in both previously treated and previously untreated patients. The discovery of ALK gene rearrangements and the development of crizotinib have transformed the treatment landscape in advanced NSCLC and paved the way for the development of further treatment strategies, such that patients with advanced ALK-positive NSCLC can now benefit from a long-term continuum of care with ALK inhibitors.

### acknowledgements

Medical writing support was provided by ACUMED* (Tythering, UK), an Ashfield company, part of UDG Healthcare plc, and was funded by Pfizer.

### funding

This work was supported by the Italian Association for Cancer Research and Fondazione Ricerca Traslazionale (FC). F.B. was supported by Cancer Research UK Lung Centre of Excellence Grant Funding.

### disclosure

F.B. has received honoraria and research support from Pfizer and Novartis. F.C. has received personal fees for lectures and has served on advisory boards for Pfizer, Roche and Novartis.

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