FRESH FROM THE PIPELINE

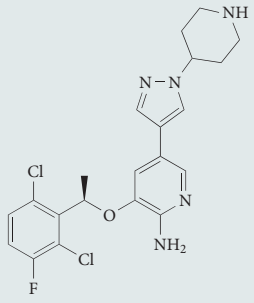
Crizotinib

Alice T. Shaw, Uma Yasothan and Peter Kirkpatrick

In August 2011 crizotinib (Xalkori; Pfizer), a small-molecule kinase inhibitor, was approved by the US Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer that is anaplastic lymphoma kinase-positive, as detected by an FDA-approved test.

Non-small-cell lung cancer (NSCLC), which accounts for ~85% of all cases of lung cancer, is a leading cause of cancer deaths worldwide[1]. It is often diagnosed at an advanced stage and has a poor prognosis; standard platinum-based chemotherapy prolongs median survival for less than 1 year[1].

However, in recent years some subgroups of patients with NSCLC who may experience substantial benefits from appropriately targeted drugs have been identified. The first such group to be identified was patients with activating mutations in the gene encoding the epidermal growth factor receptor (EGFR)[1]. Patients with *EGFR* mutations were found to have dramatic responses to two small-molecule inhibitors of EGFR kinase activity — gefitinib (Iressa; AstraZeneca) and erlotinib (Tarceva; Genentech/Roche) — which were originally approved in 2003 and 2004, respectively, for the treatment of NSCLC after failure of chemotherapy. The effectiveness of these drugs in patients with *EGFR* mutations has led to them becoming a standard treatment in this population, and has also encouraged efforts to identify other subgroups of patients with NSCLC.



Crizotinib

(*R*)-3-[1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine; $C_{21}H_{22}Cl_2FN_5O$; M_r = 450.34

Figure 1 | **Crizotinib.** The first generation of small-molecule inhibitors of the receptor tyrosine kinase MET, such as PHA-665752, were not viable clinical agents owing to their poor pharmaceutical properties and oral bioavailability[4]. Crizotinib (originally known as PF-2341066), a potent inhibitor of MET and anaplastic lymphoma kinase (ALK) that is orally bioavailable, was designed with the aid of a co-crystal structure of PHA-665752 bound to the kinase domain of MET[5].

Basis of discovery

In 2007, a study to isolate novel transforming genes in NSCLC reported the presence of a fusion gene that comprised portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*) gene in 5 out of 75 (~7%) of patients with NSCLC, who were distinct from those harbouring *EGFR* mutations[2]. As with fusions involving the *ALK* gene that had first been identified in anaplastic large-cell lymphoma (ALCL), the EML4–ALK fusion protein was shown to have transforming activity[2].

ALK encodes a tyrosine kinase, and the initial study showed that small-molecule inhibitors of ALK inhibited the growth of cells expressing EML4–ALK[2]. A subsequent analysis of 602 cell lines derived from various cancers found that ALK inhibition with small molecules including crizotinib potently suppressed the growth of a subset of cell lines known to harbour abnormalities in *ALK*, including those derived from patients with NSCLC and ALCL[3].

Drug properties

Crizotinib (FIG. 1) was discovered through studies to identify potent drug-like inhibitors of the receptor tyrosine kinase MET, the receptor for hepatocyte growth factor[4,5]. It was found to also be a potent inhibitor of ALK[4,5]. It inhibits ALK and MET phosphorylation in tumour cell lines and has antitumour activity in mice with tumour xenografts expressing EML4–ALK fusion proteins or MET[4–6].

Clinical data

The efficacy and safety of crizotinib (250 mg orally twice daily) in the treatment of locally advanced or metastatic ALK-positive NSCLC have been evaluated in two single-arm clinical trials, known as study A and study B[6]. Patients with ALK-positive NSCLC were identified using the Vysis ALK Break-Apart fluorescence *in situ* hybridization (FISH) Probe Kit in study A, and various local clinical trial assays in study B[6]. All 255 ALK-positive patients who were analysed in the two trials had received prior systemic therapy, with the exception of 15 patients in study B who had not received prior systemic treatment for locally advanced or metastatic disease[6]. The primary end point in both trials was objective response rate (ORR), which was evaluated by the investigator and by an independent radiology review panel. The duration of response was also evaluated[6].

In study A, among the 136 patients analysed at the time of data cut-off for regulatory submission (the median duration of treatment was 22 weeks), there was 1 complete response and 67 partial responses based on investigator assessments, corresponding to an ORR of 50%[6]. The median duration of response was 41.9 weeks[6].

For study B, results have been published for 82 patients with advanced ALK-positive NSCLC (identified by screening ~1,500 patients for *ALK* gene rearrangements)[7]. Treatment with crizotinib resulted in tumour shrinkage in 57% of patients and stabilized the disease in a further 33% of patients[7]. Among the 119 patients analysed at the time of data cut-off for regulatory submission (the median duration of treatment was 32 weeks), there were 2 complete responses and 69 partial responses, corresponding to an ORR of 61%[6]. The median duration of response was 48.1 weeks[6].

Indications

Crizotinib has been granted accelerated approval by the FDA for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive, as detected by an FDA-approved test[6]. This indication is based on response rate[6]. ▸

ANALYSIS | NON-SMALL-CELL LUNG CANCER

▸ Analysing issues in the treatment of NSCLC is Alice T. Shaw, M.D., Ph.D., Attending Physician, Thoracic Cancer Program, Massachusetts General Hospital, Boston, USA.

The past decade has witnessed a major shift in the treatment of advanced NSCLC. Histological subtype is clearly an important factor in selecting among standard cytotoxic chemotherapies, but the genetic subtype — the presence (or absence) of key oncogenic alterations such as activating mutations and chromosomal rearrangements — is now also crucial. This was first established with the discovery of sensitizing *EGFR* mutations in a subset of patients with NSCLC, and has now been further validated by the successful development of crizotinib for a different NSCLC subset defined by *ALK* gene rearrangements.

In Phase I and Phase II trials, crizotinib was shown to be highly active in patients with advanced ALK-positive NSCLC, with ORRs of 50–60%[7]. In the Phase I trial (study B), median progression-free survival (PFS) was 10 months[8], similar to that seen with EGFR inhibitors in advanced, *EGFR*-mutant NSCLC. This contrasts with ORRs of 10% and median PFS of less than 3 months for standard single-agent chemotherapies in unselected patients with NSCLC who have received prior chemotherapy. Based on the response rates observed in the Phase I and II studies, as well as its favourable safety profile, crizotinib was recently approved in the United States for patients with advanced, ALK-positive NSCLC, just 4 years after *ALK* gene rearrangement was reported in NSCLC[2].

One aspect of the FDA label for crizotinib that has important implications for the management of patients with ALK-positive NSCLC is that it does not specify a requirement for prior therapies. Therefore, in the United States newly diagnosed ALK-positive patients can be prescribed crizotinib in the first-line setting. Data supporting the first-line use of crizotinib are limited; in the Phase I trial the response rate among 15 previously untreated patients was 80%[8]. However, the first-line use of crizotinib for patients with advanced, ALK-positive NSCLC is expected to be substantial, and is appropriate, given the efficacy and safety data so far, as well as the results from randomized studies demonstrating the superiority of EGFR inhibitors versus platinum doublets as first-line therapy for patients with *EGFR*-mutant NSCLC.

There are currently two ongoing, randomized Phase III studies of crizotinib. The first study — known as PROFILE 1007 — is comparing crizotinib with single-agent pemetrexed (Alimta; Lilly) or docetaxel as second-line therapy in patients with advanced, ALK-positive NSCLC. The second study — known as PROFILE 1014 — will compare crizotinib with a platinum/pemetrexed combination in newly diagnosed patients with advanced, ALK-positive NSCLC. The primary end point of both studies is PFS, and overall survival is a secondary end point. The overall survival benefit of crizotinib will probably be confounded in both trials owing to crossover. However, a comparison of patients treated with crizotinib in the Phase I trial with a population of patients who never received crizotinib suggests that crizotinib may prolong survival in patients with advanced, ALK-positive NSCLC[9].

As seen with other targeted cancer drugs, patients with ALK-positive NSCLC eventually relapse on crizotinib. The development of acquired resistance is clearly the major hurdle preventing targeted therapies such as crizotinib from having an even more substantial impact on patients. Several distinct mechanisms of crizotinib resistance have been identified, including acquisition of secondary resistance mutations within the tyrosine kinase domain of ALK[10]. The development of effective strategies to overcome resistance will require understanding the precise mechanisms of resistance; hence, the molecular analysis of repeat biopsy specimens in relapsing patients is crucial. The results of these studies will facilitate the tailoring of future therapeutic strategies, and ultimately lead to improved clinical outcomes for patients with advanced, ALK-positive NSCLC.

Box 1 | Market for non-small-cell lung cancer

Analysing the market for non-small-cell lung cancer (NSCLC) is Uma Yasothan, IMS Health, London, UK.

There has been no recommended pharmacotherapy for patients who have NSCLC with disease progression after cytotoxic chemotherapy (first- or second-line) and who are resistant to erlotinib (Tarceva; Genentech/Roche) or gefitinib (Iressa; AstraZeneca). However, with the approval of crizotinib (Xalkori; Pfizer) by the US Food and Drug Administration, there is now an option for the estimated ~3–4% of patients with rearrangements in the gene encoding anaplastic lymphoma kinase (ALK).

Crizotinib is being launched into a high-value, low-volume market. In 2010, gefitinib had sales of US$350 million worldwide, and erlotinib (which is also indicated for pancreatic cancer) had sales of $1.2 billion, according to data from IMS MIDAS 2011. Potential barriers to crizotinib uptake include its high cost (up to $100,000 per year) and the willingness of physicians to obtain lung biopsy samples to identify *ALK* gene rearrangements. Pfizer is currently running two Phase III trials in patients with ALK-positive NSCLC comparing crizotinib with chemotherapy, one as a second-line treatment and one in newly diagnosed patients. Results of the first of these trials are expected in 2012. A regulatory application for crizotinib has also been accepted for review by the European Medicines Agency. Analysts' expectations for sales of crizotinib are >$500 million in peak annual sales in the United States alone, with worldwide sales of $1.3 billion by 2017 (Schott, C. *et al.* J.P. Morgan Securities report. 26 Aug 2011).

Alice T. Shaw is at Massachusetts General Hospital Cancer Center, 32 Fruit Street, Boston, Massachusetts 02114, USA.

Uma Yasothan is at IMS Health, 7 Harewood Avenue, London NW1 6JB, UK.

Peter Kirkpatrick is at Nature Reviews Drug Discovery.

e-mails: ashaw1@partners.org; UYasothan@imscg.com; p.kirkpatrick@nature.com

doi:10.1038/nrd3600

1. Janku, F. *et al.* Targeted therapy in non-small-cell lung cancer — is it becoming a reality? *Nature Rev. Clin. Oncol.* **7**, 401–414 (2010).
2. Soda, M. *et al.* Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer. *Nature* **448**, 561–567 (2007).
3. McDermott, U. *et al.* Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors. *Cancer Res.* **68**, 3389–3395 (2008).
4. Zou, H. Y. *et al.* An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res.* **67**, 4408–4417 (2007).
5. Cui J. J. *et al.* Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition Factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). *J. Med. Chem.* **54**, 6342–6363 (2011).
6. US Food and Drug Administration. FDA labeling information — Xalkori. *FDA website* [online], http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202570s000lbl.pdf (2011).
7. Kwak, E. L. *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N. Engl. J. Med.* **363**, 1693–1703 (2010).
8 Camidge, D. R. *et al.* Progression-free survival (PFS) from a phase 1 study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* **29**, 2501 (2011).
9. Shaw, A. T. *et al.* Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring *ALK* gene rearrangement: a retrospective analysis. *Lancet Oncol.* **12**,1004–1012 (2011).
10. Choi, Y, L. *et al.* EML4–ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N. Engl. J. Med.* **363**, 1734–1739 (2010).

Competing interests statement
The authors declare competing financial interests: see Web version for details.