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REVIEW

Crizotinib as a personalized alternative for targeted anaplastic lymphoma kinase rearrangement in previously treated patients with non-small-cell lung cancer

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Abstract: Crizotinib, the first clinically designed and synthesized as a tyrosine kinase inhibitor targeting mesenchymal–epithelial transition factor, indicating marked anticancer activity in patients with advanced, anaplastic lymphoma kinase-positive non-small-cell lung cancer, was approved by the US Food and Drug Administration in 2011. In this review, we focus on the efficacy of crizotinib compared with chemotherapy in advanced anaplastic lymphoma kinase-positive lung cancer and present the role of crizotinib as a personalized alternative in previously treated patients with non-small-cell lung cancer.

Keywords: crizotinib, anaplastic lymphoma kinase rearrangement, non-small-cell lung cancer

Introduction

Lung cancer is the most common cancer and the leading cause of tumor-related death worldwide, ~85%–90% of which are characterized as non-small-cell lung cancer (NSCLC).[1] For the treatments of lung cancer, the traditional methods include surgery, radiotherapy, and chemotherapy. The majority of patients (68%) with early stage NSCLC undergo surgery, and 16% patients also receive chemotherapy or radiation therapy. A total of 18% of patients with advanced-stage NSCLC are treated with chemotherapy alone, 15% radiation therapy alone, and 33% a combination therapy.[2] However, in recent years, targeted drugs shift the traditional treatment mode of NSCLC. This paradigm was first established with the discovery of epidermal growth factor receptor (*EGFR*), and *EGFR* tyrosine kinase inhibitors (TKIs) are excellent examples of personalized alternative.[3] Anaplastic lymphoma kinase (*ALK*), a member of the insulin receptor family of receptor tyrosine kinases (RTKs), as a fusion oncogene with nucleophosmin, was first identified in anaplastic large-cell lymphomas on chromosome 2p23.[4] *ALK* encodes a 1,620-amino acid transmembrane protein, including an extracellular ligand-binding domain, a transmembrane domain, and an intracellular kinase catalytic region.[5] Echinoderm microtubule-associated protein-like 4 (*EML4*) is an intracellular protein of 120 kDa, a member of echinoderm microtubule-associated protein family and microtubule stabilizing protein, and plays the role in the formation of microtubules.[5,6] *EML4-ALK* fusion gene is a new gene mutation, which is closely related to the growth and proliferation of tumor cells. Soda et al[7] identified the transforming *EML4-ALK* fusion gene in 6.7% of patients with NSCLC, resulting from a small inversion within the short arm of chromosome 2p (2p21 and 2p23), which produces a fusion protein consisting

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of the amino-terminal protein of *EML4* and the intracellular region tyrosine kinase *ALK*.[8] It is the most common *ALK* fusion gene in patients with NSCLC, and the clinical characteristics of these individuals are significantly distinct from *EGFR*-positive patients.[7] One of the distinctive clinicopathological features is more prevalent in the fluorescence in situ hybridization (FISH)-positive *ALK* rearrangement patients with the history of never smoked or a light smoking (<10 pack-years), and the other includes younger age at diagnosis and adenocarcinoma histologic analyses associated with *ALK*-positive lung cancers.[9] *EML4-ALK*-positive lung adenocarcinomas were less-differentiated grade and acinar-predominant structure observed by histology.[10] Furthermore, *EML4-ALK* expression was mutually exclusive with *EGFR* and *KRAS* mutations in sufficient tissues.[10,11] *ALK* gene rearrangements or the resulting fusion proteins in NSCLC can be detected in tumor specimens using FISH, reverse transcriptase polymerase chain reaction, and immunohistochemistry.[12] NSCLC tissues harboring *ALK* gene rearrangements are representing 3%–5% and define a distinct molecular subgroup of the tumor; a total of >60,000 new cases with *ALK*-positive are projected to occur in NSCLC annually.[5,13]

Crizotinib (PF-02341066, trade name Xalkori; Pfizer Inc., New York, NY, USA), the first clinically designed and synthesized as a TKI targeting mesenchymal–epithelial transition factor (*c-Met*), also called *MET* and hepatocyte growth factor receptor, indicating marked anticancer activity in patients with advanced, *ALK*-positive NSCLC, was approved by the US Food and Drug Administration in 2011.[14–17] In this article, the structure, mechanism, pharmacokinetics, and pharmacogenetics of crizotinib are reviewed. We have also summarized the efficacy of crizotinib compared with chemotherapy in advanced *ALK*-positive lung cancer and presented the role of crizotinib as personalized alternative in previously treated patients with NSCLC.

Structure, mechanism, and pharmacokinetics

Structure of crizotinib

Crizotinib as multitargeted TKI is a small molecule (molecular weight =450 Da),[18] oral, highly selective and potent competitive inhibitor of *ALK* with additional *MET*, *c-ros* oncogene (*ROS1*), and recepteur d'origine nantais kinase inhibitory property.[16,19] Molecular formula of crizotinib is $C_{21}H_{22}C_{l2}FN_5O$, and the chemical formula is (*R*)-3-[1-(2,6-dichloro-3-fluorophenyl) ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-l] pyridine-2-amine, which is shown in Figure 1.[20]

Mechanism

In biochemical and cellular screens for kinase selectivity, crizotinib was shown to be selective for *c-Met* and *ALK* with high potency and specificity across a panel of >120 diverse

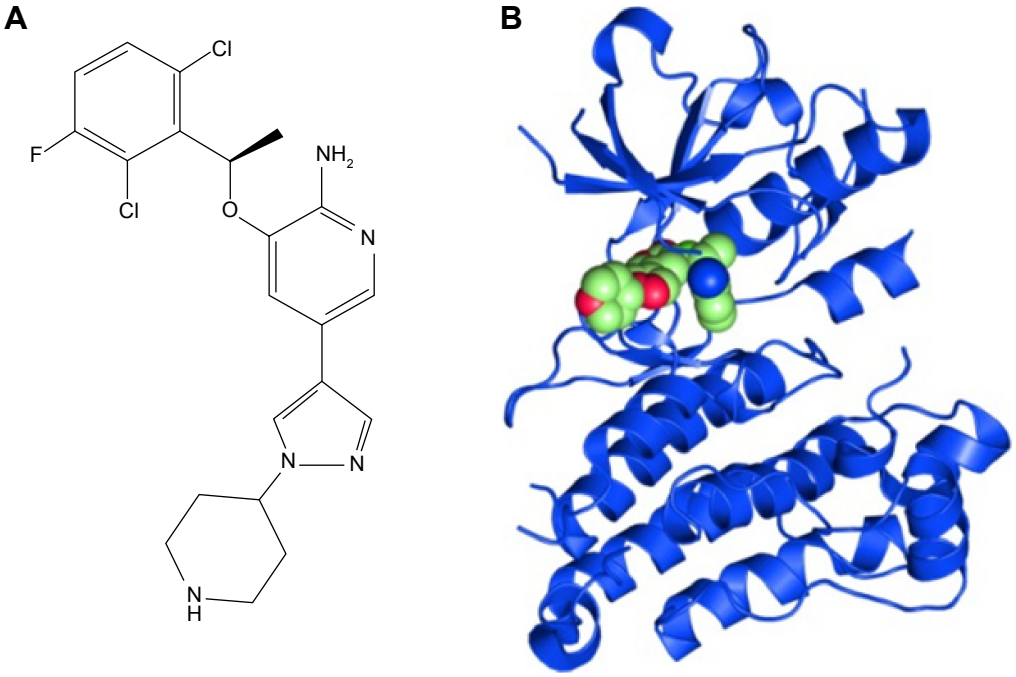

Figure 1 Chemical structure of crizotinib (**A**) and *ALK* in complex with crizotinib (**B**).
Abbreviation: *ALK*, anaplastic lymphoma kinase.

kinases.[21,22] A chromosomal inversion on chromosome 2p leads to an aberrant *EML4-ALK* fusion oncogene in NSCLC. Thus, *ALK* tyrosine kinase is constitutively activated, leading to uncontrolled cell growth and proliferation through activation of phosphoinositide 3-kinase and mitogen-activated protein kinase.[20] Apoptosis in *EML4-ALK* NSCLC cell lines and tumor shrinkage in murine models were observed when *ALK* kinase activity was inhibited via small-molecule *ALK* kinase inhibitors.[22] Crizotinib potently inhibited cell proliferation, which was associated with G1-S-phase cell cycle arrest and induction of apoptosis in *ALK*-positive anaplastic large-cell lymphomas cells but not *ALK*-negative lymphoma cells.[23] Crizotinib dose dependently inhibited the phosphorylation of *c-Met* and *ALK* and effectively inhibited downstream effector functions in vitro and in vivo.[19,24]

Pharmacokinetics and pharmacogenetics

Crizotinib was determined orally as a capsule, and clinical studies indicated 250 mg twice daily (bid) as the maximal tolerated dose in 167 patients with cancer.[25,26] Peak plasma crizotinib concentrations were achieved 4–6 hours after absorption of a single dose of 250 mg. After repeated dosing at 250 mg bid, steady-state concentrations were reached within 15 days.[26] Bioavailability was 43% (range: 32%–66%) and crizotinib exposure was influenced by food only to a minor degree.[20,25] Age, sex, race, or body weight appeared to have no effects on the single-dose crizotinib.[26] Crizotinib treated in *ALK*-positive NSCLC patients was similar to patients with other cancer types of pharmacokinetic parameters. Mean values for crizotinib peak plasma concentrations (C_{max}) and area under the plasma concentration–time curve were greater in Asian patients than in non-Asian patients.[20,26,27] Metabolization was executed primarily by cytochrome P450 3A4/5 enzymes, resulting in time-dependent inhibition of cytochrome P450 3A4 under extensive hepatic metabolism. Furthermore, crizotinib was also modulated by other drugs interacting with this cytochrome oxidase.[20,25] The lifetime incidence of central nervous system (CNS) disease in patients with advanced *ALK*-positive NSCLC approaches 50%.[28] However, crizotinib and the other small-molecule TKIs, including imatinib, erlotinib, and gefitinib, had the low penetration of the cerebrospinal fluid[29] and may require alternative dosing schemes or increased dose adjustments.[30] Local ablative therapy such as radiotherapy or surgery could be a strategy for systemic cancer control with continuation of crizotinib.[29,31] PF-06463922 (developed by Pfizer), which is a novel multitargeted *ALK* and *ROS1* TKI, a low-efflux substrate from cell lines overexpressing P-glycoprotein was designed to increase potential CNS penetration.[29,32] PF-06463922 exhibited superior potency against brain metastases compared with crizotinib and alectinib; a Phase I and II clinical trials of PF-06463922 is currently under way, and this drug can be effective in *ALK*-rearranged NSCLC patients with CNS disease in the crizotinib naïve or resistance.[29,33]

Personalized alternative for targeted *ALK*-positive in previously treated patients with NSCLC

The efficacy of crizotinib in the treatment of NSCLC has been investigated in several clinical trials, including various Phase I, II, and III studies on register (Table 1).

The first-in-man Phase I (PROFILE 1001) crizotinib trial (Funded by Pfizer and others, ClinicalTrials.gov number, NCT00585195), was designed as an open-label, multicenter dose-escalation study.[9,34,35] The trial consisted of a subgroup of 82 patients with advanced *ALK*-positive NSCLC confirmed by FISH.[14] The majority of the patients had received previous treatment. The dose-limiting toxicity was defined at 300 mg bid, in which two patients experienced grade 3 fatigue, and the maximum tolerated dose and recommended Phase II dose were defined at 250 mg bid in 28-day cycles.[17,36,37] After the mean duration 6.4 months of

Table 1 Characteristics of the clinical studies of crizotinib

Study	Trial	ID	Design	Number	PFS (months)	ORR (%)
Kwak et al[9] Camidge et al[17]	Phase I	PROFILE 1001	Single arm	149	9.7	60.8
Crinò et al[40] Kim et al[41]	Phase II	PROFILE 1005	Single arm	259	8.5	53
Shaw et al[13]	Phase III	PROFILE 1007	Second line Crizotinib vs pemetrexed or docetaxel	347	7.7	65
Solomon et al[44]	Phase III	PROFILE 1014	First line Crizotinib vs pemetrexed/cisplatin or carboplatin	343	10.9	74

Abbreviations: PFS, progression-free survival; ORR, objective response rate; ID, identification.

the treatment, an objective response rate (ORR) of 57% (95% confidence interval =46–68) was observed in the cohort. An additional group of 27 (33%) patients showed stable disease and 63 (77%) patients were still receiving treatment, and the estimated progression-free survival (PFS) at 6 months was 72%.[9,14] Based on these promising data, an expanded cohort of patients with *ALK*-positive NSCLC was subsequently enrolled.[17,38] The expansion of this trial recruited additional population that consisted of 143 characteristic patients with *ALK*-positive lung cancer. The median age was 52 years, and the ORR was 60.8% (87 of 143 evaluable patients), including three patients with a complete response (CR) and 84 with a partial response (PR).[17,39] The estimated median PFS was 9.7 months for all patients, and the median duration of response was 49.1 weeks, regardless of age, sex, and performance status. Median overall survival (OS) data are not yet mature, but the estimated 6-month and 12-month OS rates were 88% and 75%, respectively.[17]

Similar impressive clinical activity of crizotinib was observed in an ongoing global Phase II study (PROFILE 1005, NCT00932451) of advanced, *ALK*-positive NSCLC.[15] The efficacy of open-label, single-arm Phase II trial with crizotinib has been assessed in 136 patients who are *ALK*-positive.[40] At the latest update, among 901 patients with *ALK*-positive NSCLC received crizotinib therapy, the ORR of 259 patients evaluable for response was 53%, the CR in one patient and the PR in 67 patients, with median duration of response of 10.8 months and median PFS of 8.5 months. ORR was independent of age, sex, and number of prior metastatic treatment regimens.[24,40–42] These studies accelerated approval for crizotinib in *ALK*-rearranged NSCLC in many countries and granted by the US Food and Drug Administration.[17,43]

Recently, the results of two international, randomized Phase III studies of crizotinib were conducted.[15] The first Phase III trial (the second-line trial, PROFILE 1007) compared crizotinib with chemotherapy (single-agent pemetrexed or docetaxel) in 347 patients (173 to crizotinib and 174 to chemotherapy) with advanced *ALK*-positive NSCLC detected by FISH who have received one prior platinum-based chemotherapy.[13–15] PFS was the primary end point in the study, with OS as a secondary end point.[15] PFS was prolonged in the crizotinib-treated group, with the median PFS of 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group. The response rate was also obviously higher in patients treated with crizotinib (65%) as compared with chemotherapy (20%). However, there was no significant difference in OS between crizotinib and chemotherapy, and 64% of patients on chemotherapy crossed over to crizotinib at disease progression probably influenced the data.[13] Crizotinib is superior to standard chemotherapy in patients with previously treated NSCLC with *ALK* rearrangement (Table 2).

Table 2 The efficacy of crizotinib compared with standard chemotherapy in previously treated patients with NSCLC

Efficacy parameter	Crizotinib (N=173)	Pemetrexed or docetaxel (N=174)
PFS (months) (95% CI)	7.7 (6.0–8.8)	3.0 (2.6–4.3)
ORR (%) (95% CI)	65 (58–72)	20 (14–26)
Median duration of response (weeks) (range)	32.1 (2.1–72.4)	24.4 (3.0–43.6)
Median time to response (weeks) (range)	6.3 (4.4–48.4)	12.6 (5.0–37.1)

Abbreviations: NSCLC, non-small-cell lung cancer; PFS, progression-free survival; CI, confidence interval; ORR, objective response rate.

The second Phase III trial (The first-line trial, PROFILE 1014) is ongoing, comparing crizotinib with standard chemotherapy (pemetrexed plus either cisplatin or carboplatin) in newly diagnosed 343 patients with *ALK*-positive advanced NSCLC. PFS of crizotinib and standard chemotherapy was 10.9 months and 7.0 months, respectively. The ORR showed superiority of crizotinib over first-line chemotherapy.

The probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy.[44] In addition, *ROS1* (chromosome 6q22) encodes an orphan RTK related to *ALK* and belongs to the insulin receptor family.[45] Chromosomal rearrangements involving the *ROS1 RTK* gene have been reported in a subgroup of NSCLC patients, which occurs in ~1%–2% of patients with NSCLC.[46–48] All of the *ROS1*-positive NSCLCs were remarkably similar to that of *ALK*-rearranged patients, who have histologic features of adenocarcinoma, a tendency toward higher grade, young age, and never smoked. The preclinical study indicated that crizotinib could inhibit *ROS1* activity and cell growth in vitro.[45] In an expansion cohort of the Phase I study (250 mg twice daily) in 50 previously treated patients with *ROS1*-positive rearrangement advanced NSCLC, the ORR was 72%, including three CRs and 33 PRs. The median duration of response was 17.6 months, and median PFS was 19.2 months, with 25 patients (50%) still in follow-up for progression.[46] *ROS1*-rearangement could be a predictive marker for response to crizotinib; furthermore, it seems as the prognostic molecular marker in NSCLC.[48]

Safety and adverse effect

Crizotinib was generally well tolerated with the majority of adverse events (AEs), the most of which are moderate (grade 1 or 2). The frequently occurring AEs were visual effects (visual impairment, photopsia, blurred vision, vitreous floaters, photophobia, and diplopia), but the visual disorders

could disappear after discontinuation of crizotinib. Other common AEs included fatigue, decreased appetite, gastrointestinal events (nausea, diarrhea, vomiting, and constipation), peripheral edema, esophageal disorders (dyspepsia, esophagitis, and gastroesophageal reflux), altered taste, neuropathy, dizziness, and rash.[9,40,41,44]

Resistance to crizotinib

Despite the excellent efficacy, the majority of patients relapse during the first year of treatment and become resistant to crizotinib.[15] Mechanisms of the acquired crizotinib resistance can be divided into two main classes.[12] First, the target gene itself can be altered either by mutation or amplification, making tumor cells limit the drug efficacy to inhibit the kinase.[35] Choi et al[49] reported the two secondary mutations (*C1156Y* and *L1196M*) within the kinase domain of *EML4-ALK* in tumor cells, *L1196M* representing gatekeeper mutation that interferes with the binding of crizotinib and *EML4-ALK*, and the same *L1196M* gatekeeper mutation was identified in a patient with acquired resistance.[50,51] Second, crizotinib resistance is caused by the activation of alternative signaling pathways or so-called bypass tracks in *ALK*-positive NSCLCs. As an example, activation of *EGFR* signaling as a bypass signaling made resistant to crizotinib, suggesting that *EGFR* and some of its ligands may be upregulated.[15,52] Katayama et al[53] also identified aberrant activation of other kinases including marked amplification of KIT and increased autophosphorylation of *EGFR* in drug-resistant tumors from patients. Finally, *ALK*-positive NSCLC occurs through somatic kinase domain mutations, *ALK* gene fusion copy number gain, and emergence of separate oncogenic drivers, which could represent a potential resistance mechanism.[54]

Next-generation *ALK* inhibitors

Ceritinib (Zykadia; Novartis International AG, Basel, Switzerland; formerly called LDK378) is an orally available, potent, small molecule TKI of *ALK*, and it is effective in preclinical models of *ALK*-positive NSCLC.[55,56] Ceritinib has demonstrated antitumor activity in both crizotinib-naïve and crizotinib-refractory *ALK*-rearranged NSCLC patients.[57] In particular, ceritinib increased activity against *ALK* harboring *L1196M*, *G1269A*, *I1171T*, and *S1206Y* mutations, but it was ineffective at inhibiting two crizotinib-resistant *ALK* mutations, *G1202R* and *F1174C*.[32,57] Alectinib (RO5424802/CH5424802), which is being developed by Roche, is potent, selective, and orally available *ALK* inhibitor. It was first approved in multicenter, single-arm, open-label, Phase I and II study of Japan.[32,58] Based on the results of the study, alectinib could be an effective and safe option for the treatment of *ALK*-rearranged NSCLC, and it can be used to achieve strong and longlasting inhibitory effects on brain metastases.[58,59] Currently, a clinical study (NCT01588028) assessing the activity of alectinib in patients who failed to respond to crizotinib-based treatment is ongoing.[58] Brigatinib (previously known as AP26113) is a more potent inhibitor of *ALK* than crizotinib and has activity against *ALK* kinase domain mutations that confer resistance to crizotinib.[31] Brigatinib has been shown to be effective for intracranial metastasis.[59] Other *ALK* inhibitors, such as PF-06463922 (Pfizer), X-396 (Xcovery, Holding Co LLC, West Palm Beach, FL, USA), ASP3026 (Astellas Pharma Inc., Tokyo, Japan), TSR-011 (Tesaro, Inc., Waltham, MA, USA), and CEP-37440 (TEVA, Petah Tikva, Israel), are in various stages of clinical development for *ALK*-positive cancers.[31,32] Next-generation *ALK* inhibitors including ceritinib, alectinib, and brigatinib in patients have seen impressive and durable responses progressing after crizotinib, indicating that these drugs represent effective second-line treatment options.[31] Now, a number of effective treatment options raise for patients with *ALK*-rearranged NSCLC, what sequence to use these *ALK* inhibitors is yet to be determined.[31,32]

Heat shock protein 90 inhibitors

Heat shock protein 90 (Hsp90) is a molecular chaperone involved in normal cellular functions as well as tumorigenesis, which has been identified as potential anticancer agents.[32,60] Hsp90 inhibitors also showed efficacy in treating *ALK*-positive NSCLC; compared with TKIs, Hsp90 inhibitors appear to have lower response rates and side effects that are less tolerable.[32] However, Hsp90 inhibitors had limited activity against CNS metastatic tumors. The present studies encourage patients to participate in clinical trials to address the best combination or treatment strategy of Hsp90 inhibitors.[60] Immunotherapy through inhibition of programmed death 1 has demonstrated efficacy in treating advanced NSCLC.[31,61] Ongoing trials will further define the utility of Hsp90 inhibitors in NSCLC.[62]

Conclusion and future directions for drug development

Crizotinib is a promising antitumor activity for patients with *ALK* gene rearrangements in NSCLC. The clinical trials showed that crizotinib prolonged PFS, increased response rates, and improved the quality of life in patients. Crizotinib was superior to standard chemotherapy in patients with *ALK*-positive advanced NSCLC. Crizotinib for targeted *ALK* rearrangement in previously treated patients with NSCLC brings us one step closer to personalized lung cancer therapy. Though crizotinib

is well benefited for most patients who are *ALK* positive, some still go on to relapse as a result of the acquired resistance. The multiple therapeutics strategies should be implemented and developed to overcome crizotinib resistance in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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