

Crizotinib: From Chemical Entity to Anticancer Agent

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Abstract: Crizotinib is a mesenchymal-epithelial transition/anaplastic largecell kinase (MET/ALK) multi-targeted receptor tyrosine kinase inhibitor and has been rapidly and successfully developed as an inhibitor in ALK-rearranged NSCLC (non-small cell lung cancer). Lung cancer is the major cause of cancer-related mortality, accounting for over one quarter of cancer deaths. Lung cancers are generally divided into two main categories: SCLC (small cell lung cancer) and NSCLC. NSCLC accounts for approximately 85% of all lung cancers. ALK gene rearrangements are identified and targeted resulting in promising response rates for NSCLC in early studies. Considering the significance of Crizotinib in the treatment of NSCLC, the synthesis, pharmacodynamics, pharmacokinetics, therapeutic trials and adverse events are briefly overviewed in order to make more scholars, medical workers and patients have a more clear and comprehensive recognition on Crizotinib.

Key words: Crizotinib, non-small cell lung cancer, anaplastic largecell kinase inhibitor, review.

1. Introduction

Crizotinib (trade name Xalkori[®]) is an oral anti-cancer drug which is acted as an ALK (anaplastic lymphoma kinase) inhibitor and c-ros oncogene 1 (ROS1) inhibitor, approved by for treatment of some NSCLC (non-small cell lung carcinoma) in 2011 [1-3]. ALK is a receptor tyrosine kinase of the insulin receptor superfamily [4]. The expression of ALK in tissues of health humans is only found in subset of neural cells. The overexpression of ALK acts as a consequence of translocations or point mutations, which have been demonstrated to be an essential oncogenic lesion in a number of cancers especially for lung cancer. ROS1 is also a receptor tyrosine kinase with structural similarity to the ALK protein, which has been reported to be involved in cancers, especially in lung cancer [5, 6]. Lung cancer comprises 85% to 90% of cases classified as NSCLC [7-9]. It has been found that 2~7% of NSCLC tumors express genetic alterations of the ALK genes [10, 11]. ALK-positive tumors are highly sensitive to ALK inhibition, making such aberrations an important target for anticancer drug therapies. Therefore, the developing of drugs possesses

the inhibition effect both on ALK and ROS1 is badly needed in the field of treating lung cancer.

Crizotinib is commonly used as capsules in the US and some other countries. The chemical name is (R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)pyridin-2-amine [12]. The structural formula is shown in Fig. 1. It is undergoing clinical trials testing its safety and efficacy in anaplastic large cell lymphoma, neuroblastoma, and other advanced solid tumors in both adults and children. In this paper, the synthesis, pharmacodynamics, pharmacokinetics, therapeutic trials and adverse events are briefly summarized in order to make more scholars, medical workers and patients have a more clear and comprehensive recognition on this drug.

2. Synthesis

In a typical process for the synthesis of Crizotinib, 2-nitropyridin-3-ol and (R)-1-(2,6-dichloro-3-fluorophenyl)ethanol are used as starting materials. The synthetic route is shown in Fig. 2. The starting materials are treated with triphenylphosphine in tetrahydrofuran under ice bath to give (R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-nitropyridine and then reduced to (R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-

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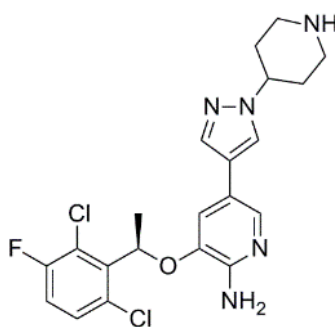


Fig. 1 The structural formula of Crizotinib.

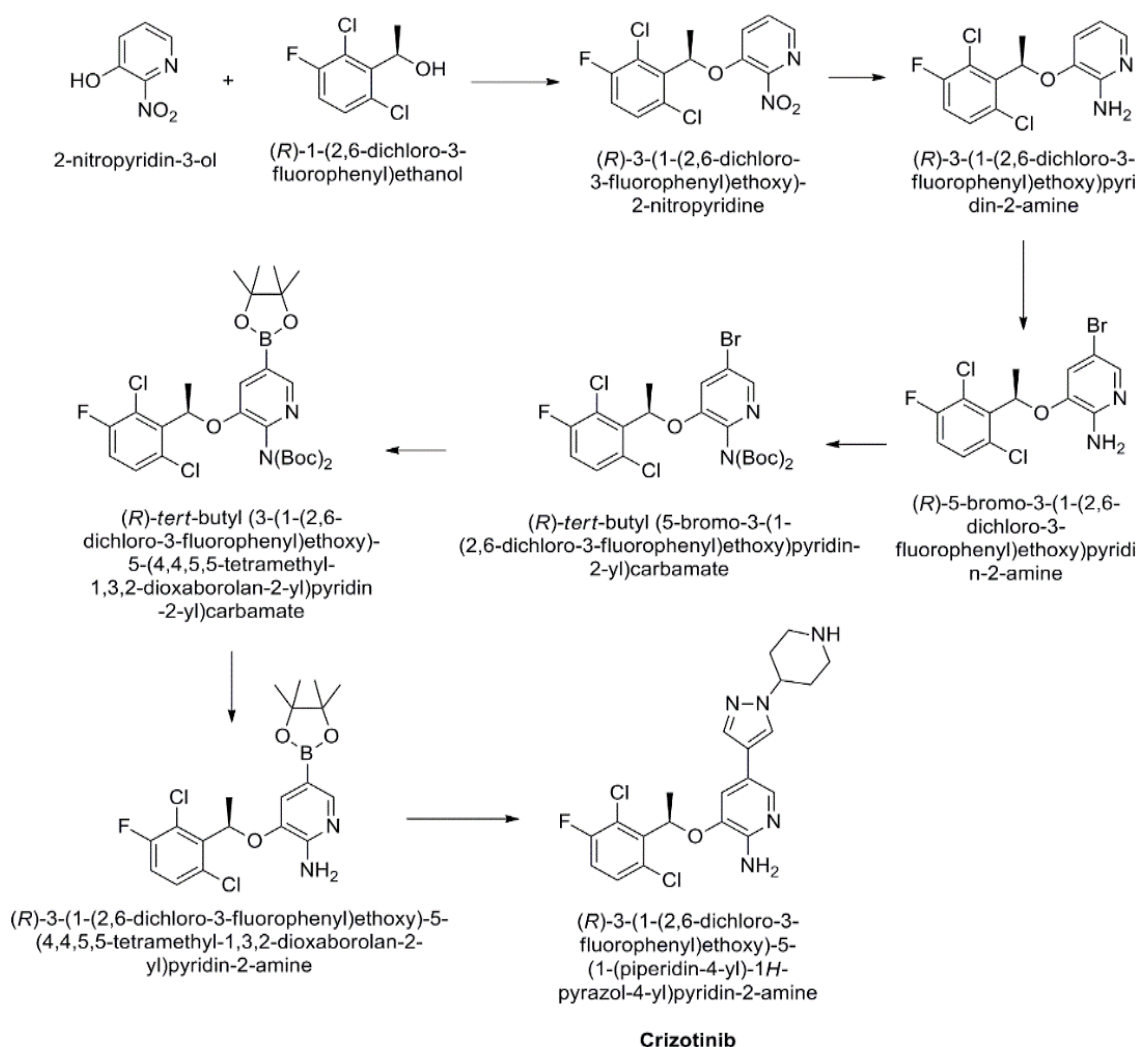


Fig. 2 The synthetic route to Crizotinib.

Table 1 The most common-adverse events and the relating incidence rates.

Events	Incidence rates
gastrointestinal disorder	43~60 %
ophthalmic disease	55~62 %
hematologic	5~10 %
cardiovascular	10 %

2-amine in a AcOH/EtOH solution under reflux. A bromination reaction is continued to give the amino-modified intermediate compound ((R)-5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-2-amine). The amine group is protected by Boc₂O and the obtained compound is treated by Bis(pinacolato)diboron. After deprotection, the as-formed

(R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine is reacted with 4-(4-bromo-1H-pyrazol-1-yl)piperidine to give the final product Crizotinib.

3. Clinical Trials

Crizotinib caused shrink or stabilization of tumors in 90% of eighty-two patients bearing the ALK fusion gene. Tumors shrank occurred at least 30% among 57% of people treated. The majorities had adenocarcinoma, and had never smoked or were former smokers. They had undergone treatment with an average of three other drugs prior to receiving Crizotinib, and only ten percent were expected to respond to standard therapy. They were given 250 mg Crizotinib two times one day for a median duration about 180 days. A phase 3 trial compares crizotinib to standard second line chemotherapy in the treatment of ALK-positive NSCLC. Additionally, a phase 2 trial studies patients meeting similar criteria who have received more than one line of prior chemotherapy. Crizotinib is also being tested in clinical trials of neuroblastoma and advanced disseminated anaplastic large-cell lymphoma [13-16].

4. Pharmacology

Crizotinib was evaluated against a panel of more than 120 kinases in biochemical assays and twelve cell-based phosphorylation assays, and was determined to be nearly 20-fold more selective for ALK and MET compared with other kinases evaluated. Crizotinib inhibited nucleophosmin (NPM)-ALK phosphorylation in Karpas299 or SU-DHL-1

anaplastic large cell lymphoma cells (mean IC₅₀ value, 24 nmol/L), and inhibited cell proliferation and induced apoptosis in NPM-ALK dependent Karpas299 or SU-DHL-1 cell lines. Furthermore, crizotinib also inhibited ALK phosphorylation and growth in a NPM-ALK-dependent Karpas299 tumor xenograft model. 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 lymphoma cells (IC₅₀ values, about 30 nmol/L). Oral administration of crizotinib to severe combined immunodeficient-beige mice bearing Karpas299 anaplastic large cell lymphoma tumor

Xenografts resulted in dose-dependent antitumor efficacy, with complete regression of all tumors at the 100 mg/kg/day dose within 15 days of initial administration of the compound. A strong correlation was observed between antitumor response and inhibition of NPM-ALK phosphorylation and induction of apoptosis in tumor tissue. In addition, inhibition of key NPM-ALK signaling mediators, including phospholipase C gamma, STAT3, and Akt, by crizotinib was observed at concentrations or dose levels that correlated with inhibition of NPM-ALK phosphorylation and function [14, 17].

5. Pharmacokinetics

There was no food effect on the pharmacokinetics of crizotinib, which was verified by a 11-patients involved food effect sub-study. There was no significant difference from the absorption of a single 250 mg dose of crizotinib after a high-fat, high-calorie meal to a single 250 mg dose of crizotinib taken on an empty stomach. The peak plasma concentration (C_{max}) was reached 4 hours after a single dose of crizotinib. A steady-state concentration of crizotinib was reached after 15 days of repeated administration of crizotinib 250 mg orally twice a day, with a half-life ($T_{1/2}$) of around 43-51 hours. The mean steady-state trough plasma level for crizotinib 250 mg taken twice a day (the recommended Phase II dose) was 274 ng/mL or 57

nM of free drug, which exceeded the target efficacy levels predicted for the inhibition of MET (about 13 nM) and ALK (about 26 nM) based on preclinical mouse models [17, 18].

6. Adverse Effects

Table 1 summarizes the most common-adverse events and the incidence rates in the above-mentioned clinical trial [19]. The gastrointestinal disorder and ophthalmic disease are the main adverse events with incidence rates of 43~60 % and 55~62 %, respectively. Otherwise, hematologic and cardiovascular are also emerged with incidence rates of 5~10 % and 10 %, respectively.

7. Conclusions

In summary, we introduced the basic information, synthesis, clinical trials, pharmacology, pharmacokinetics and adverse effects of Crizotinib in this paper. We hope the review may provide some guidance for the clinical use of Crizotinib.

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