

# Personalized treatment strategies for non-small-cell lung cancer in Chinese patients: the role of crizotinib

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**Abstract:** Anaplastic lymphoma kinase (*ALK*) rearrangement is an oncogene targeted with approved drugs second to epidermal growth factor receptor (*EGFR*) in lung cancer. Crizotinib was developed and introduced into clinical practice rapidly and successfully after the discovery of *ALK* rearrangement in non-small-cell lung cancer. Chinese and other Asian patients treated with crizotinib seem to have lower toxicity and higher efficacy compared with other ethnicities. Crizotinib showed potent antitumor activity and manageable toxicity in mesenchymal–epithelial transition factor (*c-Met*)/*ROS1*-positive non-small-cell lung cancer patients, but prospective clinical trials are still needed to confirm its efficacy and safety. Crizotinib appears to be effective against tumors originating from various organs that harbor *ALK* abnormalities. In the near future, we would classify the tumors by their genetic information beyond organs, such as *ALK*oma, *EGFR*oma, and *RAF*oma, and a single compound could be used for many different types of cancer in different organs. The major challenge of the widespread use of crizotinib in clinical practice is establishing convenient diagnostic techniques for the detection of *ALK/c-Met/ROS1*. In the present study, we reviewed the application of crizotinib in Chinese patients.

**Keywords:** NSCLC, crizotinib, *ALK*, *c-Met*, *ROS1*

## Introduction

Since the discovery of the epidermal growth factor receptor (*EGFR*) mutation in 2004, personalized treatment based on genomic variations has significantly changed lung cancer clinical practice in the past 10 years. *EGFR* tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have opened the gate of precise medicine and become a standard therapy for patients with non-small-cell lung cancer (NSCLC) harboring the *EGFR* mutation. *EGFR* inhibitors came first and then target driver gene was discovered. Conversely, the anaplastic lymphoma kinase (*ALK*) rearrangement in NSCLC was discovered prior to the development of an effective inhibitor. Thus, the development of the *ALK* inhibitor crizotinib became a typical model in personalized lung cancer treatment. The first clinical trial of crizotinib, PROFILE 1001,<sup>1</sup> was conducted for unselected patients with solid tumors in 2007. During the same year, *ALK* rearrangement was also first reported and a diagnostic fluorescence in situ hybridization (FISH) assay was developed for NSCLC. Fortunately, two NSCLC *ALK*-positive patients were enrolled in this Phase I trial and experienced a significant disease control. Subsequently, crizotinib was widely used in *ALK*-positive lung cancer patients. Only 4 years later in 2011, crizotinib was approved by the US Food and Drug Administration, a relatively short period from laboratory to market.

Crizotinib was approved by the Chinese Food and Drug Administration for *ALK*-positive patients in any line setting in 2013. It was only based on results of PROFILE

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1001, 1005,<sup>2</sup> and 1007,<sup>3</sup> when the mature results of PROFILE 1014<sup>4</sup> and 1029<sup>5</sup> were not available. The crizotinib was not covered by the Chinese health insurance system, and most patients could not tolerate the financial burden. The charitable project of crizotinib in People's Republic of China was started in April 2014. Chinese mainland citizens over 18 years of age with low income could apply for free crizotinib if they paid for the drug during the initial 4 months of treatment. The reduced economical burden greatly enhances patient adherence. To date, more than 3,000 Chinese *ALK*-positive patients have taken crizotinib in this charitable project (internal data provided by Pfizer). This review focused on the role of crizotinib in personalized treatment in People's Republic of China.

## Pharmacology, mode of action, and pharmacokinetics of crizotinib

Crizotinib (PF-02341066) is a potent and selective small-molecule inhibitor of MET kinase,<sup>6</sup> *ALK*,<sup>7,8</sup> and ROS.<sup>9</sup> Crizotinib competes with ATP for binding to the catalytic pocket, which inhibits the receptor tyrosine kinase downstream signaling pathways that are critical for growth and survival.

The pharmacokinetics of crizotinib were assessed in 15 Chinese patients (seven males and eight females) with advanced *ALK*-positive NSCLC who were enrolled in PROFILE 1005.<sup>10</sup> The median time for crizotinib to achieve peak concentration was 4–6 hours after absorption, which was similar to the first 80 patients of various ethnicities enrolled in PROFILE 1001.<sup>1</sup> The mean  $C_{max}$  of crizotinib was 117 ng/mL and  $AUC_{inf}$  was 2,711 ng h/mL. Following attainment of  $C_{max}$ , plasma concentrations of crizotinib declined in a multi-exponential manner with an average half-life terminal elimination of approximately 39 hours, which was slightly shorter than that in the 80 patients mentioned earlier, whose average terminal half-life was 43–51 hours. The plasma concentrations of crizotinib reached a steady state within 15 days and increased with a median accumulation ratio of 5.2 days. The geometric mean values for the apparent clearance were 57.7 L/h and 59.7 L/h, following 15 and 29 days of dosing, respectively, which were lower than those observed after a single dose (92.3 L/h), indicating that crizotinib exhibited nonlinear pharmacokinetics due to autoinhibition of CYP3A4.

Compared with non-Asian patients, Asian patients had higher crizotinib exposure. A comparison study evaluated crizotinib pharmacokinetics in 95 patients, including 32 Asian and 63 non-Asian patients, with advanced malignancies.<sup>11</sup> The mean  $AUC_{tau-ss}$  and  $C_{max-ss}$  were, respectively, 56% and 70% higher in Asian than in non-Asian patients (body weight adjustment accounted for 30% of the difference)

after repeated crizotinib, with median trough concentrations 41%–59% (median 50%) higher. An analysis of 167 patients from PROFILE 1001 included 42 Asian and 125 non-Asian patients and showed that mean values for crizotinib  $C_{max}$  and AUC in Asian patients were 1.57-fold (90% confidence interval, 1.16–2.13) and 1.50-fold (90% confidence interval, 1.10–2.04) those seen in non-Asian patients, respectively.<sup>12</sup> Another analysis included 8,973 pharmacokinetic samples from 1,214 patients treated with crizotinib in Phase I, II, and III trials; 43.1% were Asian patients.<sup>13</sup> The  $AUC_{ss}$  in Asian patients were over 25% higher than typical  $AUC_{ss}$  values in non-Asian patients.

## Diagnosis of *ALK* rearrangements in People's Republic of China

The prevalence of *ALK* rearrangements is 3.3%–11.6% in Chinese patients<sup>14–16</sup> similar to other Asian patients,<sup>17,18</sup> slightly greater than that in non-Asian patients,<sup>18,19</sup> and much lower than EGFR mutations – about 30% in Chinese patients.<sup>16</sup> Currently, three major methods are used for the detection of *ALK* rearrangements in lung cancer; ie, break-apart FISH, Ventana immunohistochemistry (IHC), and polymerase chain reaction (PCR). All three methods were recommended by Chinese expert consensus opinion<sup>20</sup> and approved as companion diagnostic tests by the Chinese Food and Drug Administration, which is quite different from other guidelines developed in the US and EU.

FISH is the standard method for the detection of *ALK* rearrangements in lung cancer globally. However, the application of FISH was restricted mainly by its cost-effectiveness and the lack of experienced pathologists in People's Republic of China.

IHC is much more rapid and affordable. Ventana IHC was developed by Roche for detecting *ALK* rearrangements. The sensitivity and specificity of Ventana IHC are 100% and 99%, respectively,<sup>21–26</sup> as shown in Table 1; thus, Chinese experts recommend the Ventana IHC as a diagnostic test for *ALK* rearrangements. This test has also been approved in Europe but still under consideration of National Comprehensive Cancer Network/College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines. A prospective observational trial of diagnosis of *ALK* rearrangements in unselected NSCLC patients using Ventana IHC in People's Republic of China was launched in 2013.<sup>27</sup> The primary objective is to obtain epidemiological data in unselected Chinese patients with *ALK*-positive NSCLC. The estimated enrollment is 10,000, and 3,000 patients have been enrolled to date.

**Table 1** The sensitivity and specificity of Ventana IHC and PCR compared with FISH

Reference	Ventana IHC		PCR	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Ying et al <sup>21</sup>	100	98	98	95
Demidova et al <sup>22</sup>	100	100	88	100
Wang et al <sup>23</sup>	100	98.2	95.5	87
Mino-Kenudson et al <sup>24</sup>	100	99	–	–
Minca et al <sup>25</sup>	100	100	–	–
Wynes et al <sup>26</sup>	90	96	–	–

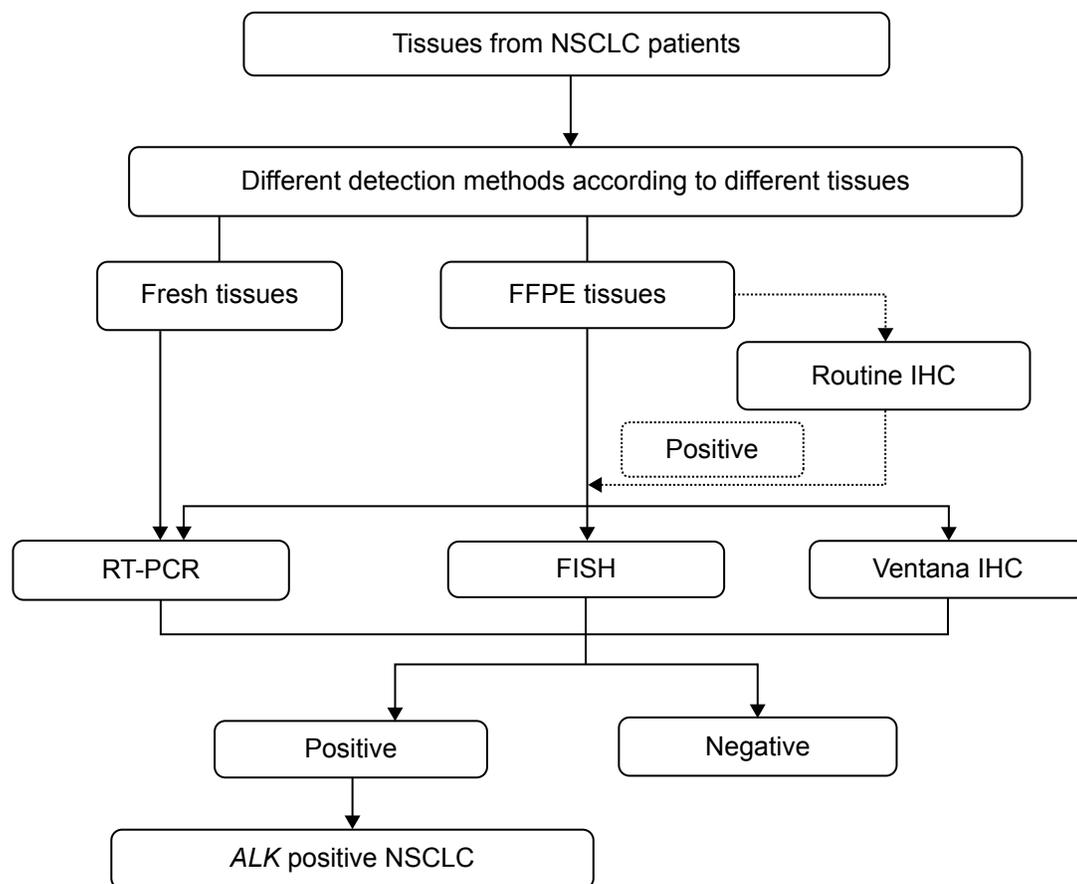
**Note:** –, the data were not provided in the article.

**Abbreviations:** FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction.

The reverse transcription (RT)-PCR method is the least subjective methodology for the detection of *ALK* rearrangements.<sup>28</sup> However, it requires high-quality RNA or is unable to detect the unknown fusion partners.<sup>15,23,29–31</sup> RT-PCR is also recommended by the Japan Lung Cancer Society but not by the National Comprehensive Cancer Network or College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines. The three types of PCR recommended by Chinese expert consensus opinion include quantitative RT-PCR, rapid

amplification of cDNA ends-coupled PCR sequencing, and specific primer-based RT-PCR coupling direct sequencing.<sup>20</sup>

The three *ALK* detection methods have advantages and disadvantages, as mentioned earlier. However, both Ventana IHC and RT-PCR have high sensitivity and specificity compared with FISH (Table 1). The methods used by clinicians in People's Republic of China to detect *ALK* arrangements differ according to the equipment available. The *ALK* test procedures used in People's Republic of China are shown in Figure 1.



**Figure 1** *ALK* testing procedures used in the People's Republic of China.

**Abbreviations:** NSCLC, non-small-cell lung cancer; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; RT-PCR, reverse transcription-polymerase chain reaction; FISH, fluorescence in situ hybridization.

## Efficacy of crizotinib in ALK-positive patients

The efficacy and safety of crizotinib were confirmed through a series of clinical trials named PROFILE (Table 2). PROFILE 1001 is a Phase I dose-escalation trial that was the first to find a target population with *ALK*-positive and embedded biomarker in patient's selection in the early stage of drug development. PROFILE 1005 is a Phase II trial that selected patients with *ALK* rearrangements to evaluate the efficacy and safety of crizotinib. Based on the results of these two trials, *ALK* rearrangement was defined as a definitive target biomarker. Subsequent Phase III trials, either second line (PROFILE 1007) or first line (PROFILE 1014 and PROFILE 1029), were based on biomarker selection. The results are shown in Table 3. All PROFILE trials showed good consistency; higher objective response rate (ORR), longer progression-free survival (PFS), overall survival, and better safety compared to chemotherapy; these are the characteristics of precise cancer treatment.

Asian patients accounted for 28%–46% of the overall population in the PROFILE series (Table 3).<sup>2–4,32</sup> Asian patients had higher response rates than non-Asian patients, possibly related to the higher crizotinib exposure. Twenty-three Chinese patients were enrolled in PROFILE 1005 and 1007. The ORR was 73.9%,<sup>33</sup> similar to that in Asian patients but higher than in non-Asian patients.

Although ORR was higher in Asian patients, the PFS was similar among ethnicities, as shown in Table 3. The median PFS of the 23 Chinese patients enrolled in PROFILE 1005 and 1007 was 7.0 months.<sup>32</sup> Several retrospective analyses of Chinese patients reported median PFS of 6.0–7.6 months.<sup>34</sup>

## Safety and tolerability of crizotinib

The normal *ALK* function in adult humans is unknown, but it is involved in gut development<sup>35</sup> and retinal axon targeting<sup>36</sup> in *Drosophila*. Therefore, the predominant adverse events (AEs) of crizotinib were visual effects and gastrointestinal events, which may represent on-target anti-*ALK* effects. The AEs of 1,255 patients taking crizotinib in three trials (PROFILE 1001, 1005, and 1007) were analyzed.<sup>37</sup>

The most common gastrointestinal events were nausea (49%), diarrhea (44%), vomiting (41%), and constipation (29%). The incidence of visual impairment was 42%. Most AEs mentioned earlier were grade 1–2 in severity, which was similar to other reports and our clinical experience in Chinese patients.<sup>34,38–40</sup> The most common treatment-related grade 3/4 AEs were neutropenia (7%) and elevated alanine aminotransferase (ALT) (6%) and aspartate aminotransferase (AST) (<3%) levels. Among the AE grades, neutropenia and elevated ALT and AST levels occurred in 11%, 21%, and 15% patients, respectively.<sup>37,38,41</sup>

The incidence of AEs based on ethnicity differs slightly. The incidence of AEs was higher in non-Asian patients compared with Asian patients in the subgroup analysis of 901 patients enrolled in PROFILE 1005.<sup>42</sup> An analysis of 95 patients (32 non-Asian and 63 Asian patients) with advanced malignancies taking crizotinib showed that Asian patients had a higher incidence of low-grade AEs (eg, gastrointestinal, visual impairment) but a lower incidence of high-grade AEs (eg, increased ALT).<sup>11</sup> The treatment-related grade 3 and/or 4 AEs occurred in 2.4% (9/379) and 6.7% (35/522) and grade 5 serious AEs in 1.1% [4/379] and 1.3% [7/522] of Asian and non-Asian patients, respectively. Due to AEs, 12% of Asian patients and 18% of non-Asian patients discontinued their treatment. In another pooled analysis of 1,053 patients from PROFILE 1005 and 1007, Asian patients were less susceptible to sinus bradycardia compared with non-Asian patients ( $P=0.039$ ),<sup>43</sup> indicating that crizotinib was slightly safer in Asian patients.

## Overcoming resistance to crizotinib

Nearly all patients develop resistance to crizotinib. The mechanism of resistance includes secondary mutations in the tyrosine kinase domain of *ALK*, *ALK* copy number gain, the aberrant activation of other driver genes, and several unknown mechanisms.<sup>44,45</sup>

The second-generation *ALK* TKIs, such as ceritinib (LDK378),<sup>46</sup> alectinib (RO5424802),<sup>47</sup> and AP26113,<sup>48</sup> showed strong capability in patients resistant to crizotinib. Ceritinib was approved by the US Food and Drug

**Table 2** The designs of PROFILE 1001, 1005, 1007, 1014, and 1029

NCT identifier	Other ID numbers	Phase	Line	Population	Chinese included or not	Target	Convention
NCT00585195	PROFILE 1001	I	Any line	Global	No	<i>ALK/c-Met/ROS1</i>	Crizotinib
NCT00932451	PROFILE 1005	II	≥2	Global	Yes	<i>ALK</i>	Crizotinib
NCT00932893	PROFILE 1007	III	2	Global	Yes	<i>ALK</i>	Crizotinib vs pemetrexed/docetaxel
NCT01154140	PROFILE 1014	III	I	Global	Yes	<i>ALK</i>	Crizotinib vs PC/PP
NCT01639001	PROFILE 1029	III	I	East Asian	Yes	<i>ALK</i>	Crizotinib vs PC/PP

**Abbreviations:** PC, pemetrexed plus carboplatin; PP, pemetrexed plus cisplatin.

**Table 3** The efficacy of crizotinib in Asian and non-Asian populations

ID Numbers	Number of patients		ORR (%)				PFS (months)			
	Overall	Asian (%)	Overall	Non-Asian	Asian	Chinese	Overall	Non-Asian	Asian	Chinese
PROFILE 1001 <sup>32</sup>	149	41 (28)	60.8	54.8	76.9	–	9.7	–	–	–
PROFILE 1005 <sup>2</sup>	259	93 (36)	59.8	54	70	73.9	8.1	–	–	7
PROFILE 1007 <sup>3</sup>	347	157 (45)	65	–	75	–	7.7	7.1	8.1	–
PROFILE 1014 <sup>4</sup>	343	157 (46)	74	72	70	–	10.9	–	13.6	–

**Note:** –, the data were not available.

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

Administration in early 2014 and alectinib has been approved by the Japanese government.

In addition to novel drugs, National Comprehensive Cancer Network guidelines recommended new strategies for patients resistant to crizotinib according to response evaluation criteria in solid tumors criteria. Patients with asymptomatic progression can continue taking crizotinib. The patients with symptomatic progression in the brain or an isolated extracranial lesion can receive local treatment and continue taking crizotinib. Patients with symptomatic progression in multiple lesions can change to chemotherapy. An analysis of 194 patients from PROFILE 1005 and 1007 was conducted; 120 (62%) patients continued taking crizotinib beyond disease progression because the investigators believed that ongoing clinical benefits could be obtained. The patients who continued taking crizotinib had significantly longer overall survival from the time of progressive disease (median 16.4 months vs 3.9 months; hazard ratio, 0.27;  $P < 0.0001$ ).<sup>49</sup>

### Basket trial: crizotinib in different tumors

An increasing number of driver genes are being discovered in solid tumors, including NSCLCs. Based on different driver genes, NSCLC was subdivided in different rare diseases. Innovative clinical trials have been performed, including basket trials. The basket trial is defined as testing of one drug against the same genetic abnormality in different organs. The *ALK* abnormality has been discovered in many solid tumors, including anaplastic large-cell lymphoma,<sup>50</sup> inflammatory myofibroblastic tumor,<sup>51</sup> diffuse large B-cell lymphoma,<sup>52</sup> esophageal squamous cell carcinoma,<sup>53</sup> and several other tumors.<sup>54,55</sup> Tumors originating from various organs carrying abnormal *ALK* as an essential growth driver were defined as “*ALKoma*”.<sup>56</sup> Crizotinib appears to be effective against tumors originating from various organs that harbor *ALK* abnormalities.<sup>57,58</sup> There is an ongoing basket clinical trial (A8081013, ClinicalTrials.gov identifier NCT01121588) evaluating the safety and clinical activity of crizotinib in patients with *ALK*-positive malignancies

other than NSCLC. There is no basket trial of crizotinib in People’s Republic of China so far. In future, tumors could be classified based on genetic information beyond organs, such as *EGFRoma* and *RAFoma* and a single compound could be used for many cancer types in different organs. Similar to *ALKoma* cancers, *EGFRoma* and *RAFoma* cancers could be treated using EGFR TKIs and RAF TKIs.

### Umbrella trial: crizotinib in lung cancers with different genetic abnormalities

The umbrella trial is another innovative clinical trial in which several drugs are tested against multiple genetic abnormalities within one type of tumor, such as lung cancer. Crizotinib showed antitumor activities in lung cancer patients with *c-Met* or *ROS1* abnormalities and is particularly suitable for an umbrella trial.

### Crizotinib in patients with *ROS1* rearrangements

*ROS1* rearrangement was discovered in NSCLC in 2007.<sup>59</sup> The researchers detected the activation of oncogenic kinases in 41 NSCLC cell lines and over 150 Chinese NSCLC patients using a phosphoproteomic approach. ROS was identified to have high tyrosine kinase phosphorylation in the HCC78 cell line and one patient tumor sample.

The frequency of *ROS1* was approximately 1.0%–2.0% in Chinese patients,<sup>60,61</sup> similar to other ethnicities.<sup>62,63</sup> However, the frequency of *ROS1* rearrangements in the triple-negative (without *EGFR/KRAS* mutations or *ALK* rearrangements) population was 8.2%, higher than that in the nonselected population.<sup>64</sup>

Shaw et al<sup>65</sup> reported the results of 50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement in an expansion cohort of the PROFILE 1001. The AEs of crizotinib were similar to those in NSCLC patients with *ALK* rearrangements. The efficacy of crizotinib was better in patients with *ROS1* rearrangements than with *ALK* rearrangements. The ORR was 72%, including three complete responses. The median PFS was 19.2 months. One

ROS1 trial in Asian patients is ongoing (ClinicalTrials.gov identifier: NCT01945021).

## Crizotinib in patients with de novo c-Met abnormalities

Preliminary results on the safety and efficacy of crizotinib in NSCLC patients with *c-Met* amplification were reported in the 2014 American Society of Clinical Oncology, which was part of the ongoing Phase I trial (A8081001, ClinicalTrials.gov identifier: NCT00585195).<sup>40</sup> The *c-Met* amplification status was divided into the following four categories: negative (MET/CEP7 ratio  $\leq 1.8$ ), low (MET/CEP7 ratio  $\geq 1.8$  to  $\leq 2.2$ ), intermediate ( $> 2.2$  to  $< 5$ ) and high ( $\geq 5$ ). CEP7 refers to the chromosome 7 centromere. At data cutoff, 13 patients with amplified *c-Met* were treated with crizotinib. The median duration of response was 35 weeks (95% confidence interval, 16–112). The AEs were similar to crizotinib in *ALK*-positive patients; most were grade 1 in severity. The antitumor activity and general tolerability of crizotinib were first indicated in a prospective clinical trial.

De novo c-Met expression was detected using IHC in NSCLC patients in Guangdong Lung Cancer Institute in People's Republic of China.<sup>66,67</sup> c-Met overexpression was defined as more than 50% tumor cells with moderate- to high-intensity staining. Thirteen patients with c-Met overexpression treated with crizotinib were evaluable for response; six experienced partial response (PR), two stable disease, and five progressive disease. One patient died of interstitial lung disease attributed to crizotinib, suggesting that c-Met overexpression could be a predictive factor of crizotinib.

De novo c-Met overexpressions/amplifications coexisting with *EGFR* mutations, *KRAS* mutations, and *ALK* rearrangements were analyzed in Guangdong Lung Cancer Institute in People's Republic of China. The definition of overexpression was as mentioned earlier and amplification was detected using FISH.<sup>68</sup> Seven patients with concomitant de novo c-Met overexpression and *EGFR* mutations received first-line EGFR TKIs. The ORR was 71.4% (5/7). One patient with concomitant de novo c-Met overexpression and *EGFR* mutations developed intrinsic resistance to first-line crizotinib. Five patients with concomitant de novo c-Met overexpressions and *ALK* rearrangements received crizotinib, and the response rate was 80%. The patient with concomitant de novo c-Met overexpression and *KRAS* mutation was resistant to crizotinib. Based on these results, NSCLC patients with concomitant de novo c-Met overexpression and other driver genes can have diverse responses to TKIs, which may depend on the predominant pathway in the tumor.<sup>69,70</sup>

## Crizotinib in patients with acquired c-Met abnormalities

*c-Met* amplification was found in 13%–33% of patients with acquired resistance to EGFR TKIs<sup>71,72</sup> and is the second most common EGFR TKIs resistance mechanism, following the T790M mutation. The sensitivity to EGFR TKIs was restored by the inhibition of c-Met signaling in a gefitinib-resistant HCC827 cell line.<sup>73</sup>

Patients with acquired resistance to EGFR TKIs were enrolled in a Phase I trial (ClinicalTrials.gov identifier: NCT01121575) to receive dacomitinib combined with crizotinib. The preliminary results showed that toxicity was manageable and the clinical activity was promising.<sup>74</sup> A retrospective analysis of 80 advanced NSCLC patients with acquired resistance to first-line EGFR TKIs from People's Republic of China was conducted. Twenty-three of the 80 patients (28.8%) had *c-Met* amplifications, including four patients taking crizotinib after resistance to EGFR TKIs. Among the three patients treated with crizotinib plus gefitinib, two attained PR and one attained stable disease.<sup>72,75</sup>

The preclinical and clinical data showed that *c-Met*-positive patients would benefit from crizotinib or crizotinib combined with EGFR TKIs and exhibit good tolerance. The major challenge when prescribing crizotinib to *c-Met*-positive patients is defining which *c-Met* state is predictive of the effect of crizotinib: c-Met amplification, overexpression, or mutation, and defining the standard detection methods and standard cutoff value of each method.

## Conclusion

Crizotinib has played an important role in the development of precise treatments due to its unique antitumor PROFILE. Crizotinib is efficacious in Chinese NSCLC patients with *ALK* rearrangements and its toxicity is manageable. The application of crizotinib in Chinese *c-Met*/*ROS1*-positive NSCLC patients is promising but prospective clinical trials are required to confirm its efficacy and safety. *ALK*/*c-Met*/*ROS1*-positive patients account for approximately 10% of lung cancer cases, meaning about 10% lung cancer patients could benefit from crizotinib. The major challenge for prescribing crizotinib in clinical practice is establishing convenient diagnostic techniques for the detection of *ALK*/*c-Met*/*ROS1*. This review of crizotinib provides a reference for integrating genetic information in the classification of lung cancer and other tumors in the near future. Cancers might be classified as *ALK*Koma, *EGFR*oma, and *RAF*oma and treated with *ALK* TKIs, *EGFR* TKIs, and *RAF* TKIs, respectively.

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## Author contributions

Fei-Yu Niu and Yi-Long Wu designed the outline, searched literature, drafted and critically revised the manuscript, and approved the final manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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