Treating patients with *ALK*-positive non-small cell lung cancer: latest evidence and management strategy

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Bin-Chi Liao, Chia-Chi Lin, Jin-Yuan Shih and James Chih-Hsin Yang

***Abstract*:** Rearrangements in anaplastic lymphoma kinase (ALK) gene and echinoderm microtubule-associated protein-like 4 (EML4) gene were first described in a small portion of patients with non-small cell lung cancer (NSCLC) in 2007. Fluorescence *in situ* hybridization is used as the diagnostic test for detecting an *EML4–ALK* rearrangement. Crizotinib, an ALK inhibitor, is effective in treating advanced *ALK*-positive NSCLC, and the US Food and Drug Administration approved it for treating *ALK*-positive NSCLC in 2011. Several mechanisms of acquired resistance to crizotinib have recently been reported. Second-generation ALK inhibitors were designed to overcome these resistance mechanisms. Two of them, ceritinib and alectinib, were approved in 2014 for advanced *ALK*-positive NSCLC in the US and Japan, respectively. Heat shock protein 90 (Hsp90) inhibitors also showed activity against *ALK*-positive NSCLC. Here we review the recent development of crizotinib, ceritinib, alectinib and other second-generation ALK inhibitors as well as Hsp90 inhibitors. We also discuss management strategies for advanced *ALK*-positive NSCLC.

Keywords: alectinib, ceritinib, crizotinib, *EML4–ALK* rearrangement, heat shock protein 90 inhibitor, non-small cell lung cancer

Introduction

In the era of molecular targeted therapy, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib, erlotinib and afatinib have been demonstrated to prolong progression-free survival (PFS) and preserve the quality of life when used as the first-line treatment for patients with *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) [Mok *et al.* 2009; Maemondo *et al.* 2010; Sequist *et al.* 2013; Yang *et al.* 2013].

In 2007, Soda and colleagues first described the rearrangements in the anaplastic lymphoma kinase (ALK) gene and the echinoderm microtubule-associated protein-like 4 (EML4) gene in a small proportion of patients with NSCLC [Soda *et al.* 2007, 2008]. Around 2–5% of NSCLC patients harboured this gene rearrangement [Soda *et al.* 2007; Kwak *et al.* 2010]. *EML4–ALK* rearrangement was identified as an oncogene and EML4–ALK fusion protein was found to possess transforming activity and oncogenic potential [Soda *et al.* 2007]. ALK inhibitors were effective *in vitro* for cell lines and *in vivo* for mouse models of tumours harbouring the *EML4–ALK* rearrangement [Koivunen *et al.* 2008; Soda *et al.* 2008]. The clinicopathological features of these patients included younger age, never/light smokers and adenocarcinoma histology (predominantly signet-ring cell subtype) [Inamura *et al.* 2008, 2009; Rodig *et al.* 2009; Shaw *et al.* 2009]. *EML4–ALK* rearrangements are typically mutually exclusive with *EGFR* mutations or *K-RAS* mutations [Wong *et al.* 2009; Gainor *et al.* 2013b].

In a retrospective study, malignant pleural effusions of patients with *EGFR* wildtype lung adenocarcinoma were tested for *ALK* rearrangement. All patients were not treated with any ALK inhibitor. The survival of patients with *EML4–ALK* rearrangement was better than that of patients without

Correspondence to:
Chia-Chi Lin, MD, PhD
Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan
cclin1@ntu.edu.tw

Bin-Chi Liao, MD
Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Jin-Yuan Shih, MD, PhD
Department of Internal Medicine, National Taiwan University Hospital, Taiwan
Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

James Chih-Hsin Yang, MD, PhD
Department of Oncology, National Taiwan University Hospital, Taiwan
Graduate Institute of Oncology and Cancer Research Center, College of Medicine, National Taiwan University, Taipei, Taiwan

EML4–ALK rearrangement, although this study enrolled only patients with malignant pleural effusion, which may potentially lead to biases [Wu *et al.* 2012]. There were several genes reported to be fused to *ALK*, but the incidence was quite low [Takeuchi et al. 2009; Togashi *et al.* 2012].

Crizotinib, a multitargeted tyrosine kinase (including ALK, MET and ROS1) inhibitor, is effective in treating patients with *ALK*-positive (referred to as *EML4–ALK* rearrangement) advanced NSCLC [Cui *et al.* 2011]. In 2011, this drug received approval from the US Food and Drug Administration (FDA) in treating advanced *ALK*-positive NSCLC using the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) based on the results of early phase clinical trials. Phase III clinical trials had been conducted to compare crizotinib monotherapy with standard second-line and first-line cytotoxic chemotherapy for advanced *ALK*-positive NSCLC patients [Shaw *et al.* 2013; Solomon *et al.* 2014]. Because of the rarity of *ALK*-positive NSCLC, immunohistochemical staining is a reliable screening tool to identify *ALK*-positive NSCLC and to reduce the cost of general screening using standard methods [Jokoji *et al.* 2010; Yi *et al.* 2011; Park *et al.* 2012; Conklin *et al.* 2013]. Crizotinib is effective in treating some subsets of *ALK*-negative NSCLC, such as tumours harbouring *ROS1* rearrangement and tumours with *de novo MET* amplification [Ou *et al.* 2011b; Bergethon *et al.* 2012; Yasuda *et al.* 2012]. Subjects without *ALK*-positive NSCLC are not covered in detail in this review.

Ceritinib, a second-generation ALK inhibitor, which is more potent against ALK than crizotinib but not active against MET, was approved by the FDA in 2014 for advanced *ALK*-positive NSCLC pretreated with crizotinib [Shaw *et al.* 2014]. Alectinib, another second-generation ALK inhibitor, was approved in Japan in 2014 for advanced *ALK*-positive NSCLC. Heat shock protein 90 (Hsp90) inhibitors were also effective in treating *ALK*-positive NSCLC [Normant *et al.* 2011]. However, drugs in this class have not yet been approved by any regulatory agencies. Here, we review the recent development of crizotinib, ceritinib, alectinib and other second-generation ALK inhibitors, as well as Hsp90 inhibitors. We also discuss management strategies for advanced *ALK*-positive NSCLC.

A literature review of clinical studies published between January 2007 and July 2014 was conducted using PubMed and MEDLINE, with keyword entry of 'non-small cell lung cancer', '*EML4–ALK* rearrangement', 'crizotinib', 'ceritinib', 'alectinib' and 'heat shock protein 90 inhibitor'. A manual search of abstracts presented at major oncology meetings was also performed.

First-generation ALK inhibitor: crizotinib

Overview of clinical development of crizotinib

Crizotinib was approved under the FDA's accelerated approval programme in 2011 based on the results of two single-arm clinical trials mentioned below [Kwak *et al.* 2010; Kim *et al.* 2012]. In a phase I study (PROFILE 1001), 149 patients with advanced *ALK*-positive NSCLC underwent treatment with crizotinib at a dose of 250 mg twice daily. Most patients (71%) were never-smokers and 97% of the patients had adenocarcinoma histology. The overall response rate (ORR) was 60.8% and the median PFS was 9.7 months. The estimated overall survival (OS) rates at 6 months and 12 months were 87.9% and 74.8%, respectively [Camidge *et al.* 2012]. Visual effects, nausea and diarrhoea were the most commonly reported adverse effects (AEs). The global single-arm phase II study (PROFILE 1005) of crizotinib in treating advanced *ALK*-positive NSCLC after the progression of at least one line of cytotoxic chemotherapy revealed an ORR of 59.8% and a median PFS of 8.1 months [Kim *et al.* 2012].

A phase III study (PROFILE 1007) compared crizotinib with pemetrexed or docetaxel chemotherapy after failing one prior platinum-based chemotherapy. A total of 347 patients with advanced *ALK*-positive NSCLC were randomised, and it was observed that the median PFS (primary endpoint) was significantly longer in the crizotinib group (7.7 months) compared with the chemotherapy group (3.0 months) [hazard ratio (HR): 0.49, 95% confidence interval (CI) 0.37–0.64; $p < 0.001$). ORRs were 65% in the crizotinib group and 20% in the chemotherapy group ($p < 0.001$). Patients in the crizotinib group reported greater reduction of lung cancer related symptoms and improvement in the overall quality of life compared with the chemotherapy group [Shaw *et al.* 2013]. The common AEs are listed in Table 1. The most common grade 3 or 4 AE was elevated aminotransferase levels, which developed in 16% of patients who underwent crizotinib treatment. Grade 3 or 4 neutropenia developed in 13% of patients in the crizotinib group.

Table 1. Selected clinical studies of ALK inhibitors for advanced *ALK*-positive NSCLC.

Drug	Study name or ClinicalTrials.gov identifier	Phase	Population	Comparator	*n*	ORR	PFS	Adverse effects or remarks
Crizotinib	PROFILE 1007 Shaw *et al.* [2013]	III	Platinum-based chemotherapy pretreated	Pemetrexed or docetaxel	347	65% *versus.* 20% ($p < .001$)	7.7 *versus* 3.0 months (HR: 0.49, 95% CI 0.37–0.64; $p < .001$)	Visual disorder (60%), diarrhoea (60%), nausea (55%), vomiting (47%), constipation (42%), elevated aminotransferase levels (38%), oedema (31%), fatigue (27%)
	PROFILE 1014 Solomon *et al.* [2014]	III	Treatment naïve, nonsquamous NSCLC	Platinum plus pemetrexed	343	74% *versus.* 45% ($p < .001$)	10.9 *versus* 7.0 months (HR 0.45, 95% CI 0.35–0.60; $p < .001$)	Visual disorder (71%), diarrhoea (61%), oedema (49%), vomiting (46%), constipation (43%), elevated aminotransferase levels (36%), upper respiratory infection (32%), abdominal pain (26%)
Ceritinib	ASCEND-1 Shaw *et al.* [2014]	I	Advanced malignancy*	No	114	58% (95% CI 0.48–0.67)	7.0 months (95% CI 5.6–9.5)	Nausea (82%), diarrhoea (75%), vomiting (65%), fatigue (47%), and increased ALT level (35%)
	NCT01685060	II	Chemotherapy and crizotinib pretreated	No	NA	NA	NA	Ongoing clinical trial
	NCT01685138	II	Crizotinib-naïve	No	NA	NA	NA	Ongoing clinical trial
	ASCEND-4	III	Treatment naïve, nonsquamous NSCLC	Platinum plus pemetrexed	NA	NA	NA	Ongoing clinical trial
	ASCEND-5	III	Platinum-based chemotherapy and crizotinib pretreated	Pemetrexed or docetaxel	NA	NA	NA	Ongoing clinical trial

(Continued)

Table 1. (Continued)

Drug	Study name or ClinicalTrials.gov identifier	Phase	Population	Comparator	*n*	ORR	PFS	Adverse effects or remarks
Alectinib[$]	AF-001JP[‡] Seto *et al.* [2013]	I/II	ALK-inhibitor-naïve	No	46	93.5%, (95% CI 82.1–98.6)	NA	Dysgeusia (30%), increased AST level (28%), increased blood bilirubin level (28%), increased blood creatinine level (26%), rash (26%), constipation (24%), stomatitis (15%), and myalgia (13%).
	AF-002JGGadgeel *et al.* [2014]	I/II	Crizotinib pretreated	No	47	55%	NA	Fatigue (30%), myalgia (17%), and peripheral oedema (15%)
	NCT01871805	II	Chemotherapy and crizotinib pretreated	No	NA	NA	NA	Ongoing clinical trial
	ALEX	III	Treatment naïve	Crizotinib	NA	NA	NA	Ongoing clinical trial
AP26113	NCT01449461 Gettinger *et al.* [2014b]	I/II	Crizotinib pretreated or ALK inhibitor naïve	No	57	Crizotinib pretreated: 69% (95% CI 54–81%)	Crizotinib pretreated: 10.9 months	Nausea (34%), diarrhoea (26%), fatigue (22%), and vomiting (16%)
	ALTA	II	Crizotinib pretreated	No	NA	NA	NA	Ongoing clinical trial

*Advanced malignancies were not restricted to NSCLC.
[$]This drug was approved only in Japan as of September 2014.
[‡]This study was conducted in Japan with Japan Pharmaceutical Information Center, number JapicCTI-101264.
ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; NA, not available; ORR, overall response rate; PFS, progression-free survival.

Interestingly, ORRs and PFS were different between the pemetrexed (29% and 4.2 months, respectively) and docetaxel groups (7% and 2.6 months, respectively). ORR was higher than that of the general population who underwent second-line chemotherapy with pemetrexed [Hanna *et al.* 2004]. Other retrospective studies also demonstrated that *ALK* positivity was a predictive factor of pemetrexed efficacy [Camidge *et al.* 2011; Lee *et al.* 2011].

Another phase III study (PROFILE 1014) compared crizotinib monotherapy with pemetrexed plus cisplatin chemotherapy as the first-line of treatment for advanced *ALK*-positive nonsquamous NSCLC. A total of 343 patients were randomised and the PFS (primary endpoint) was observed to be significantly longer in the crizotinib group (median 10.9 *versus* 7.0 months; HR 0.45, 95% CI 0.35–0.60; $p < .001$). ORR was 74% in the crizotinib group and 45% in the chemotherapy group [Solomon *et al.* 2014].

The OS results were immature in the aforementioned two phase III studies. The common AEs of crizotinib therapy are listed in Table 1. Other less common AEs had been reported, such as QTc prolongation, bradycardia, hypogonadism, renal cysts and interstitial pneumonitis [Ou *et al.* 2011, 2013; Weickhardt *et al.* 2012, 2013; Tamiya *et al.* 2013; Lin *et al.* 2014]. The management of these AEs has been reviewed elsewhere [Rothenstein and Letarte, 2014].

Activity against central nervous system metastases

The activity of crizotinib in central nervous system (CNS) metastases is still debatable [Gainor *et al.* 2013a; Maillet *et al.* 2013; Costa *et al.* 2015]. Many treatment strategies, such as high-dose crizotinib and high-dose crizotinib in combination with high-dose pemetrexed, had been reported to treat CNS disease [Gandhi *et al.* 2013; Kim *et al.* 2013c]. Some experts suggested that isolated CNS disease progression after crizotinib therapy should be treated with radiotherapy while continuing crizotinib therapy [Takeda *et al.* 2013]. A retrospective analysis of patients who developed RECIST-defined progressive disease (PD) in PROFILE 1001 and PROFILE 1005 studies revealed that 62% (120/194) of the patients continued crizotinib therapy after PD. Most of them had good performance status (ECOG PS 0-1) and 51% of them had brain metastases as the sole site of PD. The authors concluded that this treatment strategy may provide survival benefit [Ou *et al.* 2014a].

Mechanisms of crizotinib resistance

Despite the initial treatment response of crizotinib, PD inevitably develops after a period of treatment. The mechanisms of crizotinib resistance had been studied, and one of these mechanisms is a secondary mutation in the kinase domain of *ALK*, for example, the 'gatekeeper mutation' of substitution of leucine with methionine at position 1196 (L1196M) [Choi *et al.* 2010]. Other resistance mutations had been reported (Table 2) [Choi *et al.* 2010; Sasaki *et al.* 2010, 2011; Zhang *et al.* 2011; Doebele *et al.* 2012; Katayama *et al.* 2012; Lovly and Pau, 2012; Huang *et al.* 2013; Kim *et al.* 2013b; Ou *et al.* 2014b]. In addition to the secondary mutation, activation of alternative pathway (EGFR and KIT), *ALK* amplification, epithelial–mesenchymal transition (EMT) and insulin-like growth factor 1 receptor (IGF-1R) pathway activation also resulted in crizotinib resistance [Katayama *et al.* 2012; Tanizaki *et al.* 2012; Yamada *et al.* 2012; Kim *et al.* 2013; Kobayashi *et al.* 2013a; Lovly *et al.* 2014; Yamaguchi *et al.* 2014]. In some patients, the mechanism of acquired resistance remains unknown [Costa and Kobayashi,. 2012].

Novel approaches to overcome crizotinib-acquired resistance had been reported. The most common strategy is to use second-generation ALK inhibitors to overcome resistance mediated by secondary *ALK* mutations (discussed in detail below). Other strategies, such as combination therapy with Hsp90 inhibitors, EGFR inhibitors, KIT inhibitors (e.g. imatinib) or IGF-1R inhibitors, had been reported [Sasaki *et al.* 2010, 2011; Katayama *et al.* 2012; Tanizaki *et al.* 2012; Yamada *et al.* 2012; Kim *et al.* 2013; Lovly *et al.* 2014; Yamaguchi *et al.* 2014]. Other strategies of crizotinib therapy are under development. A phase Ib trial of crizotinib in combination with immunotherapeutic agent ipilimumab (an anti-CTLA-4 monoclonal antibody) is ongoing [ClinicalTrials.gov identifier: NCT01998126]. Continuous treatment with crizotinib beyond disease progression is another strategy to extend the benefit of crizotinib therapy [Ou *et al.* 2014a]. A randomised phase II trial of crizotinib plus pemetrexed *versus* pemetrexed alone in patients with *ALK*-positive nonsquamous NSCLC who have progressed after previous benefit from crizotinib

Table 2. Characteristics of second-generation ALK inhibitors.

Drugs	Molecular targets other than ALK	Activity against L1196M	Activity against C1156Y	Activity against G1202R	Activity against other crizotinib-resistant mutations	No activity	Mechanism of acquired resistance
Ceritinib	IGF1-R, InsR, STK22D	Yes	No	No	G1269A, S1206Y, I1171T, V1180L	1151T-ins, L1152P, F1174C	F1174C, G1202R
Alectinib	GAK, LTK	Yes	Yes	No	G1269A, S1206Y, L1152R, F1174L, 1151T-ins	F1174V	I1171T, V1180L, G1202R
AP26113	ROS1, $EGFR^{del19/T790M}$	Yes	Yes	Yes	G1269A, S1206Y, D1203N, F1174C, 1151T-ins, G1269S, I1171T, E1210K, F1245C, S1206R*	NA	NA
ASP3026	ROS1, ACK	Yes	NA	NA	NA	NA	NA
PF-06463922	ROS1	Yes	NA	Yes	G1269A	NA	NA
TSR-011	TRK-A, TRK-B, TRK-C	Yes	NA	NA	NA	NA	NA
RXDX-101	ROS1, TRK-A, TRK-B, TRK-C	Yes	Yes	NA	NA	NA	NA
X-396	MET	Yes	Yes	NA	NA	NA	NA
CEP-37440	FAK	NA	NA	NA	NA	NA	NA

*S1206R confers to greatest resistance to AP26113 among the tested crizotinib-resistant mutations.
ALK, anaplastic lymphoma kinase; NA, not available.

therapy is ongoing [ClinicalTrials.gov identifier: NCT02134912].

Second-generation ALK inhibitors

Second-generation ALK inhibitors were designed to have more potent activity against ALK, to overcome crizotinib-resistant mutations and to have better activity in CNS disease. Many novel agents are under development as mentioned below. The characteristics of second-generation ALK inhibitors are listed in Table 2. Those drugs that were in phase II/III development are listed in Table 1 and those in phase I/II development are listed in Table 3.

Ceritinib

Ceritinib (LDK378) is an orally administered potent ALK inhibitor derived from the compound NVP-TAE684 [Galkin *et al.* 2007; Marsilje *et al.* 2013]. In preclinical studies, this drug demonstrated greater antitumour potency than crizotinib, and displayed activity against some crizotinib-resistant mutations (Table 2) [Friboulet *et al.* 2014]. In a phase I study (ASCEND-1) [ClinicalTrials.gov identifier: NCT01283516] (Table 1), 750 mg once daily was determined as the maximum tolerated dose (MTD) with the dose-limiting toxicities (DLT) of diarrhoea, vomiting, dehydration, elevated aminotransferase levels and hypophosphataemia. Among the 114 patients who received ceritinib at least 400 mg/day, ORR was 58% and the PFS was 7.0 months. Among the 80 patients who had been previously treated with crizotinib, ORR was 56% and 19 patients with crizotinib-resistant disease underwent a tumour biopsy before ceritinib therapy. *ALK* mutation and *ALK* amplification were detected in some of the responders, but other responders had neither *ALK* mutation nor *ALK* amplification. Among the patients who were crizotinib-naïve and treated with ceritinib at least 400 mg/day, ORR was 62%. The common AEs are listed in Table 1. The most common grade 3 or 4 AEs were increased ALT level (21%), increased aspartate aminotransferase (AST) level (11%) and diarrhoea (7%), All of these AEs were reversible after discontinuation of ceritinib therapy [Shaw *et al.* 2014].

Ceritinib received accelerated approval from the FDA in April 2014 for patients with metastatic *ALK*-positive NSCLC who were previously treated

with crizotinib. An updated report of ASCEND-1 study disclosed the efficacy data of the expansion cohort, in which all of the patients were treated with a starting dose of 750 mg/day. A total of 246 patients with *ALK*-positive NSCLC were enrolled, including 163 ALK inhibitor-pretreated (crizotinib or alectinib) and 83 ALK inhibitor-naïve patients. ORRs were 58.5%, 54.6% and 66.3% in the overall population, ALK inhibitor-pretreated group and ALK inhibitor-naïve group, respectively. The median PFS periods were 8.2 and 6.9 months in the overall population and ALK inhibitor-pretreated group, respectively. The median PFS in the ALK inhibitor-naïve group was not reached and the PFS rate at 12 months was 61.3%. In addition to the AEs mentioned above, around 4% of the patients developed interstitial lung disease/pneumonitis, and 9.4% (24/255, including 9 non-NSCLC patients) of the patients discontinued the study drug because of the AEs. However, regarding its activity in CNS disease, 124 patients had brain metastases at baseline, and 10 and 4 patients had measurable lesions in the ALK inhibitor-pretreated and ALK inhibitor-naïve groups, respectively. The intracranial ORRs were 40% and 75%, respectively. The authors concluded that ceritinib therapy had a high rate of durable responses and prolonged PFS in both ALK inhibitor-pretreated group and ALK inhibitor-naïve patients [Kim *et al.* 2014]. Ceritinib treatment showed activity in patients with brain metastases. Ongoing phase II and phase III clinical trials of ceritinib therapy for patients with advanced *ALK*-positive NSCLC are listed in Table 1.

Alectinib

Alectinib (RO5424802/CH5424802) is a highly selective and orally administered ALK inhibitor. Preclinical data revealed that alectinib had activity against some crizotinib-resistant mutations (Table 2) [Sakamoto *et al.* 2011; Kinoshita *et al.* 2012; Kodama *et al.* 2014a]. Alectinib showed potent efficacy against intracranial tumour in mouse models [Kodama *et al.* 2014b]. It had no activity against MET, ROS1 and some crizotinib-resistant mutations (Table 2) [Ou *et al.* 2014b].

In a phase I/II study (AF-001JP study) conducted in Japan (Table 1), patients with *ALK*-positive and ALK inhibitor-naïve NSCLC were treated with alectinib. In the phase I portion, there were no DLT or AEs of grade 4 up to the highest dose, and 300 mg twice daily was the recommended phase II dose. In the phase II portion, 43 out of 46 (93.5%) treated patients had objective responses. The common AEs are listed in Table 1. Grade 3 AEs were recorded in 26% of the patients, and the most common grade 3 AE was decreased neutrophil count and increased blood creatine phosphokinase (4%). No grade 4 AEs were recorded [Seto *et al.* 2013; Yang, 2013]. Based on this study, alectinib was approved in Japan in July 2014 for advanced *ALK*-positive NSCLC.

In another study conducted in Japan, 35 patients were enrolled and 29 patients (83%) had been pretreated with one or more than one ALK inhibitors. Among 28 patients pretreated with crizotinib, the ORR was 58.3% (95% CI 36.6–77.9). Two patients with measurable brain tumours were observed to have complete response at the first assessment [Nakagawa *et al.* 2014].

In the US, a phase I/II study (AF-002JG study) [ClinicalTrials.gov identifier: NCT01588028] of 600 mg twice a day was selected as the recommended phase II dose in patients with crizotinib-resistant *ALK*-positive NSCLC. Among the 47 enrolled patients, 44 patients could be assessed for drug activity and the ORR was 55%. Of 32 patients with CNS metastases, ORR was 52% [Gadgeel *et al.* 2014].

V1180L (gatekeeper) and I1171T mutations conferred resistance to alectinib, and ceritinib might overcome these alectinib-resistant mutations [Katayama *et al.* 2014]. Ongoing studies of alectinib therapy for patients with advanced *ALK*-positive NSCLC are listed in Table 1. One of these ongoing studies (ALEX) [ClinicalTrials.gov identifier: NCT02075840], directly compares alectinib with crizotinib in treatment-naïve advanced *ALK*-positive NSCLC patients.

AP26113

AP26113 is a potent and orally active inhibitor of ALK. In preclinical data, this drug demonstrated activity against ROS1 and most crizotinib-resistant mutations, including G1202R [Zhang *et al.* 2010; Squillace *et al.* 2013]. This drug has activity against activating *EGFR* mutations and $EGFR^{T790M}$ resistance mutation while sparing native EGFR (Table 2) [Rivera *et al.* 2012; Camidge *et al.* 2013]. In a phase I/II study [ClinicalTrials.gov identifier: NCT01449461], early onset pulmonary symptoms developed in 14% of patients with a starting dose of 180 mg/day. In 28 patients with a starting dose of 90 mg/day for 7 days followed by an

Table 3. Novel ALK inhibitors in early phase clinical study.

Drugs	ClinicalTrials.gov identifier	Phase	*n*	ORR	Adverse effects
ASP3026	NCT01401504	I	16	50% (crizotinib pretreated ALK-positive NSCLC)	Fatigue, vomiting, nausea and constipation
PF-06463922	NCT01970865	I/II	NA	NA	NA
TSR-011	NCT02048488	I/II	5	60% (crizotinib pretreated ALK-positive NSCLC)	NA
RXDX-101	NCT02097810	I/II	NA	NA	Asthenia, paresthesia, nausea, and diarrhea
X-396	NCT01625234	I/II	11	55% (ALK-positive NSCLC)	Nausea, rash, vomiting, fatigue, oedema, and pruritus
CEP-37440	NCT01922752	I	NA	NA	NA

ALK, anaplastic lymphoma kinase; NA, not available; ORR, overall response rate.

escalation to 180 mg/day, none of them developed pulmonary symptoms during the first 7 days at 90 mg or the first 7 days at 180 mg. This dosing strategy was chosen as the phase II dosage. In the phase II part, 57 patients were enrolled and ORR was 69% among the 51 crizotinib-pretreated patients and 100% among the 6 ALK inhibitor-naïve patients. The median PFS of the 49 crizotinib-pretreated patients with follow-up scans was 10.9 months. A total of 9 out of 13 patients (69%) with brain metastases responded to AP26113 therapy. The common AEs are listed in Table 1 [Gettinger *et al.* 2014a, 2014b]. A phase II trial of AP26113 (ALTA) [ClinicalTrials.gov identifier: NCT02094573] is ongoing for advanced crizotinib-pretreated *ALK*-positive NSCLC.

ASP3026

ASP3026 is a potent ALK and ROS1 inhibitor. In mouse models, this drug showed potent antitumour activity against *ALK*-positive NSCLC cells expressing crizotinib-resistant L1196M mutation [Mori *et al.* 2014]. In a phase I study [ClinicalTrials.gov identifier: NCT01401504], a dose level of 525 mg/day was chosen as a recommended phase II dose. The common AEs are listed in Table 3. ORR was 50% among 16 patients and the median PFS was 5.5 months (95% CI 3.7–11) [Maitland *et al.* 2014].

PF-06463922

PF-06463922 is a potent, macrocyclic inhibitor of ALK and ROS1. This drug has low propensity for P-glycoprotein 1 mediated efflux and good passive permeability in order to facilitate its CNS penetration [Johnson *et al.* 2014]. In preclinical studies, this drug demonstrated activity in mice with tumour xenograft that expressed ALK and some crizotinib-resistant mutations, including G1202R (Table 2). This drug achieved brain exposure of 20–30% of its plasma level in mice and regressed the brain tumours [Johnson *et al.* 2013; Zou *et al.* 2013a, 2013b]. A phase I/II study of PF-06463922 in patients with advanced *ALK*- or *ROS1*-positive NSCLC is ongoing [ClinicalTrials.gov identifier: NCT01970865].

TSR-011

TSR-011 is a potent ALK and tropomyosin-related kinase (TRK) A, B and C (encoded by *NTRK1*, *NTRK2* and *NTRK3*, respectively) inhibitor. In preclinical studies, this drug showed activity against crizotinib-resistant L1196M mutation (Table 2) [Wilcoxen *et al.* 2012]. In a phase I/IIa study [ClinicalTrials.gov identifier: NCT02048488], 23 patients were enrolled (including five *ALK*-positive NSCLC). The DLT included dysaesthesia and QTc prolongation [Weiss *et al.* 2014]. Rearrangement in *NTRK1* had been reported in a small portion of NSCLC patients without known oncogenic alterations. Treatment with inhibitors of TRKA kinase inhibited cell growth [Vaishnavi *et al.* 2013]. TSR-011 might have activity in this patient group.

RXDX-101

RXDX-101 (former name: NMS-E628) is an inhibitor of ALK, ROS1 and TRK A, B and C. In

preclinical studies, this drug demonstrated *in vitro* and *in vivo* activity against *ALK*-positive NSCLC and some crizotinib-resistant mutations (Table 2) [Ardini *et al.* 2009, 2011]. This drug passed through the blood–brain barrier in animal models and controlled intracranial tumours [Ardini *et al.* 2011]. In a phase I study, RXDX-101 was administered to patients with advanced solid tumours with relevant molecular alterations. One patient with *ALK*-positive NSCLC achieved PR and another patient with *ALK*-positive NSCLC had prolonged stable decease (SD). No DLT had been observed in all the tested dose levels. The common AEs (mainly grade 1–2) are listed in Table 3 [De Braud *et al.* 2014a, 2014b]. A global phase I/II study was initiated in patients with cancer confirmed to be positive for ALK, ROS1 and TRK A, B and C molecular alterations, especially NSCLC, colorectal cancer, prostate cancer, papillary thyroid cancer, pancreatic cancer and neuroblastoma [ClinicalTrials.gov identifier: NCT02097810].

X-396

X-396 is an ALK and MET inhibitor. It was more potent inhibitor of ALK and less potent inhibitor of MET compared with crizotinib. This drug also had activity against some crizotinib-resistant mutations (Table 2). In combination with the mTOR inhibitor, rapamycin, X-396 displayed synergistic growth inhibition [Lovly *et al.* 2011]. The efficacy results and the common AEs of a phase I/II study [ClinicalTrials.gov identifier: NCT01625234] are listed in Table 3. Doses up to 225 mg were well tolerated. The enrolment is ongoing in the expansion cohort [Horn *et al.* 2014].

CEP-37440

CEP-37440, an analogue of CEP-28122, is an ALK and FAK inhibitor [Shanthi *et al.* 2014]. Preclinical studies demonstrated activity of CEP-28122 against *ALK*-positive human cancer cells and tumour xenograft mouse models [Cheng *et al.* 2012]. The development of CEP-28122 was terminated because severe lung toxicity was developed in animal studies [Wang *et al.* 2014]. A phase I trial of CEP-37440 [ClinicalTrials.gov identifier: NCT01922752] for patients with advanced and metastatic solid tumours is ongoing.

Summary of ALK inhibitors

Crizotinib provides benefits to patients with advanced *ALK*-positive NSCLC in the first-line, second-line or heavily pretreated settings, with the PFS being around 7–10 months. Resistance disease inevitably developed after crizotinib therapy. Crizotinib-resistant *ALK* mutations (e.g. L1196M and G1269A) were one of the resistance mechanisms. Brain metastasis was another cause of PD. Novel ALK inhibitors were active against various crizotinib-resistant *ALK* mutations and brain metastases. Ceritinib is approved by the FDA for crizotinib-pretreated *ALK*-positive NSCLC. In Japan, alectinib is also available for *ALK*-positive NSCLC in the setting of either crizotinib-naïve or crizotinib-pretreated disease. These two novel ALK inhibitors gained accelerated approvals based on phase I/II studies, and confirmatory phase III studies are needed to determine the efficacy and AEs in different clinical setting. However, these aforementioned clinical trials enrolled crizotinib-pretreated patients, but the mechanisms of crizotinib resistance in these patients were not all the same. Some of these patients underwent cytotoxic chemotherapy before entering the clinical trials and clonal repopulation of crizotinib-sensitive cells might develop during chemotherapy. This situation cannot be classified as a mechanism of crizotinib resistance. Tumours that develop resistance under an ALK inhibitor therapy warrant repeat biopsies to identify the mechanism of drug resistance, although this procedure is not current standard of care and should be performed under clinical trial settings.

Even the resistance mechanisms of ceritinib (F1174C and G1202R) and alectinib (I1171T, V1180L and G1202R) had been identified (Table 2) [Friboulet *et al.* 2014; Ou *et al.* 2014b; Katayama *et al.* 2014]. Ceritinib was active against alectinib-resistant I1171T and V1180L mutations, but both ceritinib and alectinib were ineffective against G1202R mutation. Other novel ALK inhibitors, such as PF-06463922 and AP26113, have activity against G1202R and could be effective in treating patients who developed this mutation [Politi and Gettinger, 2014]. We encourage patients with *ALK*-positive NSCLC to participate in clinical trials to address the best sequence, combination, intercalation or novel therapeutic strategy for ALK inhibitors and to extend survival for patients [Gainor and Shaw 2013].

Hsp90 inhibitors in ALK-positive NSCLC

Hsp90 is a molecular chaperone that guides the normal folding, proteolytic turnover, intracellular disposition of regulators of cell growth and

survival [Whitesell and Lindquist, 2005]. Hsp90 is also a chaperone involved in the stabilisation of many oncoproteins and has been implicated in tumourigenesis [Trepel *et al.* 2010]. In *ALK*-positive NSCLC, the tumour is addicted to the fusion protein resulting from chromosomal rearrangements and this protein is thought to be a client of Hsp90 [Neckers and Workman, 2012]. Hsp90 inhibitors are effective in treating these patients in early clinical studies and four Hsp90 inhibitors (IPI-504, ganetespib, AUY922 and AT13387) are currently under clinical investigation in *ALK*-positive NSCLC patients [Pillai and Ramalingam, 2014].

IPI-504

Retaspimycin hydrochloride (IPI-504) is an Hsp90 inhibitor. In preclinical studies, the degradation of *EML4–ALK* fusion protein was induced by IPI-504 therapy and it resulted in the inhibition of downstream signalling pathways, induction of growth arrest and apoptosis [Normant *et al.* 2011]. In a phase II trial of IPI-504 monotherapy for patients with molecularly defined NSCLC, two out of three patients with *ALK*-positive NSCLC responded to IPI-504 therapy and the remaining one patient had prolonged SD. The most common AEs were fatigue, nausea and diarrhoea (grades 1 and 2). Grade 3 or higher liver function abnormality was observed in 11.8% of the patients [Sequist *et al.* 2010]. A phase II study of IPI-504 for *ALK*-positive NSCLC [ClinicalTrials.gov identifier: NCT01228435] was terminated early because of slow patient recruitment and competing studies.

Ganetespib

Ganetespib (STA-9090) is a nongeldanamycin triazolone-containing Hsp90 inhibitor. In preclinical studies, ganetespib demonstrated activity against *KRAS* mutant, *EGFR* mutant (including $EGFR^{del\ 19}$ and $EGFR^{L858R/T790M}$), *ERBB2* mutant and *c-MET* amplification in NSCLC in animal models [Acquaviva *et al.* 2012; Shimamura *et al.* 2012; Ying *et al.* 2012]. In *ALK*-positive NSCLC cell lines, ganetespib induced loss of EML4–ALK expression and depletion of oncogenic signalling proteins [Sang *et al.* 2013]. Ganetespib overcame multiple forms of crizotinib resistance, including some secondary *ALK* mutations, and ganetespib in combination with novel ALK inhibitors other than crizotinib also led to increased activity [Sang *et al.* 2013]. In addition to *ALK*-positive NSCLC cell lines, cancer cells driven by oncogenic rearrangement of *ROS1* and *RET* were sensitive to ganetespib [Sang *et al.* 2013].

In a phase II study of ganetespib monotherapy for genotypically defined advanced NSCLC, 99 patients were enrolled and ORR was reported to be 4%. All of these responders (n=4) were patients with crizotinib-naïve *ALK*-positive NSCLC. The treatment duration of the responders ranged from 7.4 to 21 months. Three out of the remaining four patients with *ALK*-positive NSCLC achieved SD as the best response. The median PFS of these 8 patients was 8.1 months, which was longer than the patients without *ALK* rearrangement (HR, 0.223; 95% CI 0.085–0.582) [Socinski *et al.* 2013]. The most common AEs were diarrhoea (81.8%), fatigue (57.6%), nausea (41.4%), decreased appetite (37.4%) and constipation (26.3%). Two patients experienced treatment-related death (one cardiac arrest and one renal failure) [Socinski *et al.* 2013].

A phase II study of ganetespib for *ALK*-positive NSCLC [ClinicalTrials.gov identifier: NCT01562015] and a phase I study of ganetespib plus crizotinib for crizotinib-naïve advanced *ALK*-positive NSCLC [ClinicalTrials.gov identifier: NCT01579994] are ongoing. Ganetespib is under clinical development in combination with docetaxel in patients with advanced NSCLC, which is not restricted to *ALK*-positive NSCLC (GALAXY-2) [ClinicalTrials.gov identifier: NCT01798485] [Proia *et al.* 2012; Ramalingam *et al.* 2013, 2014].

AUY922

AUY922 is a potent isoxazole-based nongeldanamycin Hsp90 inhibitor, which acts *via* cytostasis, apoptosis, invasion and angiogenesis to inhibit tumour growth and metastasis [Eccles *et al.* 2008]. A phase II study [ClinicalTrials.gov identifier: NCT01124864] of AUY922 for advanced NSCLC enrolled 121 patients. A total of 6 out of 21 patients (29%) with *ALK*-positive NSCLC achieved PR, and 4 of the 6 responders were crizotinib-naïve. The estimated PFS rate at 18 weeks was 42%. The most common AEs were eye disorder (77%), diarrhoea (74%) and nausea (46%) [Felip *et al.* 2012]. A phase II study of AUY922 for advanced NSCLC pretreated with crizotinib [ClinicalTrials.gov identifier: NCT01752400] and a phase Ib study of combination therapy of ceritinib plus AUY922 for crizotinib-pretreated

ALK-positive NSCLC [ClinicalTrials.gov identifier: NCT01772797] are ongoing. In addition to *ALK*-positive population, investigators also tested the efficacy of AUY922 in *HER2*-mutant/amplification, *EGFR* mutant (including $EGFR^{T790M}$ resistance mutation, exon 20 mutation and other uncommon mutations), *BRAF* mutant and *ROS1* or *RET* rearrangement in NSCLC [ClinicalTrials.gov identifier: NCT01922583, NCT01854034, NCT01646125] [Garon *et al.* 2013; Nogova *et al.* 2014].

AT13387

AT13387 is a high-affinity Hsp90 inhibitor [Woodhead *et al.* 2010]. Preclinical studies demonstrated its activity against *EGFR* mutant and *c-MET*-amplified NSCLC [Graham *et al.* 2012]. A phase I/II study of AT13387 alone or in combination with crizotinib for *ALK*-positive and crizotinib-pretreated patients [ClinicalTrials.gov identifier: NCT01712217] is ongoing.

Summary of Hsp90 inhibitors

Hsp90 inhibitors had shown activity against *ALK*-positive NSCLC in early phase studies and even overcame crizotinib-resistant mutations [Katayama *et al.* 2012; Sang *et al.* 2013]. However, Hsp90 inhibitors had limited activity against CNS metastatic tumours and their clinical benefits were restricted to patients without CNS metastases. However, the AEs of Hsp90 inhibitor therapy were higher than with second-generation ALK inhibitors. While there are many second-generation ALK inhibitors available in clinical practice or clinical trial settings, the development of Hsp90 inhibitors should be influenced. Novel approaches such as combination therapy with crizotinib or second-generation ALK inhibitors in either crizotinib-naïve or crizotinib-pretreated patients are under investigation. We encourage patients to participate in clinical trials to address the best combination or treatment strategy of Hsp90 inhibitors.

Conclusion

In patients with advanced *ALK*-positive NSCLC, crizotinib therapy was deemed to be indispensable. After disease progression, second-generation ALK inhibitors, ceritinib and alectinib, provided opportunities to overcome acquired resistance and achieve tumour control. Second-generation ALK inhibitors are not widely available around the world and cytotoxic chemotherapy is still the standard of care. We hope clinical trials are able to develop the next generation of ALK inhibitors to overcome resistance, be effective in treating CNS metastases, and extend survival in patients. Hsp90 inhibitors are currently not available in daily practice. We still rely on clinical trials to identify the best way to incorporate these drugs into clinical practice.

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Conflict of interest statement

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