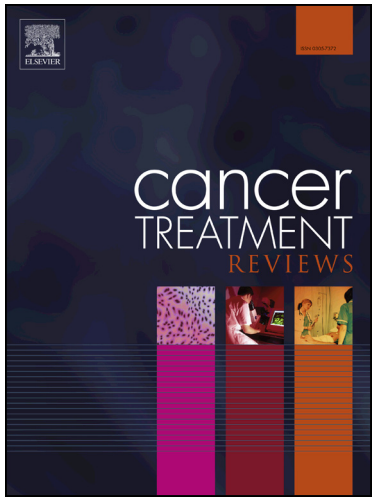

Anti-Tumour Treatment

The accelerated path of ceritinib: Translating pre-clinical development into clinical efficacy

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Title: The accelerated path of ceritinib: translating pre-clinical development into clinical efficacy

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ABSTRACT

The discovery of anaplastic lymphoma kinase (*ALK*)-rearranged non–small-cell lung cancer (NSCLC) in 2007 led to the development and subsequent approval of the ALK inhibitor crizotinib in 2011. However, despite its clinical efficacy, resistance to crizotinib invariably develops. There is now a next generation of ALK inhibitors, including two that have been approved—ceritinib and alectinib—and others that are in development—brigatinib, lorlatinib and X-396. Ceritinib and the other next-generation ALK inhibitors are more potent than crizotinib and can overcome tumor cell resistance mechanisms. Ceritinib gained US Food and Drug Administration approval in 2014 following accelerated review for the treatment of patients with *ALK*-positive (*ALK*+)

metastatic NSCLC who have progressed on or are intolerant to crizotinib.In pre-clinical studies, itdemonstrated more potent inhibition of ALK than crizotinib in enzymatic assays, more durable responses in xenograft models andthe ability to potently overcome crizotinib resistance mutations in vitro (including the gatekeeper mutation). There is also evidence for crizotinib penetration across the blood-brain barrier. In clinical trials, ceritinib has demonstrated durable responses and progression-free survival in ALK-inhibitor–pre-treated and –naïve NSCLC patients, including high overall and intracranial response rates in those with central nervous system metastases. Selective gastrointestinal toxicity of ceritinib, such as diarrhea, nausea and vomiting is generally manageable with prophylactic medication and prompt dose reduction or interruption. Future progress in treating *ALK*+ NSCLC will focus on determining the optimal sequencing of therapies and strategies to overcome acquired resistance, an ongoing challenge in treating *ALK*-mutation–driven tumors.

Keywords: Anaplastic Lymphoma Kinase, Carcinoma, Non–Small-Cell Lung, Ceritinib, Drug Resistance, Neoplasm

INTRODUCTION

The development of molecularly targeted therapies has been a paradigm shift in the treatment of non–small-cell lung cancer (NSCLC) [1]. In 2004, discovery of epidermal growth factor receptor (*EGFR*) driver mutations in a subgroup of patients with NSCLC helped researchers identify patients who substantially benefited from EGFR tyrosine kinase inhibition, which led to the eventual approval of EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy for *EGFR*-mutation-positive NSCLC [2,3]. In 2007, a chromosomal rearrangement of anaplastic lymphoma kinase (*ALK*) that resulted in the fusion with echinoderm microtubule-associated protein-like 4 (*EML4*) was identified [4,5].

This *ALK-EML4* rearrangement results in constitutive activity and is a potent oncogenic driver in NSCLC. Several other variants of *ALK* rearrangements have subsequently been identified in NSCLC, all resulting in constitutive activation [6]. Approximately 2%–6% of NSCLC patients exhibit *ALK*-positive (*ALK*+) NSCLC [7], with higher rates observed in a clinically enriched (younger, never-smokers [8-10]) population of adenocarcinoma patients.

The discovery of ALK rearrangements sparked the characterization and rapid clinical development of several specific ALK inhibitors (ALKis). Crizotinib was the first ALKi to be approved by the US Food and Drug Administration (FDA) for *ALK*+ NSCLC in 2011 along with a companion diagnostic fluorescence in situ hybridization (FISH) assay that has become the gold standard for the detection of *ALK*-rearranged NSCLC [11,12]. Crizotinib has demonstrated activity against *ALK*-rearranged NSCLC in pre-clinical and clinical studies [11,13,14] studies, with a clinical response rate of approximately 60% and median progression-free survival (PFS) of 8–11 months [13-15]. However, patients who initially derive benefit from crizotinib invariably progress and a subset of patients exhibit intrinsic resistance [16-18].

The central nervous system (CNS) is the most common site of disease recurrence in patients treated with crizotinib [19]. Crizotinib has shown suboptimal penetration across the blood-brain barrier [20], which may lead to CNS resistance in some patients; isolated CNS failures have been identified in patients treated with crizotinib [21]. In a recent retrospective analysis of crizotinib phase 3 studies (PROFILE 1005 and 1007), the intracranial response rate was lower than systemic responses among patients with brain metastases (overall response rate (ORR) 18% (95% confidence interval (CI) 5–40) and 53% (95% CI 43–63), respectively) [22].

A number of molecular resistance mechanisms have also been identified with crizotinib treatment, the most common being the gatekeeper L1196M mutation [23]. This secondary mutation that develops within the ALK tyrosine kinase domain gives rise to a change in the adenosine 5'-triphosphate (ATP)-binding pocket of the receptor and interferes with inhibitor

binding. Such mutations preserve the dominance of *ALK* signaling in the crizotinib-resistant state and therefore may remain sensitive to other ALKis [23,24]. This resistance mutation may be analogous to the *EGFR* T790M mutation in the ATP-binding pocket of *EGFR*, which is the most common mechanism of resistance in *EGFR*-mutated lung cancer [23]. *ALK*-independent resistance mechanisms can also occur through activation of alternative downstream signaling pathways, such as heat shock protein 90, EGFR or phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathways [23,25].

A number of next-generation ALKis that exhibit greater potency relative to crizotinib have been characterized. Ceritinib was the first next-generation ALKi approved by the FDA, followed by alectinib; others in various stages of development include X-396 [26], lorlatinib [23] and brigatinib [27,28]. This review will provide a brief overview of these next-generation ALKis before focusing on ceritinib, specifically the pre-clinical and clinical data leading to FDA approval. We also discuss clinical considerations for patients treated with ceritinib and future directions for treatment of patients with *ALK*-rearranged NSCLC.

NEXT-GENERATION ALKis

X-396

X-396 is a potent, orally available, small molecule TKI that was effective in vitro against NSCLC tumor cell lines engineered to express ALK mutations associated with acquired resistance to crizotinib [29]. Preliminary results from an ongoing phase 1/2 study of X-396 (NCT01625234) demonstrated a partial response in 55% of 11 evaluable patients with ALK+ NSCLC (including ALKi-naïve and ALKi–pre-treated patients), and two patients who achieved responses had CNS metastases. Enrollment is ongoing in the expansion cohort of this study [26].

Lorlatinib

Lorlatinib is a potent and brain-penetrant ATP-competitive small molecule inhibitor of ALK and ROS1 that exhibits anti-tumor efficacy in pre-clinical xenograft models harboring crizotinib-resistance mutations, as well as an ALK-driven intracranial model [30,31]. Results for 33 patients with ALK+ NSCLC and 11 patients with ROS1+ NSCLC from the phase 1 arm of a phase 1/2 clinical trial (NCT01970865) were recently reported. An objective response rate of 44% was reported for 34 patients evaluable for tumor response. Of these, 25 patients were evaluable for intracranial responses, 14 with measurable CNS target lesions; the objective intracranial response rate was 36% [32]. This study is ongoing, with an estimated completion date of October 2017.

Brigatinib

Brigatinib is an orally available ALKi with demonstrated potent inhibition of tumor cell lines harboring ALK mutations associated with crizotinib resistance [28]. Brigatinib was granted breakthrough therapy designation by the FDA in October 2014 on the basis of its early phase I/II trial data (NCT02094573). Recent results from this study reported a 74% objective response rate in 78 evaluable patients with ALK+ NSCLC, the majority of whom were crizotinib pre-treated (70/78; 90%). A post hoc independent radiological review of patients with brain metastases at baseline reported responses in 8 of 15 patients with measurable lesions at baseline and nine of 30 patients with non measurable lesions at baseline. A phase 2 trial (NCT02094573) of patients with ALK+ NSCLC pre-treated with crizotinib is currently ongoing and the randomized phase 3 ALTA-1L study (NCT02737501) to investigate brigatinib vs crizotinib in patients with ALK+ NSCLC is currently recruiting patients [33].

Alectinib

Alectinib is an orally available, highly selective and potent ALKi that has exhibited anti-tumor efficacy in vitro and in vivo against crizotinib-resistant tumor models [34,35].

Alectinib was first approved for use in Japan in July 2014 based on data from a phase 1/2 study in ALKi-naïve Japanese patients with ALK+ NSCLC (AF-001JP). Following the phase 1 arm of this study, which established that alectinib was well-tolerated with no dose-limiting toxicities reported at a maximal dose of 300 mg twice daily (BID), the phase 2 arm reported an objective response rate of 93.5% in 46 patients treated at 300 mg BID [36].

More recently, a phase 1/2 study (NCT01588028) in crizotinib–pre-treated Western patients with ALK+ NSCLC found no dose-limiting toxicity with alectinib at doses up to 600 mg BID, which was selected as the phase 2 dose. Results from the phase 2 arm of this study reported objective responses in 55% of 44 patients evaluable for efficacy [37]. Intracranial responses were also reported in 52% of the 21 patients with CNS metastases at baseline. This dose has been further evaluated in two single-arm phase 2 trials, one including 87 patients from the United States and Canada (NCT01871805), and the other 138 patients from 16 different countries (NCT01801111) [38,39]. Both trials enrolled patients with crizotinib-refractory ALK+ NSCLC. Objective responses of 48% and 49% were reported for the 69 evaluable patients in the North American study and the 122 evaluable patients in the global study, respectively. Objective intracranial responses were reported for 52% of 67 patients with CNS disease at baseline in the North American study and 57% of 35 patients with measurable CNS lesions at baseline in the global study.

In December 2015, alectinib was granted FDA approval for the treatment of patients with ALK+ NSCLC previously treated with crizotinib, and a randomized phase 3 trial comparing alectinib to chemotherapy in patients with ALK+ NSCLC previously treated with chemotherapy and crizotinib is ongoing (NCT02604342). In addition, two randomized phase 3 trials, one in Japanese patients (J-ALEX study, JapicCTI-132316) and one global study (ALEX study, NCT02075840) are currently ongoing to evaluate alectinib vs crizotinib in treatment-naïve patients with ALK+ NSCLC.

CERITINIB

Ceritinib is a highly selective and potent orally available next-generation ALKi, the first to be approved by the FDA (April 2014) for the treatment of patients with *ALK*+ metastatic NSCLC who have progressed on or are intolerant to crizotinib [40,41]. Ceritinib was granted breakthrough therapy status and was the first agent to achieve FDA approval based primarily on pivotal phase 1 study results demonstrating impressive safety and efficacy in *ALK* mutation-positive patients with advanced NSCLC who had relapsed on crizotinib [40,41].

Ceritinib development and pre-clinical activity

Ceritinib is a highly selective and potent inhibitor of ALK [42,43]. Ceritinib was found to inhibit ALK with 20-fold greater potency than crizotinib in enzymatic assays (half maximal inhibitory concentration (IC_{50}) 0.15 nM vs 3 nM; Table 1). Similarly, ceritinib was 28-fold and 39-fold more potent than crizotinib in two *ALK*-rearranged NSCLC cell lines, H2228 and H3122 (IC_{50} 3.8 nM vs 107 nM and IC_{50} 6.3 nM vs 245 nM, respectively) [43]. Unlike crizotinib, which is a dual ALK and mesenchymal-epithelial transition factor (MET) kinase inhibitor [44], ceritinib does not affect MET. Ceritinib has been found to inhibit kinases for proto-oncogene receptor tyrosine kinase (ROS1) and insulin growth factor-1 receptor (IGF-1R), although it is most active against ALK [42]. With ceritinib, IC_{50} values in Ba/F3 cell lines expressing ROS1, IGF-1R, and MET were 142 nM, 410 nM, and 1339 nM, respectively.

Ceritinib was also found to be a potent inhibitor of tumor growth in vivo (100% tumor regression in the H2228 rodent model) and has achieved more durable antitumor activity than crizotinib (Fig. 2) [43]. Following 2 weeks of treatment, marked tumor regression was observed with ceritinib and crizotinib, but animals treated with ceritinib (50 mg/kg) remained in complete remission for 4 months following withdrawal of treatment, while most crizotinib-treated mice (100 mg/kg) showed tumor outgrowth in less than 2 weeks. Interestingly, the drug exposure of crizotinib at 100 mg/kg in mice was approximately three- to five-fold greater than exposures

achieved at the maximum tolerated dose in humans (crizotinib 250 mg twice daily), while exposures of ceritinib at 25–50 mg/kg in mice are expected to be achievable in humans at a dose of 750 mg daily [43].

Ceritinib can overcome crizotinib resistance in models of acquired resistance, including cell lines established from biopsies of crizotinib-resistant NSCLC patients [43]. Ceritinib was highly active against the most common crizotinib-resistance mutations, including L1196M (the gatekeeper mutation), G1269A, S1206Y and I1171T (Table 2). Further, in xenograft models, ceritinib 25 mg/kg more effectively controlled tumor growth than crizotinib 100 mg/kg in mice that bear tumors derived from cells harboring the L1196M mutation [43]. In a tissue distribution study in rats, ceritinib crossed the blood brain barrier, with a brain-to-blood exposure (area under the concentration-time curve (AUC) from time zero to infinity) ratio of approximately 15% [40]. These in vitro and in vivo data are consistent with clinical activity of ceritinib in patients with crizotinib-resistant disease [38,41].

Ceritinib pharmacokinetic parameters and dosing

Selection of the ceritinib starting dose in the first human studies was estimated to be approximately 50 mg based on the severely toxic dose in 10% of rats with a safety factor of 10 applied. Pharmacokinetic and pharmacodynamic modeling was applied to estimate the efficacious dose in humans based on exposures associated with tumor growth inhibition in animal models. The human efficacious dose range was estimated to be between 120 and 480 mg daily [41].

In a clinical dose-escalation study, in which patients received a daily oral dose of ceritinib administered in 21-day cycles starting at 50 mg, the recommended phase 2 dose was established at 750 mg [41]. Escalation beyond 750 mg was not pursued based on a high frequency of gastrointestinal adverse effects such as low-grade nausea, vomiting and diarrhea

that would make long-term daily administration challenging, as well as a low frequency of higher grade gastrointestinal toxicities and transaminase elevations in later cycles.

At the recommended phase 2 dose, maximum concentration (C_{max}) for ceritinib was reached in approximately 6 hours and the plasma terminal half-life of ceritinib was approximately 40 hours. Mean C_{max} was 800 ± 205 ng/mL. The AUC and C_{max} increased dose proportionally over the treatment range of 50–750 mg. Following repeated daily dosing at 750 mg, steady state was reached in approximately 15 days [41]. Ceritinib exposure was found to increase in a greater than dose proportional manner after repeated doses; the terminal half-life of ceritinib was 41 hours [40]. In the fasting state, ceritinib was found to elicit tumor responses between 400 mg and 750 mg [41].

Systemic exposure of ceritinib increases when taken with food, as shown by results of a food-effect study conducted in healthy subjects. Following a single oral dose of ceritinib 500 mg taken with a high- or low-fat meal, C_{max} increased by 43% and 41%, respectively, and AUC increased by 73% and 58%, respectively, relative to fasting conditions [45]. Following a single oral dose of ceritinib 750 mg taken with a light snack, C_{max} and AUC increased by 45% and 54%, respectively, relative to the fasting state [45]. Therefore, the US prescribing information recommends patients take ceritinib 2 hours prior to or after a light meal to avoid increased systemic exposure [40]. These recommendations differ from those for crizotinib, which can be taken with or without food [12]. A study is under way to evaluate the optimal dose and timing for ceritinib administration relative to meals (NCT02299505), which should provide additional guidance on this point.

Ceritinib is highly bound to plasma proteins (97%). Ceritinib is a substrate of cytochrome P450 (CYP) 3A, and metabolic clearance occurs primarily via CYP3A enzymes. It is primarily eliminated unchanged in feces (>90%). In healthy subjects, co-administration studies performed with ketoconazole, a strong CYP3A4 inhibitor, increased ceritinib AUC by 20.9-fold and C_{max} by

22%. In addition, co-administration of ceritinib with rifampin, a strong CYP3A inducer, decreased ceritinib AUC by 70% and C_{max} by 44%. These effects on ceritinib clearance have the potential to increase adverse effects or reduce efficacy; therefore, concurrent administration of ceritinib with strong CYP3A inhibitors and inducers should be avoided [40].

Ceritinib clinical efficacy

Based on its favorable pre-clinical profile, ceritinib was investigated in ASCEND-1, a pivotal phase 1 study that included a dose-escalation phase [41]. Patients enrolled in the study were adults with locally advanced or metastatic progressive *ALK*+ cancer (as determined by FISH) who had an Eastern Cooperative Oncology Group performance status of 2 or less, with or without stable brain metastases. ASCEND-1 interim results revealed that among patients who received a ceritinib dose of 300 mg or less daily, 25% had a confirmed partial response. Among the 114 patients who received ceritinib at a dose of 400 mg or more daily, the ORR was 58% (95% CI 48–67); a similar ORR was observed for 80 patients who were previously treated with crizotinib (56%; 95% CI 45–67) [41].

One-year follow-up results of ASCEND-1 were recently reported for 246 *ALK*+ NSCLC patients treated at the recommended dose of 750 mg daily [46]. Ceritinib demonstrated a high rate of rapid and durable responses in ALK-inhibitor–naïve and ALK-inhibitor–pre-treated patients, including those with brain metastases at study entry. Brain metastases were present in 50.4% of patients at baseline; the majority of patients were heavily pre-treated, with 42.7% of patients having received three or more prior treatment regimens. The ORR was 72.3% (95% CI 61.4–81.6) in ALK-inhibitor–naïve patients (*n* = 83) and 56.4% (95% CI 48.5–64.2) in ALK-inhibitor–pre-treated patients (*n* = 163; all 163 patients received crizotinib and five patients received alectinib (investigational) after crizotinib). Median duration of response (DOR) was 17.0 months (95% CI 11.3–non estimable) for ALK-inhibitor–naïve patients and 8.3 months (95% CI 6.8–9.7) for ALK-inhibitor–pre-treated patients. Median PFS was 18.4 months (95% CI 11.1–non

estimable) and median overall survival (OS) was not reached (95% CI 19.61–non estimable) for ALK-inhibitor–naïve patients. In ALK-inhibitor–pre-treated patients, median PFS was 6.9 months (95% CI 5.6–8.7) and OS was 16.7 months (95% CI 14.8–non estimable) [46].

The intracranial disease control rate (IDCR) was also high in ALK-inhibitor–naïve and ALK-inhibitor–pre-treated patients. Retrospective analyses were conducted in 94 patients who had baseline brain metastases and at least one post-baseline magnetic resonance imaging or computed tomography tumor assessment [46]. In 19 of 94 ALK-inhibitor–naïve patients, median time to intracranial response was 9.9 weeks (range 5.4–30.1) and IDCR was 78.9% (95% CI 54.4–93.9). In 75 of 94 ALK-inhibitor–pre-treated patients, median time to intracranial response was 6.1 weeks (range 5.1–19.1) and IDCR was 65.3% (95% CI 53.5–76.0). The IDCR was similar among the 33% of patients who did not receive prior radiotherapy to the brain and the 67% of patients who did receive prior radiotherapy to the brain. Among the subgroup of 36 patients who had measureable brain lesions according to Response Evaluation Criteria in Solid Tumors at baseline, IDCR was 62.5% (95% CI 24.5–91.5) and median intracranial DOR was 8.2 months (95% CI 5.6–non estimable) in the eight ALK-inhibitor–naïve patients, and IDCR was 60.7% (95% CI 40.6–78.5) and intracranial DOR was 11.1 months (95% CI 2.8–non estimable) in the 28 ALK-inhibitor–pre-treated patients [46].

A single-arm, open-label phase 2 study, ASCEND-2, investigated the safety and efficacy of ceritinib in patients who received prior chemotherapy and progressed on crizotinib in 30 days or less [47]. Interim results showed that ceritinib demonstrated durable responses in 140 patients with or without baseline brain metastases, which was consistent with ASCEND-1 data. The ORR was 52.5% (95% CI 36.1–68.5) for the 40 patients without baseline brain metastases and 33% (95% CI 23.9–43.1) for the 100 patients with baseline brain metastases. Median DOR was 10.3 months (95% CI 7.4–16.6) and median PFS was 11.3 months (95% CI 5.7–15.6) for

patients without baseline brain metastases, while DOR was 9.2 months (95% CI 5.5–11.1) and PFS was 5.4 months (95% CI 4.7–7.2) for those with baseline brain metastases.

Interim results were also reported for a single-arm, open-label, phase 2 study of ceritinib in ALK-inhibitor–naïve patients, ASCEND-3 [48]. Ceritinib achieved a robust ORR of 67.6% (95% CI 55.7–78.0) in 74 patients without baseline brain metastases and 58% (95% CI 43.2–71.8) in 50 patients with baseline brain metastases. Median DOR was 10.8 months (95% CI 9.3–10.8) and 9.1 months (95% CI 7.5–non estimable) in patients without or with brain metastases, respectively. Median PFS was 11.1 months (95% CI 9.2–12.8) and 10.8 months (95% CI 7.3–non estimable) in patients without or with brain metastases, respectively. The PFS observed in this ASCEND-3 interim analysis [48] was similar to the PFS reported in the subgroup of ALK-inhibitor–naïve patients in ASCEND-1 at a similar duration of follow-up [41].

Ceritinib safety profile

Ceritinib has a toxicity profile that is generally manageable [20,38,40]. The incidence and types of adverse events (AEs) observed following ceritinib treatment have remained consistent across studies [20,38-41]. The AEs reported most commonly in the ASCEND-1 study were diarrhea, nausea and vomiting and were mostly grade 1 or 2. Gastrointestinal AEs leading to discontinuation occurred in one patient with grade 1 nausea [46]. Grade 3 or 4 AEs or serious AEs suspected to be treatment-related occurred in 50.8% and 11.8% of patients, respectively. The most common grade 3 or 4 AEs reported for ceritinib were increased alanine transaminase (ALT) and increased aspartate transaminase (AST), reported in 29.7% and 10.2% of patients, respectively; there were no cases of Hy's law observed [46]. Other rare but important AEs observed in studies of ceritinib were interstitial lung disease (ILD)/pneumonitis, QT interval prolongation and bradycardia [20,25,38], which were managed by dose interruptions or reductions and were reversible on discontinuation. Two on-treatment deaths considered by the

investigator to be related to ceritinib treatment were reported; one due to ILD and one as a result of multi-organ failure that occurred in the context of infection and ischemic hepatitis [46].

Of the 246 patients in the ASCEND-1 study, 73.6% required at least one dose interruption and 61.8% had at least one dose level (150 mg) reduction, with 26.0% requiring two or more dose level reductions [46]. The median average daily dose of ceritinib was 664 mg and ranged from 358 mg to 750 mg. AEs were the most common reason for dose interruption or reduction, and rates of discontinuation due to AEs were low (approximately 10%) [46].

Management of AEs with Ceritinib

The common AEs associated with ceritinib treatment can usually be managed without the need for treatment discontinuation. Appropriate management of ceritinib-associated AEs includes proactively monitoring patients, evaluating concomitant medications or existing co-morbidities that may contribute to AEs, promptly treating gastrointestinal toxicities and offering dose interruptions and modifications as needed [25,42]. For the majority of patients in whom dose interruption or modification is required, therapy can be reinitiated at a lower dose (150 mg reduction) following improvement. Data from the ASCEND-1 dose escalation phase showed dose interruptions generally lasted for 8 days or less [41].

Treating physicians should monitor patients' liver function; if ALT/AST elevations occur, these can be managed through dose interruption, after which patients may resume ceritinib therapy [25,38]. If diarrhea occurs, prompt dose adjustment of antidiarrheal medication is recommended [49,50]. Mild nausea and vomiting may be managed using antiemetic therapy according to practice guidelines and clinical judgment [51]. More significant diarrhea, nausea and/or vomiting require dose interruption; therapy may be reinitiated at a lower dose (150 mg reduction) following symptom resolution [40]. In patients for whom gastrointestinal toxicity is a concern, providing supportive care medication at the start of treatment may be a helpful strategy. A recently reported case series found proactive management of gastrointestinal AEs prevented

the need for ceritinib dose modification due to gastrointestinal toxicity in eight of nine patients [42].

According to labeling guidance, patients should take ceritinib on an empty stomach (e.g. not within 2 hours of a meal) [40]; some investigators have advised patients to take ceritinib at bedtime or with a light snack to help mitigate nausea. Food effect studies in healthy subjects have shown that a lower single dose of ceritinib (500 mg) taken with food resulted in less frequent gastrointestinal AEs; however, this trend was not observed with the 750 mg dose taken with food [45]. It should be considered that taking ceritinib with food may lead to systemic exposure exceeding 750 mg, which may increase exposure-related AEs [41]. Data anticipated from a randomized, open-label study evaluating lower doses of ceritinib (450 mg and 600 mg) taken with a low-fat meal compared with 750 mg taken on an empty stomach will help elucidate the safety and efficacy of this approach (NCT02299505).

AE PROFILES OF OTHER ALKis

It is now recommended that patients with *ALK* mutations be treated with multiple lines of ALKis. As a result, it may be valuable to consider the toxicities reported for each agent from their pivotal or most recent trials, which suggest some similarities and differences. In evaluating the reported AE rates, however, clinicians should bear in mind that these rates were based on different patient populations (e.g. approximately 66% of patients in ASCEND-1 were pre-treated with an ALKi [46]; whereas none were in the pivotal crizotinib study [13]).

Crizotinib Safety Profile

Gastrointestinal toxicities (diarrhea, nausea, vomiting and constipation) were among the most commonly reported AEs for crizotinib, although few at grade 3/4 were reported [14]. Crizotinib was associated with a high rate of grade 1/2 vision disorders (60% in the pivotal study) [12-15]. Elevated ALT levels were reported frequently with crizotinib (38%) and this was also the most

commonly reported grade 3/4 AE (16%). One case in the pivotal study met the criteria for Hy's law with fatal hepatic failure occurring after the data cutoff date [14]. There were two cases (1%) of ILD/pneumonitis with crizotinib in the pivotal study [13]. The rate of treatment-related serious AEs with crizotinib was 12% and treatment-related AEs led to permanent discontinuation of crizotinib in 6% of patients [14].

Alectinib Safety Profile

Most recent safety data for alectinib come from two single-arm Phase 2 studies, one of which was conducted globally [38] and one in North America [39]. In the global study, the most common AEs with alectinib were constipation (33%), fatigue (26%) and peripheral edema (25%) and the most common treatment-related AEs were myalgia (17%), constipation (15%), fatigue (14%) and asthenia (11%). The incidence of grade 3/4 AEs was low (1%–3%). Overall, 21% of patients had dose interruptions or reductions and 8% of patients permanently discontinued alectinib because of an AE. Four patients died as a result of AEs, but only one (intestinal perforation) was considered possibly related to study treatment [38].

In the North American study, the most common AEs with alectinib were constipation (36%), fatigue (33%), myalgia (24%) and peripheral edema (23%). Serious AEs were reported in 15% of patients. Two patients died; one patient on anticoagulants died from a hemorrhage, which the investigator judged as related, and one patient had disease progression and a history of stroke, which was judged not related to treatment. Dose interruption was needed by 36% of patients and dose reductions were reported in 16% of patients. Two patients discontinued treatment because of AEs [39].

A head-to-head comparison of the tolerability of alectinib and crizotinib will be possible with results of the ALEX study, with an estimated study completion of December 2017.

Brigatinib Safety Profile

In the ongoing Phase 1/2 study with brigatinib, the most common reported AEs were nausea (52%), fatigue (42%), diarrhea (40%), headache (33%) and cough (32%) [33]. The most common grade ≥3 AEs were increased lipase (9%), dyspnea (7%), fatigue (4%) and increased amylase (4%). The most common serious AEs were dyspnea (7%) and pneumonia (6%). Seven of 79 patients (9%) discontinued the study due to AEs. Overall, 9% of patients reported pulmonary events within 7 days of treatment initiation. The rate was lower in patients who started on 90 mg daily (QD) (4%) than those who started immediately on the full 180 mg QD dose (14%). No reports of pulmonary events after dose escalation in patients who received 90 mg QD for 7 days followed by 180 mg QD were found.

Lorlatinib Safety Profile

In the Phase 1 dose-escalation study of lorlatinib, treatment-related AEs were reported in 37% of patients and one patient discontinued from treatment due to objective disease progression. The most common reported AEs were hypercholesterolemia (47%) and peripheral neuropathy (27%) and edema (23%). Hypercholesterolemia was the most common grade ≥3 treatment-related AE, occurring in 10% of patients. One dose-limiting toxicity (CNS effects) was reported for a patient receiving the 200 mg dose [52].

X-396 Safety Profile

In the Phase 1 study of X-396, the most common drug-related AEs (mostly grade 1–2) included rash (31%), nausea (31%), vomiting (29%), fatigue (26%) and edemas (17%). Dose limiting toxicities occurred in two patients; one as a result of fluid overload (at 200 mg), the other due to rash (250 mg). A dose of 225 mg was generally tolerable [26].

DISCUSSION

Ceritinib has demonstrated clinically meaningful durable responses in ALK-inhibitor–resistant and ALK-inhibitor–naïve patients, including those with brain metastases, with a generally

manageable, consistent AE profile [38,40,41]. Brain metastases remain a complication of NSCLC, and the brain was the most common site of disease progression following acquired resistance to crizotinib [42]. Positive results were observed among patients with baseline brain metastases treated with ceritinib. The IDCR was approximately 62%–78% in ASCEND-1, with higher responses in ALK-inhibitor–naïve patients [46].

Since the discovery of *ALK* rearrangements in 2007, the treatment landscape continues to evolve and questions remain regarding the optimal timing and sequence of therapy. Crizotinib has demonstrated efficacy in the first-line setting, with results of the Phase 3 PROFILE 1014 trial showing significant improvement in PFS and ORR with crizotinib compared with standard pemetrexed-platinum chemotherapy [15]. Crizotinib is currently being assessed in a Phase 3 study in the adjuvant setting in patients with early stage *ALK*+ NSCLC (NCT02201992). A Phase 3 study to assess ceritinib in the first-line setting (ASCEND-4, NCT01828099) is under way. Ceritinib is also being studied vs standard chemotherapy in a Phase 3 study of patients previously treated with chemotherapy and crizotinib (ASCEND-5, NCT01828112). Results have demonstrated the efficacy of ceritinib in patients who progressed on crizotinib [38,40,41]. A recent retrospective analysis also demonstrated the benefit of sequential ceritinib in crizotinib-resistant patients; sequential treatment resulted in a median combined PFS of 17.4 months [53]. Support for the potential role of ceritinib as a first-line therapy comes from data showing an improved ORR and PFS in crizotinib-naïve vs crizotinib–pre-treated patients [46]. Additional support comes from an adjusted indirect comparison showing significantly prolonged PFS and OS with ceritinib compared with crizotinib among patients who were crizotinib naïve [54]. Alectinib is also being assessed in Phase 3 studies in the first-line setting (ALEX, NCT02075840) and compared to standard chemotherapy in patients who have been previously treated with chemotherapy and crizotinib (NCT02604342). A number of other ALKis remain under investigation [55,56].

With the expanding armamentarium, further insights into acquired resistance mechanisms as well as CNS penetration and activity of ALKis will be needed. Many tumors remain *ALK* dependent and may respond to more potent ALKis, although acquired resistance will remain a challenge [27]. Ceritinib and other ALKis have demonstrated activity against gatekeeper and other mutations that lead to crizotinib resistance [26,33,42,52,57]. This suggests that patients may be able to derive benefit from multiple, sequential ALKis. However, some resistance mutations are a challenge, such as the G1202R mutation. This mutation, which causes steric hindrance, has shown a high level of resistance to crizotinib, ceritinib, alectinib and other ALKis [18]. Resistance mechanisms that employ bypass signaling pathways will require a re-evaluation of current treatment algorithms focusing on sequencing vs combination approaches. These clinical challenges call for additional management strategies and highlight the role of rebiopsy to guide the selection of therapies based on the molecular resistance mechanisms identified [23,56]. Given the expanding role of immunotherapy in NSCLC, studies to evaluate the combination of immune checkpoint inhibitors with ALKis are also ongoing (i.e. NCT02511184 and NCT02393625). Results from these ongoing trials are awaited to help guide future management strategies in this evolving treatment landscape.

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Provision of study materials: Tony SK Mok and Laura Chow

Collection and/or assembly of data: Tony SK Mok and Laura Chow

Data analysis and interpretation: All authors

Manuscript writing/revision: All authors

Final approval of manuscript: All authors

Conflict of Interest

Tony SK Mok has been an advisor for and received honoraria from AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Serono, MSD, Janssen, Clovis Oncology, BioMarin, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Vertex Pharmaceuticals, Aveo/Biodesix, Bristol-Myers Squibb; he has been an advisor for geneDecode; he has received honoraria from GlaxoSmithKline and Prime Oncology; and he has ownership interests in Sanomics Limited.

Lucio Crino has received honoraria from Novartis, AstraZeneca and Boehringer Ingelheim; and he has been advisor for Pfizer, Novartis and AstraZeneca.

Enriqueta Felip has been a consultant for and received honoraria from Eli Lilly, Pfizer, Roche, Boehringer Ingelheim and MSD; and he has received lecture fees from AstraZeneca and Novartis.

Ravi Salgia has nothing to disclose.

Tommaso De Pas has nothing to disclose.

Daniel SW Tan has received research grants from Novartis; he has been an advisor for Novartis, Boehringer Ingelheim and Pfizer.

Laura QM Chow has been a consultant, advisor and steering committee member for Novartis, and she has received honoraria and/or travel and accommodation support for those activities; she has received honoraria and travel and accommodation support as an advisor for Merck; she has received honoraria as a consultant for Amgen; and her institution has received research funding from Novartis, BMS, Merck, Genentech/Roche, AstraZeneca-Medimmune, Astellas/OSI, GlaxoSmithKline/NCCN, Venti-Rx, Lily/Imclone and Pfizer

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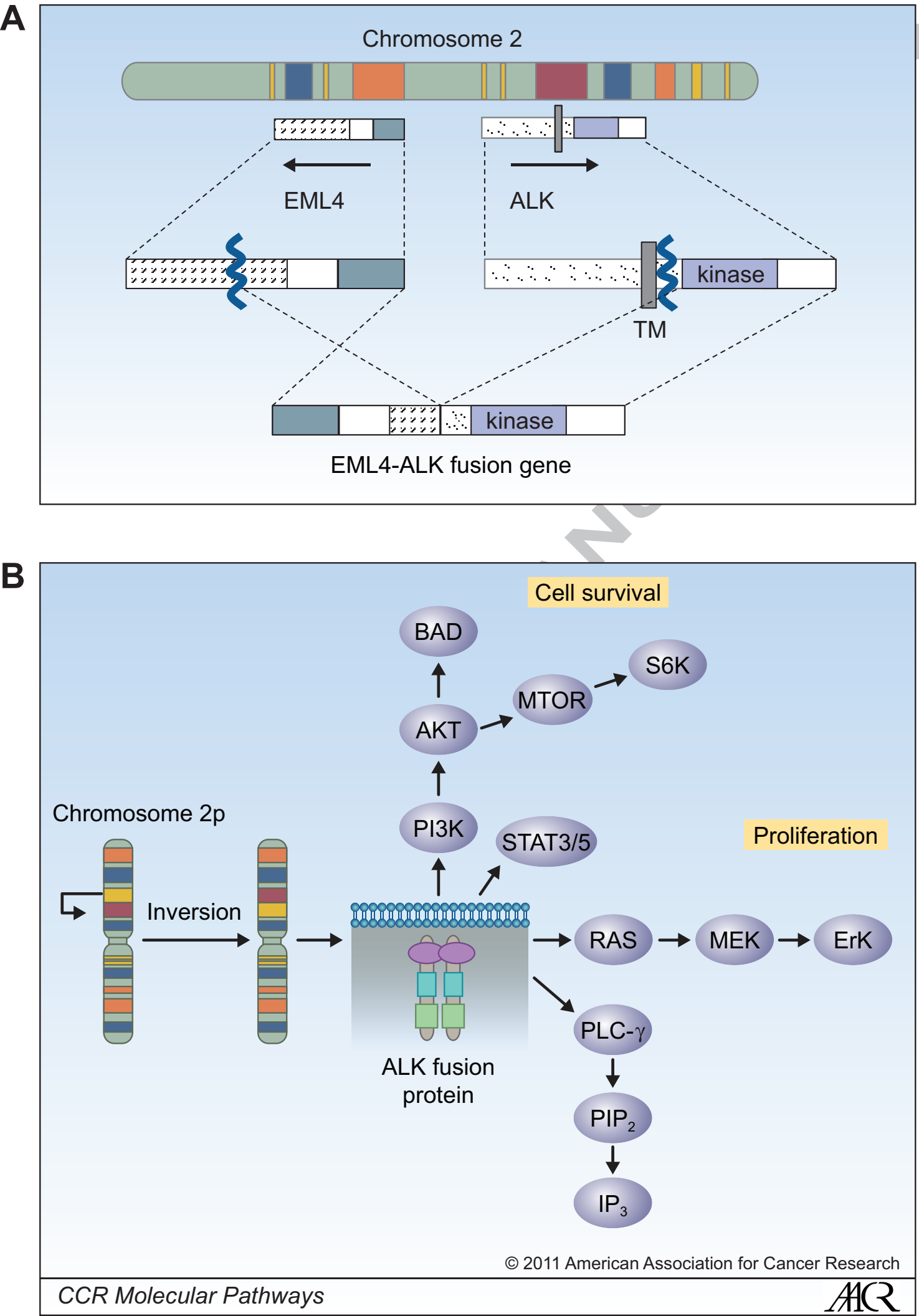
Figure Captions

Figure 1. Schematic of *ALK* fusion oncogene and downstream signaling pathways. Inversion within the short arm of chromosome 2 and ligation of *EML4* and *ALK* leads to constitutive dimerization and activation of *EML4-ALK* (**A**), reprinted from Tamura K, Tamura K. J Phys Chem Biophys 2012;2:108 (© 2012 Tanaka T, et al.) [57]. *EML4-ALK* activates major signaling pathways, including Ras/Mek/Erk, PI3K/AKT and STAT3 cascades (**B**), reprinted with permission from Shaw AT, Solomon B. Clin Cancer Res 2011;17:2081–2086. © 2011 *AACR*.

Abbreviations: ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4.

Figure 2. Durable antitumor activity of ceritinib in vivo using treatment-naïve H2228 xenograft models. Tumor-bearing animals demonstrated tumor regression following high-dose crizotinib (100 mg/kg) or ceritinib (25 mg/kg or 50 mg/kg) once daily for 14 days. Arrow indicates when treatments were stopped. Animals were monitored for progression following withdrawal of treatment for up to 4 months. Tumor volumes are presented as mean ± standard deviation (n = 8). Reprinted with permission from Friboulet L et al. Cancer Discov 2014;4:662–673 [43].


A
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kinase
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EML4-ALK fusion gene
B
Cell survival
BAD
S6K
MTOR
AKT
Chromosome 2p
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STAT3/5
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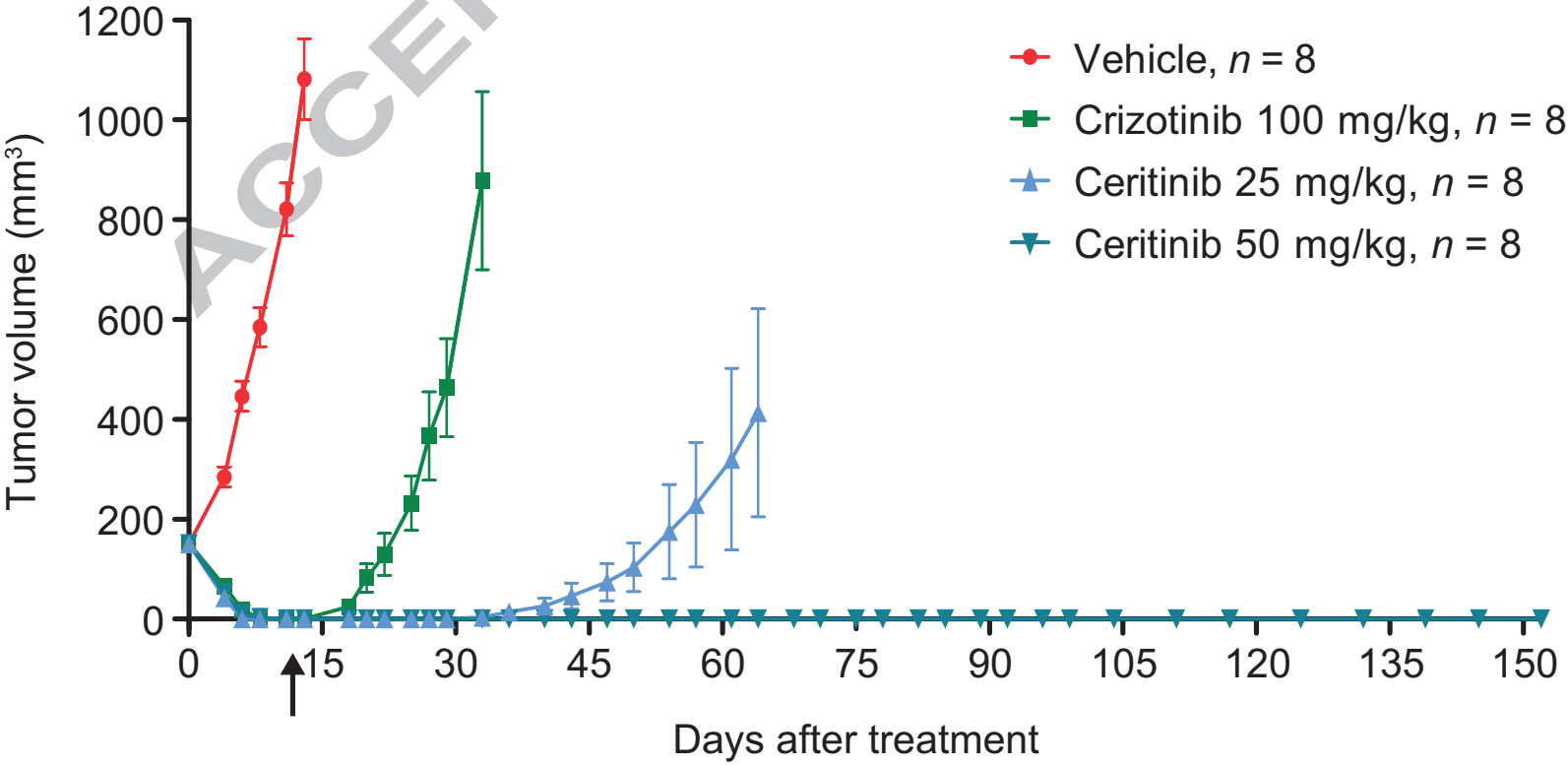

Table 1. Pre-clinical activity of approved and investigational ALK inhibitors [43,58-60].

Drug	**Molecular targets**	**ALK IC_{50}**	***ALK* mutation(s) targeted**
Crizotinib	ALK, MET, ROS1	3 nM	-
Ceritinib	ALK, IGF-1R, ROS1	0.15 nM	L1196M, C1156Y, I1171T
Alectinib	ALK	1.9	L1196M, C1156Y, F1174L
Brigatinib	ALK, EGFR, ROS1	0.62	F1174C, L1196M, F1245C, G1269S
Lorlatinib	ALK, ROS1	1.3	L1196M
X-396	ALK	>0.4	L1196M, C1156Y

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentration; IGF-1R, insulin-like growth factor 1 receptor; MET, mesenchymal-epithelial transition factor; NA, not applicable; ROS1, proto-oncogene receptor tyrosine kinase.

Table 2. Ceritinib overcomes crizotinib-resistant *ALK* mutations in vitro in Ba/F3 models; IC_{50} values in cell survival assay in engineered *EML4-ALK* mutant cells for crizotinib or ceritinib.

	Crizotinib IC_{50} (nM)	**Fold (WT)**	**Ceritinib IC_{50} (nM)**	**Fold (WT)**
Parental	744	48	668	391
WT V1	16	1	1.7	1
L1196M V1	319	20.4	7.5	4.4
G1269A V1	130	8.3	2.2	1.3
S1206Y V1	124	7.9	1.5	0.9
I1171T V1	52	3.4	2.4	1.4
1151Tins V1	561	36	91	53
G1202R V1	221	14	74	43

Adapted with permission from Friboulet L et al. Cancer Discov 2014;4:662–673 [43].

Abbreviations: ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; IC_{50}, half maximal inhibitory concentration; WT, wild type.