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ADIS DRUG EVALUATION

Alectinib: A Review of Its Use in Advanced ALK-Rearranged Non-Small Cell Lung Cancer

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Abstract Alectinib (Alecensa®) is a second-generation, orally active, potent and highly selective inhibitor of anaplastic lymphoma kinase (ALK). Alectinib is approved for the treatment of ALK fusion-gene positive, unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) in Japan, where it has been given orphan drug designation. Approval was based on a phase 1–2 study in ALK inhibitor-naive patients with ALK-rearranged advanced NSCLC who received twice-daily alectinib 300 mg. In the phase 2 portion, 93.5 % of patients achieved an objective response. Treatment response was rapid, with a partial response achieved in two-thirds of patients within 3 weeks (cycle 1). Patient follow-up is ongoing, and after approximately 2 years, 19.6 % of patients had achieved a complete response, and the 2-year progression-free survival rate is 76 %. During treatment with alectinib (median follow-up approximately 8 months), there was no progression of CNS lesions among patients with known CNS metastases at baseline (although prior radiation therapy may have confounded results). In preclinical models, alectinib was active against most ALK fusion-gene mutations related to crizotinib resistance, and preliminary results from clinical trials indicate efficacy in crizotinib-refractory NSCLC. Alectinib was generally well tolerated in clinical trials, and there were no treatment-related grade 4 adverse events or deaths. The most common grade 3 treatment-related adverse events were decreased neutrophil counts and increased creatinine phosphokinase. While more data are needed to confirm the efficacy of alectinib and to evaluate its activity in crizotinib-resistant disease, the drug provides a very promising option for the treatment of ALK-rearranged advanced NSCLC.

Alectinib in advanced, ALK-rearranged, non-small cell lung cancer (NSCLC): a summary

Second-generation, oral, potent, selective inhibitor of ALK
Active in most ALK fusion gene mutations related to crizotinib resistance in preclinical models
Alectinib 300 mg twice daily achieved an objective response in 93.5 % of ALK-inhibitor-naive patients with ALK-rearranged, advanced NSCLC
Preliminary results suggest activity against CNS metastases
Preliminary results indicate efficacy in crizotinib-refractory patients
Generally well tolerated

This article is part of the topical collection on Lung Cancer.

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1 Introduction

Non-small cell lung cancer (NSCLC), which accounts for 84 % of all lung cancer cases in the US, is associated with high rates of mortality [1]. The majority of patients with NSCLC are not diagnosed until the disease is locally advanced (stage IIIA/B) or metastatic (stage IV), and prognosis is poor [1].

The use of molecular targeted therapy in genetically defined subsets of NSCLC patients in the last decade has improved outcomes compared with standard chemotherapy regimens [2]. Several genetic alterations responsible for the initiation or maintenance of NSCLC have been identified as oncogenic drivers, including anaplastic lymphoma kinase (ALK) gene rearrangements [2]. ALK was initially identified as the receptor tyrosine kinase in a novel fusion gene resulting from a chromosomal translocation in anaplastic large cell lymphoma (ALCL) [3]. Increased expression of ALK and ALK rearrangement have also been detected in other tumours, and in 2007 the fusion gene echinoderm microtubule-associated protein-like 4 (EML4)-ALK was identified in 3–6 % of NSCLC cases [3]. ALK rearrangements appear to be more prevalent in NSCLC patients who are relatively young, those who have never or rarely smoked, and tumours with adenocarcinoma histology [4].

Crizotinib was the first ALK inhibitor to be approved for the treatment of ALK-rearranged NSCLC in the US in 2011, with other regions following soon after [3]. Compared with standard chemotherapy regimens, crizotinib achieved dramatically improved results and quickly became the standard of care for patients with ALK-rearranged NSCLC [2, 5]. However, crizotinib is associated with resistance [6], and it penetrates the blood–brain barrier poorly (the brain is a common site of NSCLC metastases) [7, 8], highlighting the need for second-generation ALK inhibitors. The first of these to be approved was ceritinib (in the US in April 2014) [9] and, most recently, alectinib (Alecensa®) was approved for the treatment of ALK-rearranged NSCLC in Japan in July 2014 [10].

This article reviews the pharmacological characteristics, therapeutic efficacy and tolerability of alectinib in patients with locally advanced or metastatic ALK-rearranged NSCLC.

2 Pharmacodynamic Properties

This section provides a brief summary of the pharmacodynamic properties of alectinib, which have been reviewed in detail elsewhere [3, 11].

2.1 General Properties

Alectinib is an orally active, potent and highly selective ALK inhibitor [11, 12]. In cell-free assays, the concentration of alectinib at which 50 % inhibition of ALK enzyme activity (IC_{50}) occurred was 1.9 nM, and the dissociation constant for ALK in an adenosine triphosphate (ATP)-competitive manner was 2.4 nM [11]. Alectinib had weak or no inhibitory activity against protein kinases ($n = 24$) other than tyrosine kinase, and when its activity was compared in a series of kinases (including mutated kinases), only 3 [ALK, cyclin-G-associated kinase (GAK) and leukocyte tyrosine kinase receptor (LTK)] of 402 showed >50 % inhibition at 10 nM [11].

EML4-ALK fusion is mutually exclusive with the appearance of epidermal growth factor receptor (EGFR) or Kirsten rat sarcoma (KRAS) mutations in NSCLC [13]. Alectinib inhibited proliferation of NSCLC cells (NCI-H2228) expressing EML4-ALK, but not ALK fusion-negative NSCLC cell lines including HCC827 cells (EGFR mutation) or A549 cells (KRAS mutant) [11]. Alectinib did not demonstrate antitumour activity against mesenchymal epithelial growth factor (c-MET)-, fibroblast growth factor receptor (FGFR2)-, or ERBB2-amplified cancer cell lines, further demonstrating the drug's selectivity for cancer cells with genetic alterations of ALK [11].

In tumour-bearing mice, oral alectinib once daily induced dose-dependent tumour growth inhibition [the effective dose in 50 % of the group (ED_{50}) was 0.46 mg/kg] and regression in the model of NCI-H2228, which is a NSCLC cell line expressing EML4-ALK [11]. In contrast, in the mouse model of A549, a NSCLC cell line that expresses the KRAS mutant and not ALK fusions, there was almost no antitumour activity following alectinib treatment. In the NCI-H2228 mouse model, alectinib 20 mg/kg resulted in rapid tumour growth inhibition of 168 % compared with controls receiving vehicle ($p < 0.001$) after 11 days of treatment, and after the treatment period there was no tumour regrowth throughout a 4-week drug-free period [11]. Similarly, in another study in mice bearing EML4-ALK-positive xenograft tumours, the efficacy of alectinib 60 mg/kg once daily for 21 days continued beyond treatment, with no tumour regrowth throughout a 4-week drug-free period. In contrast, tumour volume increased during the drug-free period following crizotinib 100 mg/kg/day for 21 days [14].

2.2 Resistance

Alectinib has a unique chemical scaffold that is distinct from the scaffold of other available ALK inhibitors (Fig. 1) and, thus, it may overcome resistance to other ALK inhibitors caused by mutations [14].

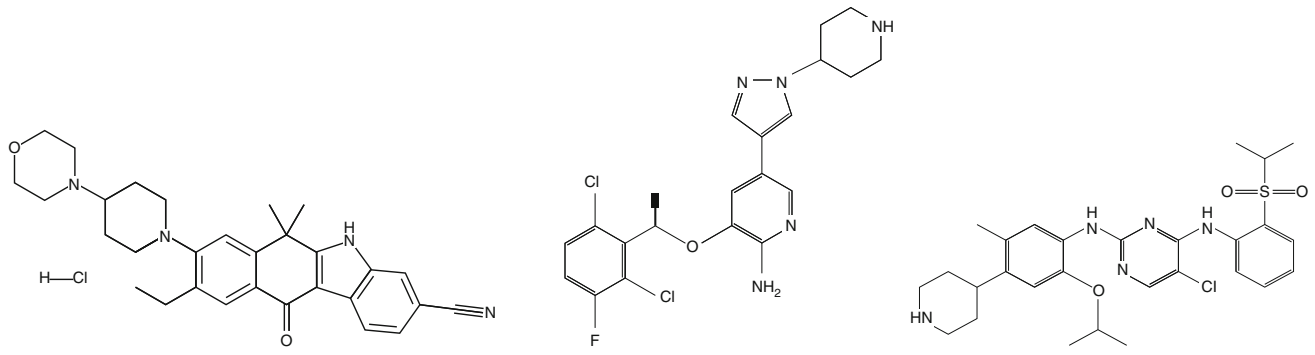

Fig. 1 Chemical structures

In in vitro studies and in preclinical models, alectinib was active against most of the EML4-ALK mutations related to crizotinib resistance [11, 14]. Substantial inhibitory potency was achieved with alectinib using recombinant glutathione S-transferase-fused ALK [inhibitory constant (K_i) = 0.83 nM] and the L1196M gatekeeper mutation of ALK (K_i = 1.56 nM), which is considered to be the most predictable mutation and is associated with resistance to crizotinib [11]. In contrast, the affinity of crizotinib for L1196M was >10-fold weaker than its affinity for native ALK. In cells expressing native EML4-ALK and the L1196M mutant, alectinib blocked cellular phosphorylation of ALK in a concentration-dependent manner [11].

In mice, alectinib treatment achieved significant ($p < 0.001$) tumour regression of native EML4-ALK- and L1196M-driven tumours, whereas, crizotinib did not result in significant growth inhibition of L1196M-driven tumours [11]. Furthermore, alectinib demonstrated potency against tumours remaining after treatment with crizotinib for 21 days in a mouse model of EML4-ALK-positive NCI-H2228 cells [14]. Switching from crizotinib to alectinib resulted in a significant ($p < 0.001$) reduction in tumour size. The apoptosis-inducing potency of alectinib in the NCI-H2228 tumours was higher than crizotinib, as determined by the induced cleavage of an apoptotic marker (PARP) [14].

Alectinib also resulted in brain tumour regression and a survival benefit in an intracranial tumour implantation mouse model of the NCI-H2228 cell line [15]. After 4 days of treatment with oral alectinib 60 mg/kg, intracranial tumours were significantly decreased versus vehicle treated mice ($p < 0.0001$). In contrast, in mice treated with oral crizotinib 100 mg/kg, there was no significant change in tumour size compared with the vehicle-treated group. Survival time in the alectinib group was significantly longer than in the crizotinib ($p = 0.0065$) or vehicle ($p = 0.006$) groups [15].

Alectinib demonstrated substantial inhibitory potency against cells expressing EML4-ALK G1269A (the second most common resistance mutation), C1156Y, F1174L, 1151Tins and L1152R, but was less potent against the ALK G1202R mutation, all of which have been associated with resistance to crizotinib [14]. Similarly, in mice bearing tumours driven by ALK mutations related to crizotinib resistance, alectinib was effective against each mutant-driven cell except for the cell line expressing G1202R, and the IC_{50} ratio of each cell line expressing EML4-ALK mutations, except for ALK G1202R, to the parent Ba/F3 cell line was higher with alectinib (8.3- to 57-fold) than crizotinib (1.3- to 5.1-fold) [14]. Furthermore, treatment with alectinib 60 mg/kg resulted in significant tumour regression of EML4-ALK G1269 driven tumours but not EML4-ALK G1202R driven tumours, whereas crizotinib 100 mg/kg caused no tumour growth inhibition of either of these EML4-ALK mutant-driven tumours [14]. Case study reports of patients with ALK-rearranged NSCLC who progressed on crizotinib confirm that the ALK G1202R mutation confers high-level resistance to alectinib [16].

Results of an in vitro study suggest that resistance to alectinib may develop [17]. Exogenously added receptor ligands of EGFR and HGF (a ligand of the MET receptor) reduced the susceptibility of ALK-rearranged NSCLC cells (NCI-H2228) to alectinib, indicative of a resistance mechanism via activation of bypass signals triggered by these receptor ligands [17].

3 Pharmacokinetic Properties

In the phase 1 portion ($n = 24$) of a phase 1–2 study in ALK inhibitor-naive patients in Japan, escalating dosages of alectinib 20–300 mg twice daily were administered in fasting (20–300 mg doses) and non-fasting (240 and 300 mg doses) conditions; dosage was capped at 300 mg twice daily based on information regarding the additive formulation in Japan [18]. At steady state (day 21 of cycle 1) and in fasting conditions, the maximum plasma level

(C_{max}) was reached at 2.00–4.61 h, and the area under the plasma concentration–time curve (AUC) from time zero to 10 h increased in an approximately linear manner [18]. Plasma exposure at steady state was similar in fasting and nonfasting conditions; however, the time to reach C_{max} (t_{max}) was greater in nonfasting conditions (Table 1). Based on the results of the phase 1 portion of this trial, the highest dosage of twice-daily alectinib 300 mg was selected for the phase 2 portion. Table 1 illustrates the pharmacokinetic parameters of the 300 mg dosage. No dose-limiting toxicities were observed with alectinib dosages of up to 300 mg twice daily, and the maximum tolerated dose was not identified [18].

Alectinib is primarily metabolized by the cytochrome P450 (CYP) 3A4 enzyme, and most of the drug is excreted in the faeces [10].

Because of the selection of the highest alectinib 300 mg dosage for ongoing treatment, a higher strength 150 mg capsule is being developed to reduce the number of capsules required for a therapeutic dose [19]. The exposure of 2 × 150 mg capsules was similar to that of 7 × 40 plus 1 × 20 mg capsules in a crossover, bioequivalence study in Japanese patients ($n = 34$) with ALK-rearranged advanced NSCLC with or without prior crizotinib treatment (reported in an abstract and poster) [19]. At steady state, the effect of food on the pharmacokinetics of the alectinib 150 mg capsule was considered to be negligibly small, although exposure (C_{max} and AUC) was ≈20 % higher in nonfasting than in fasting conditions.

In the phase 1, dose-escalating portion of an ongoing US phase 1–2 study in patients ($n = 47$) refractory to crizotinib who received alectinib 300–900 mg twice daily, the 600 mg twice-daily dosage was determined as the recommended dosage for the phase 2 portion [20]. The mean AUC_{10} of alectinib after multiple dosages of 300–600 mg twice daily was dose dependent.

Table 1 Pharmacokinetics of alectinib at steady state in patients with ALK-rearranged advanced non-small cell lung cancer. Results are from the phase 1 portion of an open-label, multicentre phase 1–2 study [18]

Parameter[a]	Alectinib 300 mg bid	
	Fasting[b] ($n = 6$)	Non-fasting ($n = 6$)
C_{max} (ng/mL)	575	528
C_{trough} (ng/mL)	463	425
AUC_{10} (ng·h/mL)	4,970	4,220
t_{max} (h)	3.99	5.32

AUC_{10} area under the plasma concentration-time curve from time zero to 10 h, *bid* twice daily, *C_{max}* maximum plasma concentration, *C_{trough}* minimum plasma concentration, t_{max} time to C_{max}

[a] Parameters were measured after 21 days' treatment

[b] Patients fasted for 2 h prior to alectinib administration and 1 h after

4 Clinical Evaluation

This section focuses on the use of oral alectinib in an open-label, single-arm, multicentre phase 1–2 study in ALK-inhibitor-naive patients with ALK-rearranged, advanced NSCLC in Japan [18]. The phase 1 portion evaluated escalating doses of twice-daily alectinib 20–300 mg (Sect. 3), and in the phase 2 portion, patients received twice-daily alectinib 300 mg without food [18]. Treatment was given until disease progression, intolerable adverse effects or withdrawal of consent. Tumours were assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 at the end of each 21-day cycle for four cycles and every two cycles thereafter.

All patients had received ≥1 prior chemotherapy regimen for metastatic disease [18]. The mean age of patients in the phase 2 portion was 48 years, and 59 % had never smoked. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 was required for eligibility, and 57 % had an ECOG performance status of 1. ALK fusion gene expression was tested using immunohistochemistry (IHC) and confirmed using fluorescence in-situ hybridization (FISH); reverse transcription polymerase chain reaction was also used for some samples [18].

The phase 1 portion of the study primarily evaluated pharmacokinetic parameters (Sect. 3) and safety [18]. In the phase 2 portion, the primary endpoint was the objective response rate [comprising complete (tumour disappears) and partial response (>30 % tumour shrinkage)], which was determined by an independent review committee and confirmed by a subsequent scan [18]. Analyses were performed in the intent-to-treat population. Preliminary results of studies evaluating the efficacy of alectinib in patients pretreated with crizotinib are also briefly discussed (Sect. 4.2) [19, 21].

4.1 ALK-Inhibitor-Naive Patients

In the phase 1 portion ($n = 24$) of the phase 1–2 study, all 20 patients with measurable lesions at baseline achieved tumour shrinkage, with 17 (85 %) achieving a partial response [18]. All patients who received dosages of alectinib >160 mg twice daily achieved at least a partial response. The mean duration of alectinib treatment was 11.8 months (range 3–18 months), with a median follow-up period of 12.05 months.

In the phase 2 portion (all 46 patients had measurable disease at baseline), after a median follow-up of 7.6 months, an objective response was achieved in 93.5 % of patients, and disease control (complete or partial response or stable disease) was achieved in 95.7 % [18]. Two (4.3 %) patients achieved a complete response, 41 (89.1 %) had a partial response, and none had progressive

disease (two patients who withdrew early had an unknown response) (Fig. 2).

Response to treatment was observed early, with a partial response achieved in 30 (65 %) patients within 3 weeks (cycle 1) and 40 (87 %) patients within 6 weeks (cycle 2) [18].

Patient follow-up is ongoing, and precise estimation of progression-free survival is yet to be determined [18]. Results were recently presented after follow-up of approximately 2 years (reported in an abstract [22]), at which time the objective response rate remained at 93.5 %, with nine (19.6 %) patients achieving a complete response. Disease had progressed in 12 patients (26.1 %), nine had died, and the 2-year progression-free survival rate is 76 %. As of February 2014, 31 of 46 patients continued to receive alectinib (one beyond disease progression) [22].

In a post-hoc analysis of response, the authors reported no differences based on age, sex, ECOG performance status, body mass index, number of previous chemotherapy regimens for metastatic disease, history of treatment with pemetrexed, types of ALK assay, and status of brain metastases, but data were not shown [18].

During treatment with alectinib, there was no progression of CNS lesions among patients with known CNS metastases at baseline [15 (33 %) patients]; 12 patients had radiotherapy prior to treatment, which may have affected outcomes by controlling the brain metastases [18]. Two of the three patients who had not received prior radiation continued alectinib for >300 days without progression of brain metastases.

4.2 Patients Previously Treated with Crizotinib

Of the 24 crizotinib-pretreated patients (including 20 who had failed crizotinib treatment) with measurable disease at baseline in the Japanese bioequivalence study (Sect. 3), 14 (58.3 %) achieved a partial response with alectinib 300 mg twice daily; tumours were assessed on days 31 and 59, and then every 56 days [19]. In addition, three patients had an unconfirmed partial response and three patients had stable disease. Figure 3 illustrates tumour shrinkage achieved in individual patients based on previous treatment. A more recent review of this patient group (median follow-up 141 days) reported that 13 patients, four with prior brain irradiation, continued on study treatment without progression (reported in an abstract) [23].

In the efficacy assessment of the phase 1 portion of an on-going US phase 1–2 study in patients ($n = 44$) with crizotinib-refractory NSCLC receiving alectinib 300–900 mg twice daily, the objective response rate at a median follow-up of 126 days was 55 %, with one (2 %) confirmed complete response, and 14 (32 %) confirmed and nine (20 %) unconfirmed partial responses [20]. In addition, 16 (36 %) patients had stable disease and the remaining four (9 %) had progressive disease. Among the 21 patients with CNS metastases at baseline, the objective response rate was 52 %, according to independent radiological review. Six (29 %) patients had a complete response (three unconfirmed), five (24 %) had partial responses (one unconfirmed), eight (38 %) had stable disease and the remaining two (10 %) had progressive disease [20].

5 Tolerability

Twice-daily alectinib 300 mg was generally well tolerated in the phase 1–2 study [18] and the bioequivalence study [19], and no grade 4 adverse events or deaths were reported during either trial.

In the phase 2 portion of the phase 1–2 study, serious treatment-related adverse events occurred in four (9 %) patients, including radius fracture, tumour haemorrhage, sclerosing cholangitis, and allergic alveolitis; one patient

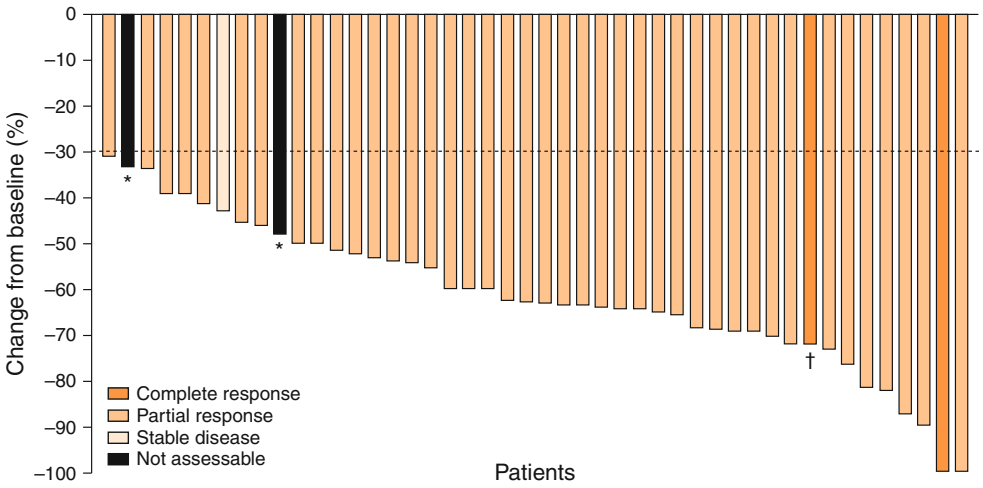

Fig. 2 Waterfall plot showing best percentage change in tumour size from baseline in individual ALK-inhibitor-naive patients ($n = 46$) with ALK-rearranged non-small cell lung cancer who received twice-daily alectinib 300 mg [18]. *Asterisk* indicates indeterminate response after early discontinuation due to safety reasons. *Dagger* indicates complete response according to RECIST criteria. Reproduced from Seto et al. [18], with permission

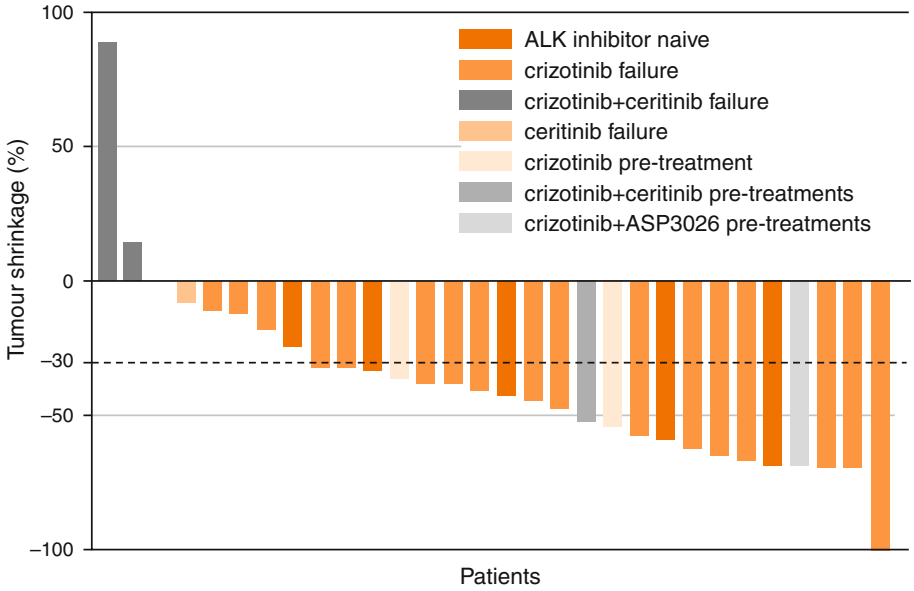

Fig. 3 Waterfall plot showing tumour shrinkage achieved with alectinib 300 mg twice daily based on previous therapy in patients with ALK-rearranged non-small cell lung cancer. Reproduced from Nakagawa et al. [19], with permission

experienced brain oedema, which was not thought to be related to treatment [18]. Four patients discontinued alectinib due to adverse events, and treatment was suspended for <21 days due to adverse events in 22 (48 %) patients, none of whom required dose reduction [18].

Most patients (93 %) experienced a treatment-related adverse event, but 94 % of all events (118 of 125) were of grade 1 or 2 in severity [18]. The most common treatment-related adverse events were dysgeusia (all grade 1), increased AST and increased bilirubin levels (Fig. 4). Interestingly, the rash (almost all cases were grade 1 or 2) related to alectinib was different to that associated with EGFR tyrosine kinase inhibitors. After approximately 2 years of alectinib treatment, the tolerability profile was similar to that reported previously [22].

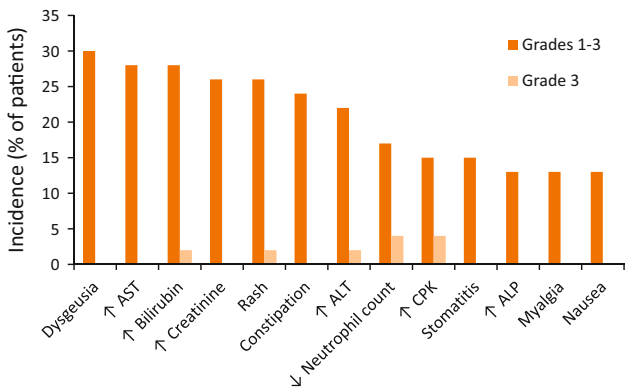

Fig. 4 Treatment-related adverse events associated with twice-daily alectinib 300 mg in patients with ALK-rearranged advanced non-small cell lung cancer. Adverse events reported in ≥10 % of patients ($n = 46$) in the phase 2 portion of a phase 1–2 study [18]. *ALP* alanine phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CPK* creatinine phosphokinase

6 Dosage and Administration

In Japan, alectinib is approved for the treatment of ALK fusion-gene positive, unresectable, advanced or recurrent NSCLC [10]. The recommended adult dosage in Japan is 300 mg twice daily orally [10]. However, the maximum tolerated dose was not identified in the phase 1 portion of the Japanese phase 1–2 study, and in ongoing international, phase 2 and 3 trials, patients are receiving twice-daily alectinib 600 mg. The effect of ethnic differences on the pharmacokinetics of alectinib is being evaluated in an ongoing trial (NCT01588028).

ALK-positive NSCLC should be confirmed with an approved diagnostic test using FISH and IHC procedures [10]. It is recommended that alectinib be taken on an empty stomach, and treatment should be continued until disease progression or unacceptable toxicity. The efficacy and safety of alectinib have not been confirmed in patients not previously treated with chemotherapy [10].

The prescribing information should be consulted for further information regarding contraindications, warnings and precautions, as well as for recommended dose adjustments in patients experiencing treatment-related toxicities.

7 Current Status of Alectinib in Non-Small Cell Lung Cancer

Alectinib has orphan drug status in Japan and is in phase 2 development in the US, where the drug has breakthrough therapy designation.

In the phase 2 portion of the open-label, multicentre, Japanese trial in ALK inhibitor-naive patients with ALK-

rearranged, advanced NSCLC, alectinib achieved very high objective response rates and was generally well tolerated. Patient follow-up is ongoing, and the 2-year progression-free survival rate is 76 %. Also in this study, there was no progression of brain metastases during alectinib therapy indicative of effective CNS penetration and activity, although more data are needed to confirm its efficacy in patients with CNS disease. Alectinib had preclinical activity against most ALK fusion gene mutations related to crizotinib resistance and preliminary results in clinical trials indicate efficacy in crizotinib-refractory NSCLC. Thus, alectinib may offer a therapeutic option for patients with acquired resistance to crizotinib. However, resistance to alectinib is also likely in some patients, and an important aspect of ongoing care will be to develop personalized treatment strategies according to resistance mechanisms [24].

Ceritinib, the other second-generation ALK-inhibitor, has also demonstrated activity in ALK-inhibitor-naive and crizotinib-refractory patients with ALK-rearranged advanced NSCLC [8]. How alectinib and ceritinib will compare in the treatment of these patient populations remains to be seen.

On-going studies will provide valuable evidence that will assist in positioning alectinib and other ALK inhibitors in treatment algorithms. For example, phase 3 trials [one multinational (ALEX; NCT02075840) and one in Japan (JapicCTI-132316)] are currently comparing alectinib and crizotinib in ALK-inhibitor-naive patients with ALK-rearranged NSCLC.

While more data are needed to confirm the efficacy of alectinib and to evaluate its activity in crizotinib-resistant disease, the drug provides a very promising option for the treatment of ALK-rearranged advanced NSCLC.

Data selection sources: Relevant medical literature (including published and unpublished data) on alectinib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 3 November 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

Search terms: Alectinib, AF802, CH5424802, RG7853, RO5424802.

Study selection: Studies in patients with non-small cell lung cancer who received alectinib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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