

# FDA Approval: Alectinib for the Treatment of Metastatic, ALK-Positive Non-Small Cell Lung Cancer Following Crizotinib

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## Abstract

On December 11, 2015, the FDA granted accelerated approval to alectinib (Alecensa; Genentech) for the treatment of patients with anaplastic lymphoma receptor tyrosine kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This approval was based on two single-arm trials including 225 patients treated with alectinib 600 mg orally twice daily. The objective response rates (ORR) by an independent review committee in these studies were 38% [95% confidence interval (CI), 28–49] and 44% (95% CI, 36–53); the median durations of response (DOR) were 7.5 months and 11.2 months. In a pooled analysis of 51 patients with measurable disease in the central nervous system (CNS) at baseline, the CNS ORR was 61% (95% CI, 46–74); the CNS DOR was 9.1 months. The primary safety analysis population included 253 patients. The most com-

mon adverse reactions were fatigue (41%), constipation (34%), edema (30%), and myalgia (29%). The most common laboratory abnormalities were anemia (56%), increased aspartate aminotransferase (51%), increased alkaline phosphatase (47%), increased creatine phosphokinase (43%), hyperbilirubinemia (39%), hyperglycemia (36%), increased alanine aminotransferase (34%), and hypocalcemia (32%). Dose reductions due to adverse reactions occurred in 12% of patients, whereas 27% of patients had alectinib dosing interrupted for adverse reactions. Permanent discontinuation of alectinib due to adverse reactions occurred in only 6% of patients. With the clinically meaningful ORR and DOR as well as the safety profile observed in these trials, alectinib was determined to have a favorable benefit-risk profile for the treatment of the indicated population. *Clin Cancer Res*; 22(21); 5171–6. ©2016 AACR.

## Introduction

A 2007 report first described the finding that tumors in a small number of patients with non-small cell lung cancer (NSCLC) harbored a rearrangement in the anaplastic lymphoma receptor tyrosine kinase (ALK) gene and the echinoderm microtubule-associated protein-like 4 (EML4) gene (referred to hereafter as "ALK rearrangement;" ref. 1), resulting in an EML4-ALK fusion protein that in preclinical studies demonstrated the potential to result in malignant transformation (2). Based on this observation, clinical development of ALK inhibitors was pursued in hopes of developing more effective treatments for the estimated 2% to 7% of NSCLC patients with tumors harboring ALK rearrangements (3). Some patient and tumor risk factors that appear to be associated with the presence of ALK rearrangement are younger age, light- or never-smoking status, adenocarcinoma histology,

and stage IV disease (3). ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component (4).

Crizotinib, a multitargeted tyrosine kinase inhibitor that targets ALK, was the first kinase inhibitor approved for the treatment of ALK-positive, metastatic NSCLC. The FDA granted accelerated approval of crizotinib in 2011 (5) and traditional approval of crizotinib in 2013 (6, 7). Acquired resistance to crizotinib develops in the majority of tumors during treatment with crizotinib. Mechanisms of resistance include mutations in the ALK tyrosine kinase domain and activation of alternative signaling pathways (8–10). In addition to resistance, another mechanism of treatment failure is the development of brain metastases. A retrospective analysis of two studies assessing crizotinib for the treatment of patients with advanced ALK-positive NSCLC reported that, among patients without brain metastases at the time of enrollment who developed progressive disease, 20% developed brain metastases (11).

In April 2014, the FDA granted accelerated approval to ceritinib, an ALK inhibitor, for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib. In the single-arm trial providing the primary data that led to the approval of ceritinib, the objective response rate (ORR) was 44%, with a median duration of response of 7.4 months (12, 13). Approximately 60% of patients required at least one dose reduction, and dose modification related to gastrointestinal (GI) toxicities of diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients (12).

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Alectinib is a tyrosine kinase inhibitor that targets ALK and ret proto-oncogene (RET) kinase. In June 2013, the FDA granted alectinib breakthrough therapy designation based on the preliminary evidence of clinical activity in patients with metastatic, ALK-positive NSCLC previously treated with crizotinib, including activity in patients with central nervous system (CNS) metastases. The FDA review of the new drug application (NDA) for alectinib for this indication is summarized in this article.

## Chemistry, Manufacturing, and Control

Alectinib is a low solubility drug. Alecensa (Genentech) 150-mg oral capsules do not exhibit rapid dissolution across the physiologic pH range (14). The capsule formulation containing sodium lauryl sulfate (SLS; as solubilizing agent) was administered in the two efficacy clinical trials [studies NP28761 (NCT01871805) and NP28673 (NCT01801111)]. SLS is a surfactant and a known GI mucosal irritant that may be associated with GI adverse effects, including nausea, vomiting, diarrhea, and abdominal pain. The recommended dose of alectinib (600 mg twice daily) results in oral ingestion of an amount of SLS daily that is higher than the amount of SLS previously approved by the FDA in other oral products. Therefore, the concentration of SLS posed a regulatory challenge. To support the necessity of this concentration of SLS, Roche/Genentech conducted additional studies demonstrating that the bioavailability of alectinib was decreased below a minimal concentration of SLS. Roche/Genentech will continue to closely monitor the incidence of GI disorders in clinical studies and postmarketing settings.

## Nonclinical Pharmacology and Toxicology

Pharmacology studies demonstrated that alectinib is a reversible kinase inhibitor that targets ALK and RET. In an *in vitro* screening assay, alectinib did not result in inhibition of other kinases, including ROS1, at clinically significant concentrations. Alectinib suppressed activation of ALK and was able to inhibit mutated versions of ALK that have been identified in patients whose disease has progressed following treatment with crizotinib. In addition, the major metabolite of alectinib, M4, identified at high levels in both humans and animals, showed comparable inhibitory activity against ALK and RET.

Alectinib administration resulted in inhibition of tumor growth in mice implanted intracranially with the NCI-H2228 tumor cell line carrying an EML4-ALK fusion protein, suggesting that alectinib can cross the blood-brain barrier and may have activity against brain metastases. Alectinib had broad tissue distribution, including the brain; levels of radioactivity in brain tissues were similar to those in the plasma of animals administered radiolabeled alectinib, further supporting penetration of alectinib across the blood-brain barrier.

The predominant target organs of alectinib toxicity in the rat and monkey were the GI tract, adrenal gland, liver, and respiratory system. Alectinib was phototoxic, aneugenic in *in vivo* micronucleus assays, and embryotoxic at maternally toxic doses. Cardiovascular assessments in monkeys suggested a potential for bradycardia and hypotension (15).

## Clinical Pharmacology

In patients with ALK-positive NSCLC, alectinib exposure increased in a dose-proportional manner at doses ranging from

460 mg to 900 mg under fed conditions after a single dose and after repeated doses. Its exposure accumulated about 6-fold at steady state with twice-daily dosing. The administration of a single 600-mg dose with an FDA-specified high-fat, high-calorie meal resulted in a 3.1-fold increase in the combined exposure of alectinib and its major similarly active metabolite, M4. The approved product labeling recommends that alectinib be taken with food to improve bioavailability and GI tolerability. The elimination half-life is 33 hours for alectinib and 31 hours for M4. No clinically meaningful effect on the combined exposure of alectinib plus M4 was observed in clinical studies following coadministration of alectinib with a strong CYP3A inhibitor (posaconazole), a strong CYP3A inducer (rifampin), or an acid-reducing agent (esomeprazole). No dose adjustment is recommended for patients with mild hepatic impairment or mild-to-moderate renal impairment (16). A study (NCT02621047) is ongoing to determine an appropriate dose for patients with moderate to severe hepatic impairment.

## Clinical Trial Design

Two multicenter, single-arm trials (studies NP28761 and NP28673) provided the primary clinical data for the review of the alectinib NDA. Both were designed to include dose-escalation and dose-expansion parts; however, the recommended phase II dose for alectinib was determined in NP28761 prior to dose escalation in NP28673. Inclusion criteria for both studies included age  $\geq 18$  years, metastatic or stage IIIB NSCLC not amenable to curative therapy, documented ALK rearrangement based on an FDA-approved test, progression of disease on crizotinib, Eastern Cooperative Oncology Group (ECOG) performance status (PS)  $\leq 2$ , and adequate organ function. At the time these studies were conducted, FDA-approved testing for ALK rearrangement involved fluorescence *in situ* hybridization performed on formalin-fixed, paraffin-embedded tissue specimens. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available on the FDA website (17).

The primary endpoint for both studies was ORR as determined by central independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1). In addition to duration of response (DOR), secondary endpoints included CNS objective response rate (CORR) and CNS duration of response (CDOR) in patients with measurable disease in the CNS at baseline assessed by IRC neurological specialized radiologists using both RECIST v1.1 and Response Assessment in Neuro-Oncology (RANO) criteria (18). Safety evaluations included physical examinations, laboratory evaluations, electrocardiograms, and assessment of adverse events. During the course of the studies, the primary analysis population for response endpoints was modified to the Response Evaluable (RE) population, defined as patients with measurable disease at baseline by IRC assessment who received at least one dose of alectinib.

## Efficacy

There were 87 patients enrolled in the expansion portion of NP28761 and 138 patients in NP28673 who received alectinib 600 mg twice daily; this "As Treated" population comprises the primary efficacy population evaluated by the FDA. Demographic and disease characteristics are presented in Table 1. The RE

**Table 1.** Demographic and baseline disease characteristics of patients in the "As Treated" populations for studies NP28761 and NP28673

Characteristic	NP28761 (N = 87)	NP28673 (N = 138)
Median age, years (range)	54 (29–79)	52 (22–79)
Age ≥65 years	18%	10%
Race		
Caucasian	84%	67%
Asian	8%	26%
Gender		
Female	55%	56%
Male	45%	44%
ECOG PS 0 or 1	90%	91%
Never or former smokers	100%	98%
Adenocarcinoma histology	94%	96%
Prior chemotherapy	74%	80%
Stage IV disease	99%	99%
Brain metastases	60%	60%
Measurable <sup>a</sup> brain metastases	18%	25%

<sup>a</sup>Measurable by RECIST v1.1 criteria.

population proposed by Roche/Genentech as the primary analysis population excluded 18 patients (21%) in NP28761 and 16 patients (12%) in NP28673 who did not have measurable disease at baseline per IRC assessment. By RECIST criteria, patients without measurable disease at baseline whose disease has not progressed can be qualified as having either complete response or stable disease; an assessment of partial response is not possible in the setting of no baseline measurable disease. With this knowledge, the decision was made to include ORR in the "As Treated" population per both IRC and investigator assessment in product labeling. ORR and DOR results are presented in Table 2.

Results of pooled analyses of CNS-related secondary endpoints in patients with measurable disease in the CNS at baseline are presented in Table 3. An exploratory analysis of CORR and CDOR in patients with and without a history of prior CNS radiation was conducted by the FDA. CNS responses were observed in both patients who had ( $n = 35$ ) and had not ( $n = 16$ ) received prior CNS radiation (CORR 57% and 69%, respectively), and CDOR was similar across these subgroups (19).

## Safety

The primary safety analysis population included 253 patients from NP28761 and NP28673 exposed to alectinib at a dose of 600 mg twice daily. The median age was 53 years, 14% of patients were ≥65 years old, 74% were Caucasian, and 18% were Asian. Baseline characteristics were otherwise similar to those of the efficacy populations. Median duration of exposure was 9.3 months. Common adverse reactions and laboratory abnormalities are presented in Table 4. Grades 3 to 4 adverse

reactions and laboratory abnormalities occurring in ≥2% of patients are presented in Table 5. Other adverse reactions of interest based on reported adverse reaction profiles for agents of the same class include vision disorder (10%), bradycardia (7.5%), interstitial lung disease/pneumonitis (0.4%), and prolonged QT interval (0.4%).

Serious adverse reactions occurred in 19% of patients; the most frequently reported were pulmonary embolism, dyspnea, and hyperbilirubinemia, each occurring in 3 patients (1.2%). The incidence of fatal adverse reactions was 2.8%; death was attributed to hemorrhage in 2 patients and to intestinal perforation, dyspnea, pulmonary embolism, and endocarditis in 1 patient each. Dose reductions due to adverse reactions occurred in 12% of patients, whereas 27% of patients had alectinib dosing interrupted due to adverse reactions. Grades 3 to 4 AST and/or ALT elevations led to discontinuation of alectinib in 4 patients (1.6%), and grade 3 bilirubin elevations led to discontinuation in 3 patients (1.2%). While no Hy's law cases were identified among patients with elevated liver function tests, 2 patients (0.8%) with grades 3 to 4 AST/ALT elevations had documented drug-induced liver injury based on liver biopsy. The U.S. Prescribing Information (USPI) for alectinib recommends monitoring liver laboratory tests every 2 weeks during the first 2 months of treatment, and then periodically during treatment.

Grade 3 myalgia, defined as a composite term incorporating the preferred terms myalgia and musculoskeletal pain, occurred in 3 patients (1.2%). Of these, only one had creatine phosphokinase (CPK) measured close to the time of the event; this patient had grade 3 CPK elevation. Based on laboratory shift data, CPK elevations occurred in 43% of 218 patients with CPK laboratory data available. Ten patients (4.6%) experienced grade 3 CPK elevation; among these patients, concomitant myalgia was reported in 3 (one grade 3, two grade 1), whereas the remaining patients were asymptomatic (15). There were no cases of grade 4 myalgia or CPK elevation, and there were no cases meeting the criteria for rhabdomyolysis as defined by the National Cholesterol Education Program Advisory Panel (CPK >10 times the upper limit of normal, with renal compromise; ref. 20). These events were adequately managed with interruption and/or dose reduction of alectinib, and no patient discontinued alectinib due to myalgia or CPK elevation. The USPI for alectinib recommends measurement of CPK every 2 weeks during the first month of treatment and in patients reporting unexplained muscle pain, tenderness, or weakness.

## Discussion

Alectinib received accelerated approval based on determination of a favorable benefit–risk profile considering the surrogate endpoint of ORR along with duration of response and the safety profile of alectinib as determined in two single-arm trials.

**Table 2.** Efficacy results in studies NP28761 and NP28673

Efficacy parameter	NP28761 (N = 87)		NP28673 (N = 138)	
	IRC assessment <sup>a</sup>	Investigator assessment	IRC assessment <sup>a</sup>	Investigator assessment
ORR (95% CI)	38% (28–49)	46% (35–57)	44% (36–53)	48% (39–57)
Number of responders	33	40	61	66
Median DOR, months (95% CI)	7.5 (4.9–NE)	NE (4.9–NE)	11.2 (9.6–NE)	7.8 (7.4–9.2)
Median duration of follow-up, months	4.8	4.8	10.9	7.0

Abbreviations: CI, confidence interval; NE, not estimable.

<sup>a</sup>Eighteen patients in NP28761 and 16 patients in NP28673 did not have measurable disease at baseline as per IRC assessment and were classified as nonresponders in the IRC analysis.

**Table 3.** CNS efficacy endpoints' pooled analyses (NP28761 and NP28673)

Efficacy parameter	Patients with measurable CNS disease at baseline (n = 51)	
	RECIST v1.1 criteria	RANO criteria
CORR (95% CI)	61% (46–74)	51% (35–67)
Median CDOR, months (95% CI)	9.1 (5.8–NE)	9.1 (7.4–NE)

Abbreviations: CI, confidence interval; NE, not estimable.

Limitations of single-arm trials include the potential for known and unknown patient selection bias and the lack of controlled safety data. Continued approval for this indication requires verification of clinical benefit in a confirmatory trial. The confirmatory trial (the ALEX study, NCT02075840), assessing alectinib versus crizotinib in treatment-naïve patients with ALK-positive, advanced NSCLC, is currently ongoing. The results of a randomized trial conducted in Japan, J-ALEX, that assessed alectinib 300 mg twice daily versus crizotinib in 207 ALK inhibitor-naïve patients with ALK-positive NSCLC were recently reported to show a progression-free survival advantage for alectinib over crizotinib (21). The ALEX study will determine whether similar findings are observed in a global population treated with alectinib 600 mg twice daily.

For NSCLC, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (22, 23). The observed ORRs of 38% and 44% by IRC-based assessment in NP28761 and NP28673, respectively, are clinically meaningful when considering the intended patient population: patients with ALK-positive NSCLC who have progressed following therapy with crizotinib. The DOR data bolster the assessment of a clinically meaningful benefit. Demonstration of significant clinical benefit compared with ceritinib was not required for alectinib, as ceritinib was approved under accelerated approval.

In addition to ORR and durability, the effects on CNS metastases were strongly supportive. The incidence of brain metastases in NSCLC patients has been reported as 16% to 36% in various population-based and cohort studies (24–27). In a randomized trial of crizotinib for the first-line treatment of ALK-positive NSCLC, 27% of patients had brain metastases at the time of enrollment (28). In addition, a retrospective analysis of two

**Table 4.** Common adverse reactions (incidence  $\geq$ 20%) and laboratory abnormalities (incidence  $\geq$ 30%) in NP28761 and NP28673

Alectinib 600 mg b.i.d. (n = 253)	
Adverse reaction	All grades
Fatigue	41%
Constipation	34%
Edema	30%
Myalgia	29%
Laboratory abnormality	
Anemia	56%
Increased aspartate aminotransferase	51%
Increased alkaline phosphatase	47%
Increased creatine phosphokinase <sup>a</sup>	43%
Hyperbilirubinemia	39%
Hyperglycemia <sup>b</sup>	36%
Increased alanine aminotransferase	34%
Hypocalcemia	32%

Abbreviation: b.i.d., twice daily.

<sup>a</sup>n = 218 for creatine phosphokinase (with baseline values missing for 91 of these patients).

<sup>b</sup>n = 152 for fasting blood glucose (with baseline values missing for 5 of these patients).

**Table 5.** Most common grades 3–4 adverse reactions and laboratory abnormalities (incidence  $\geq$ 2%) in NP28761 and NP28673

Alectinib 600 mg b.i.d. (n = 253)	
Adverse reaction	Grades 3–4
Dyspnea <sup>a</sup>	3.6%
Laboratory abnormality	
Increased alanine aminotransferase	4.8%
Increased creatine phosphokinase <sup>b</sup>	4.6%
Lymphopenia <sup>c</sup>	4.6%
Hypokalemia	4.0%
Increased aspartate aminotransferase	3.6%
Hypophosphatemia	2.8%
Hyperbilirubinemia	2.4%
Hyperglycemia <sup>d</sup>	2.0%
Hyponatremia	2.0%
Anemia	2.0%

Abbreviation: b.i.d., twice daily.

<sup>a</sup>Includes one grade 5 event.

<sup>b</sup>n = 218 for creatine phosphokinase (with baseline values missing for 91 of these patients).

<sup>c</sup>n = 217 for lymphocytes (with baseline values missing for 5 of these patients).

<sup>d</sup>n = 152 for fasting blood glucose (with baseline values missing for 5 of these patients).

studies assessing crizotinib for the treatment of patients with advanced, ALK-positive NSCLC reported that among patients without brain metastases at the time of enrollment who developed progressive disease, 20% were diagnosed with brain metastases (11). In NP28761 and NP28673, 60% of patients had CNS metastases at baseline; this high proportion is not surprising in a population of patients with metastatic, ALK-positive NSCLC previously treated with crizotinib. It is also possible that patients with brain metastases were preferentially referred to these studies based on preclinical and early clinical evidence of possible antitumor activity in the CNS with alectinib (29–31). Assessment of the treatment effect of alectinib in the CNS was prospectively undertaken in NP28761 and NP28673. The assessment of CNS disease by an IRC composed of neuroradiologists increased confidence in the validity of these assessments, as did the consistency of the observed treatment effect using RECIST v1.1 and RANO criteria.

Despite a high concentration of SLS, a known GI mucosal irritant, in the studied formulation of alectinib, the GI adverse event profile did not negatively affect the tolerance of alectinib. Based on the review of the safety data for alectinib, dose-modification recommendations for grades 3 and 4 CPK elevations were included in product labeling, as were recommendations for assessment of CPK during treatment with alectinib. The high incidence of CPK elevation observed with alectinib was not expected based on preclinical toxicology data and the reported safety profiles of the approved ALK inhibitors, crizotinib and ceritinib. It should be noted that CPK is not routinely included in the serum chemistry tests done during clinical trials of oncology drugs. CPK was included as part of routine laboratory testing in NP28761 from the beginning, but was not added in NP28673 until partway through the study. The ongoing ALEX study includes CPK as part of the serum chemistry panel obtained throughout treatment on study. This will help to more accurately define the incidence of CPK elevation for both alectinib and crizotinib, and allow for a direct comparison.

Whether treatment of patients with ALK-positive NSCLC with alectinib in the first-line setting can delay occurrence or

progression of disease in the CNS compared with first-line treatment with crizotinib is not currently known. Time to CNS progression is a secondary endpoint in the ALEX study, which may provide an answer to this question. Studies are still needed to address optimal sequencing of ALK inhibitors in the treatment of patients with metastatic, ALK-positive NSCLC.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

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