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

Erin Larkins[1], Gideon M. Blumenthal[1], Huanyu Chen[2], Kun He[2], Rajiv Agarwal[3], Gerlie Gieser[3], Olen Stephens[3], Eias Zahalka[1], Kimberly Ringgold[1], Whitney Helms[1], Stacy Shord[4], Jingyu Yu[4], Hong Zhao[4], Gina Davis[1], Amy E. McKee[1], Patricia Keegan[1], and Richard Pazdur[1]

[1]Office of Hematology and Oncology Products, FDA, Silver Spring, Maryland
[2]Office of Biostatistics, FDA, Silver Spring, Maryland
[3]Office of Pharmaceutical Quality, FDA, Silver Spring, Maryland
[4]Office of Translational Sciences, FDA, Silver Spring, Maryland

Running Title: Alectinib for ALK-Positive Non–Small Cell Lung Cancer

Corresponding author:
Erin Larkins
U.S. Food and Drug Administration, Office of Hematology and Oncology Products
10903 New Hampshire Avenue
Building 22, Room 2346
Silver Spring, MD 20993
Phone: 240-402-4286
Fax: 301-796-9849
E-mail: erin.larkins@fda.hhs.gov

Disclosure of Potential Conflicts of interest: No potential conflicts of interest were disclosed.

Abstract

On December 11, 2015, the FDA granted accelerated approval to alectinib (ALECENSA®; Genentech, Inc.) 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 independent review committee in these studies were 38% (95% CI, 36-52) 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 common 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, while 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 and the safety profile observed in these trials, alectinib was determined to have a favorable benefit-risk profile for the treatment of the indicated population.

Introduction

A 2007 report first described the finding that tumors in a small number of non-small cell lung cancer (NSCLC) patients 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) (1), resulting in an EML4-ALK fusion protein which 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 2-7% of NSCLC patients with tumors harboring ALK rearrangements (3). Some patient and tumor factors which 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 multi-targeted tyrosine kinase inhibitor which targets ALK, was the first kinase inhibitor approved for the treatment of ALK-positive metastatic NSCLC. Crizotinib was granted accelerated approval in 2011 (5) and traditional approval 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, 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 leading to 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).

Alectinib is a tyrosine kinase inhibitor that targets ALK and ret proto-oncogene (RET) kinase. In June 2013, FDA granted alectinib breakthrough therapy designation based on 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) metastasis. 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®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 [BID]) 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 post-marketing.

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 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 radiolabelled 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 co-administration 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 2 dose for alectinib was determined in NP28761 prior to dose escalation in NP28673. Inclusion criteria for both studies included age ≥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) ≤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 BID; this "As Treated " population comprises the primary efficacy population evaluated by FDA. Demographic and disease characteristics are presented in Table 1. The RE 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 both per 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 BID. 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. Grade 3-4 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; 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, while 27% of patients had alectinib dosing interrupted due to adverse reactions. Grade 3-4 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 elevations of liver function tests, 2 patients (0.8%) with Grade 3-4 AST/ALT elevations had documented drug-induced liver injury based on liver biopsy. The U.S. Prescribing Information (USPI) for alectinib recommends monitoring of 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), while 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 upper limit of normal with renal compromise) (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. 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, assessing alectinib 300 mg BID versus crizotinib in 207 ALK inhibitor-naïve patients with ALK-positive NSCLC, were recently reported to show a PFS 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 BID.

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 bolsters the assessment of a clinically meaningful benefit. Demonstration of significant clinical benefit compared to ceritinib was not required for alectinib as ceritinib was approved under accelerated approval.

In addition to the ORR and durability, the effects on CNS metastases were strongly supportive. The incidence of brain metastases in NSCLC patients has been reported as 16-36% 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 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 anti-tumor 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 Grade 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 part way 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 to 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.

References

1. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-7.
2. Soda M, Takada S, Takeuchi K, Choi YL, Enomoto M, Ueno T, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-7.
3. Fan L, Feng Y, Wan H, Shi G, Niu W. Clinicopathological and demographical characteristics of non-small cell lung cancer patients with ALK rearrangements: a systematic review and meta-analysis. PLoS One 2014;9:e100866.
4. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol 2013;8:823-59.
5. USPI crizotinib (issue date August 2011) [PDF on the Internet]; 2011 [cited 2016 Apr 5]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202570s000lbl.pdf.
6. USPI crizotinib (revision date November 2013) [PDF on the Internet]; 2013 [cited 2016 Apr 5]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202570s006lbl.pdf.
7. Malik SM, Maher VE, Bijwaard KE, Becker RL, Zhang L, Tang SW, et al. U.S. Food and Drug Administration approval: crizotinib for treatment of advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase positive. Clin Cancer Res 2014;20:2029-34.
8. Esfahani K, Agulnik JS, Cohen V. A systematic review of resistance mechanisms and ongoing clinical trials in ALK-rearranged non-small cell lung cancer. Front Oncol 2014;4:174.
9. Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, et al. Mechanisms of acquired resistance in ALK-rearranged lung cancers. Sci Transl Med 2012;4:120ra17.

10. Doebele RC, Pilling AB, Aisner DL, Kutateladze TG, Le AT, Weickhardt AJ, et al. Mechanisms of resistance to crizotinib in patients with ALK rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-82.
11. Costa DB, Shaw AT, Ou SI, Solomon BJ, Riely GJ, Ahn M, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol 2015;33:1881-8.
12. USPI ceritinib (issue date April 2014) [PDF on the Internet]; 2015 [cited 2016 Apr 5]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755lbl.pdf.
13. Khozin S, Blumenthal GM, Zhang L, Tang S, Brower M, Fox E, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res 2015;21:2436-9.
14. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. Chemistry review(s); 2015 [cited 2016 Feb 9]; [45 p.]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000ChemR.pdf. Files updated daily.
15. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. Pharmacology review(s); 2015 [cited 2016 Apr 18]; [154 p.]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000PharmR.pdf. Files updated daily.
16. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. Clinical pharmacology and biopharmaceutics review(s); 2015 [cited 2016 Apr 11]; [81 p.]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000ClinPharmR.pdf. Files updated daily.

17. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) [about 13 screens] [cited 2016 Jun 20]. Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
18. Lin NU, Lee EQ, Aoyama H, Barani IJ, Baumert BG, Brown PD, et al. Challenges relating to solid tumor brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. Lancet Oncol 2013;14:e396-406.
19. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. Medical review(s); 2015 [cited 2016 Apr 8]; [127 p.]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000MedR.pdf. Files updated daily.
20. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002;40:567-72.
21. Nokihara H, Hida T, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK+* NSCLC): primary results from the J-ALEX study. J Clin Oncol 34, 2016 (suppl; abstr 9008).
22. Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: a US Food and Drug Administration trial-level and patient-level analysis. J Clin Oncol 2015;33:1008-14.
23. Guidance for industry: clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics [PDF on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 [cited 2016 Apr 15]. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM259421.pdf.

24. Sorenson JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. J Clin Oncol 1988;6:1474-80.
25. Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002;94:2698-705.
26. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22:2865-72.
27. Mujoomdar A, Austin JH, Malhotra R, Powell CA, Pearson GD, Shiau MC, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology 2007;242:882-8.
28. Solomon BJ, Mok T, Kim D, Wu Y, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371:2167-77.
29. Kodama T, Hasegawa M, Takanashi K, Sakurai Y, Kondoh O, Sakamoto H. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. Cancer Chemother Pharmacol 2014;74:1023-8.
30. Inoue A, Nishio M, Kiura K, Seto T, Nakagawa K, Maemondo M, et al. One-year follow-up of a phase I/II study of a highly selective ALK inhibitor CH5424802/RO5424802 in ALK-rearranged advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2013;8:S1204 (abstract P3.11-034).
31. Gadgeel S, Ou S, Chiappori AA, Riely G, Lee R, Garcia L, et al. A phase 1 dose escalation study of a new ALK inhibitor, CH5424802/RO5424802, in ALK+ non-small cell lung cancer (NSCLC) patients who have failed crizotinib (AF-002JG/NP28761, NCT01588028). J Thorac Oncol 2013;8:S199 (abstract O16.06).

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[a] brain metastases	18%	25%

[a]Measurable by RECIST v1.1 criteria

Table 2. Efficacy results in studies NP28761 and NP28673

Efficacy parameter	NP28761 (n=87)		NP28673 (n=138)	
	IRC assessment[a]	Investigator assessment	IRC assessment[a]	Investigator assessment
Objective response rate (95% CI)	38% (28, 49)	46% (35, 57)	44% (36, 53)	48% (39, 57)
Number of responders	33	40	61	66
Median duration of response, 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

[a]18 patients in NP28761 and 16 patients in NP28673 did not have measurable disease at baseline as per IRC assessment and were classified as non-responders in the IRC analysis.
CI, confidence intervals; NE, not estimable

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
CNS objective response rate (95% CI)	61% (46, 74)	51% (35, 67)
Median CNS duration of response, months (95% CI)	9.1 (5.8, NE)	9.1 (7.4, NE)

Table 4. Common adverse reactions (incidence ≥20%) and laboratory abnormalities (incidence ≥30%) in NP28761 and NP28673

Alectinib 600 mg BID (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[a]	43%
Hyperbilirubinemia	39%
Hyperglycemia[b]	36%
Increased alanine aminotransferase	34%
Hypocalcemia	32%

[a]n=218 for creatine phosphokinase (with baseline values missing for 91 of these patients)
[b]n=152 for fasting blood glucose (with baseline values missing for 5 of these patients)

Table 5. Most common grade 3-4 adverse reactions and laboratory abnormalities (incidence ≥2%) in NP28761 and NP28673

Alectinib 600 mg BID (n=253)	
Adverse reaction	Grades 3-4
Dyspnea[a]	3.6%
Laboratory abnormality	
Increased alanine aminotransferase	4.8%
Increased creatine phosphokinase[b]	4.6%
Lymphopenia[c]	4.6%
Hypokalemia	4.0%
Increased aspartate aminotransferase	3.6%
Hypophosphatemia	2.8%
Hyperbilirubinemia	2.4%
Hyperglycemia[d]	2.0%
Hyponatremia	2.0%
Anemia	2.0%

[a]Includes one grade 5 event
[b]n=218 for creatine phosphokinase (with baseline values missing for 91 of these patients)
[c]n=217 for lymphocytes (with baseline values missing for 5 of these patients)
[d]n=152 for fasting blood glucose (with baseline values missing for 5 of these patients)