Clinical Cancer Research

FDA Approval: Ceritinib for the Treatment of Metastatic Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer

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Abstract

On April 29, 2014, the FDA granted accelerated approval to ceritinib (ZYKADIA; Novartis Pharmaceuticals Corporation), a breakthrough therapy-designated drug, for the treatment of patients with anaplastic lymphoma kinase (ALK)–positive, metastatic non–small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The approval was based on a single-arm multicenter trial enrolling 163 patients with metastatic ALK-positive NSCLC who had disease progression on (91%) or intolerance to crizotinib. Patients received ceritinib at a starting dose of 750 mg orally once daily. The objective response rate (ORR) by a blinded independent review committee was 44% (95% CI, 36–52), and the median duration of response (DOR) was 7.1 months. The ORR by investigator assessment was similar. Safety was evaluated in 255 patients. The most common adverse reactions and laboratory abnormalities included diarrhea (86%), nausea (80%), increased alanine transaminase (80%), increased aspartate transaminase (75%), vomiting (60%), increased glucose (49%), and increased lipase (28%). Although 74% of patients required at least one dose reduction or interruption due to adverse reactions, the discontinuation rate due to adverse reactions was low (10%). With this safety profile, the benefit–risk analysis was considered favorable because of the clinically meaningful ORR and DOR. *Clin Cancer Res; 21(11); 2436–9. ©2015 AACR.*

Introduction

In the new era of personalized medicine, treatment decisions for patients with advanced non–small cell lung cancer (NSCLC) continue to evolve as we move from a histology-based approach to one guided by targeting specific genetic alternations in the tumor that are responsible for the initiation and maintenance of cancer. Potentially targetable oncogenes in NSCLC have been identified in over half of lung adenocarcinomas and about 30% of squamous cell lung carcinomas (1, 2). The discovery of the *ALK* gene rearrangement in 2007 as an oncogenic "driver" mutation in about 5% of patients with NSCLC paved the way for the development of the ALK tyrosine kinase inhibitor (TKI) crizotinib, which received FDA accelerated approval in 2011 and traditional (i.e., regular) approval in 2013 (3–5).

Acquired resistance to crizotinib usually develops within the first year of treatment. Mechanisms of resistance include alterations in the *ALK* oncogene via secondary mutations and development of bypass oncogenic signaling pathways. Ceritinib (LDK378) is an ALK TKI, which in nonclinical models of acquired crizotinib resistance has been shown to inhibit some ALK secondary mutations (6–9). On March 6, 2013, the FDA granted ceritinib breakthrough therapy designation based on preliminary evidence of clinical activity in patients with metastatic ALK-positive NSCLC previously treated with crizotinib. The FDA review of the new drug application (NDA) for ceritinib for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib is summarized below.

Nonclinical Pharmacology and Toxicology

In biochemical and cellular assays, ceritinib inhibited ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS proto-oncogene 1 receptor kinase (ROS1) at clinically relevant concentrations. Ceritinib significantly inhibited hERG channel activity on HEK293 cells transfected with hERG cDNA. In monkeys administered a single dose of ceritinib, QT/QTc prolongation was observed in 1 of 4 animals with no drug-related effects on blood pressure, heart rate, or body temperature. Target organs of ceritinib-mediated toxicity in rats and monkeys included the pancreas, biliopancreatic ducts, bile ducts, and gastrointestinal (GI) tract (10).

Clinical Pharmacology

Following single-dose oral administration, maximal plasma concentrations (C_{max}) were reached in 4 to 6 hours, and the terminal half-life was 41 hours. Systemic exposure increased in a greater than dose proportional manner following repeat daily

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doses of 50 mg to 750 mg with an accumulation ratio of 6.2 after administration of 750 mg once daily for 3 weeks. Compared with fasting conditions, a high-fat meal increased ceritinib area under the concentration–time curve (AUC_{inf}) by 73% and C_{max} by 41%, and a low-fat meal increased ceritinib AUC_{inf} by 58% and C_{max} by 43% after a single 500-mg dose administered to healthy subjects.

Ceritinib is primarily metabolized by CYP3A and inhibits CYP3A and CYP2C9 *in vitro*. Coadministration with ketoconazole (a strong CYP3A inhibitor) increased ceritinib exposure by 2.9-fold, and coadministration with rifampin (a strong CYP3A inducer) decreased ceritinib exposure by 70% in healthy subjects. Ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro* (11).

Clinical Trial Design

The primary source of clinical data was a first-in-human, multicenter, single-arm trial (study X2101, NCT01283516) of ceritinib in 304 adult patients with ALK-positive advanced tumors. The trial consisted of a dose-escalation phase to determine the maximum tolerated dose and recommended dose and an expansion phase to characterize the efficacy, safety, and pharmacokinetics of ceritinib. Inclusion criteria included age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, adequate organ function, and ALK translocation detected by FISH in $\geq$15% of tumor cells (12, 13).

During the dose-escalation phase, 59 patients received ceritinib, 50 to 750 mg orally once daily. Dose-limiting toxicities were observed in 6 patients and consisted of diarrhea in 3 patients and vomiting, dehydration, hypophosphatemia, and transaminitis in 1 patient each. Based on the Bayesian logistic regression model used in the trial (14, 15), dose escalation to 900 mg was possible but did not occur due to the high frequency of persistent grade 1–2 nausea, vomiting, and diarrhea, and occurrence of grade 3–4 ALT and aspartate aminotransferase (AST) increases with treatment beyond the first cycle. Therefore, the 750-mg daily dose of ceritinib was chosen as the recommended dose.

During the expansion phase, 163 patients with metastatic ALK-positive NSCLC with disease progression on or intolerance to crizotinib received ceritinib, 750 mg once daily. The primary efficacy endpoint was objective response rate (ORR; complete plus partial responses) by investigator assessment per RECIST version 1.0. Based on the FDA's recommendation, the protocol was amended to include response evaluation by a blinded independent review committee (BIRC). Duration of response (DOR) was a secondary endpoint. Safety evaluations included regular physical examinations, laboratory evaluations, and electrocardiograms.

Efficacy

The median age of patients in the study X2101 was 52 years, and 87% of patients were under age 65. Baseline characteristics included female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), 2 or more prior therapies (84%), and adenocarcinoma histology (93%). Sites of extrathoracic metastasis included brain (60%), liver (42%), and bone (42%).

The ORR was 44% [95% confidence intervals (CI), 36%–52%] and 55% (95% CI, 47%–62%) according to BIRC and investigator assessments, respectively. The median DOR was 7.1 (95% CI, 5.6 to not estimable) and 7.4 (95% CI, 5.4–10.1) months according to BIRC and investigator assessments, respectively. The median time to response was 6 weeks by both assessments.

Exploratory subgroup analyses showed an ORR of 64% (95% CI, 49–77) in Asian patients and 36% (95% CI, 27–46) in Caucasian patients according to BIRC assessment with a DOR of 6.9 and 7.1 months, respectively. The ORR was 66% (95% CI, 49–80) in patients with ECOG 0 and 37% (95% CI, 29–46) in patients with ECOG $\geq$ 1, with a DOR of 9.7 and 5.6 months, respectively.

Fourteen patients treated at 750 mg had brain metastases at baseline that were considered to be target lesions by the investigator. In these 14 patients, the overall intracranial response rate was 50% (95% CI, 23–77) per investigator assessment. These responses were observed in 4 patients who had previously received an ALK inhibitor and in 3 patients who had not. In 42% of 77 patients previously treated with crizotinib who had progressive disease on ceritinib, the central nervous system (CNS) was the only site of relapse.

Safety

The primary safety analysis included 255 patients from study X2101 (246 with NSCLC and 9 with other cancers) who received ceritinib at a dose of 750 mg daily. Baseline characteristics were similar to those of the efficacy population. The median duration of exposure was 27 weeks (range, 0.4–82). Common adverse reactions with an incidence $\geq$ 25% were diarrhea (86%), nausea (80%), vomiting (60%), abdominal pain (54%), fatigue (52%), decreased appetite (34%), and constipation (29%). The most common laboratory abnormalities (incidence $\geq$ 25%) were decreased hemoglobin (84%), increased alanine aminotransferase (ALT, 80%), increased AST (75%), increased creatinine (58%), increased glucose (49%), decreased phosphate (36%), and increased lipase (29%). Less common clinically significant adverse reactions included neuropathy (17%), vision disorder (9%), prolonged QT interval (4%), and bradycardia (3%). Grade 3–4 adverse reactions occurring in $\geq$ 2% of patients included diarrhea (6%), fatigue (5%), nausea (4%), vomiting (4%), interstitial lung disease (ILD)/pneumonitis (3%), and abdominal pain (2%). Serious adverse reactions occurred in 40% of patients and included convulsion, pneumonia, ILD/pneumonitis, dyspnea, dehydration, hyperglycemia, and nausea. There were no cases of Hy's law, a measure based on concurrent elevations in ALT and total bilirubin used to estimate a drug's potential to cause severe drug-induced liver injury (16). Fatal adverse reactions were reported in 5% of patients and included pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each).

The incidence rate of adverse reactions requiring dose reduction or interruption was 74%. The study protocol allowed a maximum of 3 dose reductions from the recommended dose in decrements of 150 mg and prohibited re-escalation during subsequent treatment cycles. Most patients (59%) required at least one dose reduction, with 39%, 16%, and 4% of patients requiring 1, 2, and 3 dose reductions, respectively. The median time to first dose reduction was 7 weeks. The most frequent adverse reactions (reported in $\geq$10% of patients) leading to dose reduction or interruptions were increased ALT (29%),

nausea (20%), increased AST, vomiting, and diarrhea (16% each). Adverse reactions leading to discontinuation occurred in 10% of patients, and the most frequent (≥1% patients) were pneumonia, pneumonitis, and decreased appetite.

Exposure–Response Relationships

No significant exposure–response relationships were identified for the primary efficacy endpoint of ORR. Higher systemic exposure appeared to be associated with more frequent and earlier safety events, including overall grade 3–4 adverse reactions, and individual adverse reactions such as ≥ grade 3 ALT/AST elevation and ≥ grade 2 hyperglycemia. Higher systemic exposure appeared to be associated with earlier and more frequent dose reductions or interruptions. No significant relationships were identified between systemic exposure and GI tract adverse reactions. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation (11).

Discussion

The benefit–risk profile for ceritinib in the treatment of patients with ALK-positive metastatic NSCLC with progression on or intolerance to crizotinib was considered to be favorable based on the high ORR, the long DOR, and the toxicity profile (Table 1). Ceritinib was a breakthrough therapy–designated product, which allowed close collaboration between the sponsor and FDA throughout the development program. The sponsor submitted an NDA 3 years after the original IND submission and FDA approval occurred 4 months later.

Over half of the patients in study X2101 had brain metastasis at enrollment, which is consistent with findings that about 20% to 50% of patients with NSCLC develop brain metastasis during the course of their disease and that the CNS may be a sanctuary site in patients with ALK-positive NSCLC treated with crizotinib (17–19). Although ceritinib showed early evidence of activity in a small number of patients with target lesions in the brain, the CNS also appeared to be a relatively common primary site of disease progression, and more data are needed to adequately assess the drug's CNS activity.

The reasons for the higher ORR in Asian patients are not entirely clear. Although it has been suggested that the higher ORR in Asian patients may be partly due to pharmacokinetic differences, ceritinib's exposure based on C_{max} and AUC at steady state appears to be similar in Asian and non-Asian patients (20). Future studies should explore the role of ethnicity in predicting response to ALK inhibitors taking into account both intrinsic (e.g., genetics and pharmacokinetics) and extrinsic (e.g., diet and environment) factors in influencing response to treatment (21).

Anecdotal reports from patients and investigators suggest that GI tolerability may improve when ceritinib is taken with food, but given the increased drug exposure with food, administration with food may also increase the occurrence of non–GI-related toxicities. To address this concern, one postmarketing requirement is to conduct a clinical trial to evaluate the systemic exposure and safety of a lower dose of ceritinib taken with a meal compared with that of 750 mg of ceritinib taken in the fasted state in patients with metastatic ALK-positive NSCLC. The goal of this trial is to obtain more data on an appropriate dose of ceritinib taken with a meal that provides similar systemic exposure to that of the 750-mg dose taken under a fasted state and potentially improves GI tolerability.

Ceritinib can cause hyperglycemia, likely as a result of its inhibitory effects on IGF-1R and InsR. In study X2101, compared with all other patients, the risk of hyperglycemia was 5.7 times higher (95% CI, 3.2–10.1) for patients with a history of diabetes or glucose intolerance and 2.4 times higher (95% CI, 1.2–4.8) for patients with concomitant use of steroids. The hyperglycemic effect of ceritinib on patients with baseline blood glucose levels of greater than 200 mg/dL is unknown, because this was an exclusion criterion in the protocol. Although lipase and amylase elevations were frequently seen, only one case of acute pancreatitis was reported in a supportive trial.

There are currently limited data on the activity of crizotinib in patients with ALK-positive metastatic NSCLC who were first treated with, and had disease progression on, ceritinib or other ALK inhibitors currently under development (22, 23). Therefore, future clinical trials should explore the optimal strategy for the initial selection and subsequent sequencing of therapy of ALK inhibitors in patients with ALK-positive metastatic

Table 1. Benefit–risk analysis for ceritinib in the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib

Disease	Patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib have a serious and life-threatening condition for which treatment is not addressed adequately by available therapies.
Unmet medical need	ALK-positive metastatic NSCLC patients with acquired resistance to crizotinib are often treated with standard cytotoxic chemotherapy, which is generally associated with marginal clinical benefit and significant toxicity.
Clinical benefit	Ceritinib was associated with ORR of 44% (DOR, 7.1 months) and 55% (DOR, 7.4 months) according to BIRC and investigator assessments, respectively. The activity of ceritinib was generally consistent across all clinically relevant subgroups.
Risk	The majority of patients (74%) required at least one dose reduction or interruption, primarily for gastrointestinal adverse reactions or hepatotoxicity. However, discontinuation due to adverse reactions was acceptable (10%), indicating that ceritinib-related toxicities can be reasonably managed with dose modification/interruptions and supportive care.
Uncertainties	Although ORR is considered an endpoint that can reasonably predict clinical benefit in metastatic NSCLC, no correlation with overall survival or how a patient feels or functions has yet been established. Therefore, traditional approval for ceritinib requires confirmation of clinical benefit. Additional data are needed to assess the safety and efficacy of ceritinib: • when the drug is taken with a meal, which has been shown to increase systemic exposure; • in patients with CNS metastasis; • and in the context of the optimal sequencing of ALK-inhibitor therapies.
Conclusions	Ceritinib meets the criteria for accelerated approval under the provisions of subpart H of 21CFR314. Ceritinib has a favorable benefit–risk profile for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib and is associated with a large magnitude of durable responses in a population of patients for whom available treatment options generally offer marginal clinical benefit. The risks associated with ceritinib are acceptable in the context of the disease being treated.

NSCLC to maximize the clinical benefit derived from these agents.

Similar to the initial approval of crizotinib, the accelerated approval for ceritinib was supported by an ORR of large magnitude and long duration, which is considered an endpoint reasonably likely to predict clinical benefit. Crizotinib received traditional approval based on demonstration of superior progression-free survival (PFS) compared with chemotherapy in patients with ALK-positive NSCLC whose disease progressed after platinum-based doublet chemotherapy. At the time of ceritinib's approval, two randomized trials against standard therapy with the primary endpoint of PFS to confirm ceritinib's clinical benefit in patients with metastatic ALK-positive NSCLC were ongoing. Emerging evidence suggests a high correlation between ORR and PFS in metastatic NSCLC (24). Confirmation of these findings may qualify ORR as a validated endpoint for clinical benefit in metastatic NSCLC, especially for targeted agents that have a large magnitude of durable responses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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