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ASCEND-8 pharmacokinetic, safety, and efficacy data for ceritinib 450 mg with food in patients with anaplastic lymphoma kinase–positive non-small cell lung Cancer: A clinical perspective

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ABSTRACT

Anaplastic lymphoma kinase–positive (*ALK*+) non-small cell lung cancer (NSCLC) is diagnosed in up to 126,000 patients worldwide annually. Ceritinib is a next-generation ALK-targeted tyrosine kinase inhibitor that is approved for the treatment of patients with metastatic *ALK*+ NSCLC. In December 2017, the US Food and Drug Administration–approved dose of ceritinib was changed from 750 mg/day under fasting conditions to 450 mg/day taken with food for the treatment of patients with *ALK*+ NSCLC. This change was implemented on the basis of data from studies designed to investigate ways to reduce the frequency of gastrointestinal adverse events noted in patients enrolled in several ASCEND clinical trials that evaluated a ceritinib 750-mg fasted dose as either first- or second/third-line treatment. This review highlights and discusses published findings from the ASCEND-8 food-effect trial and includes commentary from physicians regarding their own clinical cases of patients who were enrolled in the trial and treated with either the 750-mg fasted or 450-mg fed dose of ceritinib. The review also discusses the implications of using the recently approved ceritinib 450-mg dose in the clinical setting.

1. Introduction

Anaplastic lymphoma kinase *(ALK)* gene rearrangements have been reported in 3–7% of patients with non-small cell lung cancer (NSCLC). *ALK*-positive (*ALK*+) NSCLC typically presents in young patients, light or nonsmokers, and those with adenocarcinoma histology. ALK is a transmembrane receptor tyrosine kinase that belongs to the insulin receptor superfamily; although its precise function is unclear, ALK is purported to play a role during embryonic development in the central nervous system (CNS). Furthermore, low ALK messenger RNA levels have been reported in healthy adults [1–3].

ALK was first detected in thoracic tumors as part of an *ALK* rearrangement–encoded fusion protein containing the ALK tyrosine kinase domain which functions as an oncogenic driver. To date, several ALK fusion proteins that occur in lung cancer have been described in the literature, including echinoderm microtubule–associated protein-like 4-ALK (EML4-ALK), the most common fusion reported in NSCLC tumors [2]. ALK fusion proteins are constitutively active and activate multiple signaling pathways, including mitogen-activated protein kinase/extracellular signal–regulated kinase, phosphatidylinositol-3-kinase-AKT, and Janus kinase signal transducers and activators of transcription, which are involved in promoting tumorigenesis [1]. Identification of oncogenic drivers paved the way for targeted therapies, including ALK-targeted tyrosine kinase inhibitors (TKIs), which

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALK+, anaplastic lymphoma kinase positive; AUC, area under the plasma drug concentration–time curve; AUC_{inf}, AUC from time 0 extrapolated to infinite time; CI, confidence interval; C_{max}, maximum plasma drug concentration; CNS, central nervous system; EML4-ALK, echinoderm microtubule–associated protein-like 4-ALK; FDA, US Food and Drug Administration; GI, gastrointestinal; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetic; QD, once daily; TKI, tyrosine kinase inhibitor; T_{max}, time to reach maximum plasma drug concentration

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have been evaluated in several clinical trials.

In 2011, the multikinase inhibitor crizotinib became the first ALK-targeted TKI approved by the US Food and Drug Administration (FDA) for the treatment of patients with advanced *ALK*+ NSCLC who were treatment naïve or had progressed on chemotherapy [4]. Accelerated approval was granted after crizotinib demonstrated significant improvement in overall response rate (ORR; 65–74%) and enhanced quality of life compared with chemotherapeutic agents. In the crizotinib vs chemotherapy groups, the median progression-free survival (PFS) was 10.9 vs 7.0 months (HR, 0.45; 95% confidence interval [CI], 0.35–0.60) in untreated patients and 7.7 vs 3.0 months (HR, 0.49; 95% CI, 0.37–0.64) in previously treated patients, respectively [5,6]. However, most patients developed resistance within 12–14 months of crizotinib treatment, which led to the development and subsequent approvals of second-generation ALK inhibitors ceritinib, alectinib, and brigatinib [2].

Ceritinib is an oral ALK inhibitor that has demonstrated 20 times more potency than crizotinib in enzymatic assays and notable selectivity for ALK fusions in vitro, including EML4-ALK (2 nM) and NPM-ALK (26 nM). Ceritinib has also been shown to overcome *ALK* resistance mutations (L1196M, G1269A, I1171T, and S1206Y) that arise upon treatment with crizotinib in preclinical NSCLC models [7,8]. To assess the tolerability and clinical activity of ceritinib, the multicenter ASCEND program was initiated. This comprised several ongoing clinical trials, which in total enrolled over 1400 pretreated and treatment-naïve patients with locally advanced or metastatic *ALK*+ NSCLC, as summarized below.

The ASCEND-1 trial assessed ceritinib 750 mg once daily (QD) administered under fasted conditions in ALK TKI–naïve and –pretreated patients; ORR was 72% (60/83 patients) and 56% (92/163) and median PFS was 18.4 and 6.9 months, respectively. The most frequently reported adverse events (AEs) were gastrointestinal (GI) in nature and predominantly grade 1–2, while grade 3 diarrhea and nausea (regardless of causality) were reported in 6% of patients. Frequent grade 3–4 laboratory AEs were increased alanine aminotransferase (30%) and aspartate aminotransferase (10%) [9]. Two phase II (ASCEND-2 and ASCEND-3) [10,11] and two phase III (ASCEND-4 and ASCEND-5) [12,13] trials confirmed that a ceritinib 750-mg fasted dose was efficacious and had manageable tolerability in these patients (as first-line therapy) as well as in patients progressing on chemotherapy or crizotinib.

To assess the most appropriate dosing regimen of ceritinib, food-effect studies were conducted. In one study in healthy volunteers, oral administration of ceritinib with a low-fat meal increased the maximum plasma drug concentration of ceritinib (C_{max}) and area under the plasma drug concentration–time curve (AUC) of a 500-mg dose by 43% and 58% compared with the fasted state, respectively. In another food-effect study in healthy participants, a light snack increased the C_{max} and AUC from time 0 extrapolated to infinite time (AUC_{inf}) of a 750-mg dose by 45% and 54% compared with the fasted dose, respectively. These findings led to initial instructions to take ceritinib 750 mg/day during a fasted state [14,15]. On the basis of results from the ASCEND trials and these food-effect studies, ceritinib 750 mg QD under fasting conditions was approved by the FDA for use in pretreated (April 2014) and previously untreated (May 2017) patients with advanced *ALK*+ NSCLC [15–17]. However, despite the significant antitumor activity shown by ceritinib, high rates of GI toxicity hindered its frequent use in clinical practice. The GI AEs reported in the ASCEND trials are summarized in **Table 1**. Recently published results from the first-line ASCEND-4 and third-line ASCEND-5 studies reported diarrhea in 72–85% of patients, nausea in 66–69%, and vomiting in 52–66%, which contributed to the relatively high number of patients who required dose modifications [12,13]. In the ASCEND-4 study, 80% of patients required dose interruptions or adjustments due to AEs; GI AEs accounted for 28% of dose modifications, although they led to treatment discontinuation in only 2% of patients [12].

In an effort to address these GI issues and ensure that patients may remain on treatment at an efficacious dose, a randomized phase I study (ASCEND-8; NCT02299505) evaluating the safety and efficacy of ceritinib at lower doses taken with food was initiated [18]. On the basis of the positive findings of the pharmacokinetic (PK) and preliminary safety data from the ASCEND-8 study, ceritinib 450 mg QD administered with food was approved by the FDA in December 2017 [17]. The ASCEND-8 study includes two parts: part 1 assessed PK and preliminary safety, and part 2 is evaluating efficacy and additional safety [18]. The findings from parts 1 and 2 and their clinical implications are discussed here.

2. ASCEND-8 study results

2.1. Patient eligibility and baseline demographics

The ASCEND-8 study enrolled patients with stage IIIB or IV confirmed *ALK*+ NSCLC who were treatment naïve (excluding neoadjuvant/adjuvant systemic therapy) or previously treated with one prior regimen of crizotinib (in addition ≥ 1 systemic anticancer therapy was allowed). Patients who had neurologically stable CNS metastases were also allowed into the study. Patients were randomized into one of three treatment arms: ceritinib 450 mg QD or 600 mg QD taken with a low-fat meal or 750 mg QD under fasted conditions. A low-fat meal—defined as approximately 100–500 calories and 1.5–15 g of fat—was stipulated in this study, given the modest difference reported in AUC_{inf} between a light snack, low-fat meal, and high-fat meal [18].

The ASCEND-8 study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each patient.

Overall, patient demographics were similar across the three treatment arms. The median age of patients enrolled was 56 years (range, 25–86 years), and most patients (88%) had a World Health Organization performance status of ≤ 1. Although differences were noted in baseline factors, such as the number of prior lines of anticancer therapy (27% with ≥ prior lines of therapy in 450-mg fed arm, 23% in 600-mg fed arm, 15% in 750-mg fasted arm), the number of patients who were previously treated with crizotinib was similar across the three treatment groups [18].

2.2. Analyses of PK findings

Analyses of PK parameters revealed that AUC from time 0–24 h and C_{max} were similar following a daily dose of ceritinib 450 mg administered with food and a standard 750-mg fasted dose, which indicated that systemic drug exposure is not affected by reducing the dose of ceritinib to 450 mg when taken with food. In contrast, patients in the 600-mg fed arm showed an approximately 25% higher steady-state PK exposure than those in the 750-mg fasted arm. Absorption of ceritinib was more pronounced with a high-fat meal than with a low-fat meal or light snack; however, the difference was not considered substantial, which suggests that any type of food, regardless of caloric value or fat content, could be taken with ceritinib 450 mg QD. In this study, the median time to reach maximum plasma drug concentration (T_{max}) was similar across all three treatment arms (i.e., ≈ 6 h), which indicates that there was no detectable effect of food on the T_{max} [18].

2.3. Analyses of safety and tolerability findings

Analyses of the safety of ceritinib also appeared to favor the 450-mg fed arm. In part 1 of the ASCEND-8 trial, the incidences of any-grade diarrhea (48% vs 64%), nausea (45% vs 62%), and vomiting (23% vs 42%) were lower in the ceritinib 450-mg fed arm than in the 750-mg fasted arm, respectively. Most of the GI toxicities (43%) in the 450-mg fed arm were grade 1, while no grade 3 or 4 GI AEs were reported in this arm. Conversely, hepatic toxicities of any-grade including elevated

Table 1
Summary of ceritinib GI safety data from the ASCEND clinical trials.

Clinical trial ID	Dose	Phase	Any-grade GI AEs (regardless of causality)	Ref.
ASCEND-1 NCT01283516	750-mg fasted	I	Diarrhea (87%), nausea (83%), vomiting (61%)	[9]
ASCEND-2 NCT01685060	750-mg fasted	II	Nausea (81%), diarrhea (80%), vomiting (63%)	[10]
ASCEND-3 NCT01685138	750-mg fasted	II	Diarrhea (86%), nausea (77%), vomiting (72%)	[11]
ASCEND-4 NCT01828099	750-mg fasted	III	Diarrhea (85%), nausea (69%), vomiting (66%)	[12]
ASCEND-5 NCT01828112	750-mg fasted	III	Diarrhea (72%), nausea (66%), vomiting (52%)	[13]
ASCEND-8 NCT02299505	750-mg fasted	I	Diarrhea (64%), nausea (62%), vomiting (42%)	[18]
	450-mg fed	I	Diarrhea (48%), nausea (45%), vomiting (23%)	

AE, adverse event; GI, gastrointestinal; ID, identifier; Ref, reference.

alanine aminotransferase and aspartate aminotransferase were higher in the 450-mg fed arm than in the fasted arm. Results from part 2 of the ASCEND-8 trial (n = 306) were similar, demonstrating a reduced incidence of all-grade and grade 3/4 GI toxicities in the 450-mg fed arm (75.9% and 2.8%) vs the 600-mg fed (82.6% and 8.1%) and 750-mg fasted (91.8% and 13.6%) arms [19]. Overall, the reduced rates of GI AEs in the 450-mg fed arm appeared to allow patients to better tolerate treatment with ceritinib, as fewer dose reductions were observed (24.1% in the 450-mg fed arm, 65.1% in the 600-mg fed arm, 60.9% in the 750-mg fasted arm). This finding may translate into higher median treatment exposure in the long term and maintained relative dose intensity compared with the higher fasted dose. In the ASCEND-8 trial, the 450-mg group had the highest proportion of patients with relative dose intensity of ≥ 90% [18]. The importance of preserving adequate dose intensity was previously highlighted with chemotherapy in elderly patients (≥ 70 years of age) with advanced NSCLC who demonstrated significantly improved response and overall survival rates when relative dose intensity was ≥ 80% of the initial dose [20]. Notably, patients neither discontinued treatment nor required dose reductions due to diarrhea or nausea in the ceritinib 450-mg fed arm [18].

2.3.1. Safety and tolerability findings from individual patient case studies

Beginning in August 2015, our site enrolled five eligible patients, four of whom were randomized to receive either ceritinib 450 mg with food (n = 1) or ceritinib 750 mg under fasting conditions (n = 3). The average age of these patients was 61 years; three were female and one was male; two patients were white, one was Asian, and one was black. Patient characteristics are summarized in Table 2. Overall, the most common AEs among all patients included GI complaints (diarrhea, nausea, vomiting), elevation in liver enzymes, headache, and dizziness.

Table 2
Summary of patient characteristics from the ASCEND-8 clinical trial.

Characteristic	Ceritinib 750-mg fasted dose (n = 3)	Ceritinib 450-mg fed dose (n = 1)
Mean age (range), years	60 (49–71)	63
Sex, n (%)		
Female	2 (67)	1 (100)
Male	1 (33)	0
Race, n (%)		
Asian	0	1 (100)
Black	1 (33)	0
White	2 (67)	0
Mean duration of exposure, months	23[a]	18
Permanently discontinued treatment, n (%)	2 (67)	1 (100)
Progressive disease	2 (67)	1 (100)
Serious adverse events	0	0
Prior treatments		
Chemotherapy	2 (67)	0
Crizotinib	1 (33)	1 (100)
Dose modification	1 (33)	0

[a] One patient taking ceritinib 750 mg under fasting conditions currently remains on treatment, at 35.3 months.

These AEs were managed with symptomatic treatment and/or dose reductions or interruptions. In addition, there were no reported grade 4 AEs, study drug–related discontinuations, or serious AEs in any of these four patients. In the three patients randomized to the 750-mg fasted arm, the majority of grade 1 AEs that were reported were expected and did not affect the clinical course of planned treatment. In this arm, eight grade 2 AEs were reported, with only one report of diarrhea, which was treatment related. It was managed by dose interruption, which resolved without further medical intervention. Five grade 3 AEs were reported, with only one case of nausea, which was suspected to be related to the study drug. It was also managed by dose interruption, followed by dose reduction from 750 to 600 mg. In the single patient in the 450-mg fed arm, no occurrence of GI-related AEs or any AE of grade > 1 was reported.

2.4. Analyses of patient disposition findings

In part 1 of the ASCEND-8 study, 30 patients (22%) discontinued from treatment, with similar rates seen across the three treatment arms, due to factors including AEs (5% in the 450-mg fed arm, 0% in the 600-mg fed arm, 2% in the 750-mg fasted arm) and disease progression (7% in the 450-mg fed arm, 9% in the 600-mg fed arm, 9% in the 750-mg fasted arm). The AEs leading to discontinuation were suspected to be unrelated to ceritinib in the 450-mg arm (muscle weakness [n = 1], intestinal perforation [n = 1]); the 1 AE leading to discontinuation in the 750-mg fasted arm (renal impairment) was considered to be related to ceritinib [18].

2.4.1. Patient disposition findings from individual patient case studies

Three patients in the 750-mg fasted group received ceritinib for an average of 23 months. Two of these patients discontinued ceritinib due to disease progression and lack of clinical benefit after an average of 17 months of treatment, and one patient in the 450-mg fed arm received ceritinib for 18 months. Currently, one patient in the fasted arm remains on ceritinib after 35 months of treatment. Of the three patients who were no longer on treatment, the average time to discontinuation of ceritinib was 18 months. Overall, once these patients initially experienced disease progression, they continued to receive ceritinib, as it was believed that they derived clinical benefit in both systemic and CNS disease control. All of these patients later discontinued study treatment due to worsening disease progression in the brain.

2.5. Efficacy analyses

Efficacy in part 2 of the ASCEND-8 trial was assessed in patients who were treatment naïve and had *ALK*+ disease per immunohistochemistry (450-mg fed, n = 73; 600-mg fed, n = 51; 750-mg fasted, n = 74) [19]. The median follow-up in the efficacy population was 14.3 months (range, 4.2–30.2 months). The ORR was similar between treatment arms: 78.1%, 72.5%, and 75.7% in the 450-mg fed, 600-mg fed, and 750-mg fasted arms, respectively. The median time to response was 6.3 weeks in all three treatment arms. The 18-month PFS rate was also similar between arms, with the highest rate observed in

the 450-mg fed arm: 50.8% (95% CI, 33.7%–65.7%) vs 48.6% (95% CI, 30.7%–64.3%) in the 600-mg fed arm and 40.9% (95% CI, 23.3%–57.8%) in the 750-mg fasted arm.

3. Implications for clinical practice and future perspectives

Results from the ASCEND-8 study have shown that reducing the dose of ceritinib to the current FDA-approved dose of 450 mg when taken with food vs treating with the higher, fasted dose does not significantly affect systemic drug exposure. Moreover, retrospective analyses from the first real-world assessment of ceritinib prescribed in US clinical practices were similar to efficacy analyses from part 2 of the ASCEND-8 trial, demonstrating that lower doses of ceritinib administered with food did not appear to be associated with reduced rates of complete or partial responses in patients with *ALK*+ NSCLC. In this study, complete or partial responses were observed in 23 of 35 patients (66%) in the 750-mg dose group, 7 of 10 (70%) in the 600-mg dose group, and 5 of 6 (83%) in the 450-mg dose group [21]. Interestingly, patients in the ASCEND-8 study treated with ceritinib 600 mg taken with food experienced an approximate 25% increase in drug exposure compared with those treated with the 750-mg fasting dose [18]. Although this dosage appeared to be intolerable for a higher number of patients—as indicated by more patients having ≥ 1 dose modification in the 600-mg fed arm (52%) than in the 450-mg fed arm (11%)—the higher level of drug exposure may be of clinical benefit to patients with brain metastases [15]. For example, a recent case report of a 57-year-old patient with *ALK*+ NSCLC who developed brain metastases while being treated with crizotinib demonstrated no intra- or extracranial tumor progression for 25 months after switching to ceritinib treatment, which was orally administered at 450 mg per day [22].

Preliminary safety findings from ASCEND-8 have also demonstrated that reducing the dose of ceritinib and taking it with food resulted in a more favorable safety profile and enhanced tolerability, with fewer dose reductions reported in the 450-mg fed group [18]. Moreover, a recent retrospective real-world assessment of patients with *ALK*+ NSCLC (N = 164) in the United States, the majority of whom initiated ceritinib at the 750-mg dose, reported that 52% had ≥ 1 treatment interruption, which was similar to the rate reported in the ASCEND-8 study [18,23]. These findings suggest that reducing the ceritinib dose may lower the number of patients who require dose modifications, lead to increased maintenance of a therapeutic ceritinib dose in the long term, and translate into improved efficacy compared with the previously approved higher, fasted dose. In addition, favorable effects reported in the ASCEND-8 study were observed with a dosing procedure that permitted patients to consume meals containing a wide range of fat and caloric content, which may make it easier for patients to adhere to the appropriate treatment regimen for ceritinib [18].

In our study, the patient in the 450-mg fed arm appeared to tolerate ceritinib better than the three patients in the fasted arm. We believe that this led to a better quality of life for the patient, as there were no treatment-related GI AEs necessitating a change in the study treatment schedule. A retrospective assessment of patients treated with ceritinib 750 mg (N = 164) showed that 46% had ≥ 1 inpatient hospital admission during the observation period after ceritinib initiation. Furthermore, the average healthcare cost per patient per 6 months reported in this retrospective study was $111,468, which was predominantly driven by out- and inpatient-associated costs [23]. Therefore, recommending that patients take ceritinib with food to avoid GI AEs may improve overall adherence and disease control and is likely to decrease the number of healthcare professional interventions as well as costs.

Overall, discontinuation rates during treatment were low, and similar rates were reported across the three treatment arms [18]. In the three patients from the clinical case examples who progressed during study treatment, ceritinib was continued until the primary investigator determined that there was no longer any clinical benefit. Continuation of study treatment beyond clinical progression allowed for longer disease control and postponement of local treatment, such as brain radiation or stereotactic radiosurgery intervention.

Another key implication of this study is that a large population of patients with *ALK*+ NSCLC may benefit from the change in ceritinib dose since both treatment-naïve patients and those who were previously treated with antineoplastic therapy and/or ALK inhibitors were enrolled in addition to patients who were receiving concomitant medications, such as proton pump inhibitors. Of note, previous studies have indicated that long-term administration of potent acid-reducing agents with ceritinib does not adversely affect the steady-state PK and efficacy of ceritinib in patients with *ALK*+ NSCLC [24].

4. Conclusions

Analyses of PK and preliminary safety data from the ASCEND-8 study provide support for the use of the reduced dose of ceritinib (from 750 mg QD under fasting conditions to 450 mg QD with food), which resulted in a change to the prescribing information in December 2017. Additionally, efficacy analyses demonstrated similar responses in patients who received the 450-mg fed dose and those who received the 750-mg fasted dose. Based on clinical experience, we believe that recommending that patients take the newly approved dose of ceritinib with food may positively impact overall treatment adherence, disease control, and clinical management of patients with *ALK*+ NSCLC.

Conflict of interest

Aside from medical writing support acknowledged below, all authors report no conflicts of interest related to this work.

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