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Two Phase III Studies Evaluating Ceritinib in Patients (Pts) With Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non–Small Cell Lung Cancer (NSCLC): ASCEND-4 and ASCEND-5

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BACKGROUND

- Anaplastic lymphoma kinase (*ALK*) gene rearrangements occur in approximately 2% to 7% of patients with non–small cell lung cancer (NSCLC).[1]
- Ceritinib (LDK378), is an oral, small molecule tyrosine kinase inhibitor of ALK with 20–fold greater potency than crizotinib in enzymatic assays.[2] Ceritinib demonstrated marked antitumor activity against both crizotinib-sensitive and crizotinib-resistant tumors in xenograft models of *ALK*-rearranged (ALK-positive) NSCLC.[2,3]
- The results from the first-in-human phase I study (ASCEND-1; NCT01283516) of ceritinib demonstrated substantial antitumor activity in patients with ALK-positive, advanced NSCLC with crizotinib-naïve or crizotinib-resistant disease.[4]
- Ceritinib was granted accelerated approval by the FDA in April 2014 for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.[5]
- In an updated analysis of ASCEND-1 (data cut-off date: October 31, 2013), ceritinib 750 mg/day demonstrated durable responses and prolonged progression-free survival (PFS) in both ALK inhibitor-naïve and ALK inhibitor-pretreated patients. Among the 246 patients treated with ceritinib 750 mg/day, the overall response rate was 58.5% (95% confidence interval [CI]: 52.1-64.8) and the median PFS was 8.21 months (95% CI: 6.7-10.12).[6]
  - The antitumor activity of ceritinib was demonstrated in ALK-positive NSCLC patients with or without brain metastases, regardless of prior ALK inhibitor treatment status.
- Updated data (data cut-off date: April 14, 2014) from the ASCEND-1 study will be presented.[7,8] There are two, ongoing, confirmatory, phase III, prospective, multicenter, randomized open-label studies designed to compare the antitumor activity of ceritinib with that of chemotherapy in adult patients with ALK-positive advanced NSCLC who are either:
  - Chemotherapy- and crizotinib-naive (ASCEND-4; NCT01828099) or
  - Have received prior chemotherapy and crizotinib (ASCEND-5; NCT01828112).
- The primary objective of the ASCEND-4 and ASCEND-5 studies is to compare the antitumor activity (as measured by PFS) of ceritinib vs standard chemotherapy in patients with advanced ALK-positive NSCLC.

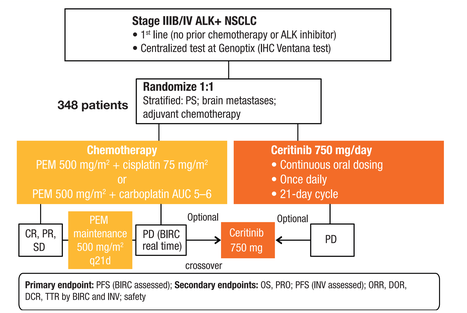
METHODS

Study Design and Treatment

- ASCEND-4 and ASCEND-5 are phase III, prospective, multicenter, randomized open-label studies (**Figure 1**).
- In each study, patients in the investigational arm receive ceritinib. The control arm treatment consists of either pemetrexed plus cisplatin/pemetrexed plus carboplatin for first 4 cycles (21 days) followed by pemetrexed maintenance in patients who did not progress (ASCEND-4 study) or pemetrexed/docetaxel (ASCEND-5 study).

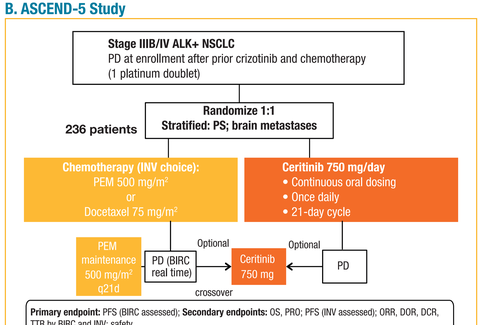
Figure 1. Study Design

A. ASCEND-4 Study



AUC, area under the curve; BIRC, Blinded Independent Review Committee; CR, complete response; DCR, disease-control rate; DOR, duration of response; IHC, immunohistochemistry; INV, investigator; ORR, overall response rate; OS, overall survival; PD, progressive disease; PEM, pemetrexed; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcomes; PS, performance status; SD, stable disease; TTR, time to response

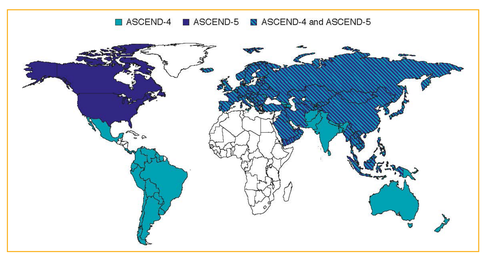
B. ASCEND-5 Study



BIRC, Blinded Independent Review Committee; DCR, disease-control rate; DOR, duration of response; INV, investigator; ORR, overall response rate; OS, overall survival; PD, progressive disease; PEM, pemetrexed; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; TTR, time to response

- Locations of ASCEND-4 and ASCEND-5 studies are shown in **Figure 2**.

Figure 2. Study Locations



Patients

- The ASCEND-4 study is recruiting previously untreated adult patients with advanced ALK-positive nonsquamous NSCLC.
  - Approximately, 348 patients will be randomized (1:1 ratio) to the 2 treatment arms.
- The ASCEND-5 study is recruiting adult patients with ALK-positive, advanced NSCLC previously treated with cytotoxic chemotherapy and crizotinib.
  - Approximately, 236 patients will be randomized (1:1 ratio) to the 2 treatment arms.
- Key inclusion and exclusion criteria for ASCEND-4 and ASCEND-5 studies are shown in **Table 1**.

Outcomes and Measurements

- The primary outcome in both studies is PFS (defined as time from date of randomization to date of first documented disease progression or date of death due to any cause), which will be assessed by Blinded Independent Review Committee per RECIST 1.1.
- Secondary outcomes include the following: overall survival (OS; defined as time from date of randomization to date of death due to any cause), overall response rate (proportion of patients with a best overall response defined as complete response [CR] or partial response [PR]), duration of response (time from date of first documented CR or PR to date of first documented disease progression or death due to any cause), disease control rate (proportion of patients with best overall response of CR, PR, or stable disease [SD]), and time to response (time from date of randomization to date of first documented response [CR or PR]).

Statistical Analyses

- PFS will be analyzed when the requisite number of PFS events has been documented. PFS distribution will be estimated using Kaplan-Meier method. PFS will be tested using log-rank test. A Cox regression model will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence interval (CI).
- A hierarchical testing procedure will be adopted, and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant favoring ceritinib.
- OS will be estimated using the Kaplan-Meier method. OS will be tested using log-rank test. A Cox regression model will be used to estimate the HR of OS, along with 95% CI.

Table 1. Key Inclusion and Exclusion Criteria for ASCEND-4 and ASCEND-5 Studies

Key Inclusion Criteria
• Age ≥ 18 years
• World Health Organization performance status 0 to 2
• ≥ 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
ASCEND-4 Specific Inclusion Criteria
• Histologically or cytologically confirmed stage IIIb or IV nonsquamous NSCLC with ALK rearrangement assessed by the Ventana IHC test (Ventana Medical Systems, Inc.) in a central laboratory
• Prior systemic anticancer therapy not allowed except neo adjuvant or adjuvant therapy
ASCEND-5 Specific Inclusion Criteria
• Histologically or cytologically confirmed stage IIIb or IV NSCLC with ALK rearrangement (per FDA-approved Vysis ALK break-apart fluorescence in situ hybridization [FISH] assay, Abbott Molecular Inc.). If documentation of ALK rearrangement is not available, the test to confirm ALK rearrangement need to be performed (at Novartis designated central laboratory), using a new tumor biopsy obtained prior to the first dose of study treatment (ceritinib or chemotherapy) or archival tumor obtained at or since the time of diagnosis prior to study entry
• Documented disease progression at study enrollment
• Must have received previous crizotinib therapy and cytotoxic chemotherapy for stage IIIb or IV NSCLC
Key Exclusion Criteria
• Known hypersensitivity to any excipients of ceritinib
• History of carcinomatous meningitis
• Presence or history of malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years
• History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis
• Other severe, acute, or chronic medical conditions
• Patient with symptomatic central nervous system (CNS) metastases who is neurologically unstable or has required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms
ASCEND-4 Specific Exclusion Criteria
• History of severe hypersensitivity reaction to platinum containing drugs,pemetrexed, or any known excipients of these drugs
ASCEND-5 Specific Exclusion Criteria
• History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
• History of severe hypersensitivity reaction to pemetrexed or docetaxel or any known excipients of these drugs

SUMMARY

- **ASCEND-4 and ASCEND-5 are the first randomized, phase III studies comparing the antitumor activity of ceritinib vs standard chemotherapy in patients with advanced ALK-positive NSCLC.**
  - **The ASCEND-5 is first randomized, phase III study enrolling patients resistant to crizotinib.**
- **In ASCEND-4 study, approximately 348 previously untreated adult patients with advanced ALK-positive nonsquamous NSCLC will be randomized (1:1 ratio) to either ceritinib or chemotherapy followed by pemetrexed alone in nonprogressors (maintenance).**
- **In ASCEND-5 study, approximately 236 adult patients with ALK-positive, advanced NSCLC previously treated with cytotoxic chemotherapy and crizotinib will be randomized (1:1 ratio) to either ceritinib or chemotherapy.**
- **The primary outcome in both studies is PFS, which will be assessed by Blinded Independent Review Committee per RECIST 1.1. The crossover design may impact the OS endpoint in both studies.**

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