ORIGINAL ARTICLE

Ceritinib plus Nivolumab in Patients with Advanced *ALK*-Rearranged Non–Small Cell Lung Cancer: Results of an Open-Label, Multicenter, Phase 1B Study

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ABSTRACT

Introduction: Induction of programmed death ligand 1 (PD-L1) expression due to constitutive oncogenic signaling has been reported in NSCLC models harboring echinoderm microtubule associated protein like 4 gene (*EML4*)–ALK receptor tyrosine kinase gene (*ALK*) rearrangements. We assessed the safety and activity of ceritinib plus nivolumab in these patients.

Methods: In this open-label, phase 1B, multicenter, dose escalation and expansion study, previously treated (with ALK receptor tyrosine kinase [ALK] inhibitor [ALKI]/chemotherapy) or treatment-naive patients with stage IIIB or IV *ALK*-rearranged NSCLC received nivolumab, 3 mg/kg intravenously every 2 weeks, plus ceritinib, 450 mg/300 mg daily, with a low-fat meal.

Results: In total, 36 patients were treated (a 450-mg cohort [n=14] and a 300-mg cohort [n=22]). In the 450-mg cohort, four patients experienced dose-limiting toxicities. In the 300-mg cohort, two patients experienced dose-limiting toxicities. Among ALKI-naive patients, the overall response rate (ORR) was 83% (95% confidence interval [CI]: 35.9–99.6) in the 450-mg cohort and 60% (95% CI: 26.2–87.8) in the 300-mg cohort. Among ALKI-pretreated patients, the ORR was 50% (95% CI: 15.7–84.3) in the 450-mg cohort and 25% (95% CI: 5.5–57.2) in the 300-mg cohort. The ORR point estimate was observed to be greater in patients who were positive for PD-L1 than in those who were negative for PD-L1, with overlapping CIs (e.g., at a cutoff $\geq$1% PD-L1, 64% of patients [95% CI: 35.1–87.2] had confirmed responses as compared with those with negative PD-L1 staining (31% [95% CI: 11.0–58.7]). The most frequently reported grade 3 or 4 adverse events were increased alanine aminotransferase level (25%), increased gamma-glutamyl transferase level (22%), increased amylase level (14%), increased lipase level (11%), and maculopapular rash (11%). The incidence of all-grade rash (grouped term) was 64% in both cohorts; grade 3 rash was reported in 29% and 14% of patients in the 450-mg and 300-mg cohorts, respectively; no grade 4 rash was reported.

Conclusion: Ceritinib plus nivolumab has activity; ORR appears to correlate with PD-L1 at baseline. Toxicity, especially rash, is more common than with either single agent.

Keywords: Ceritinib; Nivolumab; ALK; PD-1; NSCLC

Introduction

Drugs that target oncogenic driver mutations or inhibit immune checkpoints are reshaping management of NSCLC.[1] ALK receptor tyrosine kinase gene (*ALK*) rearrangements are key oncogenic drivers, occurring in 3% to 7% of patients with NSCLC.[2,3] Ceritinib (brand name Zykadia [Novartis, East Hanover, NJ]), a selective oral ALK inhibitor (ALKI), is approved for the treatment of patients with metastatic *ALK*-rearranged NSCLC, both in the first-line setting and in patients who progressed while taking crizotinib or are intolerant to it.[4] The most common adverse events (AEs) with ceritinib at a dose of 750 mg/d fasted that have been reported in clinical trials are diarrhea, nausea, vomiting, increased alanine aminotransferase (ALT) level, decreased appetite, increased aspartate aminotransferase (AST) level, fatigue, and abdominal pain, all reported in more than 30% of patients.[5-9] Recent data from a phase 1 study of ceritinib (ASCEND-8 [NCT02299505]) showed that the frequency and severity of gastrointestinal toxicities were lower with a starting dose of 450 mg/d administered with food with a dose of 750 mg/d when patients fasted, with fewer patients requiring dose reduction or interruption, resulting in a higher median relative dose intensity and comparable efficacy.[10,11] On the basis of the ASCEND-8 data, the 450-mg dose of ceritinib with food was recently approved as the recommended dose in the United States[12] and Europe.[13]

Nivolumab (proprietary name Opdivo, Bristol-Myers Squibb, NY) is a PD-1 immune checkpoint inhibitor approved by the U.S. Food and Drug Administration for metastatic NSCLC that has progressed during or after platinum-based chemotherapy[14] and approved in Europe for locally advanced or metastatic NSCLC after prior chemotherapy.[15] In two phase 3 trials, an overall survival benefit was observed with nivolumab versus with docetaxel regardless of the programmed death ligand 1 (PD-L1) expression level[16–18]; however, survival was enhanced in patients with nonsquamous NSCLC having higher PD-L1 expression.[16,17] The most frequently reported AEs with nivolumab in clinical trials were fatigue, nausea, decreased appetite, and asthenia.[16,17]

Induction of PD-L1 expression due to constitutive oncogenic signaling has been reported in NSCLC models harboring echinoderm microtubule associated protein like 4 gene (*EML4*)–*ALK* rearrangements, contributing to immune escape in these models.[19] This preclinical evidence and the demonstrated efficacy of ceritinib monotherapy in *ALK*-rearranged NSCLC and nivolumab monotherapy in stage IIIB or IV NSCLC provided a rationale to evaluate the combination ceritinib plus nivolumab in patients with *ALK*-rearranged NSCLC. This multicenter, phase 1B, dose-finding, proof-of-concept study is the first study assessing the safety and activity of the combination of ceritinib plus nivolumab in these patients.

Patients and Methods

Study Design and Participants

In this phase 1B study, patients were recruited from nine centers across eight countries. The study design included a dose escalation phase, guided by Bayesian logistic regression model (BLRM) with overdose control to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE),[20,21] followed by a two-arm expansion phase, using the RDE of the combination and enrolling ALKI-treated (one prior treatment with any ALKI except ceritinib) and ALKI-naive patients. Results from the dose escalation phase are reported in this article.

Adult patients (age $\geq$18 years) were eligible if they had histologically or cytologically confirmed stage IIIB or IV *ALK*-rearranged NSCLC with *ALK* rearrangement determined by the U.S. Food and Drug Administration–approved Vysis ALK Break-Apart Fluorescent in Situ Hybridization Probe Kit (Abbott Molecular Inc., Molecular, Des Plaines, IL) and scoring algorithm (including positivity criteria). If documentation of *ALK* rearrangement was not available, the test to confirm *ALK* rearrangement was performed at a Novartis-designated central laboratory and the result had to be available before initiation of ceritinib treatment. PD-L1 expression was not used to determine eligibility. Patients who were treatment naive or who had received prior chemotherapy regimens or ALKIs for advanced disease were eligible for the dose escalation phase. Other inclusion criteria included presence of at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1, a WHO performance status of 0 or 1, and adequate organ function and laboratory test results. Patients with asymptomatic or neurologically stable brain metastases were eligible (Supplementary Appendix).

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization. The study protocol and all amendments were reviewed and approved by the independent ethics committee or institutional review board for each center. All patients provided written informed consent before screening.

Procedures

Eligible patients received ceritinib (at assigned dose levels) once daily with a low-fat meal (fed) in continuous 28-day treatment cycles, plus nivolumab, 3 mg/kg every 2 weeks (fixed dose). The originally planned dose levels for ceritinib were 450 mg/d fed (starting dose level), 600 mg/d fed, and 300 mg/d fed. In the study, the patients were treated with ceritinib, 450 mg/d fed and 300 mg/d fed. Patients continued treatment with ceritinib and/or nivolumab until unacceptable toxicity, death, or withdrawal of consent and/or at the discretion of the investigator. For more information, please refer to the Supplementary Appendix.

Outcomes

The primary objective was to determine the MTD and/or RDE of ceritinib plus nivolumab (dose escalation phase) and to assess the preliminary antitumor activity of the ceritinib plus nivolumab combination at the RDE (dose escalation and dose expansion phases). The primary end points were dose-limiting toxicities (DLTs) in each dose cohort during the first 6 weeks of therapy and overall response rate (ORR), as assessed per the Response Evaluation Criteria in Solid Tumors version 1.1) by investigator assessment.

Secondary objectives were to assess the safety profile and efficacy based on investigator-assessed duration of response (DOR), disease control rate, and progression-free survival (PFS). Exploratory objectives included assessment of pharmacokinetics of ceritinib and nivolumab and correlation of clinical efficacy end points with baseline PD-L1 expression, as well as potential resistance biomarkers at the time of disease progression. For more information, please refer to the Supplementary Appendix.

Statistical Analysis

For dose escalation, a five-parameter BLRM using the escalation with overdose control (EWOC) principle was used for dose level selection and for determination of the MTD and RDE. Pharmacokinetic parameters for ceritinib were summarized by treatment group by using descriptive statistics, including geometric mean and geometric coefficient of variation. For maximum time, median values were provided. ORR and disease control rate were estimated, and their associated exact binomial 95% confidence intervals (CIs) were reported. PFS and DOR were analyzed by using the Kaplan-Meier method; the median value with the associated 95% CI was reported.

The data cutoff was August 30, 2017 (except for the ceritinib pharmacokinetic data, for which the cutoff was September 9, 2016). We used SAS software (version 9.4) for analyses. For more information, please refer to the Supplementary Appendix.

Results

Between June 11, 2015, and July 11, 2016, a total of 36 patients were treated; of these, 14 patients received ceritinib, 450 mg/d fed, plus nivolumab, 3 mg/kg every 2 weeks, and 22 patients received ceritinib, 300 mg/d fed,

plus nivolumab, 3 mg/kg every 2 weeks. At data cutoff, 13 patients (five in the 450-mg cohort and eight in the 300-mg cohort) were still receiving treatment and 23 patients had discontinued treatment (Supplementary Appendix). In all, 17 patients discontinued treatment because of disease progression, four because of AEs (cerebrovascular accident [study drug–unrelated], asthenia [study drug–unrelated], increased lipase level [study drug–related], and increased ALT level [study drug–related], and increased carcinoembryonic antigen level [study drug–unrelated]), and two patients did not complete treatment because of death (due to disease progression in both cases). The median duration of follow-up from treatment start to cutoff date was 24.6 months (interquartile range [IQR] 21.8–25.1) for the 450-mg cohort (25.1 months [IQR 24.5–26.1] in the ALKI-naive patients and 22.1 months [IQR 21.4–24.9] in the ALKI-pretreated patients) and 17.6 months (IQR 15.5–20.4) for the 300-mg cohort (19.6 months [IQR 15.6–20.6] in the ALKI-naive patients and 15.9 months [IQR 14.9–20.1] in the ALKI-pretreated patients).

Baseline patient demographics and disease characteristics are shown in Table 1. The baseline characteristics were similar in patients in the 450-mg and 300-mg cohorts.

The median duration of exposure to study treatment was 47.0 weeks (range 1.0–116.0) for the 450-mg cohort and 37.3 weeks (range 4.4–91.3) for the 300-mg cohort. Of the 14 patients in the 450-mg cohort, 12 were evaluable for dose-determining analysis. Two patients at each dose level were not evaluable because they did not receive the minimum required 28 days of treatment with ceritinib and/or two complete nivolumab infusions during the first 6 weeks. Four patients experienced DLTs: pancreatitis in two patients (one grade 2 [asymptomatic] and one grade 3), autoimmune hepatitis in one patient (grade 3), and both increased lipase (grade 4) and increased transaminase levels (grade 3) in

Table 1. Baseline Characteristics

Characteristic	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 14)	Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 22)
Age		
Median, y (range)	56.5 (36.0-78.0)	53.0 (35.0-66.0)
<65 y, n (%)	10 (71.4)	21 (95.5)
≥65 y, n (%)	4 (28.6)	1 (4.5)
Sex, n (%)		
Male	8 (57.1)	10 (45.5)
Race, n (%)		
Asian	6 (42.9)	8 (36.4)
White	8 (57.1)	14 (63.6)
WHO performance status, n (%)		
0	7 (50.0)	7 (31.8)
1	7 (50.0)	15 (68.2)
Smoking history, n (%)		
Never-smoker	7 (50.0)	10 (45.5)
Ex-smoker	6 (42.9)	11 (50.0)
Current smoker	1 (7.1)	1 (4.5)
Key metastatic site of cancer, n (%)		
Brain	5 (35.7)	10 (45.5)
Bone	5 (35.7)	9 (40.9)
Liver	3 (21.4)	7 (31.8)
Prior antineoplastic regimens, n (%)		
0	1 (7.1)	3 (13.6)
1	4 (28.6)	8 (36.4)
2	5 (35.7)	5 (22.7)
≥3	4 (28.6)	6 (27.3)
Prior ALKI, n (%)		
0	6 (42.9)	10 (45.5)
1	5 (35.7)	9 (40.9)
2	2 (14.3)	2 (9.1)
3	1 (7.1)	1 (4.5)

ALKI, ALK receptor tyrosine kinase inhibitor.

Table 2. All-Causality Adverse Events (in ≥10% of Patients for Grade 1 or 2 and All Grade 3 and 4 Events)

	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 14)			Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 22)		
Preferred Term, n (%)	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Diarrhea	12 (85)	0	0	12 (55)	1 (5)	0
ALT level increased	6 (43)	2 (14)	0	6 (27)	7 (32)	0
AST level increased	6 (43)	1 (7)	0	8 (36)	1 (5)	0
Vomiting	6 (43)	1 (7)	0	7 (32)	1 (5)	0
Nausea	6 (43)	0	0	8 (36)	0	0
Amylase level increased	4 (29)	2 (14)	0	4 (18)	3 (14)	0
Blood creatinine level increased	3 (21)	0	0	8 (36)	0	0
Rash	4 (29)	2 (14)	0	5 (23)	0	0
Maculopapular rash	3 (21)	2 (14)	0	4 (18)	2 (9)	0
Fatigue	2 (14)	2 (14)	0	5 (23)	1 (5)	0
Headache	5 (36)	0	0	5 (23)	0	0
Upper respiratory tract infection	5 (36)	0	0	5 (23)	0	0
Back pain	4 (29)	1 (7)	0	3 (14)	1 (5)	0
Cough	4 (29)	0	0	5 (23)	0	0
Decreased appetite	4 (29)	0	0	5 (23)	0	0
GGT level increased	1 (7)	2 (14)	0	0	5 (23)	1 (5)
Pyrexia	2 (14)	0	0	6 (27)	1 (5)	0
Blood ALP level increased	2 (14)	1 (7)	0	5 (23)	0	0
Lipase level increased	1 (7)	0	2 (14)	3 (14)	1 (5)	1 (5)
Pruritus	3 (21)	0	0	5 (23)	0	0
Upper abdominal pain	2 (14)	0	0	5 (23)	0	0
Arthralgia	3 (21)	0	0	4 (18)	0	0
Noncardiac chest pain	2 (14)	1 (7)	0	3 (14)	0	0
Anaemia	2 (14)	1 (7)	0	2 (9)	0	0
Constipation	0	0	0	5 (23)	0	0
Abdominal pain	3 (21)	0	0	0	1 (5)	0
Stomatitis	3 (21)	0	0	1 (5)	0	0
Hypophosphatemia	2 (14)	1 (7)	0	0	0	0
Macular rash	2 (14)	1 (7)	0	0	0	0
Hypothyroidism	2 (14)	0	0	1 (5)	0	0
Pericardial effusion	0	0	1 (7)	0	0	0
Dyspepsia	1 (7)	0	0	3 (14)	0	0
Pancreatitis	1 (7)	1 (7)	0	0	0	0
Asthenia	1 (7)	0	0	2 (9)	1 (5)	0
Influenza-like illness	0	0	0	4 (18)	0	0
Deterioration of general physical health	0	0	0	0	1 (5)	0
Autoimmune hepatitis	0	1 (7)	0	0	0	0
Conjunctivitis	0	0	0	3 (14)	0	0
Pneumonia	1 (7)	1 (7)	0	1 (5)	0	0
Nasopharyngitis	2 (14)	0	0	0	0	0
Head injury	1 (7)	0	0	0	1 (5)	0
Blood bilirubin level increased	2 (14)	0	0	3 (14)	0	0
Transaminase levels increased	0	2 (14)	0	0	1 (5)	0
Weight decreased	2 (14)	0	0	1 (5)	0	0
Neutrophil count decreased	2 (14)	0	0	0	0	0
Hepatic enzyme levels increased	0	1 (7)	0	0	0	0
Hyperglycemia	1 (7)	1 (7)	0	2 (9)	1 (5)	0
Hypokalemia	0	0	1 (7)	0	1 (5)	0
Hyperamylasemia	0	0	0	0	1 (5)	0
Hyponatremia	0	0	0	0	1 (5)	0
Musculoskeletal pain	1 (7)	0	0	4 (18)	0	0
Neck pain	1 (7)	0	0	3 (14)	0	0
Musculoskeletal chest pain	0	0	0	3 (14)	0	0
Muscular weakness	0	0	0	1 (5)	1 (5)	0

(continued)

Table 2. Continued

Preferred Term, n (%)	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 14)			Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 22)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Dizziness	2 (14)	0	0	2 (9)	0	0
Cerebrovascular accident	0	1 (7)	0	0	0	0
Seizure	0	0	0	0	1 (5)	0
Insomnia	2 (14)	0	0	3 (14)	0	0
Anxiety	0	0	0	1 (5)	0	0
Mental status changes	0	1 (7)	0	0	0	0
Renal impairment	0	1 (7)	0	0	0	0
Dyspnea	0	2 (14)	0	2 (9)	0	0
Pulmonary edema	0	0	0	0	0	1 (5)
Dry skin	2 (14)	0	0	3 (14)	0	0
Papular rash	2 (14)	0	0	1 (5)	0	0
Drug eruption	1 (7)	0	0	0	1 (5)	0
Xeroderma	0	1 (7)	0	0	0	0

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transferase.

one patient. Of the 22 patients in the ceritinib 300-mg cohort, 20 were evaluable for dose-determining analysis and two experienced DLTs: increased ALT level in two patients (both grade 3 with no bilirubin level increase). Both dose levels satisfied the BLRM EWOC criteria. The dose of 600 mg/d fed was not used because of toxicities noted in the 450-mg fed group.

AEs regardless of study drug relationship in at least 20% of patients (in any cohort) are shown in Table 2. The most frequently reported AE in the overall population (N = 36) was diarrhea (69%); only one patient (in the 300-mg cohort) had grade 3 or 4 diarrhea. Other frequently reported AEs (≥30%) in the overall population (N = 36) were increased ALT level (58%), increased AST level (44%), vomiting (42%), nausea (39%), increased amylase level (36%), increased blood creatinine level (31%), rash (31%), and maculopapular rash (31%). The most frequently (in >10% of all patients [n = 14]) reported grade 3 or 4 AEs in the ceritinib 450-mg cohort were increased ALT level, increased amylase level, rash, maculopapular rash, fatigue, increased γ-glutamyl transferase (GGT) level, increased lipase level, dyspnea, and increased transaminase levels (all reported in 14.3% of patients). The most frequently (in >10% of all patients [n = 22]) reported grade 3 or 4 AEs in the 300-mg/d cohort were increased ALT level in 32%, increased GGT level in 27%, and increased amylase level in 14%.

When pooled terms were used, rash was a common AE (Table 3). Overall, 64% of patients experienced development of rash-related events regardless of study drug relationship, including 19% of patients with grade 3 or 4 rash-related events (see Table 3). The proportion of patients with rash-related events was similar in the 450-mg cohort (64%) and the 300-mg cohort (64%). However, the proportion of patients with grade 3 or 4 rash-related events was 29% in the 450-mg cohort and 14% in the 300-mg cohort. Overall, the incidence of rash was 93% in the Asian patients and 46% in the non-Asian patients (see Table 3). Most patients (50% in each cohort) experienced the initial onset of rash during the first 6 weeks of treatment; however, it was not considered a DLT as per the study protocol.

Among the overall 36 patients, AEs requiring ceritinib dose change were reported in 12 patients (33%) and AEs leading to dose interruptions (either drug or both) were reported in 29 patients (81%) (Table 4). On the basis of these safety findings, including DLTs and rash-related events, the safety committee (investigators and Novartis) decided to investigate an alternative dosing regimen.

The preliminary efficacy of ceritinib plus nivolumab combination according to whether prior ALKI treatment was received is shown in Table 5. The confirmed ORR (by investigator) in ALKI-naive patients was 69% (95% CI: 41.3–89.0) (one complete response [CR] and 10 partial responses [PRs]); the ORR was 83% (95% CI: 35.9–99.6) in the 450-mg cohort (all PRs) and 60% (95% CI: 26.2–87.8) in the 300-mg cohort (one CR and five PRs). The ORR in ALKI-pretreated patients was 35% (95% CI: 15.4–59.2); the ORR was 50% (95% CI: 15.7–84.3) in the 450-mg cohort (all PRs) and 25% (95% CI:5.5–57.2) in the 300-mg cohort (all PRs).

The Kaplan-Meier analysis results of median PFS and DOR with low sample sizes need to be interpreted with caution. In the ceritinib 450-mg cohort, the median DOR was 11.2 months (95% CI: 3.7–not estimable [NE]) in the ALKI-pretreated patients (n = 4), whereas it was not reached in the ALKI-naive patients (n = 5) (95% CI: 3.9–NE), as a high proportion of responders were censored

among the ALKI-naive patients (three of five patients [60%]). In the ceritinib 450-mg cohort, the estimated event-free rates at 6 months and 10 months were 80% (four of five responders at risk) (95% CI: 20.4–96.9) in the ALKI-naive patients and 75% (three of four responders at risk) (95% CI: 12.8–96.1) in the ALKI-pretreated patients. In the ceritinib 300-mg cohort, the median DOR was not reached for either ALKI-naive (n = 5) (95% CI: 3.8–NE) or ALKI-pretreated patients (n = 3) (95% CI 7.4–NE) owing to the high proportion of responders censored: five of six patients (83%) among the ALKI-naive patients and two of three patients (67%) among the ALKI-pretreated patients. In the ceritinib 300-mg cohort, the estimated event-free rates at 10 months were 83% (five of six responders at risk) (95% CI: 27.3–97.5) in the ALKI-naive patients and 67% (two of three responders at risk) (95% CI: 5.4–94.5) in the ALKI-pretreated patients. Because of the high proportion of responders censored, we need to interpret the results with caution. The best percentage change from baseline in target lesions for the ALKI-naive and ALKI-pretreated patients is shown in Supplementary Figure 2.

Across both cohorts, the median PFS time was not reached in the ALKI-naive patients and was 4.6 months (95% CI: 2.1–13.6) in the ALKI-pretreated patients (Fig. 1) (data for each dose level are provided in Supplementary Table 2); the proportion of patients censored was 10 of 16 (62.5%) among the ALKI-naive patients versus four of 20 (20.0%) among the ALKI-pretreated patients. The corresponding estimated PFS rates at 12 months were 67.5% (95% CI: 38.4–85.1) and 35.0% (95% CI: 15.7–55.2), respectively.

In the ceritinib 450-mg cohort, the median PFS was 6.4 months (95% CI: 0.8–13.7, with seven of eight patients [88%] having events) in the ALKI-pretreated patients (n = 8), whereas it was not reached in the ALKI-naive patients (n = 6) (95% CI: 1.8–NE, with three of six patients [50%] having events) (see Table 5), as a high proportion of patients were censored among ALKI-naive patients (three of six patients [50%]). In the ceritinib 450-mg cohort, the estimated event-free rates at 12 months were 67% (95% CI: 19.5–90.4) in the ALKI-naive patients and 38% (95% CI: 8.7–67.4) in the ALKI-pretreated patients (see Table 5). In the ceritinib 300-mg cohort, the median PFS was 3.7 months (95% CI: 1.8–NE, with nine of 12 patients [75%] having events) in the ALKI-pretreated patients (n = 12), whereas it was not reached in ALKI-naive patients (n = 10) (95% CI: 1.9–NE, with three of 10 patients [30%] having events), as a high proportion of patients were censored among the ALKI-naive patients (seven of 10 patients [70%]). In the ceritinib 300-mg cohort, the estimated event-free rates at 12 months were 67% (95% CI: 27.2–88.1) in the ALKI-naive patients and 33% (95% CI: 10.3–58.8) in the ALKI-pretreated patients.

Among the 15 patients with brain metastases at baseline, six were ALKI naive, of whom four had a confirmed response (three PRs and one CR) and nine were ALKI-pretreated, of whom two had a confirmed PR (Supplementary Table 2).

In total, 30 patients had baseline tumor tissue available for PD-L1 staining using the immunohistochemistry 28-8 pharmDx assay. At each cutoff of PD-L1 expression examined, the ORR point estimate was observed to be greater in patients who were positive for PD-L1 than in those who were negative for PD-L1, with overlapping CIs (Supplementary Table 3). For example, at a cutoff of at least 1% PD-L1, 64% of patients (95% CI: 35.1–87.2) had confirmed responses as compared with patients with negative PD-L1 staining (31% [95% CI: 11.0–58.7]) (see Supplementary Table 3).

Discussion

This study explored the combination of an ALKI (ceritinib) with a PD-1 inhibitor (nivolumab) in patients with *ALK*-rearranged NSCLC. This combination appears to have promising activity, particularly in patients with high PD-L1 expression based on an exploratory analysis; however, the combination was associated with relevant toxicity, principally rash, ALT and/or AST level increases, and lipase level increases.

Table 3. Overview of Rash

		Dose		Race	
Maximum Grade of Rash	All Patients (N = 36)	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 14)	Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 22)	Asian (n = 14)	Non-Asian (n = 22)
All grades (all causality), n (%)	23 (64)	9 (64)	14 (64)	13 (93)	10 (46)
Grade 3	7 (19)	4 (29)	3 (14)	3 (21)	4 (18)
Grade 2	8 (22)	3 (21)	5 (23)	7 (50)	1 (5)
Grade 1	8 (22)	2 (14)	6 (27)	3 (21)	5 (23)

Note: Pooled terms: maculopapular rash, rash, dry skin, macular rash, papular rash, dermatitis acneiform, drug eruption, rash erythematous, pruritic rash, blister, dermatitis, allergic dermatitis, erythema, exfoliative rash, skin exfoliation, xeroderma.

Table 4. Overview of Safety

Variable	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 14)	Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 22)	Total (N = 36)
Adverse events, n (%)			
All adverse events	14 (100)	22 (100)	36 (100)
Grade 3 or 4 adverse events	13 (93)	18 (82)	31 (86)
Adverse events (study drug-related)	14 (100)	22 (100)	36 (100)
Adverse events requiring ceritinib dose change, n (%)			
All adverse events	3 (21)	9 (41)	12 (33)
Grade 3 or 4 adverse events	0	3 (14)	3 (8)
Adverse events leading to dose interruptions (either drug or both), n (%)			
All adverse events	13 (93)	16 (73)	29 (81)
Interruption of ceritinib	12 (86)	17 (77)	29 (81)
Interruption of nivolumab	9 (64)	9 (41)	18 (50)
Grade 3 or 4 adverse events	12 (86)	11 (50)	23 (64)
Adverse events leading to discontinuation (either drug or both), n (%)			
All adverse events	5 (36)	6 (27)	11 (31)
Grade 3 or 4 adverse events	3 (21)	5 (23)	8 (22)

Recently, a phase 1/2 study (CheckMate 370) evaluated the safety and tolerability of first-line nivolumab plus crizotinib in patients with *ALK*-positive NSCLC. However, of the first 13 patients treated with nivolumab plus crizotinib, five (38%) experienced development of severe hepatic toxicities leading to discontinuation of the combination; of these, two patients died.[22]

Other second-generation ALKI are being explored in combination with immunotherapy.[23] Recently, Kim et al. presented the data from a study of alectinib plus atezolizumab[24] in which alectinib was given as a run-in from 7 days before combining with atezolizumab. The ORR reported in their study was 86% (18 out of 21 patients) and the median PFS was 21.7 months (95% CI: 13.1–NE). The incidence of treatment-related AEs with combination therapy was 52%, with grade 3 rash reported in 19% of patients.[24]

In the current study, four patients among 12 evaluable patients in the ceritinib 450-mg fed cohort experienced DLTs; the 450-mg dose satisfied the BLRM EWOC criteria. Further, the incidence of rash was higher than that observed with ceritinib monotherapy (up to 22%)[6,7,9] or nivolumab monotherapy (up to 18%).[16-18] The overall incidence of rash-related events (pooled term) was 64% and was similar at both tested dose levels; however, the incidence of grade 3 rash was higher at the 450-mg dose level (29% vs 14%). Of note, none of the patients reported grade 4 rash. The incidence of all-grade rash (pooled term) was higher in Asian patients (93% [13 of 14]) than in non-Asian patients (45% [10 of 22]); the interpretation of these results is limited owing to the small sample size. The mechanism of rash-related events with the combination ceritinib plus nivolumab is unclear. Other frequent grade 3 or 4 AEs were increased ALT level, increased GGT level, increased amylase level, and increased lipase level; however, these AEs were not increased compared with those known for either agent. The incidence of diarrhea and vomiting in the 450-mg fed cohort was higher than that reported with ceritinib, 450 mg fed, in the ASCEND-8 study,[11] perhaps because of the fact that nivolumab is also known to be associated with these AEs.[16,17] However, no increased frequency of colitis was observed and these AEs were managed by dose interruption, dose reduction, or supportive concomitant medication. The MTD was not reached, and the recommended phase 2 dose was not established. On the basis of these safety findings, an alternative dosing regimen (regimen B) is being investigated. In this alternative dosing regimen, ceritinib monotherapy is administered for two cycles before initiation of combination therapy with nivolumab to allow for safety observation and ceritinib dose reduction before initiation of combination therapy with nivolumab. Thus, the regimen was designed in such a way that ceritinib was given initially as monotherapy and nivolumab was added later with the rationale that the frequency of toxicity with the original regimen would decrease. The dose of ceritinib used in the alternative regimen was 450 mg fed, as the ceritinib

Table 5. Best Overall Response, Duration of Response, and Progression-Free Survival by Investigator Review

Variable	ALKI-Naive			ALKI-Pretreated		
	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 6)	Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 10)	Total (n = 16)	Ceritinib, 450 mg Fed, plus Nivolumab, 3 mg/kg (n = 8)	Ceritinib, 300 mg Fed, plus Nivolumab, 3 mg/kg (n = 12)	Total (n = 20)
Overall response rate, n (%) [95% CI]	5 (83) [36-100]	6 (60) [26-88]	11 (69) [41-89]	4 (50) [16-84]	3 (25) [6-57]	7 (35) [15-59]
Complete response, n (%)	—	1 (10)	1 (6)	—	—	—
Partial response, n (%)	5 (83)	5 (50)	10 (63)	4 (50)	3 (25)	7 (35)
Stable disease, n (%)	—	3 (30)	3 (19)	2 (25)	6 (50)	8 (40)
Progressive disease, n (%)	1 (17)	1 (10)	2 (13)	—	3 (25)	3 (15)
Unknown	—	—	—	2 (25)	-—	2 (10)
Disease control rate, n (%) [95% CI]	5 (83) [36-100]	9 (90) [56-100]	14 (88) [62-98]	6 (75) [35-97]	9 (75) [43-95]	15 (75) [51-91]
Duration of response, n/n (%)						
Median (95% CI) (mo)	2/5 (40)	1/6 (17)	3/11 (27)	3/4 (75)	1/3 (33)	4/7 (57)
Event-free rate, % (95% CI)	NE (3.9-NE)	NE (3.8-NE)	NE (3.9-NE)	11.2 (3.7-NE)	NE (7.4-NE)	11.9 (3.7-NE)
6 mo	80 (20-97)	83 (27-98)	82 (45-95)	75 (13-96)	100 (100-100)	86 (33-98)
10 mo	80 (20-97)	83 (27-98)	81.8 (45-95)	75 (138-96)	67 (5-95)	71 (26-92)
Progression-free survival, n/n (%)						
Median (95% CI) (mo)	3/6 (50)	3/10 (30)	6/16 (38)	7/8 (88)	9/12 (75)	16/20 (80)
Event-free rate, % (95% CI)	NE (1.8-NE)	NE (1.9-NE)	NE (5.6-NE)	6.4 (0.8-13.7)	3.7 (1.8-NE)	4.6 (2.1-13.6)
6 mo	67 (20-90)	80 (41-95)	75 (46-90)	50 (15-78)	42 (15-67)	45 (23-65)
8 mo	67 (20-90)	80 (41-95)	75 (46-90)	38 (9-67)	42 (15-67)	40 (19-60)
12 mo	67 (20-90)	67 (27-88)	68 (38-85)	37.5 (9-67)	33 (10-59)	35 (16-55)

ALKI, ALK receptor tyrosine kinase inhibitor; CI, confidence interval; NE, not estimable.

steady-state pharmacokinetics of the 450-mg fed regimen were similar to those of the 750-mg fasted regimen (on the basis of the ASCEND-8 study)[10]; therefore, the efficacy from ceritinib would not be compromised. In the study by Kim et al., alectinib was given as monotherapy during the run-in period followed by combination with atezolizumab; interestingly, in that study, safety of the combination of alectinib and atezolizumab was acceptable.[24] Both explored cohorts have demonstrated preliminary evidence of activity. As expected, the ORR was higher in the ceritinib 450-mg cohort than in the ceritinib 300-mg cohort in both ALKI-naive and ALKI-pretreated patients. The PD-L1 inhibitor durvalumab, used as a third-line or later treatment, has shown limited activity (ORR, 12%) in patients with *ALK*-positive NSCLC.[25] In the current study, the ORR was observed to be higher in patients with positive PD-L1 staining, suggesting an additive effect by combining ceritinib with nivolumab; however, because of the small sample sizes, these results need to be interpreted with caution. The PFS time in previously treated *ALK*-positive patients in this study was short; however, it has to be noted that 20 of 36 patients (56%) received at least two prior antineoplastic regimens and six of 36 patients (17%) received at least two ALKIs.

The ceritinib steady-state pharmacokinetics of the 450-mg fed regimen was similar to that of the 750-mg fasted regimen (historical data).[26] This finding is consistent with the results of the ASCEND-8 study, which demonstrated that ceritinib in a dose of 450 mg with food had comparable exposure and efficacy, with improved gastrointestinal safety than with ceritinib, 750 mg, in fasted patients with *ALK*-rearranged NSCLC.[10,11] The trough concentration of nivolumab reached steady state by cycle 8 and remained stable afterward. Accumulation of the trough concentration from the first dose to steady state was 3.7-fold, which is consistent with the published values.[27] Although some benefit was observed in patients at all PD-L1 levels, greater benefit was found in those with higher PD-L1 positivity. However, given the small sample size and the exploratory nature of this analysis, these results need to be interpreted with caution (see Supplementary Table 3). The absence of either detectable circulating tumor DNA or baseline *ALK* somatic single-nucleotide variation mutations may be associated with longer PFS; however, these results need to be interpreted with caution.[28] The major limitation of our study is smaller sample size for the exploratory analysis of ORR; future studies with a larger number of patients are needed to assess ALKIs in combination with PD-1 inhibitor in ALK-positive patients with NSCLC with higher PD-L1 positivity.

When all the data are taken together, combining ceritinib with nivolumab has been associated with an increase in toxicity, including rash (grade $\leq$3), when administered concomitantly at the recommended single-agent doses. Nevertheless, this combination appears to elicit activity, with exploratory analysis suggesting that high PD-L1 expression may enrich for patients more likely to respond. Identifying subgroups of patients with *ALK*-rearranged NSCLC who may yet benefit from adding an anti–programmed death 1 therapy to ceritinib remains a crucial challenge. On the basis of these safety findings, an alternative dosing regimen is being investigated in which ceritinib is administered as monotherapy for two cycles before initiation of the combination therapy with nivolumab.

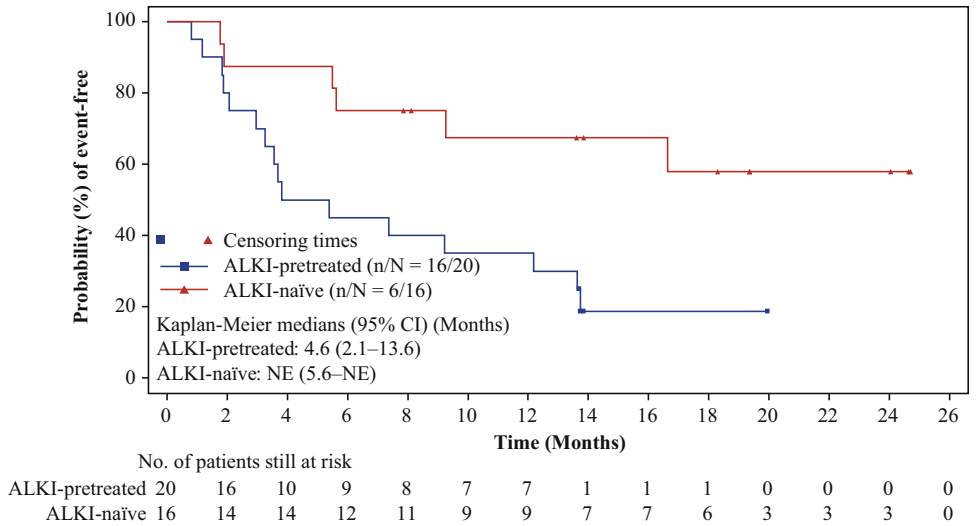

Figure 1. Progression-free survival by prior ALK receptor tyrosine kinase inhibitor (ALKI) status. CI, confidence interval; NE, not estimable.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.10.006.

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