ORIGINAL ARTICLE

Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation — Positive Advanced Non–Small Cell Lung Cancer (CheckMate 370)

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ABSTRACT

Introduction: Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, is a first-line treatment for *ALK* translocation–positive advanced non–small cell lung cancer (NSCLC); however, patients eventually progress. Immunotherapies, including the programmed death-1 inhibitor nivolumab, have resulted in durable responses and long-term overall survival in patients with NSCLC. We hypothesized that combining targeted therapy with immunotherapy could result in more patients with responses and/or more durable responses. Herein we report data from a study assessing nivolumab plus crizotinib in patients with previously untreated advanced *ALK* translocation–positive NSCLC.

Methods: Group E in CheckMate 370 was a single-arm cohort designed to evaluate the safety of first-line

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nivolumab (240 mg every 2 weeks) plus crizotinib (250 mg twice daily) in patients with *ALK* translocation–positive NSCLC. The primary endpoint of safety would be met if ≤20% of patients discontinued treatment due to treatment-related adverse events by week 17. Objective response rate was a secondary endpoint. A planned safety review occurred in November 2016; the data cutoff was May 26, 2017.

Results: Of the first 13 patients treated with nivolumab plus crizotinib, 5 (38%) developed severe hepatic toxicities leading to the discontinuation of the combination. Of these, two patients died and the presence of severe hepatic toxicities may have contributed to death. Enrollment was closed and combination treatment discontinued due to observed grade ≥3 hepatic toxicities. Five patients (38%) had a partial response.

Conclusions: These findings do not support further evaluation of nivolumab 240 mg every 2 weeks plus crizotinib 250 mg twice daily.

Keywords: Non–small cell lung cancer; PD-1 inhibitor; Nivolumab; Crizotinib; anaplastic lymphoma kinase translocation

Introduction

The identification of anaplastic lymphoma kinase (ALK) rearrangements in approximately 5% of patients with non–small cell lung cancer (NSCLC) has expanded the personalized treatment of this disease.[1-3] Crizotinib is a first-in-class receptor tyrosine kinase inhibitor of ALK, ROS1, and c-Met approved for the treatment of metastatic *ALK* translocation–positive or *ROS1*-positive NSCLC.[4] Approval in the first-line *ALK* translocation–positive setting was based on a randomized, phase 3 study that showed significantly improved progression-free survival and objective response rates with crizotinib versus platinum-doublet chemotherapy.[5] However, approximately half of patients treated with crizotinib experience progression by 1 year.

Nivolumab, a fully human immunoglobulin G4 programmed death-1 (PD-1) inhibitor antibody, was approved in the United States, the European Union, and other countries for previously treated, metastatic NSCLC[6] based on two randomized, phase 3 studies that showed significantly improved overall survival and objective response rates with nivolumab compared with docetaxel.[7-9] Additionally, nivolumab showed a favorable safety profile for the first-line treatment of metastatic or recurrent NSCLC.[10] We hypothesized that the combination of nivolumab with crizotinib could result in higher response rates, more durable responses, and improved long-term overall survival in patients with *ALK* translocation–positive disease. Herein we report the safety and tolerability, as well as best overall response, with nivolumab in combination with crizotinib for the first-line treatment of *ALK* translocation–positive advanced NSCLC.

Patients and Methods

Study Design and Treatment

CheckMate 370 is a 5-cohort, open-label phase 1/2 study of nivolumab in advanced NSCLC using nivolumab as maintenance after induction chemotherapy or as first-line treatment alone or in combination with standard of care therapies (ClinicalTrials.gov number, NCT02574078). This cohort (group E) investigated nivolumab plus crizotinib for the first-line treatment of histologically confirmed, recurrent locally advanced or metastatic NSCLC positive for an *ALK* translocation (Supplementary Fig. 1). ALK testing was performed locally and use of a U.S. Food and Drug Administration–approved test was strongly encouraged. Eligible patients were 18 years of age or older, had an Eastern Cooperative Oncology Group performance status score of 0 to 2, and had measurable disease by computed tomography within 21 days of study drug administration. Required baseline laboratory tests included white blood cell counts of at least 2,000/mL, neutrophils at least 1,500/mL, platelets at least 100 10^3/mL, hemoglobin at least 9.0 g/dL, serum creatinine within 1.5 upper limit of normal (ULN) or calculated creatinine clearance greater than 40 mL/min, aspartate aminotransferase (AST) 3.0 ULN or below, alanine aminotransferase (ALT) 3.0 ULN or below, and total bilirubin 1.5 ULN or below.

Key exclusion criteria included untreated or active central nervous system metastases, the need for systemic treatment with corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive medications within 2 weeks of study drug administration (inhaled or topical steroids and adrenal replacement steroid doses [>10 mg daily equivalent] were permitted in the absence of autoimmune disease), history of autoimmune disease, and symptomatic interstitial lung disease (except for controlled chronic obstructive pulmonary disease) before study drug administration.

Patients were assigned to receive nivolumab 240 mg intravenously over 30 minutes every 2 weeks plus crizotinib 250 mg orally twice daily, which are the U.S.-approved doses for each drug as monotherapy. Safety was evaluated continuously throughout the study and measured by the frequency of adverse events (AEs) and serious AEs occurring up to 100 days after the last dose of study drug and the frequency of clinical laboratory tests by worst toxicity grade (as assessed at screening and every cycle). AEs and laboratory abnormalities were

graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs preferred term. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors version 1.1.[11]

The primary objective of this cohort study was safety and tolerability. The regimen was defined as safe if 20% or fewer patients developed treatment-related adverse events (TRAEs) that led to discontinuation of both therapies by week 17. Objective response rate was a secondary objective.

The study protocol was approved by an institutional review board or independent ethics committee at each participating center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. Written informed consent was collected from all patients before enrollment.

Statistical Analyses

The planned enrollment for this cohort was 20 patients. Safety was analyzed in all treated patients. Descriptive statistics were conducted for AE incidence, baseline and demographic information, and laboratory tests. Time to onset was calculated from first dosing date to the event onset date. Time to resolution was calculated from the AE onset date to AE end date. The best overall response was listed for each patient. A planned safety review occurred in November 2016. The data cutoff for this analysis was May 26, 2017.

Results

This analysis included 13 patients treated with nivolumab plus crizotinib. Four additional patients were screened, but not treated due to no longer meeting study criteria, having been enrolled in error, or closure of group E enrollment. At baseline, the median age was older than typical patients with *ALK* translocation–positive NSCLC (63 years) and there were more smokers than anticipated (62% were current or former smokers)[5]; 54% of patients were male and nearly all patients had Eastern Cooperative Oncology Group performance status score of 0 or 1.

At the time of the interim safety review, 3 of the first 13 treated patients (23%) experienced grade 3 or more hepatic toxicities leading to the discontinuation of combination treatment. Enrollment to the cohort was suspended based on the results of the planned safety review. Subsequently, two additional patients developed grade 3 or more hepatic TRAEs; both of them died. The first patient presented with grade 4 treatment-related pneumonitis, grade 3 rhabdomyolysis, and grade 3 ALT/AST elevations (the cause of death was attributed to pneumonitis). The second patient presented with treatment-related grade 4 acute liver failure and died 1 week later; the death was attributed to acute respiratory failure from disease progression by the investigator. However, it is possible that the grade 4 liver failure contributed to the fatal outcome. After the death of these two patients, all ongoing patients in group E, regardless of status due to the hepatic safety signal, were immediately subject to discontinuation of combination treatment and continued to be treated with a subsequent therapy (chemotherapy or ALK inhibitor).

At the time of data cutoff, five total patients had developed grade 3 or more liver toxicity, which fully recovered with or without steroid treatment in three of the patients. The timing, treatment, and outcomes of the five patients with grade 3 or more hepatic events are presented in Figure 1. All five of these patients had ALT and AST levels within the normal range at baseline, and none of these five patients had liver metastases before enrollment.

Of the remaining eight patients enrolled and treated on the study, three additional patients had grade 1 to 2 hepatic TRAEs and fully recovered with or without intervention (dose delay and steroid treatment). A summary of individual patient baseline characteristics, treatment summary and exposure, safety, reasons for discontinuation, and tumor response for all patients as of the data cutoff on May 26, 2017, is presented in Table 1. The minimum follow-up time for this analysis was 7.2 months. Median treatment duration of the combination therapy was 1.6 months (range, 0.7 to 6.2 months), and the median number of doses received was 3.0 months (range, 1 to 14 months) for nivolumab and 49.0 months (range, 20 to 183 months) for crizotinib.

Partial responses were reported in 5 of 13 patients (38%). A best response of stable and progressive disease was observed in 2 (15%) and 3 (23%) patients, respectively (Table 1). Subsequent responses after discontinuation of combination therapy were not collected. Tumor responses could not be determined in the remaining 3 patients because of treatment discontinuation before disease assessment.

Discussion

The combination of nivolumab (240 mg every 2 weeks) plus crizotinib (250 mg twice daily) in patients with *ALK* translocation–positive NSCLC was evaluated in cohort E of CheckMate 370. The primary objective was safety and tolerability. Ongoing safety review suggested a hepatic safety signal based on the first 13 patients, leading to a suspension of enrollment and eventual permanent closure to enrollment and discontinuation of combination therapy in all patients in cohort E.

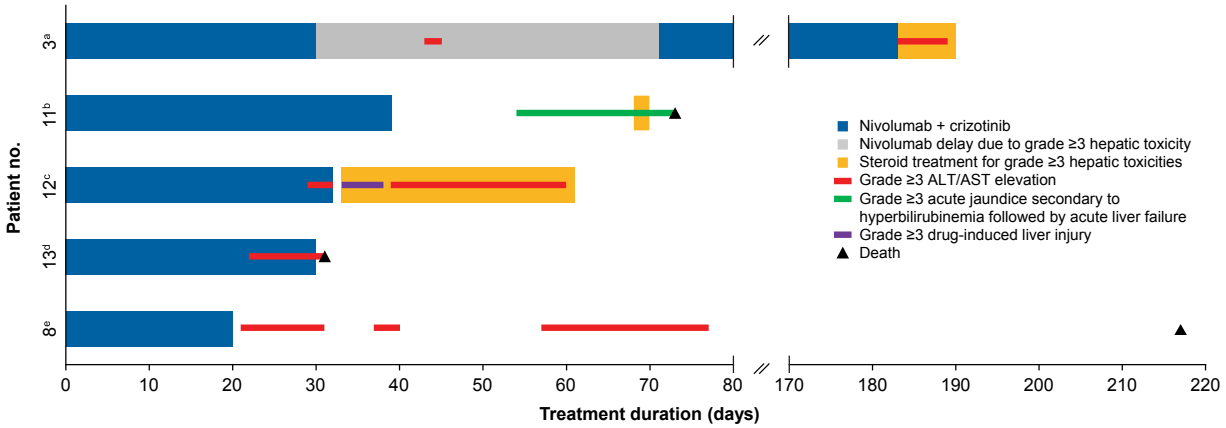

Figure 1. Patients with grade ≥3 hepatic adverse events. [a]Nivolumab was also delayed in this patient between days 85 and 113 and 113 and 169. Patient also experienced treatment-related grade 1 to 2 ALT/AST elevations throughout the treatment period and after treatment discontinuation; all ALT/AST elevations resolved. Crizotinib also was delayed between days 29 and 71. [b]Acute jaundice secondary to hyperbilirubinemia initiated on day 54 and acute liver failure initiated on day 68, neither of which resolved before death; after treatment discontinuation, the patient also experienced grade 2 ALT/AST elevations that were not treated with steroids before experiencing acute liver failure. [c]Drug-induced liver injury initiated on day 33. After treatment discontinuation and with steroid treatment, the patient's grade 3 ALT/AST elevations were improved to a lower grade and eventually resolved. [d]Grade 3 ALT/AST elevations initiated on day 22 and did not resolve before death. [e]Before and after treatment discontinuation, the patient also experienced grade 1 to 2 ALT/AST elevations before and after grade 3 ALT/AST elevations; the grade 3 ALT/AST elevations were improved to a lower grade and eventually resolved without steroids. Patient died of disease progression. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

These are the first results reported from a study combining a PD-1 inhibitor with crizotinib. Discontinuation rates due to hepatic AEs were low with single-agent nivolumab (treatment-related 0.3% to 1.5% of patients)[7,8] or crizotinib (2.3%)[5] for the treatment of advanced NSCLC; therefore, the incidence of potential overlapping toxicities was expected to be low. Nonetheless, liver function tests were monitored every 2 weeks throughout the study. In our study, the rate of discontinuation of treatment due to hepatic TRAEs with the combination regimen was higher than historical expectations based on observations with either monotherapy alone. The underlying mechanisms causing observed toxicities with this combination are currently unknown, but could be due to additive effects, drug-drug interactions (e.g., creation of reactive drug metabolites capable of interfering with cell function and inducing cell death), off-target effects, exacerbation of tyrosine kinase inhibitor–induced damage by checkpoint inhibitors, or immune-based effects, among other possibilities.

The combination of nivolumab plus ceritinib, another ALK inhibitor, for *ALK* translocation–positive advanced NSCLC is being investigated in a phase 1b study (Clinicaltrials.gov number, NCT02393625). In the first 36 patients treated with nivolumab plus ceritinib, a total of seven dose-limiting toxicities were observed, including pancreatitis (n = 2), autoimmune hepatitis (n = 1), elevated lipase (n = 1), elevated transaminases (n = 1), and elevated ALT (n = 2).[12] Hepatotoxicity was a common AE (all grade [all-causality], 69%). The most common hepatic AEs were elevated ALT (58.3%), AST (44.4%), gamma-glutamyltransferase (25.0%), and blood bilirubin (13.9%). The most common grade 3 to 4 AEs were elevated ALT (25.0%) and gamma-glutamyltransferase (22.2%). Grade 3 or higher rash occurred in 19% of patients. An objective response rate of 68.8% was reported. The initial efficacy findings and safety signals in this trial led to an amendment of the trial to evaluate an alternate dosing regimen with sequential run-in of ceritinib before combination with nivolumab. Hepatotoxicity appears to be a class effect among ALK inhibitors[4,13,14]; however, the mechanism of action for increased toxicity with these combinations (and tyrosine kinase inhibitors in general) is unknown. Differences in hepatotoxicity between crizotinib, ceritinib, and other ALK tyrosine kinase inhibitors may be due to different kinases (beyond the primary target) being targeted by different agents or other off-target effects.

Beyond alternative dosing schedules, further exploration of combining immunotherapy and other ALK inhibitors with lower observed hepatotoxicity rates, such as brigatinib, are warranted, and combination with other tyrosine kinase inhibitors targeting other membrane receptors remains an active area of research. Additional trials of ALK inhibitors combined with checkpoint inhibitors that target PD-1 (crizotinib plus nivolumab; crizotinib plus pembrolizumab), PD-1 (alectinib plus atezolizumab; lorlatinib or crizotinib plus avelumab; ensartinib plus durvalumab), and cytotoxic T

Table 1. Patient Summary

Patient No.	Baseline Characteristics				Exposure to Combination, mo	TRAEs		Reason for Discontinuation	Best Tumor Response
	Sex	Age, y	Smoking Status	ECOG PS		Event	Worst Grade		
1	F	56	Current/former	1	1.08	Fatigue	3	Disease progression	PD
						Elevated ALT	1		
						Elevated blood alkaline phosphatase	1		
						Anemia	1		
						Diarrhea	1		
2	F	63	Never	0	1.48	Constipation	3	Consent withdrawn (side effects of medication)	PR
						Elevated ALT	2		
						Visual distortion	1		
						Fatigue	1		
3	F	50	Never	0	6.01	Elevated ALT	3	TRAEs (ALT and AST elevations)	SD
						Elevated AST	3		
						Erythematous rash	3		
						Hypokalemia	3		
						Arthralgia	1		
						Headache	1		
						Visual disturbance	1		
4	M	60	Current/former	1	6.24	Hypocalcemia	1	Other (arm closed)[a]	PR
						Hypomagnesemia	1		
5	M	75	Current/former	1	2.30	Vomiting	2	Disease progression	PD
						Hypophosphatemia	2		
6	M	83	Current/former	1	1.61	Asthenia	3	Consent withdrawn	NE
						Altered consciousness	3		
						Hypomagnesemia	1		
7	M	88	Never	2	3.38	Diarrhea	2	TRAE (increased diarrhea)	PR
						Nausea	1		
						Decreased appetite	1		
8	M	55	Current/former	1	0.66	Elevated ALT	3	Other (hepatic toxicities and LFTs remained above grade 1 so patient restarted crizotinib)	PD
						Thrombocytopenia	3		
						Elevated AST	2		
						Exertional dyspnea	2		
						Pneumonitis	2		
						Decreased platelet count	2		
						Blurred vision	1		
9	M	82	Current/former	0	4.14	Elevated ALT	1	Administrative reason by sponsor[a]	PR
						Elevated AST	1		
						Hypocalcemia	1		
						Elevated creatinine	1		
						Fatigue	1		
10	F	72	Current/former	1	3.29	None		Administrative reason by sponsor[a]	SD

(continued)

Table 1. Continued

Patient No.	Baseline Characteristics				Exposure to Combination, mo	TRAEs		Reason for Discontinuation	Best Tumor Response
	Sex	Age, y	Smoking Status	ECOG PS		Event	Worst Grade		
11	F	56	Current/former	1	1.28	Acute liver failure	4	Administrative reason by sponsor[b]	NE
						Hypotension	2		
						Vomiting	2		
						Nausea	2		
12	M	60	Never	1	1.05	Drug-induced liver injury	4	TRAE (drug-induced liver injury)	PR
						Elevated ALT	3		
						Elevated AST	3		
						Elevated LDH	2		
13	F	75	Never	1	0.99	Pneumonitis	5	Death	NE
						Pneumonia	4		
						Sepsis	4		
						Elevated ALT	3		
						Elevated AST	3		
						Rhabdomyolysis	3		
						Acute myocardial infarction	3		

[a]Treatment was discontinued immediately in all ongoing patients regardless of status due to the hepatic safety signal in the study.
[b]Discontinuation was due to a TRAE (hepatic safety signal).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; LDH, lactate dehydrogenase; LFT, liver function test; M, male; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event.

lymphocyte antigen-4 (crizotinib plus ipilimumab) are being investigated for the treatment of advanced NSCLC (Clinicaltrials.gov identifiers: NCT01998126, NCT02511184, NCT02013219, NCT02584634, NCT02898116, and NCT01998126, respectively); however, to our knowledge, preliminary results have not yet been reported.

The number of patients receiving nivolumab plus crizotinib with an objective response was less than anticipated based on those who responded to crizotinib monotherapy for the first-line treatment of advanced NSCLC.[5] Efficacy outcomes were likely compromised by a high rate of early discontinuation.

In conclusion, this cohort study of nivolumab plus crizotinib did not meet the primary endpoint of safety and tolerability for the first-line treatment of *ALK* translocation–positive advanced NSCLC. The findings of this study do not support further evaluation of nivolumab 240 mg every 2 weeks plus crizotinib 250 mg twice daily.

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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.2018.02.022.

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