ORIGINAL ARTICLE

Comparative Efficacy of Ceritinib and Crizotinib as Initial *ALK*–Targeted Therapies in Previously Treated Advanced NSCLC: An Adjusted Comparison with External Controls

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ABSTRACT

Introduction: Crizotinib and ceritinib have been developed to treat advanced or metastatic NSCLC by inhibiting anaplastic lymphoma receptor tyrosine kinase gene (*ALK*). No randomized trial has compared these treatments head-to-head. We compared efficacy outcomes between patients receiving ceritinib and an external control group receiving crizotinib, both as initial *ALK*-targeted therapies for previously treated advanced or metastatic *ALK*-positive NSCLC.

Methods: Individual patient data for the ceritinib-treated patients were drawn from two single-arm trials (ASCEND-1 and ASCEND-3); published summary data for the crizotinib-treated patients were extracted from three trials (PROFILE 1001, PROFILE 1005, and PROFILE 1007). To adjust for cross-trial differences, average baseline characteristics were matched using propensity score weighting. Overall survival (OS), progression-free survival (PFS), and overall response rate were then compared between treatment groups.

Results: Before matching, the ceritinib-treated patients (n = 189) were significantly different from the crizotinib-treated patients (n = 557) in the distribution of race and number of prior regimens. After matching, all available baseline characteristics were balanced. Compared with crizotinib, ceritinib was associated with longer OS (hazard ratio = 0.59, 95% confidence interval: 0.46–0.75) and longer PFS (median 13.8 versus 8.3 months, hazard ratio = 0.52, 95% confidence interval: 0.44–0.62) in Cox proportional hazards models. The 12-month OS was 82.6% with ceritinib and 66.0% with crizotinib in a Kaplan-Meier analysis (log-rank $p < 0.001$). There was no significant difference in overall response rate between ceritinib and crizotinib.

Conclusions: In an adjusted comparison across separate clinical trials, ceritinib was associated with prolonged OS and PFS compared with crizotinib when used as initial *ALK*-targeted therapy for previously treated *ALK*-positive NSCLC.

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Keywords: ALK; NSCLC; ceritinib; crizotinib; indirect comparison

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Introduction

Lung cancer is the worldwide leading cause of cancer death and is typically diagnosed at an advanced stage.[1,2] More than 85% of lung cancers are classified as NSCLC,[3] for which chemotherapy is at best only moderately active, with response rates of approximately 20%.[4,5] Effective targeted therapies developed against specific molecular subtypes of NSCLC such as *EGFR* and anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) have further expanded the therapeutic opportunities and have led to significant improvement in survival.[6,7]

Approximately 2% to 7% of patients with stage III or IV NSCLC harbor *ALK* fusions.[8] These patients tend to be younger, associated with light or never-smoking status, and have a propensity for development of brain metastases.[9,10] The occurrence of brain metastases is estimated to be up to 50% in patients treated with first-generation *ALK* inhibitors.[11] Two *ALK*-targeted therapies, crizotinib and ceritinib, have been approved for the treatment of *ALK*-positive NSCLC. Crizotinib has been demonstrated to improve progression-free survival (PFS) compared with chemotherapy in both the first-line[12] (median PFS 10.9 months versus 7.0 months, respectively) and second-line[13] (median PFS 7.7 months versus 3.0 months, respectively) settings. Ceritinib, a second-generation *ALK* inhibitor, has been shown to be effective in the treatment of advanced or metastatic *ALK*-positive NSCLC, including for crizotinib-pretreated patients. In the phase I ASCEND-1 clinical trial, the overall response rate (ORR) was 56.4% with a median PFS of 6.9 months among patients with prior use of crizotinib.[14] Among crizotinib-naive patients, more than 70% achieved ORR and the median PFS was 18.4 months.[14]

Recent studies have revealed potential differences in efficacy between these two *ALK*-targeted therapies. According to preclinical data, ceritinib is 20 times as potent as crizotinib against *ALK*.[15] In addition, ceritinib has been shown to be active in patients in whom resistance to crizotinib has developed, with impressive tumor responses observed in brain metastases.[16,17] To date, no randomized controlled trial (RCT) has compared crizotinib and ceritinib, although each has been investigated in multiple clinical trials.[13,14,18–20] In the absence of head-to-head RCTs, comparative efficacy in advanced oncology settings, including *ALK*-positive NSCLC, is often based on comparisons with external controls.[11,21–23] One technique that can reduce bias in such comparisons is the use of propensity score matching to achieve baseline similarity across treatment groups. These steps include a comparison of trial designs and study settings, selection of patients based on shared inclusion/exclusion criteria, and matching of multiple known baseline prognostic factors on the basis of a propensity score model. Studies reporting an estimated treatment effect derived by this method have been supported by results from RCTs.[24,25]

The present study attempted to compare efficacy outcomes for ceritinib with those in an external control population receiving crizotinib in two cohorts balanced through propensity score matching. We then compared the overall survival (OS), PFS, and ORR of patients receiving ceritinib with those of the external comparator receiving crizotinib, with both treatments used as the initial *ALK*-targeted therapy for chemotherapy-treated *ALK*-positive NSCLC.

Materials and Methods

Study Populations and Data Sources

The evidence for the efficacy of ceritinib and crizotinib in crizotinib-naive advanced or metastatic *ALK*-positive NSCLC is based on five clinical trials. Two single-arm studies are available for ceritinib in this population: the phase I trial ASCEND-1[14,20] (NCT01283516 [data cutoff date April 14, 2014]) and the phase II trial ASCEND-3[26] (NCT01685138 [data cutoff date June 27, 2014]). Three trials are available for crizotinib, including the phase I single-arm study PROFILE 1001[18] (NCT00585195 [data cutoff date January 2, 2012]), the phase II single-arm study PROFILE 1005[19] (NCT00932451 [data cutoff date February 1, 2011]), and the phase III, open-label RCT of crizotinib and chemotherapy PROFILE 1007[13] (NCT00932893 [data cutoff date March 30, 2012]). These data represent the most recent, publically available crizotinib trial data in which the relevant population and outcomes of interest are reported. The doses assigned in the ceritinib and crizotinib arms in these trials are consistent with label recommendations (750 mg orally once daily for ceritinib; 250 mg orally twice daily for crizotinib).

These five trials had generally consistent study designs (Supplementary Table 1). All trials enrolled adult patients with locally advanced or metastatic *ALK*-positive NSCLC. Patients with stable or controlled brain metastases were allowed. Baseline Eastern Cooperative Oncology Group performance status (ECOG PS) ranged between 0 and 2 within all studies except for PROFILE 1005, in which approximately 17% of patients had a baseline ECOG PS of 3. All trials allowed prior treatment for advanced or metastatic *ALK*-positive NSCLC, but only the ASCEND-3 and PROFILE 1001 trials specifically excluded patients previously treated with *ALK*-targeted agents. PROFILE 1005 allowed at least one prior chemotherapy, and PROFILE 1007 trial allowed only one prior platinum-based chemotherapy; the other trials did not limit the number or type of prior systemic therapies.

Individual patient data (IPD) from the ceritinib trials were obtained from Novartis Pharmaceuticals Corporation. IPD from the crizotinib trials were not publically available, so published summary statistics from the crizotinib trials were used in the current analyses. In particular, data on baseline characteristics and response rates were extracted from published literature and publically available regulatory briefing documents and reports.[27,28] Rates of OS and PFS at multiple time points were extracted from published Kaplan-Meier curves using Engauge Digitizer software[29] and the approach described in Guyot et al. 2012,[30] which is consistent with the National Institute for Health and Care Excellence technical support guidelines.[31]

As a first step toward harmonizing the study populations receiving ceritinib and crizotinib, a shared set of inclusion and exclusion criteria was applied to all trials. All present analyses included data only from patients who had (1) received at least one prior systemic therapy and (2) not been previously treated with an *ALK*-targeted agent. Thus, in the crizotinib trials, published baseline characteristics and outcomes were extracted specifically for the subgroup of previously treated patients. In the ceritinib trials, IPD for all previously treated and crizotinib-naive patients were included.

Outcome Measures

OS, PFS, and ORR were defined similarly across trials. OS was defined as the time from treatment initiation (or from randomization for PROFILE 1007) to death due to any cause. PFS was defined as the time from treatment initiation (or from randomization for PROFILE 1007) to disease progression (defined by Response Evaluation Criteria in Solid Tumors [RECIST]) or death due to any cause, whichever occurred first. Durations of OS and PFS in patients without observed events were censored at the last day on which they were known to be event-free. ORR was defined as the proportion of patients with a best overall complete response (CR) or partial response (PR) determined by specified criteria (i.e., RECIST version 1.0 for phase I trials, RECIST version 1.1 for phase II and III trials).

Statistical Methods

To assess comparability of the ceritinib-treated population and the external control group receiving crizotinib, baseline characteristics were compared between these treatment groups. All baseline variables that were available and consistently defined in all trials were included: age, sex, race, tumor histologic type (e.g., adenocarcinoma), ECOG PS (0 versus $\geq$1), and number of prior regimens (1, 2, or $\geq$3). Comparisons were conducted using chi-square tests.

To make an adjusted comparison between the ceritinib- and crizotinib-treated patients, propensity score weighting was used to adjust for baseline differences between the populations.[32,33] Specifically, individual ceritinib-treated patients were assigned statistical weights that adjusted for their overrepresentation or underrepresentation relative to the crizotinib-treated population such that after weighting, average baseline characteristics were balanced between the treatment groups. The statistical weights were based on a propensity score model incorporating all available baseline characteristics. The propensity score model

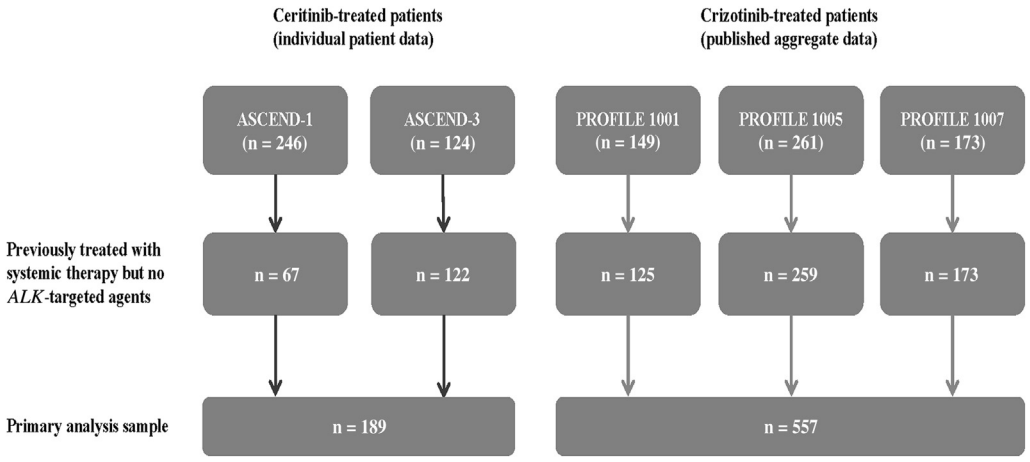

Figure 1. Patient selection of pooled ceritinib- and crizotinib-treated populations. Individual patient data for ceritinib-treated patients were pooled from two single-arm trials (ASCEND-1 and ASCEND-3). Summary baseline characteristics and efficacy outcomes for crizotinib-treated patients were extracted from three published studies (PROFILE 1001, PROFILE 1005, and PROFILE 1007). Previously treated patients without prior exposure to anaplastic lymphoma receptor tyrosine kinase gene (*ALK*)-targeted therapies were selected as the primary analysis sample.

Table 1. Primary Analysis: Baseline Characteristics before and after Matching

Baseline Characteristics	Pooled Ceritinib Population		Pooled Crizotinib Population
	Prematch (n = 189)	Postmatch (n = 189; n_{eff} = 143)	As Reported (n = 557)
Median age, y	55.0	52.0	52.0
Female	56.6	54.0	54.0
Asian[a]	55.0	37.6	37.6
ECOG performance status of 0	34.9	32.2	32.2
No. prior regimens[a]			
1	48.7	45.1	45.1
2	28.0	21.8	21.8
≥3	23.3	33.1	33.1
Adenocarcinoma	94.7	95.0	95.0

Note: Reported as percentages unless otherwise specified.
[a]*p* Values < 0.05 were considered statistically significant for comparisons between pooled ceritinib and crizotinib trials before matching.
n_{eff}, effective sample size after weighting; ECOG, Eastern Cooperative Oncology Group.

was estimated on the basis of IPD available for the ceritinib-treated patients and the published summary data available for the crizotinib-treated patients.[34–36]

After matching, efficacy outcomes were compared between balanced treatment groups using statistical tests that incorporated the propensity score weights. For OS and PFS, weighted Kaplan-Meier curves were generated and compared using weighted log-rank tests. Hazard ratios (HRs) comparing ceritinib and crizotinib were estimated using weighted Cox proportional hazards models. The proportional hazards assumption was tested both before and after matching. ORRs were compared using weighted chi-square tests.

Four sensitivity analyses were conducted to explore additional baseline adjustments involving ethnicity, brain metastases, single-arm versus randomized trial design, and smoking status. The first sensitivity analysis was conducted to match on the proportion of white versus nonwhite patients, whereas the primary analysis adjusted for the proportion of Asian versus non-Asian patients because of a potentially higher response rate to crizotinib among Asian patients revealed in previous studies.[11,18,37] In the present study, non-Asian and nonwhite individuals comprised only 1% of ceritinib- and 5% of crizotinib-treated patients. In the second sensitivity analysis, the presence of baseline brain metastases was additionally adjusted for considering brain metastases as one of the prognostic factors associated with poor outcomes in *ALK*-positive NSCLC. Because the baseline information with brain metastases was not available in PROFILE 1001, the second sensitivity analysis included only the subset of crizotinib trials (PROFILE 1005 and PROFILE 1007) that reported brain metastases. The third sensitivity analysis excluded PROFILE 1007, the only RCT included in the study (all other trials were single-arm), to investigate potential confounding of the external control group by randomization to chemotherapy. Lastly, given the impact of smoking status on NSCLC clinical outcomes, the fourth sensitivity analysis added smoking status at baseline to the list of characteristics used for adjustment, excluding the ASCEND-3 trial, in which data on smoking status were not available.

Table 2. Primary Analysis: Comparisons of OS, PFS, and Response Rate before and after Matching

Efficacy Outcomes[a]	Pooled Ceritinib Population		Pooled Crizotinib Population	*p* Values	
	Prematch (n = 189) [A]	Postmatch (n = 189; n_{eff} = 143) [B]	As reported (n = 557) [C]	[A] vs. [C]	[B] vs. [C]
OS					
Median, mo	NR (19.6-NR)	NR (19.6-NR)	20.5 (19.9-29.6)		
1-year OS rate, %	83.5 (75.6-89.0)	82.6 (74.9-91.1)	66.0 (62.1-70.2)	<0.001[b]	<0.001[b]
HR (ceritinib vs. crizotinib)	0.49 (0.33-0.74)	0.59 (0.46-0.75)	Reference	<0.001[b]	<0.001[b]
PFS					
Median, mo	13.8 (11.1-NR)	13.8 (11.1, NR)	8.3 (7.3-9.3)		
1-year PFS rate, %	56.5 (47.5-67.1)	58.2 (47.9-70.7)	37.2 (33.3-41.5)	<0.001[b]	<0.001[b]
HR (ceritinib vs. crizotinib)	0.56 (0.43-0.73)	0.52 (0.44-0.62)	Reference	<0.001[b]	<0.001[b]
Response rate					
ORR (CR + PR), %	66.7 (59.9-73.4)	68.3 (60.8-75.7)	61.2 (57.2-65.3)	0.181	0.102
CR, %	0.0	0.0	1.4 (0.4-2.4)	0.098	0.010[b]
PR, %	66.7 (59.9-73.4)	68.3 (60.8-75.7)	59.8 (55.7-63.9)	0.093	0.049[b]

[a]Ranges in parentheses are 95% confidence intervals.
[b]*p* Values < 0.05 were considered statistically significant for comparisons between pooled ceritinib and crizotinib trials.
OS, overall survival; PFS, progression-free survival; N_{eff}, effective sample size after weighting; NR, not reached; HR, hazard ratio; ORR, overall response rate; CR, complete response; PR, partial response.

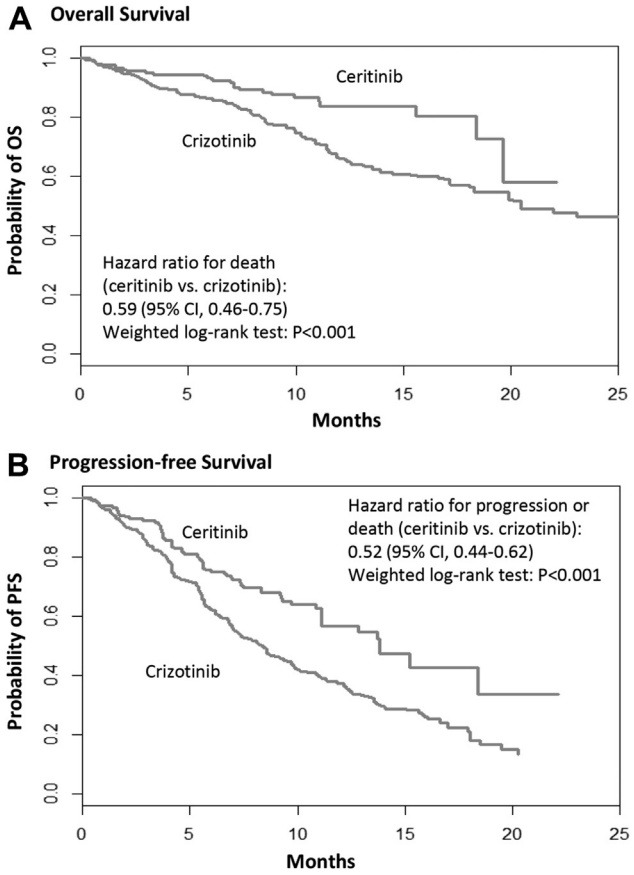

Figure 2. Overall survival (OS) and progression-free survival (PFS) between balanced ceritinib- and crizotinib-treated populations. (*A*) Kaplan-Meier estimates of OS after matching adjustment. The median OS was not reached with ceritinib as compared with 20.5 months with crizotinib. (*B*) Kaplan-Meier estimates of PFS after matching adjustment. The median PFS was 13.8 months with ceritinib as compared with 8.3 months with crizotinib. CI, confidence interval.

All analyses were conducted using SAS 9.3 software (SAS Institute Inc., Cary, NC) and R 2.15.2 software (R Foundation for Statistical Computing). Statistical significance was assessed at the 5% level.

Results

The pooled ceritinib trials included 189 patients who had at least one prior systemic treatment and were naive to *ALK*-targeted agents, including 67 patients from ASCEND-1 and 122 from ASCEND-2. The pooled crizotinib trials consisted of 557 previously treated patients, including 125 patients from PROFILE 1001, 259 from PROFILE 1005, and 173 randomized to the crizotinib arm in PROFILE 1007. Selection of the primary analysis sample is described in Figure 1. Efficacy outcomes in the included trials are summarized in Supplementary Table 2.

Before matching, the ceritinib-treated patients included a significantly higher proportion of Asians (55.0% versus 37.6% [$p < 0.001$]) compared with the crizotinib-treated patients. The distribution of number of prior regimens was significantly different between the two populations, with more heavily pretreated patients in the pooled crizotinib trials ($p = 0.028$). After matching adjustment, all baseline characteristics were exactly balanced between the two populations (Table 1). After weighting adjustment, the effective sample size for the ceritinib-treated patients, which measures the statistical information available after weighting, was 143 (the number of actual subjects included in the analyses remained 189 before and after weighting).

After matching, the 1-year OS rate was significantly higher among the ceritinib-treated patients than among the crizotinib-treated patients (82.6% versus 66.0% [$p < 0.001$]). Ceritinib was associated with a significantly lower hazard of death compared with crizotinib (HR = 0.59, 95% confidence interval: 0.46–0.75) (Table 2 and Fig. 2*A*). The 1-year PFS rate among the ceritinib-treated patients was significantly higher than that among the crizotinib-treated patients after matching (58.2% versus 37.2% [$p < 0.001$]). Ceritinib was also associated with significantly longer median PFS compared with crizotinib (median 13.8 versus 8.3 months, HR = 0.52, 95% confidence interval: 0.44–0.62) (Fig. 2*B*). Prematching analyses based on the unweighted sample produced similar results for OS and PFS. The proportional hazards assumption was validated for all analyses of OS and PFS, both before and after matching.

Before matching, the patients who received ceritinib had response rates similar to those of the patients who received crizotinib, as measured by CR (0% versus 1.4% [$p = 0.098$]), PR (66.7% versus 59.8%, [$p = 0.093$]), and ORR (66.7% versus 61.2% [$p = 0.181$]). After matching adjustment, there was a significant difference in CR (0% in ceritinib versus 1.4% with crizotinib [$p = 0.010$]) and PR (68.3% in ceritinib versus 59.8% with crizotinib, [$p = 0.049$]). ORR did not differ significantly between treatment groups.

The estimated comparative efficacy of ceritinib and crizotinib was consistent across the four sensitivity analyses after additional baseline adjustment (Table 3). In the first sensitivity analysis, the prevalence of whites was lower among the ceritinib population than among the crizotinib population (43.9% versus 57.2%) before matching and was exactly balanced at 57.2% after matching adjustment. In the second sensitivity analysis, the proportion of patients with brain metastases at screening in the ceritinib treatment group was more than double that in the crizotinib treatment group (38.6% versus 18.0%) before matching but was balanced at 18.0% in both groups after matching. In the third sensitivity analysis, which was based only on single-arm trials, the ceritinib-treated patients had a

Table 3. Sensitivity Analyses: Comparisons of OS and PFS before and after Matching

Additional Baseline Adjustment Criteria	HRs for Ceritinib vs. Crizotinib (95% CI)			
	Prematch		Postmatch	
1. Matching on prevalence of whites	n = 189 vs. n = 557	*p* Value	n_{eff} = 152 vs. n = 557	*p* Value
OS	0.49 (0.33-0.74)	<0.001	0.58 (0.45-0.74)	<0.001
PFS	0.56 (0.43-0.73)	<0.001	0.53 (0.44-0.62)	<0.001
2. Adjusting for baseline brain metastases (excluding PROFILE 1001)	n = 189 vs. n = 432		n_{eff} = 128 vs. n = 432	
OS	0.47 (0.32-0.71)	<0.001	0.50 (0.38-0.67)	<0.001
PFS	0.53 (0.40-0.69)	<0.001	0.46 (0.38-0.56)	<0.001
3. Including only single-arm trials (excluding PROFILE 1007)	n = 189 vs. n = 384		n_{eff} = 85 vs. n = 384	
OS	0.48 (0.32-0.72)	<0.001	0.63 (0.47-0.83)	0.001
PFS	0.60 (0.46-0.79)	<0.001	0.55 (0.45-0.68)	<0.001
4. Adjusting for baseline smoking status (excluding ASCEND-3)	n = 67 vs. n = 557		n_{eff} = 43 vs. n = 557	
OS	0.54 (0.32-0.93)	0.026	0.43 (0.33-0.54)	<0.001
PFS	0.50 (0.34-0.74)	<0.001	0.41 (0.35-0.49)	<0.001

Note: Ranges in parentheses are 95% confidence intervals. *p* Values < 0.05 were considered statistically significant for comparisons between pooled ceritinib and crizotinib trials.
OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI: confidence interval; N_{eff}, effective sample size after weighting.

higher proportion of Asians compared with the pooled crizotinib-treated patients (55.0% versus 33.9%) and a lower number of prior regimens (rates with one, two, or three or more regimens of 48.7%, 28.0%, and 23.3% versus 20.5%, 31.6%, and 47.9%, respectively); these differences were eliminated by matching. Finally, in the fourth sensitivity analysis, the proportion of individuals who had ever smoked was higher among the ceritinib-treated patients than among the crizotinib-treated patients before matching (53.7% versus 33.1%) but was balanced at 33.1% after matching.

Discussion

This study has estimated the comparative efficacy of ceritinib and crizotinib among patients with previously treated, crizotinib-naive advanced or metastatic *ALK*-positive NSCLC. In the absence of a head-to-head RCT, an adjusted comparison was made across separate clinical trial populations. Both before and after adjustment for cross-trial differences, ceritinib was associated with significantly prolonged OS and PFS compared with crizotinib. In particular, after adjustment, ceritinib was associated with an additional 17% of patients surviving for 1 year compared with crizotinib, and with a 5.5-month increase in median PFS. This level of improvement in median PFS is highly clinically significant for second-line metastatic NSCLC treatment, in which prior therapeutic improvements in median PFS have ranged from 0.4 to 4.7 months.[13,38]

As the present study was a comparison of non-randomized treatment groups, the baseline similarity of those groups is paramount. The fact that all treatment groups were followed in clinical trial settings, with regular follow-up visits and imaging, provides an important initial level of similarity. Multiple steps were taken to further ensure similarity. First, a review of the clinical trials indicated highly similar designs and outcome definitions. Differences in inclusion and exclusion criteria were addressed by further sample selection (i.e., including only previously treated patients who were naive to *ALK*-targeted agents). The primary analysis then adjusted for all patient characteristics that were available from all of the studied trials, which included multiple important prognostic factors in *ALK*-positive NSCLC (i.e., age, sex, race, ECOG PS, number of prior regimens, and tumor histologic type). Sensitivity analyses were conducted to adjust for additional patient characteristics that were available only in subsets of trials, including brain metastases, smoking status, and potential for randomization to chemotherapy. In particular, patients' race/ethnicity was adjusted for in the main and sensitivity analyses. The primary analysis adjusted for the proportion of Asian versus non-Asian patients whereas the sensitivity analysis matched on the proportion of white versus nonwhite patients. These analyses were conducted to ensure balance in baseline patient race/ethnicity owing to a potentially higher response rate to crizotinib among Asian patients demonstrated in previous studies.[11,18,37] The overall list of patient characteristics used for adjustment represents, by design, the characteristics considered important by the trial investigators and co-authors, and it was consistent with previously reported prognostic factors for NSCLC outcomes.[11,13,14,18] Longer

durations of OS and PFS with ceritinib versus crizotinib were consistently observed across the primary and sensitivity analyses. In addition, the changes in estimated outcomes after adjustments for known baseline prognostic factors were in the expected directions. Adjustment for the higher baseline prevalence of brain metastases in the ceritinib-treated patients resulted in improved comparative outcomes for ceritinib, as would be expected given the known poor prognosis for patients with brain metastases. Likewise, given the known negative effect of smoking history on NSCLC clinical outcomes, the adjustment for the higher baseline prevalence of ex- and current smokers among the ceritinib-treated patients contributed, as would be expected, to better comparative efficacy for ceritinib.

There are inherent limitations to this study. The absence of publically available patient-level data for the crizotinib-treated patients necessitated the use of study-level data to facilitate patient matching. Moreover, as a comparison of nonrandomized treatment groups from trials with small to moderate sample sizes, the potential for confounding due to unobserved or unadjusted differences between treatment groups remains an important limitation. However, study populations were well matched in the current analyses in terms of multiple patient characteristics including age, sex, race, ECOG PS, number of prior regimens, and histologic type (adenocarcinoma versus not). Further, differences in definitions of tumor response (i.e., use of RECIST 1.0 versus RECIST 1.1) may have limited comparisons of ORR. In addition, unrelated to confounding, the OS and PFS data might have been immature for some of the trials at the time of the present study.

As new treatment options for *ALK*-positive NSCLC emerge, evidence of comparative efficacy is needed to inform clinical and economic decisions. Direct, randomized head-to-head comparisons are the accepted standard for comparative evidence, yet they are not always available at the time decisions need to be made. This is particularly relevant for late-stage oncology settings, such as advanced or metastatic *ALK*-positive NSCLC, in which accelerated access to novel targeted therapies has generally preceded availability of phase III data. Thus, although propensity score matching of external controls cannot replace a direct head-to-head randomized comparison, it can provide some preliminary insights to comparative efficacy.[11,21–23] In the present study, the comparison of patients who received ceritinib with external controls who received crizotinib, in which all patients were followed in clinical trial settings and adjustments were made for multiple patient characteristics, represents the best available comparative evidence for these treatments as initial *ALK*-targeted therapies.

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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 http://dx.doi.org/10.1016/j.jtho.2016.05.029.

References

1. National Cancer Institute. SEER stat fact sheets: lung and bronchus cancer. Surveillance, Epidemiology, and End Results (SEER) program. http://seer.cancer.gov/statfacts/html/lungb.html. Accessed March 2, 2015.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225–249.
3. American Cancer Society. Lung cancer (non-small cell). http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf. Accessed February 15, 2014.
4. Socinski MA, Crowell R, Hensing TE, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132:277s–289s.
5. Baggstrom MQ, Stinchcombe TE, Fried DB, et al. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. *J Thorac Oncol*. 2007;2:845–853.
6. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer, version 4.2014. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Fort Washington, PA: National Comprehensive Cancer Network; 2014:1–147.
7. Villaruz LC, Socinski MA. Personalized therapy for non-small cell lung cancer: which drug for which patient? *Semin Thorac Cardiovasc Surg*. 2011;23:281–290.
8. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res*. 2008;14:4275–4283.
9. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res*. 2009;15:5216–5223.
10. Kang HJ, Lim HJ, Park JS, et al. Comparison of clinical characteristics between patients with ALK-positive and EGFR-positive lung adenocarcinoma. *Respir Med*. 2014;108:388–394.
11. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol*. 2011;12:1004–1012.
12. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167–2177.
13. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385–2394.

14. Felip E, Kim D, Mehra R, et al. 1295P—Efficacy and safety of ceritinib in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): An update of ASCEND-1. *Ann Oncol*. 2014;25(suppl 4):iv426–iv470.
15. Thomas RK. Overcoming drug resistance in ALK-rearranged lung cancer. *N Engl J Med*. 2014;370:1250–1251.
16. Katayama R, Khan TM, Benes C, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *Proc Natl Acad Sci U S A*. 2011;108:7535–7540.
17. Gainor JF, Tan DS, De Pas T, et al. Progression-free and overall survival in alk-positive nsclc patients treated with sequential crizotinib and ceritinib. *Clin Cancer Res*. 2015;21:2745–2752.
18. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol*. 2012;13:1011–1019.
19. Riely GJ, Evans TL, Salgia R, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Paper presented at the International Association for the Study of Lung Cancer Chicago Multidisciplinary Symposium in Thoracic Oncology. September 6–8, 2012; Chicago, IL.
20. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;370:1189–1197.
21. Di Lorenzo G, Casciano R, Malangone E, et al. An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples. *Expert Opin Pharmacother*. 2011;12:1491–1497.
22. Signorovitch JE, Wu EQ, Betts KA, et al. Comparative efficacy of nilotinib and dasatinib in newly diagnosed chronic myeloid leukemia: a matching-adjusted indirect comparison of randomized trials. *Curr Med Res Opin*. 2011;27:1263–1271.
23. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood*. 2006;108:2165–2172.
24. Kuss O, Legler T, Börgermann J. Treatments effects from randomized trials and propensity score analyses were similar in similar populations in an example from cardiac surgery. *J Clin Epidemiol*. 2011;64:1076–1084.
25. Smeeth L, Douglas I, Hall AJ, et al. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br J Clin Pharmacol*. 2009;67:99–109.
26. Felip E, Orlov S, Park K, et al. ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) [abstract]. Presented at the 2015 American Society of Clinical Oncology meeting. May 29–June 2, 2015; Chicago, IL. Available at http://meetinglibrary.asco.org/print/1999356. Accessed August 21, 2015.
27. Australian Government, Department of Health, Therapeutic Goods Administration. Australian Public Assessment Report for Crizotinib. Australian Government Department of Health Therapeutic Goods Administration, 2014. https://www.tga.gov.au/auspar/auspar-crizotinib. Accessed September 15, 2014.
28. National Institute for Health and Care Excellence Single Technology Appraisal: Crizotinib for the second line treatment of ALK positive non-small cell lung cancer (TA296; manufacturer's submission). http://www.nice.org.uk/guidance/ta296/resources/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-fusion-gene-previously-treated-crizotinib-pfizer2. Accessed September 15, 2014.
29. Engauge digitizer [computer program]. Version 4.1. http://markummitchell.github.io/engauge-digitizer/. Accessed July 29, 2014.
30. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9.
31. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf. Accessed March 2, 2015.
32. Hirano K, Imbens GW. Estimation of causal effects using propensity score weighting: an application to data on right heart catheterization. *Health Serv Outcomes Res Methodol*. 2001;2:259–278.
33. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
34. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010;28:935–945.
35. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health*. 2012;15:940–947.
36. Signorovitch J, Erder MH, Xie J, et al. Comparative effectiveness research using matching-adjusted indirect comparison: an application to treatment with guanfacine extended release or atomoxetine in children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 2):130–137.
37. Nishio M, Hirsh V, Kim D-W, et al. Efficacy, safety, and patient-reported outcomes with crizotinib versus chemotherapy in Asian patients in a phase III study of previously treated advanced ALK-positive non-small cell lung cancer [abstract]. *J Thorac Oncol*. 2013;8(suppl 2):S198–S199.
38. Petrelli F, Borgonovo K, Cabiddu M, et al. Biological agents alone or in combination as second-line therapy in advanced non-small-cell lung cancer: systematic review of randomized studies. *Expert Rev Anticancer Ther*. 2012;12:1299–1312.