

## Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With *ALK*-Positive Non–Small-Cell Lung Cancer

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### A B S T R A C T

#### Purpose

Alectinib has shown activity in the CNS in phase I and II studies. To further evaluate this activity, we pooled efficacy and safety data from two single-arm phase II studies (NP28761 and NP28673; [ClinicalTrials.gov](http://ClinicalTrials.gov) identifiers: NCT01871805 and NCT01801111, respectively) in patients with *ALK*-positive non–small-cell lung cancer (NSCLC).

#### Patients and Methods

Both studies included patients with *ALK*-positive NSCLC who had previously received crizotinib; all patients received alectinib 600 mg twice per day. The primary end point in both studies was independent review committee (IRC)-assessed objective response rate (ORR; by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Additional end points (all by IRC) included CNS ORR (CORR), CNS disease control rate (CDCR), and CNS duration of response (CDOR).

#### Results

One hundred thirty-six patients had baseline CNS metastases (60% of the overall study populations); 50 patients (37%) had measurable CNS disease at baseline. Ninety-five patients (70%) had prior CNS radiotherapy; 55 patients completed the CNS radiotherapy more than 6 months before starting alectinib. Median follow-up time was 12.4 months (range, 0.9 to 19.7 months). For patients with baseline measurable CNS disease, IRC CORR was 64.0% (95% CI, 49.2% to 77.1%), CDCR was 90.0% (95% CI, 78.2% to 96.7%), and median CDOR was 10.8 months (95% CI, 7.6 to 14.1 months). For patients with measurable and/or nonmeasurable baseline CNS disease, IRC CORR was 42.6% (95% CI, 34.2% to 51.4%), CDCR was 85.3% (95% CI, 78.2% to 90.8%), and median CDOR was 11.1 months (95% CI, 10.3 months to not evaluable). CORR was 35.8% (95% CI, 26.2% to 46.3%) for patients with prior radiotherapy ( $n = 95$ ) and 58.5% (95% CI, 42.1% to 73.7%) for patients without prior radiotherapy ( $n = 41$ ). As previously reported, alectinib was well tolerated, regardless of baseline CNS disease.

#### Conclusion

Alectinib showed good efficacy against CNS metastases, in addition to systemic activity, in crizotinib-refractory *ALK*-positive NSCLC.

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### INTRODUCTION

Crizotinib was the first anaplastic lymphoma kinase (*ALK*) inhibitor to receive US Food and Drug Administration (FDA) approval for the treatment of advanced *ALK*-positive non–small-cell lung cancer (NSCLC) in 2011.<sup>1,2</sup> However, although patients initially respond well to crizotinib, the majority eventually experience progressive disease (PD).<sup>3,4</sup>

Approximately 15% to 30% of all patients with lung cancer develop brain metastases, and the incidence is increasing, possibly as a result of better diagnostic methods<sup>5</sup> or longer systemic progression-free survival (PFS) on targeted therapies. In addition, the CNS is a common site of progression for patients with *ALK*-positive NSCLC treated with crizotinib; the CNS was the first site of PD in 70% of patients with known brain me-

tastases (30 of 43 patients) during crizotinib treatment.<sup>6</sup> Further, the overall incidence of CNS metastases in patients with *ALK*-positive NSCLC can increase to approximately 60% after first-line crizotinib.<sup>7,8</sup> The CNS was also a common site of PD in studies of ceritinib (approved for patients with *ALK*-positive NSCLC previously treated with crizotinib).<sup>7</sup> Together, these findings highlight a need for new treatments that can offer both systemic efficacy and CNS disease control for patients with *ALK*-positive NSCLC.

Alectinib, a potent and highly selective *ALK* inhibitor, was granted approval by the Japanese Ministry of Health, Labor, and Welfare for *ALK* inhibitor-naïve patients with *ALK*-positive NSCLC in 2014 on the basis of the phase I/II AF-001JP study, which demonstrated an objective response rate (ORR) of 93.5% (95% CI, 82% to 99%), including two complete responses (CRs) and 41 partial responses (PRs).<sup>9</sup> Patient follow-up for this study is ongoing, and to date, 19.6% of patients have achieved a CR, and the 2-year PFS rate is 76% (95% CI, 60% to 87%).<sup>10,11</sup>

Phase II studies have confirmed the efficacy of alectinib in crizotinib-refractory patients with *ALK*-positive NSCLC. The North American phase II NP28761 (ClinicalTrials.gov identifier: NCT01871805) study demonstrated an ORR by central independent review committee (IRC) of 52.2% (95% CI, 39.7% to 64.6%) and a disease control rate (DCR) of 79.1% (95% CI, 67.4% to 88.1%).<sup>12</sup> The global phase II NP28673 (ClinicalTrials.gov identifier: NCT01801111) trial reported similar rates; IRC ORR was 50% (95% CI, 41% to 59%), whereas DCR was 79% (95% CI, 70% to 86%).<sup>8</sup> Data from these studies supported the accelerated FDA approval of alectinib in December 2015 for the treatment of patients with *ALK*-positive NSCLC who have experienced PD on or are intolerant to crizotinib.

Alectinib has also demonstrated activity in the CNS in phase I and II studies.<sup>8,12</sup> To further evaluate the efficacy of alectinib in the CNS, we pooled efficacy and safety data for patients with CNS disease from the phase II NP28761 and NP28673 studies.

## PATIENTS AND METHODS

### Study Design

Full study details are provided in the primary publications for the NP28673<sup>8</sup> and NP28761<sup>12</sup> studies. NP28761 and NP28673 were single-arm, phase II, open-label, multicenter studies. NP28761 was conducted at 27 sites in North America, and NP28673 was a global study conducted at 56 sites in 16 countries. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocols were approved by local institutional review boards or ethics committees at each participating site. Patients provided written informed consent.

Enrollment periods differed between the two studies. In NP28761, patients were enrolled between May 3, 2012, and August 4, 2014. This duration included the phase I dose-finding stage; for the phase II part, the first patient received treatment on September 4, 2013. In NP28673, patients were enrolled between June 20, 2013, and April 23, 2014.

### Inclusion and Exclusion Criteria

Eligible patients had advanced or metastatic NSCLC that was previously confirmed as *ALK*-positive by an FDA-approved test (Vysis LSI break-apart fluorescence in situ hybridization; Abbott, Chicago, IL; retesting was not required). Patients were age  $\geq$  18 years, had an Eastern Cooperative Oncology Group performance status of  $\leq$  2, had adequate organ function, and had measurable disease according to Response

Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In addition, patients were required to have PD on crizotinib according to RECIST version 1.1. Patients previously irradiated (whole-brain radiotherapy [WBRT] or stereotactic radiosurgery permitted; data on radiation type not captured) in the CNS had to have stable brain disease (no obvious clinical symptoms and no clinical deterioration) at study entry and be off corticosteroid treatment; both conditions had to be met for at least 2 weeks before the first dose of alectinib.

In both studies, patients were excluded if they had brain or leptomeningeal metastases that were symptomatic in nature and/or required treatment. Patients were also excluded from both studies if they had received prior therapy with an *ALK* inhibitor other than crizotinib. Patients could be chemotherapy naïve or have received prior platinum-based chemotherapy.

### Procedures

All patients received oral alectinib 600 mg twice daily with a meal. Patients continued treatment with alectinib until PD, unacceptable toxicity, or withdrawal of consent. A minimum washout period of 7 days was required between the last dose of crizotinib and the first dose of alectinib.

### Study End Points

The primary end point in both studies was ORR by IRC using RECIST version 1.1 in the response-evaluable population, with a coprimary end point in NP28673 of ORR by IRC in patients previously treated with chemotherapy. The key protocol-defined secondary end point was CNS ORR (CORR) by IRC; other secondary end points included duration of response (DOR), PFS, CNS DOR (CDOR), and safety.

### Assessments

Tumor response and progression, including CNS response and progression, were assessed according to RECIST version 1.1 by IRC. A separate IRC assessing CNS disease consisted of specialist neuroradiologists who were blinded to systemic response. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). All patients underwent baseline tumor imaging, including computed tomography of the chest and abdomen, as well as brain imaging. CNS assessment was performed prospectively by regular brain imaging; magnetic resonance imaging was the most commonly used method; in the pooled population, 85 patients (62.5%) were assessed with magnetic resonance imaging, 38 (27.9%) with computed tomography, and 13 (9.6%) with both methods. The frequency of response or progression assessments, including brain scans, was the same regardless of baseline CNS metastases status. However, scans were taken every 6 weeks in the NP28761 study and every 8 weeks in NP28673.

### Statistical Analysis

CNS end points were assessed in the following two populations: patients with measurable CNS disease at baseline and patients with measurable and/or nonmeasurable CNS disease at baseline, on the basis of RECIST version 1.1 by IRC. CORR was defined as objective tumor response rate (CR and PR) of CNS lesions in patients who had baseline CNS disease, on the basis of RECIST version 1.1 by IRC. CNS DCR (CDCR) was defined as the percentage of patients who had a best overall CNS response of PR, CR, or stable disease (SD) on the basis of RECIST version 1.1 by IRC. CDOR was defined as the time from the first observation of a CNS response until the first observation of CNS progression or death from any cause on the basis of RECIST version 1.1 by IRC. For patients with only nonmeasurable disease, response could be classed as CR, SD, or PD, but not PR.

The Clopper-Pearson method was used to construct 95% CIs for response rates. Kaplan-Meier analysis of time-to-event data (DOR) was used to estimate median event times, and the Brookmeyer-Crowley method was used to calculate two-sided 95% CIs. All analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

## RESULTS

A total of 225 patients were enrolled onto the two studies (n = 87 in NP28761 and n = 138 in NP28673; Appendix Table A1, online only). Here, we report data for the pooled CNS population only, on the basis of a data cutoff of April 27, 2015, for both studies.

### Patients

This pooled CNS analysis included 136 patients (60% of the overall pooled population of the two studies) with baseline CNS disease; patient characteristics are listed in Table 1. Briefly, the median age was 51 years (range, 22 to 75 years); most patients had an Eastern Cooperative Oncology Group performance status of 1 (54%) and were younger than 65 years of age (90%). Fifty patients (37%) had measurable CNS disease at baseline, whereas 86 patients (63%) had only nonmeasurable CNS disease.

In total, 95 patients (70%) had received prior CNS radiotherapy, with 55 completing this radiotherapy greater than 6 months before starting alectinib. In patients with measurable CNS disease, 34 (68%) had received prior CNS radiotherapy, but

the majority of these patients (25 of 34 patients) had completed the radiotherapy greater than 6 months before starting alectinib.

### Prior Crizotinib Treatment

Median time on prior treatment with crizotinib was 350 days (interquartile range, 250 to 607 days), and the median time from last dose of crizotinib to first dose of alectinib was 15 days (range, 7 to 676 days). The best response on crizotinib was PR in 49% of patients, SD in 27% of patients, and PD in 19% of patients.

### Efficacy

At data cutoff (April 27, 2015), the median duration of follow-up was 12.4 months (range, 0.9 to 19.7 months). In the group with measurable CNS disease at baseline, 32 of 50 patients had a CNS response, resulting in an IRC CORR of 64.0% (95% CI, 49.2% to 77.1%), with 11 CRs (22.0%) observed (Table 2 and Fig 1). The CDCR was 90.0% (95% CI, 78.2% to 96.7%) and the median CDOR was 10.8 months (95% CI, 7.6 to 14.1 months) after 56% of events.

For patients with measurable and/or nonmeasurable CNS disease at baseline, the IRC CORR was 42.6% (95% CI, 34.2% to 51.4%), with 37 CRs (27%) observed (Table 2). The CDCR was 85.3% (95% CI, 78.2% to 90.8%) and the median CDOR was 11.1 months (95% CI, 10.3 months to not evaluable) after 45% of events (Table 2).

In patients with measurable CNS disease at baseline, CORR was 64.7% in white patients (n = 34) and 62.5% in Asian/other patients (n = 16). In patients with measurable and/or nonmeasurable CNS disease at baseline, CORRs were 43.8% and 38.7% in white (n = 105) and Asian/other patients (n = 31), respectively.

### CORR by Prior Brain Radiation Therapy

The CORR was 35.8% (95% CI, 26.2% to 46.3%) in patients who had received prior radiation (n = 95) and 58.5% (95% CI, 42.1% to 73.7%) in patients who had not received prior radiation (n = 41; Table 3 and Fig 1). In patients who had received radiation ≤ 6 months (n = 40) versus greater than 6 months prior (n = 55), the CORRs were 27.5% (95% CI, 14.6% to 43.9%) and 41.8% (95% CI, 28.7% to 55.9%), respectively. The CDCR in both patient groups was greater than 85%. CRs were seen in 18% of patients with and 49% of patients without prior radiotherapy. For the 50 patients with measurable CNS disease at baseline, the CORR was 61.8% (95% CI, 43.6% to 77.8%; CR rate, 12%) in patients who had received prior radiation (n = 34) and 68.8% (95% CI, 41.3% to 89.0%; CR rate, 44%) in patients who did not receive prior radiation (n = 16; Appendix Table A2, online only).

### Time-to-Event Summary for PFS

Overall, 83 (61%) of 136 patients with baseline CNS metastases had a PFS event at the time of data cutoff. The median time to event was 8.3 months (95% CI, 5.9 to 11.2 months), and the 6-month event-free rate was 58.0% (95% CI, 49.6% to 66.4%). For patients with measurable CNS disease only, 31 patients (62%) had an event, and the median time to event was 9.2 months (95% CI, 7.4 to 15.9 months); the 6-month event-free rate was 67.9% (95% CI, 54.9% to 80.9%). For patients without baseline CNS disease,

**Table 1.** Pooled Baseline Characteristics for Patients Who Had Measurable and/or Nonmeasurable CNS Disease at Baseline

Characteristic	Pooled Population (N = 225)
Patients with CNS disease at baseline, No. (%)	136 (60)
Baseline characteristic, No.	136
Age, years	
Median (range)	50.9 (22-75)
< 65, No. (%)	123 (90)
≥ 65, No. (%)	13 (10)
Sex, No. (%)	
Male	58 (43)
Female	78 (57)
Race, No. (%)	
White	105 (77)
Asian	23 (17)
Other	8 (6)
ECOG PS, No. (%)	
0	46 (34)
1	74 (54)
2	16 (12)
Smoking status, No. (%)	
Current	2 (2)
Former	40 (29)
Never	94 (69)
Histology, No. (%)	
Adenocarcinoma	128 (94)
Other	8 (6)
Prior chemotherapy, No. (%)	
Yes	109 (80)
No	27 (20)
Median time since last dose of crizotinib, days (range)	15.0 (7-676)
Radiation therapy, No. (%)	
No prior brain radiation	41 (30)
Prior brain radiation	95 (70)
Within 4 weeks of start of alectinib	7 (5)
> 4 weeks to ≤ 6 months before start of alectinib	33 (24)
> 6 months before start of alectinib	55 (40)

NOTE. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

**Table 2.** Pooled Analysis of IRC CORR and CDCR for Patients With CNS Disease at Baseline

Response	Measurable Baseline CNS Disease (n = 50)	Measurable and/or Nonmeasurable Baseline CNS Disease (n = 136)
CNS response rate		
Responders, No.	32	58
CORR, % (95% CI)	64.0 (49.2 to 77.1)	42.6 (34.2 to 51.4)
Best overall response, No. (%)		
Complete response	11 (22.0)	37 (27.2)
Partial response	21 (42.0)	21 (15.4)
Stable disease	13 (26.0)	58 (42.6)
Progressive disease	3 (6.0)	12 (8.8)
Missing or unevaluable	2 (4.0)	8 (5.9)
CDCR		
No.	45	116
% (95% CI)	90.0 (78.2 to 96.7)	85.3 (78.2 to 90.8)
Median CDOR, months (95% CI)	10.8 (7.6 to 14.1)	11.1 (10.3 to NE)
Patients included in analysis, No. (%)	32 (100.0)	58 (100.0)
Patients with event, No. (%)	18 (56.3)	26 (44.8)

NOTE. Responses evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Abbreviations: CDCR, CNS disease control rate; CDOR, CNS duration of response; CORR, CNS objective response rate; IRC, independent review committee; NE, not evaluable.

67 patients (59.8%) had an event, and the median time to event was 7.6 months (95% CI, 5.6 to 13.0 months); the 6-month event-free rate was 58.0% (95% CI, 48.7% to 67.3%). These results are similar to those for the overall populations of the two phase II studies.

**Site of Progression**

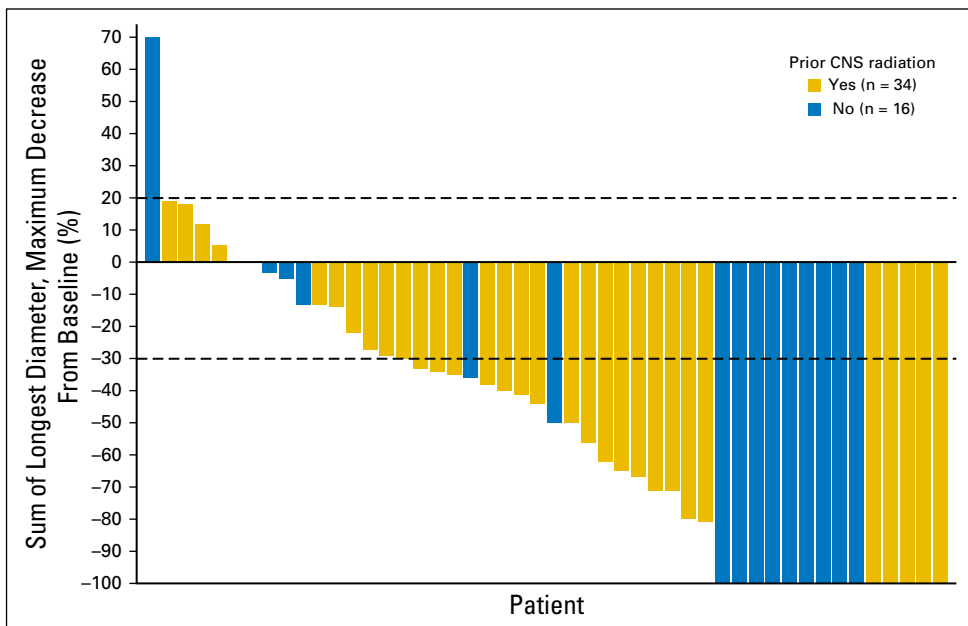
At the data cutoff (April 27, 2015), with a median follow-up time of 12.4 months (range, 0.9 to 19.7 months), only 17% of patients in the overall pooled population (n = 225) had PD in the CNS, as assessed by the IRC systemic read, and 11% had the CNS as the sole site of PD (Table 4). Of the 112 patients identified by the IRC systemic read as not having CNS disease at baseline, only 8% developed CNS metastases.

**Safety**

The safety profile of alectinib was consistent with previous studies<sup>9,13</sup> and similar to the overall populations of the phase II studies<sup>8,12</sup> (Table 5). There were low rates of dose reductions (14.7%) and withdrawals (5.9%) as a result of adverse events, confirming that alectinib was well tolerated in patients with measurable and/or nonmeasurable CNS lesions.

**DISCUSSION**

Although patients with ALK-positive NSCLC initially respond well to the current standard treatment of crizotinib (National Comprehensive Cancer Network guidelines V6.2015),<sup>2</sup> the majority will



**Fig 1.** Waterfall plot of best CNS response in patients with baseline measurable CNS disease by prior CNS radiation.

**Table 3.** IRC CORR by Prior Radiation Therapy

Response	All Patients With CNS Metastases* (n = 136)	
	Prior Radiation (n = 95)	No Prior Radiation (n = 41)
Responders (CORR), %	35.8	58.5
95% CI	26.2 to 46.3	42.1 to 73.7
Complete response, No. (%)	17 (17.9)	20 (48.8)
Partial response, No. (%)	17 (17.9)	4 (9.8)
Stable disease, No. (%)	48 (50.5)	10 (24.4)
Progressive disease, No. (%)	9 (9.5)	3 (7.3)
Missing/unevaluable, No. (%)	4 (4.2)	4 (9.8)
CDCR, No. (%)	82 (86.3)	34 (82.9)
95% CI (%)	77.7 to 92.5	67.9 to 92.9

NOTE. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Responses evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). Abbreviations: CDCR, CNS disease control rate; CORR, CNS objective response rate; IRC, independent review committee.  
\*Patients who had both measurable and/or nonmeasurable disease at baseline.

eventually experience PD within 1 year.<sup>3,4,14</sup> The CNS is a common site of progression for crizotinib-treated patients, with 70% of patients experiencing CNS progression as a new or nontarget lesion during treatment,<sup>6</sup> possibly as a result of poor CNS exposure to crizotinib.<sup>15</sup> New treatments are needed, not only to overcome acquired resistance to crizotinib, but also to achieve better clinical efficacy in the CNS.

The phase II NP28673 and NP28761 studies have demonstrated that alectinib has both systemic and CNS efficacy in crizotinib-refractory *ALK*-positive NSCLC.<sup>8,12,13</sup> Combining data from these two studies helps to characterize the role of alectinib in the CNS, as the larger patient numbers increase the precision of the pooled results and broaden the population profile. In this pooled analysis of patients with baseline CNS disease from these two studies, alectinib demonstrated good CNS efficacy, with IRC CORRs of 64.0% and 42.6% for patients with measurable and patients with measurable and/or nonmeasurable CNS disease at baseline, respectively. For patients with measurable and/or nonmeasurable CNS disease at baseline, 37 CRs (27%) were observed, demonstrating that alectinib can provide CNS benefit regardless of whether the disease is measurable according to RECIST. Importantly, the responses observed in the CNS were durable, with a CDOR of approximately 11 months, and were comparable to those observed for the overall systemic disease assessment.<sup>12,16</sup>

The promising CNS efficacy profile of alectinib in this pooled analysis is supported by previous clinical and preclinical results, which have suggested that alectinib is effective at controlling brain metastases. Preclinical studies showed that alectinib induced brain

tumor regression in mouse models.<sup>17</sup> In addition, the phase I/II AF-001JP study of alectinib in *ALK*-positive NSCLC reported no progression of brain metastases during alectinib therapy.<sup>9</sup> In the Japanese bioequivalence study (JP28927; JapicCTI-132186), alectinib demonstrated efficacy in patients with *ALK*-positive NSCLC who had baseline brain metastases, with a reported response rate of 65%.<sup>18</sup> Results from the phase I dose-finding part of NP28761 reported an ORR of 52% in patients with baseline brain metastases, including 29% with a CR.<sup>13</sup> Although the current pooled analysis did not include any patients with leptomeningeal metastases, alectinib has been shown to be active in patients with *ALK*-positive NSCLC with leptomeningeal metastases.<sup>19,20</sup>

The *ALK* inhibitor ceritinib has also shown some efficacy in the CNS, although patient numbers are still relatively low. Overall, 10 of 29 patients with *ALK*-positive NSCLC and measurable brain disease at baseline had an objective CNS response with ceritinib, giving a CORR of 34.5% (95% CI, 17.9% to 54.3%).<sup>21</sup> The different CORRs reported with ceritinib and alectinib may potentially be a result of different rates of efflux from the brain, which could affect the therapeutic concentrations of these agents in the CNS.<sup>22</sup> In NP28761, paired CSF and systemic plasma samples showed alectinib penetration of the CNS, supporting a linear relationship between CSF and free alectinib concentrations in plasma.<sup>13</sup> Furthermore, in preclinical models of intracranial metastases, alectinib demonstrated a high brain-to-plasma ratio and was transported independently of the efflux transporter, P-glycoprotein.<sup>17</sup> Conversely, preclinical models of ceritinib reported restricted brain accumulation in the presence of P-glycoprotein or breast cancer resistance protein.<sup>23</sup>

**Table 4.** Incidence of Progression in the CNS in the Pooled Population

Pooled NP28673 and NP28761 Population	No. of Patients (%)			
	All Patients (N = 225)	Patients With PD (n = 120*)	Patients With CNS Disease at Baseline (n = 113*)	Patients Without CNS Disease at Baseline (n = 112*)
Patients with CNS PD	39 (17)	39 (33)	30 (27)	9 (8)
Patients with CNS as only site of PD	24 (11)	24 (20)	18 (16)	6 (5)

Abbreviation: PD, progressive disease.  
\*On the basis of independent review committee systemic read.



**Table 5.** Summary of Safety Data in the Pooled CNS Population With Measurable and/or Nonmeasurable Disease at Baseline

AE	No. (%) of Patients (n = 136)
Total patients with at least one AE	135 (99.3)
Grade 3 to 5 AEs	52 (38.2)
Serious AEs	28 (20.6)
AE leading to treatment withdrawal	8 (5.9)
Total deaths	40 (29.4)

NOTE. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Abbreviation: AE, adverse event.

In this pooled analysis, only 29% of patients with baseline CNS disease had received prior CNS radiation within the last 6 months, and only 5% had received CNS radiation within 1 month of starting alectinib. CORRs of 35.8% and 58.5% were observed for patients with CNS metastases with and without prior radiotherapy, increasing to 61.8% and 68.8%, respectively, for patients with measurable CNS disease only, suggesting that alectinib has clinical efficacy irrespective of radiation history. The observed CR rates (12% to 49%, depending on subgroup) are much higher than the 5% to 6% CR rates historically noted with WBRT,<sup>24,25</sup> with the higher CR rates in patients without prior radiation likely a result of a lower disease burden in these patients. These data suggest that alectinib has CNS efficacy that is at least equivalent to the systemic efficacy observed. However, the results of this retrospective pooled analysis must be evaluated in the context of the small sample numbers for some subgroups and the single-arm design of the two studies.

The safety profile of alectinib in this combined analysis was consistent with previous studies,<sup>8,9,12,13</sup> confirming that alectinib is well tolerated in patients with or without baseline CNS metastases. Standard WBRT can have physiologic and neurologic adverse effects, with many patients experiencing a decline in cognitive function.<sup>26</sup> Stereotactic radiosurgery, increasingly used as an alternative to WBRT, can reduce these adverse effects but may decrease effectiveness when targeting large numbers of metastases.<sup>27</sup> In addition, both types of radiation can result in areas of radionecrosis, which may require corticosteroids. A systemic drug treatment able to target all brain lesions with minimal toxicity could therefore offer clear advantages versus current standards of care.

In conclusion, this pooled analysis supports the results of previous alectinib studies, suggesting that alectinib has good CNS efficacy in *ALK*-positive NSCLC. Two ongoing phase III, head-to-head studies are comparing the systemic and CNS efficacy of alectinib versus crizotinib for patients with *ALK*-positive NSCLC who are *ALK* inhibitor naïve (global ALEX study, NCT02075840; Japanese J-ALEX study, JapicCTI-132316). Preliminary results from J-ALEX were recently presented; the PFS hazard ratio for alectinib versus crizotinib was 0.34 (99.6826% CI, 0.17 to 0.70;  $P < .001$ ). Median PFS was not reached with alectinib (95% CI, 20.3 months to not reached) and was 10.2 months with crizotinib (95% CI, 8.2 to 12.0 months). Patients were not stratified according to baseline CNS metastases, but subgroup analyses found that the PFS hazard ratio for alectinib versus crizotinib in patients with baseline brain metastases was 0.08 (95% CI, 0.01 to 0.61).<sup>28</sup>

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non–Small-Cell Lung Cancer

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**Appendix**

<b>Table A1.</b> Baseline Characteristics for the Overall Study Populations	
Characteristic	No. (%) of Patients (N = 225)
<b>Sex</b>	
Male	100 (44.4)
Female	125 (55.6)
<b>Age, years</b>	
Median (range)	53.0 (22-79)
< 65	195 (86.7)
≥ 65	30 (13.3)
<b>Disease stage</b>	
IIIB	3 (1.3)
IV	220 (97.8)
Recurrence	2 (0.9)
<b>Histology</b>	
Adenocarcinoma	215 (95.6)
Other	10 (4.4)
<b>Race</b>	
Asian	43 (19.1)
Black or African American	4 (1.8)
White	166 (73.8)
Other	12 (5.3)
<b>ECOG PS</b>	
0	74 (32.9)
1	129 (57.3)
2	22 (9.8)
<b>Smoking status</b>	
Current smoker	3 (1.3)
Never-smoker	150 (66.7)
Former smoker	72 (32.0)
<b>Measurable CNS lesions</b>	
Patients with measurable CNS lesions at baseline	50 (22.2)
Patients with only nonmeasurable CNS lesions at baseline	85 (37.8)
Patients with no CNS lesions at baseline	90 (40.0)
<b>Prior chemotherapy</b>	
Chemotherapy-naïve patients	51 (22.7)
Patients treated with prior chemotherapy	174 (77.3)

NOTE. Data cutoff for both NP28673 and NP28761 was April 27, 2015. Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

**Table A2.** CORR by Prior Radiation in Patients With Measurable CNS Metastases at Baseline

Response to Alectinib (600 mg twice a day)	All Patients With Measurable CNS Metastases (n = 50)	
	Prior Radiation (n = 34)	No Prior Radiation (n = 16)
Responders (CORR), % (95% CI)	61.8 (43.6 to 77.8)	68.8 (41.3 to 89.0)
Response, No. (%)		
Complete response	4 (11.8)	7 (43.8)
Partial response	17 (50.0)	4 (25.0)
Stable disease	10 (29.4)	3 (18.8)
Progressive disease	2 (5.9)	1 (6.3)
Missing/unevaluable	1 (2.9)	1 (6.3)

NOTE. Responses evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). Data cutoff for both NP28673 and NP28761 was April 27, 2015. Abbreviation: CORR, CNS objective response rate.