1293P

Evaluation of Ceritinib-treated Patients with Anaplastic Lymphoma Kinase Rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) and Brain Metastases in the ASCEND-1 Study

Alice T. Shaw,[1] Ranee Mehra,[2] Daniel S.W. Tan,[3] Enriqueta Felip,[4] Laura Q.M. Chow,[5] D. Ross Camidge,[6] Johan Vansteenkiste,[7] Sunil Sharma,[8] Tommaso De Pas,[9] Gregory J. Riely,[10] Benjamin J. Solomon,[11] Juergen Wolf,[12] Michael Thomas,[13] Martin Schuler,[14] Geoffrey Liu,[15] Armando Santoro,[16] Paramita Sen,[17] Anthony L. Boral,[18] Alejandro Yovine,[19] and Dong-Wan Kim[20]

[1]Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; [3]National Cancer Center, Singapore; [4]Vall d'Hebron University, Barcelona, Spain; [5]University of Washington, Seattle, Washington, USA; [6]University of Colorado, Denver, Colorado, USA; [7]University Hospital KU Leuven, Leuven, Belgium; [8]Huntsman Cancer Institute, Salt Lake City, Utah, USA; [9]Instituto Europeo di Oncologia, Milan, Italy; [10]Memorial Sloan-Kettering Cancer Center, New York, New York, USA; [11]Peter MacCallum Cancer Center, Melbourne, Victoria, Australia; [12]University Hospital Cologne, Cologne, Germany; [13]Thoraxklinik im Universitätsklinikum Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany; [14]University Hospital Essen, University Duisburg-Essen, Essen, Germany and German Cancer Consortium, Heidelberg, Germany; [15]Princess Margaret Cancer Center, Toronto, Canada; [16]IRCCS Institute Clinico Humanitas, Milan, Italy; [17]Novartis Pharma, East Hanover, New Jersey, USA; [18]Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, USA; [19]Novartis Pharma AG, Basel, Switzerland; [20]Seoul National University Hospital, Seoul, Korea

BACKGROUND

- Approximately 2–7% of patients with non-small cell lung cancer (NSCLC) exhibit rearrangements of the anaplastic lymphoma kinase gene (ALK+ NSCLC).[1]
- ALK-targeted therapy using the ALK inhibitor crizotinib achieves responses in approximately 60% of patients with advanced ALK+ NSCLC and is more effective than standard chemotherapy.[2,3]
  - However, the majority of responders develop crizotinib resistance within 1 year, frequently showing recurrence of disease in the brain.[4,5]
- In a study of patients with ALK+ NSCLC receiving crizotinib treatment, 46% of patients progressed first in the central nervous system (CNS).[6]
- Ceritinib is a novel, highly selective, orally active, small-molecule tyrosine kinase inhibitor of ALK.[7]
- Preclinical studies have shown ceritinib to inhibit ALK with a 20-fold greater potency than crizotinib.[8]
- In a preclinical study in rats, ceritinib crossed the blood brain barrier with a brain-to-blood exposure (AUCinf) ratio of approximately 15%[9] and clinical data has shown evidence for ceritinib activity in the brain.[7]
- Early efficacy data in patients from the ASCEND-1 Phase I study (NCT01283516) with ALK+ NSCLC treated with ceritinib at 750 mg showed an overall response rate (ORR) of 58.5% (95% confidence interval [CI], 52.1, 64.8).[10]
  - Updated data, to be reported at this meeting (poster number 1295P) have demonstrated a median progression-free survival (PFS) of 18.40 (95% CI, 11.10, NE) months for patients that are ALK inhibitor naïve and 6.93 (95% CI, 5.55, 8.67) months for those previously treated with an ALK inhibitor
- Here we report updated efficacy and safety data in ALK+ NSCLC patients in the ASCEND-1 study who entered the study with clinically and neurologically stable brain metastases. In addition, data on intracranial efficacy of ceritinib from post-hoc analyses of patients evaluated by magnetic resonance imaging (MRI) scans will be presented.

METHODS

Patients

- Details of the ASCEND-1 Phase I study have been reported previously.[7,10] Briefly, patients included in this analysis comprise:
  - Adult patients with ALK+ NSCLC who had investigator-identified brain metastases at baseline and who started ceritinib at a dose of 750 mg/day[10]
  - Patients who were ALK inhibitor naïve as well as patients who had received prior treatment with an ALK inhibitor

Treatment and Evaluation

- Ceritinib was administered at 750 mg once daily in continuous 21-day cycles, until unacceptable toxicity, disease progression, or withdrawal of consent.
- Treatment beyond CNS progression was permitted when there was evidence of clinical benefit, as assessed by investigator.
- Computerised tomography (CT)/MRI scans were performed in patients at baseline and every two cycles thereafter.
- Follow-up CT/MRI scans in the brain were carried out only in patients with known brain metastases at baseline
- Limited data regarding radiotherapy to the brain was collected. Details regarding the nature, location and duration of radiotherapy were not collected.
- Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Study Analyses

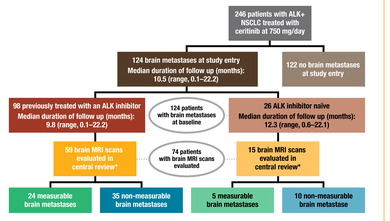
- Systemic efficacy analyses were carried out to evaluate tumour responses according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.0 criteria, PFS and duration of response (DOR).
  - Overall response rate (ORR) was summarised along with 95% CIs by prior ALK inhibitor treatment status
  - Kaplan-Meier estimates of DOR and PFS were summarised along with 95% CIs by prior ALK inhibitor treatment status
- Patients with brain metastases at study entry were identified by baseline CT and/or MRI scans.
- Baseline and follow-up brain MRI scans in patients with baseline brain metastases were centrally reviewed by two independent neuroradiologists blinded to investigator assessment and systemic response.
- In this post-hoc analysis, intracranial responses, including PFS and DOR, were evaluated in brain lesions according to RECIST v1.1 criteria.
- Intracranial disease control rate (IDCR) and overall intracranial response rate (OIRR) were summarised along with 95% CIs.
- Brain lesions were defined as measurable using the RECIST v1.1 criteria (longest diameter ≥10 mm).
- The data cut-off date was 14 April 2014.

RESULTS

Patients

- Of the 246 ALK+ NSCLC patients enrolled in the ASCEND-1 trial and treated with ceritinib 750 mg/day, 124 had brain metastases at study entry, as per investigator assessment.
  - Among the 124 patients with brain metastases at study entry, 26 were ALK inhibitor naïve while 98 had previously been treated with an ALK inhibitor (**Figure 1**)
- Most patients had adenocarcinoma histology, were aged <65 years and had good performance status (Eastern Cooperative Oncology Group Performance Status ≤1; **Table 1**).
- Caucasian and Asian represented the predominant races and accounted for 98% of the patient cohort (**Table 1**).

Figure 1. Patient Stratification



*Remaining patients either had CT scans or scans that were not available
ALK, anaplastic lymphoma kinase gene; CT, computerised tomography; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer

Table 1. Patient and Disease Characteristics in Patients with ALK+ NSCLC and Brain Metastases at Baseline

Characteristic	NSCLC with Prior ALK Inhibitor (n=98)	NSCLC ALK Inhibitor Naive (n=26)	All NSCLC (N=124)
Age, years			
Median (range)	51 (24–80)	53 (27–73)	51 (24–80)
Sex, n (%)			
Female	57 (58)	17 (65)	74 (60)
Predominant race, n (%)			
Caucasian	60 (61)	12 (46)	72 (58)
Asian	35 (36)	14 (54)	49 (40)
Other	3 (3)	0 (0)	3 (2)
Smoking history, n (%)			
Never/Former or current	65/33 (66/34)	17/9 (65/35)	82/42 (66/34)
WHO/ECOG performance status, n (%)			
0	16 (16)	6 (23)	22 (18)
1	68 (69)	16 (62)	84 (68)
2	13 (13)	4 (15)	17 (14)
3	1 (1)	0 (0)	1 (1)
Tumour histology, n (%)			
Adenocarcinoma	92 (94)	24 (92)	116 (94)
Other/missing	6 (6)	2 (8)	8 (6)
Extracranial metastatic lesions			
Lung	66 (67)	20 (77)	86 (69)
Lymph nodes	93 (95)	22 (85)	115 (93)
Bone	61 (62)	13 (50)	74 (60)
Liver	43 (44)	12 (46)	55 (44)
Number of prior treatment regimens, n (%)			
0	0 (0)	3 (12)	3 (2)
1	11 (11)	13 (50)	24 (19)
2	28 (29)	4 (15)	32 (26)
≥3	59 (60)	6 (23)	65 (52)
Prior radiotherapy to the brain, n (%)	68 (69)	15 (58)	83 (67)
Median time from prior radiotherapy to the brain to first dose of study drug, months (range)	6.5 (0–38)	4.6 (1–21)	6.1 (0–38)
Median time from initial diagnosis to first dose of study drug, months (range)	24 (3–174)	9 (2–109)	21 (2–174)

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; WHO, World Health Organization

Efficacy

Systemic Efficacy

- Ceritinib achieved objective responses in 69 (55.6% [95% CI: 46.5, 64.6]) of the 124 patients with ALK+ NSCLC and brain metastases based on investigator assessment (**Table 2**).
  - Patients who were ALK inhibitor naïve had an ORR of 73.1% (95% CI: 52.2, 88.4), while patients previously treated with an ALK inhibitor had an ORR of 51% (95% CI: 40.7, 61.3) (**Table 2**)
- Responding patients who were ALK inhibitor naïve had a median DOR of 12.6 months (95% CI: 5.5, non evaluable [NE]); responding patients who were previously treated with an ALK inhibitor had a median DOR of 6.9 months (95% CI: 5.4, 8.3).
- Median PFS was 9.7 months (95% CI: 4.6, NE) in patients who were ALK inhibitor naïve and 6.9 months (95% CI: 4.9, 8.4) in patients previously treated with an ALK inhibitor.

Intracranial Efficacy

- Of the 124 ALK+ NSCLC patients with brain metastases at baseline, 74 patients had MRI scans available for central evaluation according to RECIST v1.1. The remaining patients either had CT scans or scans that were not available.
  - Of the 74 patients with MRI scans available, 15 were ALK inhibitor naïve and 59 had been previously treated with an ALK inhibitor
- Patient and disease characteristics in the 74 patients with MRI evaluations were comparable to those shown for the overall patient subgroup with brain metastases at baseline (n=124).
  - Among these 74 patients, 29 had brain lesions that were measurable at baseline (RECIST v1.1; longest diameter ≥10 mm) and 45 had non-measurable lesions (**Figure 1; Table 3**)
  - Among the 29 patients with measurable brain lesions by MRI, five were ALK inhibitor naïve while 24 had previously been treated with an ALK inhibitor
- Ceritinib achieved objective responses in 10 (34.5%, [95% CI: 17.9, 54.3]) of the 29 patients with ALK+ NSCLC and measurable brain metastases (**Tables 4 and 5**).
- Five patients with non-measurable brain metastases showed complete response following treatment with ceritinib (**Table 4**).
- IDCR was 67.6% (50/74, [95% CI: [95% CI: 55.7, 78.0]) in patients with ALK+ NSCLC with brain metastases evaluated by MRI scans (**Table 4**).
- Ceritinib achieved durable intracranial responses in patients with measurable brain metastases at baseline, with a median DOR in brain that was non-estimable (95% CI: NE, NE) in patients who were ALK inhibitor naïve and of 6.9 months (95% CI: 2.8, NE) in patients who had previously been treated with an ALK inhibitor.
- Intracranial median PFS was also non-estimable (95% CI: 4.2, NE) in patients who were ALK inhibitor naïve, and was 7.0 months (95% CI: 4.2, 9.8) in patients who had been previously treated with an ALK inhibitor (**Table 6**).

Table 2. Systemic Response* to Ceritinib Treatment in Patients with ALK+ NSCLC with Brain Metastases at Baseline (RECIST v1.0)

Endpoint	NSCLC with Prior ALK Inhibitor (n=98)	NSCLC ALK Inhibitor Naive (n=26)	All NSCLC (N=124)
Complete response, n (%)	1 (1.0)	0	1 (0.8)
Partial response, n (%)	49 (50.0)	19 (73.1)	68 (54.8)
Stable disease, n (%)	22 (22.4)	2 (7.7)	24 (19.4)
Progressive disease, n (%)	7 (7.1)	0	7 (5.6)
Unknown	19 (19.4)	5 (19.2)	24 (19.4)
Overall response rate, n (%) [95% CI]	50 (51.0) [40.7, 61.3]	19 (73.1) [52.2, 88.4]	69 (55.6) [46.5, 64.6]

ALK, anaplastic lymphoma kinase; CI, confidence interval; NSCLC, non-small cell lung cancer
*Systemic response denotes best overall response in all sites of disease, including brain

Table 3. Brain Lesion Characteristics in Patients with ALK+ NSCLC and Brain Metastases by MRI at Baseline

Characteristic	NSCLC with Prior ALK Inhibitor (n=98)	NSCLC ALK Inhibitor Naive (n=26)	All NSCLC (N=124)
Types of brain mets lesions at baseline based on BIRC assessment	**n=59**	**n=15**	**n=74**
Target only, n (%)	3 (5.1)	0 (0.0)	3 (4.1)
Non-target only, n (%)	35 (59.3)	10 (66.7)	45 (60.8)
Both target and non-target, n (%)	21 (35.6)	5 (33.3)	26 (35.1)
Disease burden in brain (Sum of longest diameter at baseline for target brain lesions based on BIRC assessment) (mm)	**n=24***	**n=5***	**n=29***
Mean (SD)	36.5 (27.6)	41.2 (29.1)	37.3 (27.4)
Median (Min–max)	28 (10–116)	31 (12–88)	30 (10–116)
No. of target lesions in brain, n (%)			
1	12 (50.0)	3 (60.0)	15 (51.7)
2	5 (20.8)	0 (0.0)	5 (17.2)
≥3	7 (29.2)	2 (40.0)	9 (31.0)

ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; NSCLC, non-small cell lung cancer; SD, standard deviation
*Patients with measurable brain metastases at baseline

Table 4. Intracranial response to ceritinib treatment in patients with brain metastases at baseline by MRI (RECIST 1.1)

Endpoint	Measurable brain metastases (n=29)	Non-measurable brain metastases (n=45)
Complete response [CR], n (%)	0 (0.0)	5 (11.1)
Partial response [PR], n (%)	10 (34.5)	0 (0.0)
Stable disease [SD]*/Non-CR/Non-PD†, n (%)	7 (24.1)	28 (62.2)
Progressive disease [PD], n (%)	6 (20.7)	4 (8.9)
Unknown, n (%)	6 (20.7)	8 (17.8)
OIRR (CR + PR), n (%) [95% CI]	10 (34.5) [17.9, 54.3]	NA
IDCR‡ (CR + PR + SD*/Non-CR/Non-PD†), n (%) [95% CI]	17 (58.6) [38.9, 76.5]	33 (73.3) [58.1, 85.4]

CI, confidence interval; NA, not available; NSCLC, non-small cell lung cancer; IDCR, intracranial disease control rate; OIRR, overall intracranial response rate
*SD for measurable brain metastases
†Non-CR/Non-PD for non-measurable brain metastases
‡Limited data on prior radiotherapy to brain available

Table 5. Response of measurable brain metastases patients to ceritinib assessed by MRI according to prior ALK inhibitor status

Endpoint	NSCLC with Prior ALK Inhibitor (n=24)	NSCLC ALK Inhibitor Naïve (n=5)	All NSCLC (n=29)
Complete response [CR], n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response [PR], n (%)	7 (29.2)	3 (60.0)	10 (34.5)
Stable disease [SD], n (%)	7 (29.2)	0 (0.0)	7 (24.1)
Progressive disease [PD], n (%)	6 (25.0)	0 (0.0)	6 (20.7)
Unknown, n (%)	4 (16.7)	2 (40.0)	6 (20.7)
OIRR (CR + PR), n (%) [95% CI]	7 (29.2) [12.6, 51.1]	3 (60.0) [14.7, 94.7]	10 (34.5) [17.9, 54.3]
IDCR* (CR + PR + SD) [95% CI]	14 (58.3) [36.6, 77.9]	3 (60.0) [14.7, 94.7]	17 (58.6) [38.9, 76.5]

ALK, anaplastic lymphoma kinase; CI, confidence interval; NSCLC, non-small cell lung cancer; OIRR, overall intracranial response rate; IDCR, intracranial disease control rate
*Limited data on prior radiotherapy to brain available

Table 6. Intracranial Progression-Free Survival with Ceritinib in Patients with ALK+ NSCLC with Brain Metastases at Baseline by MRI

	Intracranial Median PFS, months* (95% CI) (n=74)	12 month Kaplan Meier Estimate of Intracranial PFS rate* (95% CI) (n=74)
All NSCLC	8.3 (4.5, 11.7)	35.1 (21.7, 48.8)
NSCLC with prior ALK inhibitor	7.0 (4.2, 9.8)	27.4 (14.3, 42.1)
NSCLC ALK inhibitor naive	NE (4.2, NE)	69.9 (30.1, 89.9)

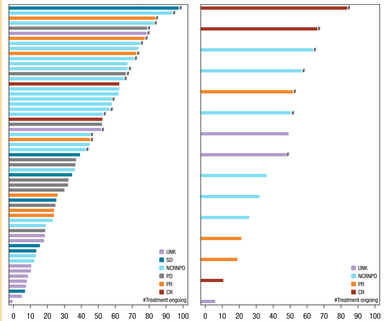
ALK, anaplastic lymphoma kinase; CI, confidence interval; NE, not estimable; NSCLC, non-small cell lung cancer; PFS, progression-free survival
*Intracranial PFS calculated as time to progression in brain + deaths due to any cause

Treatment Exposure

- Median ceritinib treatment exposure among all 124 patients with ALK+ NSCLC and brain metastases at baseline, was 36 weeks in the total cohort, and 43 and 36 weeks in the ALK inhibitor-naïve and -pretreated cohorts, respectively.
  - Median ceritinib treatment exposure among the 74 patients with MRI scans available was 41 weeks (**Figure 2**)
- The median dose intensity for patients with ALK+ NSCLC and brain metastases at baseline was 628 (range, 311-750) mg/day in the total cohort and 570 (range, 362-750) and 637 (range, 311-750) mg/day in the ALK inhibitor-naïve and -pretreated cohorts, respectively.

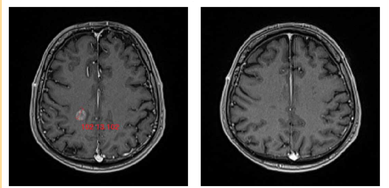
Figure 2. Response to ceritinib in patients with ALK+ NSCLC with brain metastases at baseline by MRI (retrospective, independent readings)

(A) Swimmer plot of duration of exposure and response to ceritinib



CR, complete response; CT, computerised tomography; NCRNPD, non-complete response non-progressive disease; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown

(B) MRI scans showing response in a patient pretreated with an ALK inhibitor



- The majority of patients (64%) received ceritinib therapy for more than 6 months, with almost one third (31%) receiving treatment for at least 1 year.
- The most frequent reason for treatment discontinuation amongst all patients with brain metastases at baseline (n=124) was disease progression (45.2% of patients), with similar results observed in ALK inhibitor-naïve and -pretreated patients (38.5% and 46.9%, respectively). Overall, 13 patients (10.5%) discontinued due to AEs.

Safety

- All patients experienced ≥1 AE, regardless of study drug relationship.
- The most common AEs in the 124 patients with brain metastases were nausea, diarrhoea and vomiting (**Table 7**).
- A total of 73 patients (58.9%) with brain metastases experienced ≥1 serious AE (SAE), regardless of study drug relationship.
- The most common SAEs among the 124 patients with brain metastases were convulsion (n=9), pneumonia (n=9), dyspnoea (n=5) and hyperglycaemia (n=5).
- The safety profile for ceritinib was similar among ALK inhibitor-naïve and -pretreated patients.
- There were no treatment-related deaths.

Table 7. Adverse Events (≥20% for All Grades) Among Patients with ALK+ NSCLC and Brain Metastases at Baseline

	NSCLC with Prior ALK Inhibitor (n=98)		NSCLC ALK Inhibitor Naïve (n=26)		All NSCLC (N=124)	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
Nausea	82 (83.7)	6 (6.1)	22 (88.4)	1 (3.8)	104 (83.9)	7 (5.6)
Diarrhoea	75 (76.5)	5 (5.1)	24 (92.3)	1 (3.8)	99 (79.8)	6 (4.8)
Vomiting	59 (60.2)	8 (8.2)	20 (76.9)	1 (3.8)	79 (63.7)	9 (7.3)
Alanine aminotransferase increased	40 (40.8)	26 (26.5)	14 (53.8)	10 (38.5)	54 (43.5)	36 (29.0)
Fatigue	37 (37.8)	7 (7.1)	13 (50.0)	0 (0.0)	50 (40.3)	7 (5.6)
Abdominal pain	30 (30.6)	0 (0.0)	10 (38.5)	1 (3.8)	40 (32.3)	1 (0.8)
Headache	29 (29.6)	4 (4.1)	4 (15.4)	0 (0.0)	33 (26.6)	4 (3.2)
Aspartate aminotransferase increased	28 (28.6)	10 (10.2)	9 (34.6)	2 (7.7)	37 (29.8)	12 (9.7)
Weight decreased	23 (23.5)	1 (1.0)	5 (19.2)	2 (7.7)	28 (22.6)	3 (2.4)
Asthenia	20 (20.4)	1 (1.0)	8 (30.8)	0 (0.0)	28 (22.6)	1 (0.8)
Dyspnoea	24 (24.5)	4 (4.1)	9 (34.6)	3 (11.5)	33 (26.6)	7 (5.6)
Back pain	19 (19.4)	1 (1.0)	7 (26.9)	0 (0.0)	26 (21.0)	1 (0.8)
Blood alkaline phosphatase increased	19 (19.4)	6 (6.1)	4 (15.4)	0 (0.0)	23 (18.5)	6 (4.8)
Hypokalaemia	12 (12.2)	5 (5.1)	6 (23.1)	2 (7.7)	18 (14.5)	7 (5.6)

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer

CONCLUSIONS

- **Ceritinib 750 mg/day demonstrated anti-tumour activity in patients with ALK+ NSCLC and brain metastases.**
  - **Efficacy was observed in ALK inhibitor-naïve patients as well as in patients previously treated with an ALK inhibitor; ceritinib afforded substantial efficacy in ALK inhibitor-resistant disease, with responses observed in more than half of patients**
- **Ceritinib also achieved durable intracranial responses in ALK+ NSCLC patients with brain metastases, both in patients previously untreated or treated with crizotinib.**
- **With only limited data available on prior radiotherapy in the brain, this analysis could not account for effect of prior intracranial radiation.**
- **Ceritinib was generally well tolerated in patients with ALK+ NSCLC and brain metastases, with a safety profile similar to that seen in the total ALK+ NSCLC patient population.[7]**
- **A Phase II study will be initiated at the end of 2014 to further investigate the efficacy of ceritinib in brain metastases.**

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Corresponding Author Email: ASHAW1@mgh.harvard.edu

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