June 27, 2014

Submission Request
National Comprehensive Cancer Network

RE: Updated Clinical Evidence in Support of Zykadia (ceritinib) in Anaplastic Lymphoma Kinase-Positive (ALK+) Metastatic Non-Small Cell Lung Cancer (NSCLC) Patients With or Without Prior ALK inhibitor Therapy

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Date of request:	June 27, 2014
NCCN Guidelines Panel:	Non-Small Cell Lung Cancer

To Whom It May Concern:

In addition to the submission dated May 1, 2014, we have enclosed more recent data relating to treatment with ceritinib. This information is highlighted below:

- Updated data to support the use of ceritinib in ALK+ metastatic non-small cell lung cancer with or without prior treatment with an ALK inhibitor.

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Ceritinib for the treatment of ALK+ metastatic non-small cell lung cancer
We are providing updated information regarding ceritinib as the Panel reviews the NSCLC Guidelines and the associated "NCCN Drugs and Biologics Compendium™". A phase I, multicenter, open-label, dose escalation study evaluated ceritinib, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK. Patients with asymptomatic untreated or treated central nervous system (CNS) metastases were eligible.

Table 1. Systemic response rates in patients with ALK-positive NSCLC treated with ceritinib 750 mg daily

	ALK inhibitor treated (n=163)	ALK inhibitor naïve (n=83)	All NSCLC (n=246)
CR	2 (1.2)	1 (1.2)	3 (1.2)
PR	87 (53.4)	54 (65.1)	141 (57.3)
SD	32 (19.6)	19 (22.9)	51 (20.7)
PD	16 (9.8)	0	16 (6.5)
Unknown response	26 (16.0)	9 (10.8)	35 (14.2)
ORR	89 (54.6)	55 (66.3)	144 (58.5)
95% CI	46.6, 62.4	55.1, 76.3	52.1, 64.8

All data presented as n (%); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CI, confidence interval

Among those responding NSCLC patients treated with ceritinib 750 mg daily, the median DOR was 9.69 months (95% CI 7.00, 11.40), with a 12-month DOR rate of 33%. The overall median PFS was 8.21 months (95% CI 6.70, 10.12), with a 12-month PFS rate of 39.1%.

At baseline, 124 patients had brain metastases, including 98 ALK inhibitor treated patients and 26 ALK inhibitor naïve patients. Out of these patients, a total of 14 (10 ALK inhibitor treated and four ALK

inhibitor naïve) had brain metastases measurable by RECIST 1.0 criteria. The ORR for all patients with brain metastases at baseline was 54% with a median DOR of 7.00 months. Table 2 provides additional information.

Table 2. OIRR results for patients with measurable brain metastases at baseline

Best overall response n (%)	ALK inhibitor treated (n=10)	ALK inhibitor naïve (n=4)	All NSCLC (n=14)
CR	0	1 (25.0)	1 (7.1)
PR	4 (40.0)	2 (50.0)	6 (42.9)
SD	3 (30.0)	0	3 (21.4)
PD	0	0	0
Unknown response	3 (30.0)	1 (25.1)	4 (28.6)
OIRR	4 (40.0)	3 (75.0)	7 (50.0)
95% CI	12.2, 73.8	19.4, 99.4	23.0, 77.0

All data presented as n (%); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease OIRR, overall intracranial response rate; CI, confidence interval

The most common adverse events (>20%) were diarrhea, nausea, vomiting, abdominal pain, constipation, fatigue and decreased appetite. The most common laboratory abnormalities included decreased hemoglobin, increased alanine transaminase (ALT), increased aspartate transaminase (AST), increased creatinine, increased glucose, decreased phosphate and increased lipase. The most common grade 3/4 adverse events (≥2%) were diarrhea, fatigue, nausea, vomiting, interstitial lung disease/pneumonitis and abdominal pain. The most common grade 3/4 laboratory abnormalities included increased ALT, increased AST, increased glucose, increased lipase, decreased phosphate, decreased hemoglobin and increased creatinine.

Specific changes recommended for the Guidelines & Compendium
Please add ceritinib as an option for the treatment of patients with ALK+ metastatic NSCLC with or without prior treatment with an ALK inhibitor.

FDA Status
Ceritinib is a kinase inhibitor indicated for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rationale for recommended change
Evidence of clinical benefit in patients with or without prior ALK inhibitor therapy was demonstrated in a phase I trial of ALK+ metastatic NSCLC patients treated with ceritinib.

Literature support
1. Kim DW, Mehra R, Tan D, et al. Ceritinib in Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) – Results of the ASCEND-1 Trial. Oral Presentation at American Society of Clinical Oncology;May 30-June 3, 2014;Chicago, IL. Oral Presentation 8003

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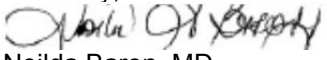
We appreciate the opportunity to provide this information for consideration by the NCCN NSCLC Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,



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Enclosures: Copies of referenced primary literature; Author disclosures included within references