May 1, 2014

Submission Request
National Comprehensive Cancer Network

RE: 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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NCCN Guidelines Panel:	Non-Small Cell Lung Cancer

To Whom It May Concern:

As the NCCN Non-Small Cell Lung Cancer Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, v.3.2014 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with ceritinib. This information is highlighted below:

- 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
This request is for the Panel to consider the addition of ceritinib in sections “NSCL-18”, “NSCL-F”, and “NSCL-H” of the Non-Small Cell Lung Cancer Guidelines and the associated “NCCN Drugs and Biologics Compendium™” based on results from a phase I trial. A phase I, multicenter, open-label, dose escalation study evaluated ceritinib, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK. In patients with NSCLC, demonstration of ALK rearrangement was required in ≥15% of tumor cells by break-apart fluorescence in situ hybridization (FISH) assay. Patients with asymptomatic untreated or treated central nervous system (CNS) metastases were eligible. In the dose-escalation phase, treatment comprised a single ceritinib dose followed by a 3-day pharmacokinetic evaluation period, and daily oral dosing in continuous 21-day treatment cycles. The starting dose was 50 mg per day. Expansion cohorts received the maximum tolerated dose of 750 mg per day.

At the time of data analysis, a total of 130 patients had been treated: 59 patients in the dose-escalation phase and 71 in the expansion phase. A total of 114 patients with NSCLC received ≥ 400 mg of ceritinib daily. The overall response rate (ORR) was 58% (95% CI, 48-67). Among the 78 patients with NSCLC who received 750 mg daily, the ORR was 59% (95% CI, 47-70). For crizotinib-pretreated patients, the ORR was 56% (95% CI, 45-67) among those who received ceritinib at a dose of ≥ 400 mg daily (45 of 80 patients) and 56% (95% CI, 41-70) among those treated with ceritinib at a dose of 750 mg daily (28 of 50 patients). Among the 34 patients who were crizotinib-naïve and who were treated with ≥ 400 mg of ceritinib daily, the ORR was 62% (95% CI, 44-78). In ALK+ NSCLC patients receiving ≥400 mg/day, the median duration of response (DOR) was 8.2 months (95% CI, 6.9-11.4) and the median progression free

survival (PFS) was 7.0 months (95% CI, 5.6-9.5). In the subgroup of 80 patients with NSCLC who had previously received crizotinib, the median PFS was 6.9 months (95% CI, 5.3 to 8.8). In the subgroup of 34 patients with NSCLC who were crizotinib-naïve, the median PFS was 10.4 months (95% CI, 4.6-NE). Among 64 patients with CNS metastases at baseline, the median PFS (daily ceritinib dose of ≥400 mg) was similar to that among 50 patients without CNS metastases (6.9 and 7.0 months, respectively; *P*= 0.37).

The most commonly reported grade 3 or 4 adverse events were ALT increase (21%), AST increase (11%), diarrhea (7%), lipase increase (7%), nausea (5%), fatigue (5%), vomiting (5%), hypophosphatemia (3%), amylase increase (2%), blood alkaline phosphatase increase (2%), and hyperglycemia (2%). The most common all-grade adverse events (incidence ≥15%) included nausea, diarrhea, vomiting, fatigue, and increased alanine aminotransferase levels. Eight patients (6%) discontinued due to adverse events. No treatment-related deaths occurred.

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
Efficacy and safety of ceritinib has been demonstrated in a phase I trial for the treatment of metastatic ALK+ NSCLC patients; these results provide evidence of clinical benefit in patients with or without prior ALK-inhibitor therapy.

Literature support

1. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. N Engl J Med. 2014 Mar 27;370(13):1189-1197.

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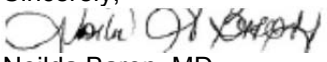
We appreciate the opportunity to provide this information for consideration by the NCCN Non-Small Cell Lung Cancer Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time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

Sincerely,



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