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Date of request: 12/11/15
NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC)

On behalf of Genentech, I respectfully request the NCCN NSCLC Guideline Panel to review the enclosed most recent data for:

- Alecensa® (alectinib): NSCLC

Specific Changes:

- Please consider the available data on the use of Alecensa in ALK+ NSCLC patients for inclusion in the NCCN Guidelines.

FDA Clearance: Alecensa was recently FDA-approved for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib.

Please refer to the product prescribing information for the full FDA-approved indications and safety information.

- Full Alecensa® prescribing information available at: http://www.gene.com/download/pdf/alecensa_prescribing.pdf

Rationale:

The FDA based their approval of Alecensa on two single-arm, open-label Phase II trials (Global NP28673, and North American NP28761) in addition to a pooled analysis of these two trials evaluating CNS efficacy in crizotinib-refractory patients.

Global NP28673 trial (Barlesi et al.):

- In this Phase II single-arm study in patients with ALK-positive NSCLC who had progressed on crizotinib, at a media follow up of 14.5 months in the response-evaluable population of 122 patients, Alecensa 600 mg twice daily demonstrated an objective response rate (ORR) of 50.8%, a median duration of response of 14.1 months, a disease control rate (DCR) of 78.7%, and a median progression-free survival (PFS) of 8.9 months.
- Treatment-related Grade 3/4 adverse events included fatigue, headache, dyspnea, diarrhea, anemia, increased bilirubin, and increased alanine and aspartate aminotransferase.
- Adverse events that resulted in dose reductions, interruptions or withdrawals were reported in 10.1%, 22.5% and 8.7% respectively.

North-American NP28761 trial (Shaw et al):

- In this Phase II single-arm study in patients with ALK-positive NSCLC who had progressed on crizotinib, at median follow up of 43 weeks in the response-evaluable population of 76

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patients, Alecensa 600 mg twice daily demonstrated an objective response rate of 52.2%, a median duration of response of 13.5 months, a DCR of 79.1%, and a median PFS of 8.1 months.
- Grade ≥3 adverse events included increased alanine and aspartate aminotransferase, increased blood creatine phosphokinase, dyspnea, hypertrigliceridemia, hypokalemia, and hypophosphatemia.
- Dose reductions, interruptions and withdrawals were reported in 16%, 36% and 2% of patients, respectively.

Pooled Analysis (Gadgeel et al.):

- In a pooled analysis of pre-specified CNS endpoints in the Global and North American trials (refer to individual trials for additional CNS data) at a median follow up of 12.4 months, the CNS ORR was 64% (CR=22%), DOR was 10.8 months and DCR was 85.3% in patients with measurable CNS metastases at baseline (n=50). In all 136 patients with CNS metastases (measureable and non-measurable), the CNS ORR was 42.6% (CR=27.2%), DOR was 11.1 months and DCR was 90%.
- In a post-hoc analysis of CNS activity by prior brain radiation therapy status, responses were observed in patients with (n=95, ORR=35.8%, CR=17.9%, DCR=86.3%) and without (n=41, ORR=58.5%, CR=48.8%, DCR=82.9%) prior brain radiation therapy.
- The percentage of patients with grade 3-5 AE's were similar between patients with baseline CNS mets (38.2%) and the overall pooled population (34.7%).

Alecensa, at a dose of 300mg twice daily, has also shown activity in patients with CNS mets in a Phase I/II single-arm, open-label study conducted by Ohe, et al. in 46 Japanese patients with crizotinib-naive NSCLC.

- At 12 months of follow up, the ORR was 93.5% for the entire population with none of the 46 enrolled patients in the Phase II portion of the trial experiencing progressive disease including the 15 patients with CNS metastases at baseline.[1]
- At a median follow up of greater than 30 months, ORR remained the same, and median PFS had not been reached. At the time of this report, median PFS in patients with CNS metastasis was estimated to be 35.3 months, and half of the patients with CNS metastases at baseline were still on treatment without progression.
- Grade 3 treatment-related adverse events included increased bilirubin, increased alanine aminotransferase, decreased neutrophil count, leukopenia, and increased blood creatine phosphokinase.

Additional data have been reported on use of Alecensa in patients with ALK-positive NSCLC.[2-4]

The following enclosures are included for your review (copyright-paid where applicable):

- Barlesi F, Dingemans AC, Ou SI, et al. Updated efficacy and safety results from a global phase II, open-label, single-arm study (NP28673) of alectinib in crizotinib-refractory *ALK*+ non-small-cell lung cancer (NSCLC). Presented at the European Cancer Conference. Vienna, Austria; September 25-September 29, 2015. ECC Poster # 3101.

- Shaw A, West H, Socinski M, et al. Updated efficacy/safety data from the phase 2 NP28761 study of alectinib in ALK+ NSCLC. Presented at 16th World Conference on Lung Cancer in Denver, CO; September 6-September 9, 2015. WCLC Oral Presentation #1261.

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- Gadgeel S, Shaw A, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pre-treated *ALK*+ NSCLC. Presented at 16th World Conference on Lung Cancer in Denver, CO; September 6-September 9, 2015. WCLC Oral Presentation #1219.

- Ohe Y, Nishio M, Kiura K, et al. A phase I/II study with a CNS-penetrant, selective ALK inhibitor alectinib in ALK-rearranged non-small cell lung cancer (ALK+ NSCLC) patients (pts): updates on progression-free survival (PFS) and safety results from AF-001JP. Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, IL; May 29-June 2, 2015. ASCO Poster #8061.

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Respectfully submitted,

Katherine Eakle, Pharm.D.

Supplemental References

1. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with *ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol. 2013;14(7):590-598.
2. Gadgeel S, Ou SH, Chiappori AA, et al. A phase 1 dose escalation study of a new ALK inhibitor, CH5424802/RO5424802, in ALK+ non-small cell lung cancer (NSCLC) patients who have failed crizotinib (AF-002JG/NP28761, NCT01588028). J Thorac Oncol 2013;8(suppl 2):S199.
3. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant alk-rearranged non-small-cell lung cancer (AF-002JG): Results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119-1128.
4. Hotta K, Hida T, Nakagawa K, et al. Updated data from JP28927 study of alectinib in ALK+ NSCLC patients with or without history of ALK inhibitor treatment. Presented at 16th World Conference on Lung Cancer in Denver, CO; September 6-September 9, 2015. WCLC Poster #346.

C#15-M0107

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