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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 Phase III trial results for:

- Alecensa® (alectinib): NSCLC

  Nokihara H, Hida T, Kondo M, et al. Alectinib versus crizotinib in ALK inhibitor naïve ALK-positive non-small cell lung cancer: Primary results from J-Alex study. Presented at the American Society of Clinical Oncology 2016 Annual Meeting in Chicago, Illinois; June 3 - June 7, 2016. ASCO Oral Presentation #9008.

  Nokihara H, Hida T, Masashi K, et al. Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naïve ALK-positive non-small cell lung cancer (ALK+ NSCLC): primary results from the J-ALEX study. Presented at the American Society of Clinical Oncology 2016 Annual Meeting in Chicago, Illinois; June 3 - June 7, 2016. ASCO abstract #9008. http://abstracts.asco.org/176/AbstView_176_167434.html

Specific Changes:
Consider the available data on the use of Alecensa in ALK-inhibitor naïve patients with ALK+ NSCLC for your updating purposes.

FDA Clearance:
Alecensa is not FDA-approved for use in the treatment of ALK-inhibitor naïve ALK+ NSCLC. Alecensa is FDA-approved for the treatment of patients with ALK+, metastatic NSCLC who have progressed on or are intolerant to crizotinib.

Please refer to the full Alecensa prescribing information for the FDA-approved indication and safety information available at: http://www.gene.com/download/pdf/alecensa_prescribing.pdf

Rationale:

Efficacy:

A Phase III, randomized, open-label study was conducted in Japan to compare the efficacy and safety of Alecensa with crizotinib for the treatment of 207 patients with ALK-inhibitor naïve, ALK+ NSCLC. At a pre-planned interim analysis, the primary endpoint of progression-free survival (PFS) had been met. The hazard ratio for PFS was 0.34 (95% CI, 0.17-0.70; p<0.0001); the median PFS was not reached for Alecensa (95% CI, 20.3-not reached) and was 10.2 months in the crizotinib arm (95% CI, 8.2-12).

Safety:
In the Alecensa arm constipation (35%) was an adverse event (AE) with greater than 30% frequency, while in the crizotinib arm nausea (74%), diarrhea (73%), vomiting (58%), visual disturbance (55%), dysgeusia (52%), constipation (44%), ALT elevation (32%), and AST elevation (31%) were seen in greater than 30% patients. Grade 3-4 AEs occurred in 26% of Alecensa patients compared with 52% of crizotinib patients, and there were

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no treatment-related deaths in either arm. AEs leading to discontinuation of the study drug were 9% in the Alecensa arm vs. 20% in the crizotinib arm.

Dosing:

This trial was conducted in Japan at a dose of 300mg twice daily (BID) due to restrictions in Japan on the maximum amount of SLS (sodium lauryl sulfate) that can be administered to humans.[1] In the US, the FDA-approved dose of Alecensa is 600mg BID. This dose has been found to be safe and effective and resulted in multi-dose exposures expected within the plateau range of antitumor response in crizotinib-progressed patients.[2,3] In addition, based on a cross-study comparison of Japanese patients who received 300mg BID in the AF-001JP study and non-Japanese patients who received 600mg BID in the AF-002JG study, Alecensa 600mg BID resulted in multi-dose exposures that met or exceeded those shown to be active with the 300mg BID dose.[2-5] In the US patient population, doses below 600mg BID may result in variable exposure and thus sub-optimal efficacy.[3]

Additional data have been reported on the use of Alecensa in patients with ALK inhibitor-naïve ALK+ NSCLC.[6,7]

Respectfully submitted,

Supplemental References

1. Food and Drug Administration. Center for Drug Evaluation and Research: application number 208434Orig1s000. medical review(s): p. 33 Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000MedR.pdf. Accessed on 6-6-2016.
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. Hsu JC, Carnac R, Henschel V, et al. Population pharmacokinetics (popPK) and exposure-response (ER) analyses confirm alectinib 600mg BID dose selection in a crizotinib-progressed or intolerant population. Presented at the American Society of Clinical Oncology 2016 Annual Meeting in Chicago, Illinois; June 3 - June 7, 2016. ASCO #e20598.
4. 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.
5. Ou SHI, Gadgeel S, Chiappori A, et al. Safety and efficacy analysis of alectinib (CH5424802/RO5424802) in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients who have failed crizotinib in a dose-finding Phase I study (AF-002JG, NCT01588028). Presented at the European Society for Medical Oncology in Amsterdam, Netherlands; September 27–October 1, 2013. ESMO Oral presentation #44 LBA.
6. 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.

7. 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.