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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 most recent clinical data and diagnostic information regarding:

- Alecensa[®] (alectinib): NSCLC

Shaw A, Peters S, Mok T, et al. Alectinib vs crizotinib in treatment-naïve advanced ALK+ NSCLC: primary results of the global phase III ALEX study (LBA9008). Presented at the American Society of Clinical Oncology 2017 Annual Meeting in Chicago, Illinois; June 2-6, 2017. #ASCO17.

Peters S, Camidge R, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer. *N Engl J Med*. E-pub Date: [published online ahead of print] June 6, 2017. DOI # 10.1056/NEJMoa1704795.

Specific Changes:

- Consider the available Phase III data on the use of Alecensa in treatment-naïve patients with ALK+ NSCLC for inclusion into the guideline.
- In addition, the recommendation listed in the NSCLC Guideline V.6.2017 Principles of Pathologic Review [NSCL-A 3 of 5] for ALK testing methodology appears inconsistent with currently available IHC (immunohistochemistry)/FISH (fluorescence in situ hybridization) concordance data. Please consider including IHC as a standalone ALK testing option.

FDA Clearance:

Alecensa is not FDA-approved for use in treatment-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:

ALEX Trial:

The ALEX trial is a randomized, open-label, Phase III study conducted to evaluate the efficacy and safety of Alecensa vs. crizotinib in 303 patients with treatment-naïve metastatic ALK+ NSCLC. The primary outcome measure of investigator-assessed progression-free survival (PFS) was significantly longer in the Alecensa arm vs. the crizotinib arm (not reached vs. 11.1 months; hazard ratio (HR)=0.47 (95% CI: 0.34-0.65); p<0.0001). The objective response rate was 83% for Alecensa vs. 76% for crizotinib (p=0.09). The central nervous system objective response rate was 59% (complete response [CR]=45%) for Alecensa vs. 26% (CR=9%) for crizotinib. The median duration of response has not been reached for Alecensa vs. 11.1 months for crizotinib (95% CI: 7.9-13). The median overall survival has not been reached for either arm.

There were more Grade 3-5 adverse events in the crizotinib arm (50%) than in the Alecensa arm (41%). Adverse events leading to treatment discontinuation, dose reduction or interruption were 13%, 21% and 25%

respectively for crizotinib vs. 11%, 16% and 19% for Alecensa. There were two treatment-related deaths in the crizotinib arm and none in the Alecensa arm.

Additional Phase III comparative data between Alecensa and crizotinib (J-ALEX) has been submitted previously. In an updated analysis, the median PFS was 25.9 months (95% CI: 20.3-NE) for Alecensa compared to 10.2 months (95% CI: 8.3-12) for crizotinib (HR=0.38 [95% CI: 0.26-0.55]; p<0.0001). Alecensa continued to demonstrate a more favorable tolerability profile with 32% Grade 3-4 adverse events vs. 56.7% for crizotinib.¹⁻²

IHC Testing

The NSCLC guideline V.6.2017 under Principles of Pathologic Review [NSCL-A 3 of 5] states that the current standard method for detecting ALK NSCLC is FISH, and that antibody and detection methods such as IHC could be used as a prescreening if confirmed by FISH testing. The discussion section only mentions an FDA approved ALK diagnostic test using FISH [MS-13]. There is also a test, however, using IHC [Ventana ALK (D5F3) CDx Assay] that has been approved by the FDA as a standalone test for detecting ALK rearrangements. This test does not require follow up testing with FISH.

The College of American Pathologists, in partnership with the International Association for the study of Lung Cancer and the Association for Molecular Pathology is in the process of updating their "*Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase inhibitors*".³ The [draft updated guideline](#) currently states: "When performing ALK testing, physicians can utilize IHC as an equivalent alternative to FISH."

Additional data have been reported on concordance between FISH and IHC.⁴⁻¹⁴

Respectfully submitted,



Supplemental References

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