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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of Takeda Oncology, I respectfully request that that the Panel consider the enclosed updated data for ALUNBRIG® (brigatinib) as monotherapy in the treatment of patients with anaplastic lymphoma kinase–positive (ALK+) non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Specific Changes: I request that the Panel please consider the following updates:

- **NSCL-22 (ALK+, Subsequent therapy):** Brigatinib as **preferred** therapy for both asymptomatic and symptomatic patients in the post-crizotinib setting.[1-4]
- Denote on page **MS-17** that brigatinib can be administered beyond Response Evaluation Criteria in Solid Tumors (RECIST)–defined progression[5]

FDA Clearance: On April 28, 2017, brigatinib was approved for the treatment of adult patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib.[1]

Rationale Summary: Updates to the ALTA trial with longer follow-up show prolonged efficacy, including a median progression-free survival (PFS) of 16.7 months and median overall survival (OS) of 34.1 months, at the recommended dose (180 mg once daily with a 7-day lead in at 90 mg once daily) in patients with or without brain metastases. Safety data were consistent with previous reports.[2-4] Additionally, an exploratory post hoc analysis from ALTA demonstrated that brigatinib administered beyond RECIST-defined progression may prolong OS compared with discontinuing brigatinib.[5]

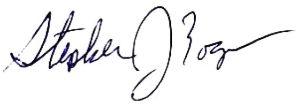
Supporting Literature:

Huber et al. reported updated ALTA data at the 2018 American Society of Clinical Oncology Annual Meeting (manuscript in preparation). ALTA is a phase 2, pivotal randomized trial of brigatinib 90 mg once daily (Arm A; n = 112) or brigatinib 180 mg once daily with a 7-day lead in at 90 mg once daily (90 → 180 mg once daily) (Arm B; n = 110). As of the reported data cut-off date, median follow-up in Arm B was 24.3 months—16 months longer than that reported in the 2017 *Journal of Clinical Oncology* publication by Kim et al.[2,3] As of this updated data cut, IRC-assessed median PFS was 16.7 months and median OS has matured to 34.1 months.[3]
The most common (≥ 3%) treatment-related AEs of grade ≥ 3 in the 90 → 180 mg once daily arm were increased blood creatine phosphokinase (13%), hypertension (5%), increased lipase (5%), pneumonitis (4%), rash (4%), increased alanine aminotransferase (4%), increased aspartate aminotransferase (3%), and hyponatremia (3%).[3]

Camidge et al. published peer-reviewed CNS efficacy results for brigatinib, including from the ALTA trial, in the *Journal of Clinical Oncology*. Median follow-up in ALTA Arm B was 11.0 months. In patients with measurable (≥ 10 mm) brain metastases at baseline who received the recommended dose (90 → 180 mg once daily; n = 18), the confirmed intracranial ORR was 67%; among the subset of patients with active brain metastases (defined as brain metastasis with no prior radiotherapy or with progression following prior radiotherapy treatment; n=15) the confirmed intracranial ORR was 73%. IRC-assessed median intracranial PFS in patients with any brain metastases at baseline in Arm B (n = 73) was 18.4 months.[4]

Langer et al. reported the results of an exploratory post hoc analysis that assessed OS in patients who continued brigatinib beyond RECIST version 1.1–defined progression in ALTA and was presented at the 2017 World Conference in Lung Cancer (manuscript in preparation). Patients in Arm B who continued brigatinib beyond progression (n = 38) had a 1-year OS rate of 66% from the time of first disease progression, compared with 31% for those who discontinued brigatinib (n = 23) (adjusted hazard ratio: 0.45; 95% CI: 0.18-1.16).[5]

Respectfully submitted,



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References:

1. Alunbrig (brigatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; 2018.
2. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol.* 2017;35(22):2490-2498.
3. Huber RM, Kim DW, Ahn MJ, et al. Brigatinib in crizotinib-refractory ALK+ non-small cell lung cancer: efficacy updates and exploratory analysis of CNS ORR and overall ORR by baseline brain lesion status. *J Clin Oncol.* 2018;36(15 suppl): abstr 9061. Manuscript in preparation.
4. Camidge DR, Kim DW, Tiseo M, et al. Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials. *J Clin Oncol.* 2018;36(26):2693-2701.
5. Langer C, Huang H, Reichmann W, et al. Overall survival (OS) after disease progression (DP) on brigatinib in patients with crizotinib-refractory ALK+ NSCLC in ALTA. *J Thorac Oncol* 2017;12(11S2):S1893-S1894. Manuscript in preparation.