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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 first-line monotherapy in the treatment of patients with anaplastic lymphoma kinase–positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have not received an ALK inhibitor (eg, crizotinib).

Specific Changes: I respectfully request that the Panel consider the following:

- **NSCL-21 (ALK+, First-line)**: Add Brigatinib (category 1) as **preferred** first-line therapy[2]

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: In the ALTA-1L trial, brigatinib demonstrated superior progression-free survival (PFS) against systemic and intracranial disease compared with crizotinib in patients with ALK inhibitor−naive ALK+ advanced NSCLC.[2,3] The risk of progression or death was significantly reduced by 51% (HR for disease progression or death, 0.49; 95% CI, 0.33 to 0.74; *P*=0.007). PFS favored brigatinib across subgroups. Brigatinib also showed improved activity in the brain compared with crizotinib, as evidenced by intracranial overall response rate (ORR) and intracranial PFS. The safety profile for brigatinib was consistent with previous reports,[4,5] and no new safety concerns were noted.

Supporting literature:

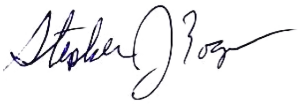
Camidge et al. reported results from the first interim analysis of ALTA-1L in *The New England Journal of Medicine*.[2] ALTA-1L is an open-label, phase 3 study in patients with ALK inhibitor−naive advanced ALK+ NSCLC. Patients were randomized 1:1 to brigatinib 180 mg once daily (with a 7-day lead in at 90 mg; n = 137) or crizotinib 250 mg twice daily (n = 138). Crossover from crizotinib to brigatinib was permitted after blinded independent review committee (BIRC)-assessed progression, following a 10-day washout period from crizotinib. The primary endpoint was BIRC-assessed PFS. Secondary endpoints included ORR, intracranial ORR, intracranial PFS, and OS.[2,3]

At the planned first interim analysis (99 events), median follow-up was 11.0 (0−20.0) months for brigatinib and 9.3 (0−20.9) months for crizotinib. PFS was significantly longer with brigatinib than crizotinib (estimated 12-month PFS, 67% vs 43%; HR for disease progression or death, 0.49; 95% CI, 0.33–0.74; *P*=0.0007).[2,3] The confirmed ORR was 71% with brigatinib and 60% with

crizotinib (*P*=0.07). The confirmed intracranial ORR among patients with measurable lesions was 78% in the brigatinib group compared with 29% in the crizotinib group (*P*=0.003). Intracranial PFS was improved with brigatinib, with a 73% reduction in risk of progression in the brain or death in patients with any baseline brain metastases. The median intracranial PFS was not reached with brigatinib compared with 5.6 months with crizotinib (estimated 12-month intracranial PFS: 67% vs 21%; HR for intracranial disease progression or death, 0.27; 95% CI, 0.13–0.54; *P*<0.0001).[2,3]

The safety profile of brigatinib was consistent with that seen in the post-crizotinib setting (ALTA),[4,5] and no new safety concerns were noted. The most common (>25% of patients overall) any-grade treatment-emergent AEs were gastrointestinal symptoms (diarrhea: brigatinib 49%, crizotinib 55%; nausea: brigatinib 26%, crizotinib 56%), increased blood creatine phosphokinase levels (brigatinib 39% vs crizotinib 15%), and increased alanine aminotransferase levels (brigatinib 19% vs crizotinib 32%).[2] Interstitial lung disease/pneumonitis at any time occurred in 4% of patients in the brigatinib group and 2% in the crizotinib group; early-onset pulmonary events occurred in 3% of patients in the brigatinib group and were not observed with crizotinib.[2]

Respectfully submitted,



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References:

1. Alunbrig (brigatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc; 2018.
2. Camidge DR, Kim HR, Ahn, M-J, et al. Brigatinib versus crizotinib in *ALK*-positive non–small-cell lung cancer. *New Engl J Med*. 2018 Sep 25. DOI: 10.1056/NEJMoa181017 [Epub ahead of print].
3. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib with ALK inibitor−naïve advanced ALK+ NSCLC: First report of a phase 3 trial (ALTA-1L) Presented at: IASLC 19th World Conference on Lung Cancer; September 23−26, 2018; Toronto, Canada [abstract 11155].
4. 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.
5. Ahn MJ, Camidge DR, Tiseo M, et al. Brigatinib in Crizotinib-Refractory ALK+ NSCLC: Updated Efficacy and Safety Results From ALTA, a Randomized Phase 2 Trial. *J Thorac Oncol* 2017;12(11S2):S1755-S1756..