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Date of request: 5/26/20

NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC)

Re: Brigatinib as preferred option for front-line ALK-positive NSCLC

On behalf of Takeda Oncology, I respectfully request the NCCN NSCLC Panel to consider updated results of the ALTA-1L study¹ in support of brigatinib as a preferred option for front-line ALK-positive NSCLC.

Suggested Changes: Please consider the following:

- **NSCL-22 – “ALK Rearrangement Positive, First-Line Therapy”:**
 - **“ALK discovered prior to 1L systemic therapy”:** Update Brigatinib (category 1) as preferred
 - **“ALK discovered during 1L systemic therapy”:** Update Brigatinib as category 1 preferred*

*ALTA-1L includes patients (26%) who received prior chemotherapy.¹

Rationale Summary: An updated analysis of the phase 3 ALTA-1L shows consistent efficacy of brigatinib with a longer follow-up of 25 months in ALK-positive, ALK inhibitor-naïve NSCLC.¹ Of note, 26% of patients in ALTA-1L have received prior chemotherapy for advanced disease. Brigatinib continued to demonstrate higher PFS compared with crizotinib (51% decrease in risk; median: 24.0 vs 11.0 mo) and higher ORR (74% vs 62%) as assessed by BIRC. The benefit was observed across all subgroups, including patients with baseline brain metastasis (HR, 0.249), without brain metastasis (HR, 0.649), with prior chemotherapy (0.438), or without prior chemotherapy (0.519). Intracranial PFS was dramatically increased with brigatinib than with crizotinib (24.0 vs 5.6 mo; HR, 0.311). Treatment duration with brigatinib was about 3 times as long as for crizotinib (24.3 vs 8.4 mo). These findings support the value of brigatinib as a preferred front-line treatment option for patients with ALK-positive NSCLC with or without brain metastasis and/or prior exposure to systemic therapy.

FDA Clearance:²

Brigatinib (ALUNBRIG®) received FDA approval for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

Supporting Literature:

ALTA-1L is an open-label, phase 3 study that randomized patients with ALK inhibitor-naïve advanced ALK+ NSCLC to brigatinib (n = 137) or crizotinib (n = 138).¹ The study included 26% of patients who received one prior systemic therapy for advanced disease and 29% of patients with baseline intracranial

metastases. Crossover from crizotinib to brigatinib was permitted after progression assessed by blinded independent review committee (BIRC) following a 10-day washout period from crizotinib. The primary endpoint, BIRC-assessed progression-free survival (PFS), has already been met at a prior interim analysis.³ An updated analysis at 25 months of median follow-up confirmed that brigatinib continued to be associated with improved BIRC-assessed PFS compared with crizotinib (24-month PFS: 48% vs 26%; HR, 0.489; 95% CI, 0.35-0.68; $P<0.0001$).¹ Median BIRC PFS was 24.0 months with brigatinib and 11.0 with crizotinib. This was consistent with investigator-assessed PFS (24-month PFS: 56% vs 24%; HR, 0.434; 95% CI, 0.31-0.61; $P<0.0001$; median PFS: 29.4 vs 9.2 months). The benefit of BIRC-assessed PFS was observed across all subgroups, including patients with baseline brain metastasis (HR, 0.249; 95% CI, 0.14-0.46), without brain metastasis (HR, 0.649; 0.44-0.97), with prior chemotherapy (HR, 0.438; 0.23-0.83), or without prior chemotherapy (HR, 0.519; 0.35-0.77). Brigatinib also improved BIRC objective response rate (ORR) (73.7% vs 61.6%; $P=0.034$). Among patients with baseline intracranial metastases, brigatinib was associated with a dramatic increase in confirmed intracranial ORR (77.8% vs 26.1%; $P=0.0014$) and a 69% reduction in risk of intracranial progression, death, or radiotherapy to the brain (median intracranial PFS: 24.0 vs 5.6 mo; HR, 0.311; 95% CI, 0.17-0.56; $P<0.0001$). In the crizotinib arm, 44% of patients crossed over to brigatinib. Overall survival (OS) was immature at this time; the number of events was 24.1% for brigatinib and 26.8% for crizotinib. Brigatinib also achieved significant improvement in health-related quality of life in several function and symptom scores.¹

Median duration of exposure was almost 3 times longer with brigatinib (24.3 months) than with crizotinib (8.4 months).¹ The safety profile of brigatinib in the front-line setting was consistent with that in the subsequent setting (ALTA) and no new safety concerns for brigatinib were noted in ALTA-1L.^{1,4} In the current study, grade 3 or 4 drug-related adverse events (AE) were observed in 55.9% with brigatinib.¹ Brigatinib was discontinued in 12.5% of patients due to AE. The most common AE (all grades) in the brigatinib arm was diarrhea (52%), creatine phosphokinase increase (46%), cough (35%), and hypertension (32%). The incidence of early-onset pulmonary events (interstitial lung disease/pneumonitis) was lower in ALTA-1L (2.9%) compared with ALTA in the subsequent setting (6.4%).^{1,4}

Respectfully submitted,



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References:

1. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib vs crizotinib in ALK inhibitor-naïve advanced ALK+ NSCLC: updated results from the phase 3 ALTA-1L trial. *Annals of Oncology*. 2019; 30(suppl_9):ix183-ix202. 10.1093/annonc/mdz446.
2. ALUNBRIG® (brigatinib) prescribing information. Takeda Oncology, Inc.
3. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018 Nov 22;379(21):2027-2039.
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 Aug 1;35(22):2490-2498.