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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of Takeda Oncology, I respectfully request the NCCN Non-Small Cell Lung Cancer (NSCLC) Guideline Panel to consider the enclosed data supporting the use of ALUNBRIG™ (brigatinib) as monotherapy in the treatment of patients with Anaplastic Lymphoma Kinase-positive (ALK+) NSCLC who have progressed on or are intolerant to crizotinib.

Specific Changes: Please consider the available data supporting the use of brigatinib for the treatment of patients with ALK+ NSCLC. Provided is a summary of brigatinib efficacy and safety data in patients with ALK+ NSCLC, including patients with brain metastases.

FDA Clearance: On April 28, 2017, the FDA approved brigatinib for the treatment of adult patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib. Brigatinib previously received Breakthrough Therapy designation from the FDA for the treatment of patients with ALK+ NSCLC whose tumors are resistant to crizotinib, and was granted orphan drug designation by the FDA for the treatment of ALK+ NSCLC. Enclosed, please find the full prescribing information[1] for the FDA-approved indication, along with supportive literature, which is summarized below.[2,3,4,5,6]

Rationale: Brigatinib yielded responses in a majority of ALK+ NSCLC patients previously treated with crizotinib, and produced a median progression free survival (PFS) of over one year. In addition, brigatinib showed efficacy in patients with brain metastases and against specific ALK kinase domain (KD) resistance mutations.

Supporting Literature: ***Kim et al.*** reported results of a Phase 2, pivotal randomized trial (ALTA) of brigatinib in patients with ALK+ NSCLC refractory to crizotinib.[2] Patients were randomized to receive brigatinib 90 mg once daily (QD) (Arm A) or brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD (90 mg →180 mg QD) (Arm B). Investigator-assessed confirmed objective response rate (ORR), by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, was the primary endpoint. Secondary endpoints included confirmed ORR by an Independent Review Committee (IRC), duration of response (DOR), PFS, central nervous system (CNS) response (IRC-assessed intracranial response rate and PFS), overall survival (OS), and safety. The data published by Kim et al in the Journal of Clinical Oncology[2] are consistent with the data reported in the full prescribing information.[1]

The results of Arm B (recommended dosing) were as follows: in Arm B (n=110), brigatinib demonstrated a confirmed investigator-assessed ORR of 54% with 4 complete responses (CR), including CR in a patient with the G1202R resistance mutation at baseline. Investigator-assessed median PFS was 12.9 months, investigator-assessed median DOR was 11.1 months, estimated 1-year OS was 80%, and median OS was not reached. IRC-assessed confirmed ORR was 53%, IRC-assessed median PFS was 15.6 months, and IRC-assessed median DOR was 13.8 months. In this same arm (Arm B), in patients with measurable (≥10 mm) brain metastases at baseline (n=18), IRC-assessed intracranial ORR was 67%, and IRC-assessed median intracranial PFS in patients with any brain metastasis at baseline (n=73) was 12.8 months.[2]

The most common treatment-emergent adverse events (AEs) of grade ≥3 were hypertension (6%/6%, Arms A/B), increased blood creatine phosphokinase (3%/9%, Arms A/B), pneumonia (3%/5%, Arms A/B),

and increased lipase (4%/3%, Arms A/B). Among all treated patients (both Arms), a subset of pulmonary AEs with early onset (median onset, 2 days [range, 1 to 9 days]) that included dyspnea, hypoxia, cough, pneumonia, or pneumonitis occurred in 14/219 (6%) patients (3%, grade ≥3); no such events with early onset occurred after escalation to 180 mg in Arm B. These events were managed with dose interruption and successful reintroduction (6/14) or continued treatment with resolution (1/14). Seven patients discontinued brigatinib due to a pulmonary event with early onset, including one patient who experienced a fatal event of pneumonia.[2]

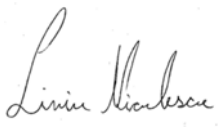
Camidge et al. reported updated results of the Phase 2 ALTA trial at the World Conference on Lung Cancer in December 2016, which included three additional months of patient follow-up.[3]

Gettinger et al. and Bazhenova et al. reported results from a Phase 1/2 dose escalation study in patients with ALK+ NSCLC, including crizotinib-treated patients, crizotinib-naive patients, and patients with brain metastases.[4,5] In patients with prior crizotinib exposure (n=71), results were as follows: confirmed investigator-assessed ORR was 62% across all doses tested; median DOR in confirmed responders was 14.5 months, and median PFS in all patients was 12.9 months. In patients in the 90 mg → 180 mg QD dose cohort, confirmed ORR was 76% (19/25), and median PFS was 16.3 months. Of 8 patients who were crizotinib-naïve, all experienced confirmed objective responses, including 3 CRs; median PFS was not reached in this group. In patients with measurable (≥10 mm) brain metastases at baseline (n=15), brigatinib resulted in a confirmed intracranial ORR of 53%, as assessed by blinded independent central review. The most common treatment-emergent AEs of grade ≥3 in all patients (n=137) were increased lipase levels (12%), pneumonia (7%), dyspnea (6%), hypoxia (6%), and hypertension (5%). A subset of pulmonary AEs with early onset occurred in 2% (1/50) of patients started at the 90 mg QD dose, and in 14% (6/44) of patients started at the 180 mg QD dose. No such events occurred in patients escalated to 180 mg QD after one week at 90 mg QD (n=32). Most events were managed with dose interruption or discontinuation and empiric treatment with steroids and/or antibiotics.[4,5]

Gettinger et al. examined brigatinib efficacy by secondary ALK KD mutations in ALK+ NSCLC patients who had progressed on crizotinib and were enrolled in the Phase 2 ALTA and Phase 1/2 trials described above.[6] Of 293 total patients with prior crizotinib therapy, baseline tumor samples were available from 32 patients. Secondary ALK KD mutations were detected in 9/32 tumor samples at baseline. Confirmed responses were observed in 69% (22/32) of patients with or without secondary ALK KD mutations. In patients with secondary ALK KD mutations, the confirmed ORR was 78% (7/9), including a patient with the G1202R mutation (identified by tissue analysis) at baseline.[6]

Summary: Brigatinib yielded responses in a majority of ALK+ NSCLC patients treated with crizotinib, and produced a median PFS of over one year. In addition, brigatinib showed efficacy in patients with brain metastases and against specific secondary ALK KD mutations.

Respectfully Submitted,



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References (enclosed):

1. ALUNBRIG™ (brigatinib) prescribing information. ARIAD Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Cambridge MA. 04/2017.
2. Kim et al. Brigatinib in patients with crizotinib-refractory ALK+ non-small cell lung cancer: a randomized, multicenter phase 2 trial. J Clin Oncol. 2017 May 5; doi: 10.1200/JCO.2016.71.5904. [Epub ahead of print]
3. Camidge et al. Brigatinib in crizotinib-refractory ALK+ NSCLC: central assessment and updates from ALTA, a pivotal randomized phase 2 trial. World Conference on Lung Cancer 2016, Dec 4-7; Abstract 4046; Poster ID: P3.02a-013
4. Gettinger et al. Activity and safety of brigatinib in ALK-rearranged non-small cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol. 2016 Dec;17(12):1683-1696.
5. Bazhenova et al. Brigatinib (BRG) in patients (pts) with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in a phase 1/2 trial. ESMO 2016, Oct 7-11; Poster 1207PD & Poster Discussion Presentation
6. Gettinger et al. Activity of brigatinib (BRG) in crizotinib (CRZ) resistant patients (pts) according to ALK mutation status. J Clin Oncol 34, 2016 (suppl; abstr 9060)