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

Re: Brigatinib following progression on next-generation ALK inhibitors

On behalf of Takeda Oncology, I respectfully request the NCCN NSCLC Panel to consider two studies^{1,2} in support of brigatinib as second-line or later-line treatment after progression on next-generation ALK inhibitors for ALK-positive NSCLC.

Suggested Changes: Please consider the following updates:

- **NSCL-23 – “ALK Rearrangement Positive, Progression on Alectinib or Brigatinib or Ceritinib”:**
 - Under “Subsequent therapy”, “Progression”: Add Brigatinib for select patients who progressed on alectinib or ceritinib
- **NSCL-22 – “ALK Rearrangement Positive, Progression on Crizotinib”**
 - Under “Subsequent therapy”, “Progression”: Add Brigatinib
 - Add footnote similar to current footnote yy: “Brigatinib is a treatment option after progression on crizotinib and alectinib or ceritinib.”

FDA Clearance:³

Brigatinib (ALUNBRIG®) received FDA accelerated approval for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Rationale Summary: Two recent studies demonstrated overall response rates (ORR) of 40% to 50% with brigatinib as second-line or later-line therapy following progression on next generation ALK inhibitors (including alectinib or ceritinib).^{1,2} These include patients with or without brain metastases, those with good or poor performance status, and those who have been heavily pretreated. Median progression-free survival (PFS) and

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overall survival (OS) with brigatinib in these studies were 6.4 to 6.6 months and 17.2 months, respectively.^{1,2} These findings support the value of brigatinib as a treatment option for patients with ALK-positive NSCLC who are refractory to next generation ALK inhibitors in a broad range of subsequent-line settings.

Supporting Literature:

At least one prior ALK inhibitor – Stinchcombe et al¹

This is a prospective phase 2 study evaluating brigatinib in patients with ALK-positive, stage IIIB/IV NSCLC who progressed on at least one next generation ALK inhibitor. Patients enrolled were heavily pretreated (median number of prior therapies: 3). Prior ALK inhibitors before the study include crizotinib (75%), alectinib (80%), ceritinib (30%), and other investigational agents. More than half of the patients had brain metastases (55%). The confirmed ORR and disease control rate (DCR) of brigatinib in 20 evaluable patients were 40% and 65%, respectively. Median PFS at a follow-up of 6.7 months was 6.4 months (patients with brain metastases: 7.8 months; without brain metastases: 10.1 months). Grade 3-4 adverse events observed include pneumonitis (10%) and 5% each of hypoxemic respiratory failure, acute renal failure, sepsis, headache, hypertension, and CPK elevation.

At least two prior ALK inhibitors – Descourt et al (BRIGALK)²

BRIGALK is a retrospective multicenter study of 104 patients pretreated with at least two ALK inhibitors. Patients in this study were also heavily pretreated (median number of prior therapies: 3); 93% received crizotinib as first-line therapy, then ceritinib as second-line therapy. Majority of these patients (74.5%) had brain metastases; 59% had good performance status (0-1) and 41% had poor performance status (≥ 2). Brigatinib was associated with 50% ORR and 78% DCR. Median PFS and median OS from brigatinib initiation were 6.6 months and 17.2 months, respectively. Ten patients (9.6%) discontinued treatment due to adverse events or by patient request.

Results of these two studies were consistent in demonstrating significant activity of brigatinib following progression on next-generation ALK inhibitors, including alectinib and ceritinib, for a broad range of clinical settings.

Respectfully submitted,

A handwritten signature in blue ink, appearing to read "S. J. Noga", with a long horizontal flourish extending to the right.

Stephen J. Noga, MD, Ph.D.

Vice President, U.S. Medical Affairs - Oncology

References:

1. Stinchcombe TE, et al. Preliminary results of single arm phase 2 trial of brigatinib in patients with disease progression after next-generation Anaplastic Lymphoma Kinase (ALK) tyrosine kinase inhibitors in ALK + Non-Small Cell Lung Cancer. Presented at: 2019 ASCO Annual Meeting. May 31-June 4, 2019. Chicago, IL. Abstract 9027.
2. Descourt R, et al. Brigatinib in pretreated patients with ALK-positive advanced NSCLC. Presented at: 2019 ASCO Annual Meeting. May 31-June 4, 2019. Chicago, IL. Abstract 9045.
3. ALUNBRIG® (brigatinib) prescribing information. Takeda Oncology, Inc.