Date of request: June 10, 2019

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

Re: Brigatinib as preferred therapy in the post-crizotinib setting based on new publication

On behalf of Takeda Oncology, I respectfully request the NCCN NSCLC Panel to consider the enclosed new analysis in support of brigatinib as a preferred option after progression on crizotinib for ALK-positive NSCLC.

Suggested Changes: Please consider the following update:

- **NSCL-22 — “ALK Rearrangement Positive, Progression on crizotinib”**:
  - Under “Subsequent therapy”: Brigatinib as preferred regimen

FDA Clearance:

Brigatinib (ALUNDRIG®) 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: Brigatinib is approved for treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. A comparative efficacy analysis using propensity score weighting showed that brigatinib was associated with significantly longer progression free survival (PFS) and overall survival (OS) compared with ceritinib. Compared with alectinib, brigatinib was associated with longer PFS.

Supporting Literature: A matching adjusted indirect comparison (MAIC) analysis that uses propensity score weighting was conducted to compare the efficacy of brigatinib with ceritinib and alectinib in the crizotinib-refractory setting. A MAIC weights subjects in the index trial such that their weighted average characteristics match those of subjects in the comparator trial; relative efficacy is estimated across balanced trial populations after matching. The ALTA trial for brigatinib served as the index trial. The comparator trials include ASCEND-1...
and ASCEND-2 for ceritinib and NP28761 and NP28673 for alectinib. Results of the analysis are summarized below (bold indicates statistical significance):

<table>
<thead>
<tr>
<th>Agents</th>
<th>Trial comparison</th>
<th>mPFS (hazard ratio [95% CI])</th>
<th>mOS (hazard ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib vs ceritinib</td>
<td>ALTA vs ASCEND-1</td>
<td>15.7 vs 6.9 mo (0.38 [0.26-0.57])</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td>ALTA vs ASCEND-2</td>
<td>18.3 vs 7.2 mo (0.33 [0.20-0.56])</td>
<td>27.6 vs 14.9 mo (0.33 [0.17-0.63])</td>
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<tr>
<td>Brigatinib vs alectinib</td>
<td>ALTA vs NP28761</td>
<td>17.6 vs 8.2 mo (0.56 [0.36-0.86])</td>
<td>27.6 vs 27.7 mo (0.70 [0.42-1.16])</td>
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<tr>
<td></td>
<td>ALTA vs NP28673</td>
<td>17.6 vs 8.9 mo (0.61 [0.40-0.93])</td>
<td>27.6 vs 26.0 mo (0.66 [0.39-1.09])</td>
</tr>
</tbody>
</table>

In the crizotinib-refractory setting, estimates of relative efficacy suggest that brigatinib may improve PFS and OS compared with ceritinib and may improve PFS compared with alectinib. Based on these findings, we respectfully request the NCCN Panel to consider brigatinib as a preferred option over ceritinib and alectinib for ALK-positive patients who are refractory to crizotinib.

Respectfully submitted,

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Vice President, U.S. Medical Affairs - Oncology

References:
2. ALUNBRIG® (brigatinib) prescribing information. Takeda Oncology, Inc.