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Date of Request: May 4, 2020
NCCN Guidelines Panel: Central Nervous System Cancers Panel

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Central Nervous System Cancers to review the enclosed data for KOSELUGO™ (selumetinib) for inclusion in the guidelines as a treatment option for pediatric patients with recurrent, refractory, or progressive low-grade glioma associated with *BRAF* aberration or neurofibromatosis type 1 (NF1).

Specific Changes:
We respectfully request for consideration the following change:

- Page BRAIN-D 1 of 15: Add selumetinib as a treatment option for recurrent or progressive disease in patients with low-grade glioma/pilocytic and infiltrative supratentorial astrocytoma/oligodendroglioma

FDA Status:
KOSELUGO™ (selumetinib) is not approved by the FDA for the treatment of glioma. KOSELUGO™ (selumetinib) is an FDA-approved MEK 1/2 inhibitor indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).[1]

Rationale:
This request is based on clinical data from a multicenter, Phase II study conducted by the Pediatric Brain Tumor Consortium (PBTC) evaluating the use of selumetinib in recurrent, refractory, or progressive pediatric low-grade glioma following treatment with at least one standard therapy (NCT01089101).[2] Patients were stratified according to histology, tumor location, NF1 status, and *BRAF* aberration status. Stratum 1 consisted of patients with World Health Organization (WHO) grade I pilocytic astrocytoma with either *KIAA1549-BRAF* fusion or $BRAF^{V600E}$ [Val600Glu] mutation. Stratum 3 consisted of patients with any NF1-associated pediatric low-grade glioma (WHO grade I and II). The results of strata 1 and 3 are presented below.

Eligible patients between the ages of 3-21 with a Lansky or Karnofsky Performance score (KPS) >60 were administered selumetinib 25 mg/m^2 orally twice daily in 28-day courses for up to 26 courses. The primary endpoint was the proportion of patients with a stratum-specific objective response, defined as a partial response (PR) or complete response (CR), as assessed by the local site and sustained for ≥8 weeks. Progression-free survival (PFS) in each strata was a secondary endpoint.

A total of 25 patients each were evaluable for efficacy in strata 1 and 3. After a median follow-up of 26.94 months, 36% (95% CI: 18-57) of patients in stratum 1 achieved a sustained PR, including 7 patients with a *KIAA1549-BRAF* fusion and 2 patients with $BRAF^{V600E}$ mutation. The median time to PR was 7.54 months (IQR: 7.31-12.40) and the 2-year PFS rate was 70% (95% CI: 47-85). After a median follow-up of 42.12 months, 40% (95% CI: 21-61) of patients in stratum 3 achieved a sustained PR. The median time to PR was 3.57 months (IQR: 1.76-5.36) and the 2-year PFS rate was 96% (95% CI: 74-99).

The most frequent grade ≥3 adverse events reported in strata 1 and 3 were elevated creatine phosphokinase (n=5) and maculopapular rash (n=5). Dose reductions due to toxicity were required in 40% and 32% of patients in strata 1 and 3, respectively. One patient in stratum 1 discontinued treatment due to grade 3 rash. Four patients in stratum 3 discontinued treatment due to grade 2 intolerable paronychia (n=1), grade 3 gastric hemorrhage (n=1), grade 2 intolerable fatigue (n=1), and grade 2 intolerable dyspnea (n=1). No deaths were reported in the study.

References submitted in support of this proposal, along with the Prescribing Information for KOSELUGO™ (selumetinib), are enclosed for your review.[1,2]

Reference(s):

1. KOSELUGO™ (selumetinib) Prescribing Information.
2. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial [article and supplementary appendix]. *Lancet Oncol*. 2019; 20(7):1011-1022.

Sincerely,

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