Genentech
A Member of the Roche Group

Submitted by:
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NCCN Guidelines Panel: Melanoma

On behalf of Genentech, Inc., I respectfully request the NCCN Melanoma Guideline Panel to review the enclosed data for:

- **Zelboraf® (vemurafenib):**

  Lewis K, Maio M, Demidov L, et al. BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients (pts) with completely resected BRAFV600+ melanoma at high risk for recurrence. Presented at the European Society for Medical Oncology 42nd Congress in Madrid, Spain; September 8-12, 2017. ESMO Oral presentation.

Specific Changes:

Please consider the recently presented data on the use Zelboraf for the adjuvant treatment of BRAF V600 mutation-positive melanoma for your updating purposes.

FDA Clearance:

- Zelboraf is not FDA-approved for the adjuvant treatment of patients with resected melanoma.
- Zelboraf is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma.

Please refer to the Zelboraf prescribing information for the full FDA-approved indication and safety information, available at: https://www.gene.com/download/pdf/zelboraf_prescribing.pdf.

Rationale:

BRIM8 is a Phase 3, international, multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the safety and efficacy of Zelboraf in patients with resected BRAF V600 mutation-positive melanoma at high risk for recurrence. Cohort 1 (n=314) included patients with Stage IIC, IIIA with ≥1 nodal metastasis >1 mm in diameter, or IIIB melanoma. Cohort 2 (n=184) enrolled patients with Stage IIIC disease. The primary endpoint was disease-free survival (DFS). The protocol pre-specified hierarchical testing of DFS in Cohort 2 prior to Cohort 1; the analysis of Cohort 1 was to be considered statistically significant only if differences in Cohort 2 were significant ($p \leq 0.05$).

In Cohort 2, the DFS difference between patients receiving Zelboraf (n=93) and placebo (n=91) was not statistically significant (HR: 0.80; 95% CI: 0.54-1.18; p=0.2598). Median DFS was 23.1 and 15.4 months in patients receiving Zelboraf and placebo, respectively. In Cohort 1, median DFS was not estimable in the Zelboraf group (n=157) and 36.9 months in the placebo group (n=157), (HR: 0.54; 95% CI: 0.37-0.78; p=0.0010). The difference could not be considered statistically significant because the primary endpoint was not met in Cohort 2.

The most common Grade 3/4 adverse events occurring in ≥2% of patients receiving Zelboraf (n=247) were arthralgia, rash, increased alanine aminotransferase, fatigue, photosensitivity reaction, and diarrhea. Secondary malignancies that occurred in ≥1% of patients treated with Zelboraf included

keratoacanthoma, cutaneous squamous cell carcinoma, and basal cell carcinoma. One Grade 5 event in the Zelboraf arm was considered unrelated to treatment.

I hope this information is helpful to you. If you have any questions, please contact me directly at (650) 255-9706 or by email at dang.joseph@gene.com.

Respectfully submitted,

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