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Submitted by:
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NCCN Guidelines Panel: Colon and Rectal Cancer

On behalf of Genentech, Inc., I respectfully request the NCCN Colon and Rectal Cancer Guideline Panels to review the following key presentation for Zelboraf® (vemurafenib) with or without irinotecan and cetuximab in patients with BRAF mutation-positive metastatic colorectal cancer (mCRC); a patient population with high unmet medical need. The abstract and oral presentation are publically accessible at www.asco.org.

- Kopetz S, McDonough SL, Morris VK, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). Presented at the 2017 ASCO Gastrointestinal Cancers Symposium in San Francisco, CA; January 18–21, 2017. ASCO GI Abstract #520. www.asco.org

Specific Changes:

- Consider the available data on the use of Zelboraf with cetuximab and irinotecan in patients with BRAF mutation-positive mCRC who have received one or two prior systemic regimens for inclusion in the NCCN Colon and Rectal Cancer Guidelines.

FDA Clearance:

- 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.
- Zelboraf is not FDA-approved for treatment of patients with BRAF mutation-positive mCRC.

Please refer to the product prescribing information for the full FDA-approved indications and safety information.

- Full Zelboraf® prescribing information available at: http://www.gene.com/download/pdf/zelboraf_prescribing.pdf

Rationale:

In the Principles of Pathologic Review section (COL-A, 4 of 5; REC-A, 5 of 6) of the Colon and Rectal Cancer Guidelines, KRAS, NRAS and BRAF mutation testing is recommended for all patients with mCRC. SWOG 1406 supports a treatment option for patients with BRAF mutation-positive mCRC who have received one or two prior systemic regimens.

Results of SWOG 1406, a Phase 2, randomized, open label, multicenter trial, were presented at the recent ASCO GI meeting. This study was conducted to evaluate irinotecan and cetuximab with or without Zelboraf in 106 patients with BRAF V600E mutation and extended RAS wild type mCRC who had received 1 or 2 prior regimens. The primary endpoint was progression-free survival (PFS) which was significantly improved in patients who received Zelboraf in addition to irinotecan and cetuximab (hazard ratio 0.42; 95% CI, 0.26-0.66; p=0.0002), with a median PFS of 4.4 vs 2 months. Response rates were 16% vs 4% (p=0.09), and disease control rates were 67% vs 22% (p<0.001) for Zelboraf, irinotecan, and cetuximab vs irinotecan and cetuximab. At the time of the presentation, overall survival results were immature.

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Grade 3/4 adverse events that occurred with a greater than 10% difference between the Zelboraf-containing arm vs. comparator arm include: neutropenia (28% vs 7%), nausea (15% vs 0%), anemia (13% vs 0%), and diarrhea (22% vs 11%). Fatigue and skin adverse event rates were similar in the 2 arms of the study, and no new safety signals were observed.

The Phase 1B study that established tolerability and preliminary activity of Zelboraf in combination with irinotecan and cetuximab in patients with BRAF mutation-positive mCRC have been published.[1] Currently, we are not aware of any additional clinical trials (completed, ongoing, or planned) for Zelboraf with irinotecan and cetuximab in patients with BRAF mutation-positive mCRC.

Respectfully submitted,

Susie Kim, Pharm.D.

Supplemental References

1. Hong DS, Van Morris K, El Osta B, et al. Phase IB Study of Vemurafenib in Combination with Irinotecan and Cetuximab in Patients with Metastatic Colorectal Cancer with BRAFV600E Mutation. Cancer Discov 2016;6:1352-1365. https://www.ncbi.nlm.nih.gov/pubmed/27729313

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