

Submitted by:
Susie Kim, Pharm.D.
Managed Care Medical Communications, Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: 650-922-6708
Email: kim.susie@gene.com
Date of request: July 21, 2017
NCCN Guidelines Panel: Colon and Rectal Cancer

On behalf of Genentech, Inc., I respectfully request the NCCN Colon and Rectal Cancer Guideline Panel to review the enclosed recent key presentation for:

- Zelboraf® (vemurafenib): BRAF mutation-positive metastatic colorectal cancer (mCRC)

Kopetz S McDonough S Lenz HJ et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). Presented at the 2017 ASCO Annual Meeting in Chicago, IL; June 2-6, 2017. ASCO Oral Presentation 3505. http://abstracts.asco.org/199/AbstView_199_194502.html

Specific Changes:

- Consider the updated trial information on the use of Zelboraf with cetuximab and irinotecan as therapy in patients with BRAF mutation-positive previously treated mCRC for inclusion in the NCCN Colon and Rectal Cancer Guidelines.

FDA Clearance:

- Zelboraf is not FDA-approved for treatment of patients with BRAF mutation-positive mCRC.
- 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 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 provides trial results for patients with BRAF mutation-positive mCRC who have received 1 or 2 prior systemic regimens.

In follow up to our previous submission, updated results of SWOG 1406, a Phase 2, randomized, open label, multicenter trial, were presented at the recent ASCO annual meeting. This study was conducted to evaluate irinotecan and cetuximab with or without Zelboraf in patients with BRAF V600E mutation and extended RAS wild type mCRC who had received 1 or 2 prior regimens. The results were reported on 99 evaluable patients (49 patients in the experimental arm) after a median follow-up of 7.3 months.

The primary endpoint of progression-free survival (PFS) was met and was significantly improved in patients who received Zelboraf in addition to irinotecan and cetuximab (hazard ratio 0.48; 95% CI, 0.31-0.75; p=0.001), with a median PFS of 4.3 vs 2 months. In the 93 patients with measurable disease, partial response rates were 16% vs 4%, and disease control rates were 67% vs 22% for Zelboraf, irinotecan, and cetuximab vs irinotecan and cetuximab, respectively.

Overall survival was not statistically significantly different in the 2 groups (hazard ratio 0.73; 95% CI 0.45-1.17; p=0.19); the median overall survival was 9.6 months vs 5.9 months in the Zelboraf vs control arm. Twenty-four patients (48%) had crossed over from the control arm to the experimental arm at the time of the report.

Grade 3/4 adverse events that occurred more frequently in the Zelboraf arm were neutropenia (33% vs 7%), diarrhea (24% vs 13%), nausea (20% vs 2%), anemia (13% vs 0%), dehydration (11% vs 7%), febrile neutropenia (11% vs 4%), and arthralgia (7% vs 0%). Rates of fatigue and rash were similar in the 2 arms of the study. Treatment discontinuation due to AEs were 16% in the Zelboraf, irinotecan, and cetuximab arm and 6% in irinotecan and cetuximab arm.

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.

I hope this information is helpful to you. Taken together this data supports a treatment option for this subgroup of patients. If you have any questions, please contact me directly at 650-922-6708 or by email at kim.susie@gene.com.

Any references supplied to you are protected under U. S. Copyright Law (Title 17, U.S. Code). No further reproduction is permitted.

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>
2. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations [supplementary appendix appears online]. *N Engl J Med* 2015;373:726-736. <https://www.ncbi.nlm.nih.gov/pubmed/26287849>
3. Desai J, Markman B, Ananda S, et al. A phase I/II trial of combined BRAF and EGFR inhibition in patients (pts) with BRAF V600E mutated (BRAFM) metastatic colorectal (mCRC): the EViCT (erlotinib and vemurafenib in combination trial) study. Presented at the 2017 ASCO Annual Meeting in Chicago, IL; June 2–6, 2017. ASCO Poster. <https://am.asco.org/>
4. Kopetz S, Desai J, Chan E, et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J Clin Oncol* 2015;33:4032-4038. <https://www.ncbi.nlm.nih.gov/pubmed/26460303>
5. Hainsworth J, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors based on molecular profiles: early results from MyPathway, an Open-Label, Phase IIa multiple basket study. Presented at the ASCO Annual Meeting in Chicago, IL; June 3–7, 2016. ASCO Oral Presentation #LBA11511. <http://www.asco.org>
6. Hurwitz H, Hainsworth J, Swanton C, et al. Targeted therapy for gastrointestinal tumors based on molecular profiles: early results from MyPathway, an open-label Phase IIa basket study in patients with advanced solid tumors. Presented at the American Society of Clinical Oncology, Gastrointestinal

Cancers Symposium in San Francisco, CA; January 21–23, 2016. ASCO GI Poster #653.
<http://gicasym.org/>

C#17-M0099