

Joan McClure, MS
Senior Vice President, Clinical Information and Publications
National Comprehensive Cancer Network
275 Commerce Dr, Suite 300
Fort Washington, PA 19034

Dear Ms. McClure:

On behalf of Bristol-Myers Squibb Company, I respectfully request the *NCCN Colon / Rectal / Anal Cancers Panel* to review the enclosed data for inclusion of the updated results from the Phase III CRYSTAL trial in the first line treatment of mCRC. The updated analysis represents an extended follow-up of 46 months, and an increased ascertainment rate of KRAS status of 89%.

Specific Changes Requested: Please consider the recently published data for updating the options for agents used in the treatment of first line mCRC patients to reflect a Category 1 listing for Cetuximab + FOLFIRI, based on the significant improvement demonstrated in Overall Survival (OS).

The referenced publication entitled “*Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As a First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status*” discusses data that have not been approved by the Food and Drug Administration (FDA).

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

Rationale: The updated results from the multicenter, randomized CRYSTAL study (n=1198) reflect a more accurate assessment of the impact of tumor KRAS mutation status, as its assessment was based upon an increased number of patients evaluable for KRAS status and an increased follow up time for survival. Study results include:

- In the ITT population, the addition of cetuximab to FOLFIRI resulted in a statistically significant improvement in OS, with the stratified HR for death 0.878 (95% CI, 0.774 to 0.995; p=0.0419), and median survival times of 19.9 months compared with 18.6 months for FOLFIRI alone.
- In the KRAS WT population, compared with those who received FOLFIRI alone, the addition of cetuximab to FOLFIRI resulted in a statistically significant improvement in:
 - Reduced risk of disease progression (median PFS, 9.9 v 8.4 months; HR, 0.696; p=.0012)
 - Overall survival (median survival, 23.5 v 20.0 months; HR, 0.796; p=.0093)
 - Odds of response (best overall response rate 57.3% v 39.7%; odds ratio, 2.069; p=.001)
 - No new safety concerns related to Cetuximab were reported.

To assist the committee with their review, I have included the following resources:

1. Erbitux (cetuximab) [package insert]. Branchburg, NJ and Princeton, NJ: Imclone LLC, a wholly-owned subsidiary of Eli Lilly and Company and Bristol-Myers Squibb Company; March 2011.
2. Van Cutsem et al. Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As a First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. [published online ahead of print April 18 2011]. JCO. 2011
<http://jco.ascopubs.org/content/early/2011/04/18/JCO.2010.33.5091.full.pdf>. Accessed April 18th, 2011.

We acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of this publication.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information

Sincerely,

A handwritten signature in black ink, appearing to read 'John Tsai', with a stylized flourish at the end.

John Tsai, MD
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NCCN Guidelines Panel: Colon/Rectal/Anal Cancers