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A Member of the Roche Group

Submitted by:
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NCCN Guidelines Panels: Colon and Rectal Panels

On behalf of Genentech, Inc., I respectfully request the NCCN Colon and Rectal Cancer Guideline Panels to review recently presented key data for:

- **Avastin® (bevacizumab):** Metastatic colorectal cancer (mCRC)

Venook A, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Presented at the American Society of Clinical Oncology 2014 Annual Meeting in Chicago, Illinois; May 30 - June 3, 2014. ASCO Abstract #LBA3.

Specific Changes:
There are no specific changes being requested. We are providing data on Avastin in mCRC for your review and consideration.

FDA Clearance: Avastin is FDA-approved for first- or second-line treatment of mCRC with 5-FU based chemotherapy or in combination with either fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.

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

Rationale:
The Cancer and Leukemia Group B (CALGB) 80405 study is a Phase III, randomized, controlled trial evaluating the use of Avastin and/or cetuximab in combination with provider's choice of FOLFOX or FOLFIRI in untreated patients with mCRC. The study was amended to eliminate the dual-biologic arm and to include patients with KRAS WT (wild type) tumors only. There was no significant difference between the two groups in the primary outcome measure of overall survival (OS) or secondary outcome of progression free survival. There was also no significant difference in OS between Avastin and cetuximab when given in combination with FOLFOX, nor when given in combination with FOLFIRI.[1] The majority of patients in this study received FOLFOX (73.4%), and there was no comparison made of one chemotherapy regimen over the other. There were more Grade ≥3 hypertension and GI (gastrointestinal)-related events in the Avastin group, and more Grade 3 rash and Grade ≥3 diarrhea in the cetuximab group. A previously presented sub-analysis from this study found that global QOL (quality of life), as well as physical, social and emotional functioning, were not significantly different across treatment arms.[2] However, there were significantly more skin symptoms, limitations in social activities due to skin condition, and concerns about appearance, as measured by the DSQL (Dermatology-Specific

Quality of Life) scale for cetuximab. Additional comparative data on the use of Avastin mCRC have been reported.[3-7]

Please refer to the following ASCO link to view this abstract:
http://abstracts.asco.org/144/AbstView_144_126013.html

Respectfully submitted,

Supplemental References

1. Venook A, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients w/ KRAS *wild type* untreated metastatic adenocarcinoma of the colon or rectum. Presented at the American Society of Clinical Oncology 2014 Annual Meeting in Chicago, Illinois; May 30 - June 3, 2014. ASCO Oral Presentation.

2. Naughton MJ, Schrag D, Venook AP, et al. Quality of life (QOL) and toxicity among patients in CALGB 80405. Presented at the American Society of Clinical Oncology 2013 Annual Meeting in Chicago, Illinois; May 31 - June 4, 2013. ASCO Abstract #3611.

3. Heinemann V, Fischer von Weikersthal L, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). Presented at the American Society of Clinical Oncology 2013 Annual Meeting in Chicago, IL; May 31 - June 4, 2013. ASCO Oral presentation.

4. Stintzing S, Jung A, Rossius L, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized Phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type KRAS (exon 2) metastatic colorectal cancer patients. Presented at the The European Cancer Congress in Amsterdam, Netherlands; September 27-October 1, 2013. ECC Oral Presentation.

5. Schwartzberg L, Rivera F, Karthaus M, et al. PEAK (study 20070509): a randomized Phase 2 study of mFOLFOX6 with either panitumumab or bevacizumab as 1st-line treatment in patients with unresectable wild-type (WT) KRAS metastatic colorectal cancer (mCRC). Presented at the 2013 Gastrointestinal Cancers Symposium in San Francisco, CA; January 24-26, 2013. ASCO GI Poster #446.

6. Karthaus M, Schwartzberg L, Rivera F, et al. Updated overall survival (OS) analysis of novel predictive KRAS/NRAS mutations beyond KRAS exon 2 in PEAK: a 1st-line Phase 2 study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) in metastatic colorectal cancer (mCRC). Presented at the The European Cancer Congress in Amsterdam, Netherlands; September 27-October 1, 2013. ECC Abstract #2262.

7. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT (study 20060141): a randomized Phase 2 study of FOLFIRI with either panitumumab or bevacizumab as second-line treatment in patients with wild- type (WT) KRAS metastatic colorectal cancer (mCRC). Presented at the 2013 Gastrointestinal Cancers Symposium in San Francisco, CA; January 24-26, 2013. ASCO GI Poster #454.