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NCCN Guidelines Panel: Colon, Rectal, and Anal Cancers

On behalf of Genentech, I respectfully request the NCCN Colon, Rectal and Anal Cancers Guideline Panel to review the enclosed data for the use of Avastin® (Bevacizumab) in the treatment of metastatic colorectal cancer (mCRC).

We acknowledge the NCCN requirement for scientific data at least 21 days prior to a Panel meeting and appreciate consideration for this newly available information.

Specific Changes: Consider revising footnote #5 on COL-C 3 of 7 in the Colon Cancer guideline and footnote #5 on REC-E 3 of 7 in the Rectal Cancer guideline where it currently states, "There is insufficient data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first-line regimen, and such continuation of bevacizumab beyond progression is not recommended."

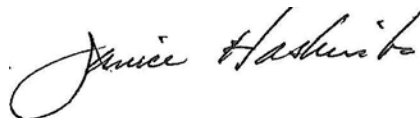
FDA Clearance: FDA has not approved Avastin in combination with chemotherapy for the treatment of mCRC in patients that progressed after receiving Avastin plus chemotherapy. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

Rationale: Results were recently presented at the 2012 American Society of Clinical Oncology (ASCO) on June 3. The Treatment Across Multiple Lines (TML) study (ML18147) is the first randomized phase III trial to evaluate the continued use of Avastin in combination with chemotherapy as a second-line treatment in patients with mCRC who progressed after receiving Avastin in combination with chemotherapy in the first-line setting.<sup>1</sup>

D. Arnold et al. reported that the TML study met the primary endpoint of overall survival (OS) demonstrating an improvement of 11.2 months vs. 9.8 months in the Avastin plus chemotherapy arm vs. standard chemotherapy only arm, respectively (HR 0.81 p=0.0062). Hypertension, venous thromboembolism and arterial thromboembolism were the most common grade 3-5 adverse events.

Additional data on the use of Avastin beyond progression in first-line mCRC including large observational registries and large retrospective analyses have been published.<sup>2-5</sup>

Respectfully submitted,



**Cited and Enclosed References**(copyright-paid where applicable):

1. Arnold D, Andre T, Bennouna J, et al. Bevacizumab (Bev) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with Bev + CT: results of a randomized Phase III intergroup study – TML (ML18147). Presented at the American Society of Clinical Oncology 2012 Annual Meeting in Chicago, IL; June 1-5, 2012. ASCO Abstract #CRA3503.
2. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26:5326-5334.
3. Cohn A, Bekaii-Saab T, Bendell J, et al. Clinical outcomes in bevacizumab (BV)-treated patients (pts) with metastatic colorectal cancer (mCRC): results from ARIES observational cohort study (OCS) and confirmation of BRiTE data on BV beyond progression (BBP). Presented at the 46th Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois; June 4-8, 2010. ASCO Poster #3596.
4. Cartwright T, Yim YM, Yu E, et al. Survival outcomes with use of bevacizumab beyond progression (BBP) in metastatic colorectal cancer (MCRC) patients. Presented at the European Multidisciplinary Cancer Congress in Stockholm, Sweden; September 23-27, 2011. EMCC Poster #6150.
5. Nadler ES, Sail KR, Chen L, et al. Retrospective observational study: bevacizumab (B) use and outcomes among metastatic colorectal cancer (mCRC) patients (pts) receiving care in the outpatient community in the United States. Presented at the 2012 Gastrointestinal Cancers Symposium in San Francisco, California; January 19-21, 2012. ASCO GI Abstract #547.
6. Avastin Prescribing Information