

June 8, 2010

Submission Request to the NCCN Guidelines Panel for Colon and Rectal Cancer

For your consideration, results from two studies were recently presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois in June 2010 on the use of Avastin® (Bevacizumab) in first- and second-line treatment of metastatic colorectal cancer (MCRC).

Two analyses from ARIES, an observational cohort study, reported results from metastatic colorectal patients who: 1) received Avastin with chemotherapy in the first-line setting and continued the use of Avastin with chemotherapy beyond first progressive disease (PD); and 2) received second-line Avastin with chemotherapy in previously Avastin-naïve patients.^{1,2} In the first analysis, Cohn et al. reported results from three groups of patients who had received first-line Avastin with chemotherapy and had experienced progressive disease. The three groups were characterized by post-progression therapy into patients who received: A) no post-PD treatment, B) post-PD treatment without Avastin, and C) continued Avastin beyond progression with chemotherapy.¹ The study looked at survival beyond progression (SBP) as the primary endpoint. Overall survival (OS), time to first PD, and safety were also reported. Sensitivity analysis was also conducted to assess the robustness of the results. Median SBP was 5.2 months, 8.5 months and 16.3 months for patients in Arms A, B, and C, respectively. Multivariate sensitivity analyses demonstrated that Avastin beyond progression was independently associated with improved SBP. The authors reported no substantial increase in the rate of Avastin-associated serious safety events among patients treated with second-line Avastin. The investigators concluded that the findings from this analysis were generally consistent with those from the previous BRiTE study.^{3,4}

In a second separate analysis also from the ARIES registry, Bekaii-Saab et al. looked at efficacy and safety outcomes from MCRC patients treated with Avastin with chemotherapy in the second-line setting.² Results were stratified by whether patients received or did not receive Avastin with chemotherapy in the first-line setting. Investigators reported that the median OS for patients who previously received Avastin was numerically longer than in patients who were Avastin-naïve (20.4 vs. 17.2 months) despite the progression-free survival (PFS) being similar between both groups of patients (7.7 vs. 7.9 months). The rates of Avastin-associated adverse events of gastrointestinal perforations, arterial thromboembolic events, bleeding, hypertension, and post-operative wound-healing were similar (<5%) in both groups and consistent with previous trials.

The MACRO trial, a Phase III multicenter, randomized non-inferiority study by the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD) reported results on the efficacy and safety of first-line MCRC patients who were treated with 6 cycles of Avastin + XELOX (Xeloda + oxaliplatin) followed by either maintenance Avastin + XELOX (Arm A) or Avastin alone (Arm B).⁵ The primary endpoint was PFS. The secondary endpoints were OS, objective response rate (ORR), time to response, response duration, number of treatment cycles, and safety. Investigators reported that there were no statistical differences in median PFS (10.4 vs. 9.7 months), median OS (23.4 vs. 21.7 months), and ORR (46% vs. 49%) between Arm A and Arm B. A preliminary safety analysis showed that Grade 3/4 adverse events seen in >2% of patients were numerically lower in Arm B for neuropathy, hand-foot syndrome, and fatigue when compared to Arm A. Diarrhea and hypertension were numerically higher when compared to Arm A. The results demonstrate that following induction with Avastin + XELOX, maintenance therapy with Avastin alone was not inferior to continuation maintenance with Avastin + XELOX.

Avastin is FDA-approved in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy in the first- or second-line treatment for patients with metastatic carcinoma of the colon or rectum. The

data on the use of Avastin from ARIES and MACRO are not a part of the current indication. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

The following enclosures are included for your review (copyright-paid where applicable):

- Cohn AL, Bekaii-Saab T, Bendell JC, 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). J Clin Oncol 28(suppl 15):284s. ASCO Abstract #3596.
- 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; Jun 4-8, 2010. ASCO Poster #3596.
- Bekaii-Saab T, Bendell J, Cohn A, et al. Bevacizumab (BV) plus chemotherapy (CT) in second-line metastatic colorectal cancer (mCRC): initial results from ARIES, a second BV observational cohort study (OCS). J Clin Oncol 28(suppl 15):284s. ASCO Abstract #3595.
- Bekaii-Saab T, Bendell J, Cohn A, et al. Bevacizumab (BV) plus chemotherapy (CT) in second-line metastatic colorectal cancer (mCRC): initial results from ARIES, a second BV observational cohort study (OCS). Presented at the 46th Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois; Jun 4-8, 2010. ASCO Poster #3595.
- Tabernero J, Aranda E, Gomez A, et al. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): the MACRO trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). J Clin Oncol 28(suppl 15):261s. ASCO Abstract #3501.
- Avastin Prescribing Information

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Cited References

1. Cohn AL, Bekaii-Saab T, Bendell JC, 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.
2. Bekaii-Saab TS, Bendell JC, Cohn AL, et al. Bevacizumab (BV) plus chemotherapy (CT) in second-line metastatic colorectal cancer (mCRC): initial results from ARIES, a second BV observational cohort study (OCS). Presented at the 46th Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois; June 4-8, 2010. ASCO Poster #3595.
3. Grothey A, Sugrue M, Purdie D, et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (PTS) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE). Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois; Jun 1-5, 2007. ASCO Poster #4036.
4. Grothey A, Sugrue M, Hedrick E, et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE). J Clin Oncol 2007;25. ASCO Abstract #4036.

5. Tabernero J, Aranda E, Gomez A, et al. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): the MACRO trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). Presented at the 46th Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois; June 4-8, 2010. ASCO Oral Abstract #3501.