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Highlights in Metastatic Colorectal Cancer From the American Society of Clinical Oncology Annual Meeting

June 3–7, 2011

Chicago, Illinois

With an introduction by:
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Introduction

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This year's American Society of Clinical Oncology (ASCO) meeting featured several important updates in the field of colorectal cancer (CRC). Perhaps one of the most important lessons relates to the role of bevacizumab in the adjuvant setting. There were numerous other important updates, including new information on the first-line study of panitumumab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX) and the second-line study of panitumumab plus leucovorin, fluorouracil, and irinotecan (FOLFIRI).

AVANT (Avastin Adjuvant) was a large, phase III study of FOLFOX versus FOLFOX plus bevacizumab versus capecitabine and oxaliplatin (XELOX) plus bevacizumab, administered in patients with resected stage III CRC.[1] FOLFOX or XELOX chemotherapy was administered for up to 6 months; bevacizumab was given for 1 year, the first 6 months with chemotherapy, and the second 6 months as monotherapy. There were no improvements in disease-free survival (DFS). A similar lack of benefit was noted in the National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant study C-O8, which randomized patients to FOLFOX or FOLFOX plus bevacizumab, with bevacizumab administered for up to 6 months with chemotherapy and up to 6 additional months as monotherapy.[2]

This lack of benefit with bevacizumab adjuvant therapy has also been observed with other agents. In the NCCTG (North Central Cancer Treatment Group) Intergroup Phase III Trial N0147, the addition of cetuximab to modified FOLFOX6 (mFOLFOX6) was of no benefit among patients with resected, stage III wild-type KRAS CRC. Results of this trial were presented at the 2010 ASCO meeting.[3] The 2009 PETACC 3 (Pan-European Trials in Alimentary Tract Cancers) phase III trial aimed to determine whether the addition of irinotecan to the de Gramont infusional fluorouracil/leucovorin adjuvant regimen would improve disease-free survival among patients with stage III colon cancer. There was no statistically significant improvement in disease-free survival or overall survival among patients who received irinotecan.[4]

Preclinical models and the activity of bevacizumab in patients with metastatic disease had raised hopes and expectations for the recent trials with this agent. The somewhat unexpected results from these studies have 2 clear messages. First, bevacizumab has no role in the treatment of adjuvant CRC. Secondly, we are reminded that the biology of CRC is complex, emphasizing the limitations of even our best preclinical models and the need for robust phase III data to guide clinical practices. The AVANT study also noted that the arms containing bevacizumab had a modestly worse overall survival (OS), a very unanticipated result, even though it was of borderline statistical significance. Interpreting unanticipated results is always rather speculative. However, understanding unanticipated results is extremely important. Although it is gratifying to receive anticipated results, this mostly confirms what is already known; those unanticipated results are what force us to consider new possibilities and what lead to a better understanding of the problem.

First, it should be noted that these survival results are based upon data that are not mature, given the overall favorable outcomes for most patients. Immature data can potentially change with further follow-up, in either a more or less favorable direction. In addition, the NSABP C-O8 study also found no difference in DFS; however, it found no evidence for a worsening of survival outcome, either. Unanticipated issues in study conduct could have complicated the survival endpoint. Specifically, patients treated with bevacizumab in the adjuvant setting may have been less likely to receive this agent when their cancer recurred, which may have impacted their OS by limiting the use of bevacizumab in the metastatic setting, where it may be most effective. In metastatic CRC, access to all active drugs has been associated with the best clinical outcomes.[5] However, the order in which any agents are used may still matter.

For example, if sequencing leads to use of an agent in the wrong line of therapy or in the wrong regimen, the benefit may be compromised or lost. This explanation may apply to the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) and to the randomized phase III study on capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in first-line advanced CRC, known as CAIRO2.[6,7] In these studies, the combination of chemotherapy, bevacizumab, and an anti-epidermal growth factor receptor (EGFR) monoclonal antibody (panitumumab and cetuximab, respectively) was found to be no better than chemotherapy plus bevacizumab. These results may have been due to excess toxicity from the full combination, limiting the use of these agents in the most effective manner.

The AVANT results could also be related to complex and unfavorable changes in tumor or host biology that are induced by a given treatment. This scenario, if indeed correct, must be respected, given its large implications for our patients. However, it must also be interpreted with extreme caution, since there is the potential for false signals and for correlations that are not causally related. The development of a more aggressive phenotype with anti-vascular endothelial growth factor (VEGF) treatment has been seen in some, but not all, preclinical models.[8-10] This phenomenon may also depend on the anti-VEGF agent used. The mechanisms of resistance to a VEGF receptor kinase inhibitor (eg, sunitinib, sorafenib, pazopanib) may not be entirely the same as the mechanisms of resistance to a VEGF ligand depletor (eg, bevacizumab or aflibercept). These mechanisms, which may be partially compensatory or homeostatic, may also be influenced by the half-life of the drug (eg, 6–24 hours vs 3 weeks).

In the clinical setting, this issue is extremely hard to model for many reasons. One of the most comprehensive attempts to address this issue looked at the rate of progression after discontinuation of bevacizumab across a number of tumor types.[11] This analysis found no evidence for acceleration or rebound after bevacizumab treatment. Additionally, there is much evidence in clinical experience and preclinical models that more aggressive tumors are simply more likely to be or become refractory to a given treatment in the first place. This issue deserves more attention in preclinical models and in the clinic. Fortunately, many such efforts are ongoing, including extensive biomarker profiling of formalin-fixed, paraffin-embedded tumor samples and profiling of multiple angiogenic factors in plasma. Given the successes reported in other areas, it is likely that this information will be a key component of next year's ASCO meeting.

Acknowledgment

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Highlights in the Treatment of Metastatic Colorectal Cancer

A Review of Selected Abstracts From the 2011 American Society of Clinical Oncology Annual Meeting and Exposition
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3509 A Multinational, Randomized Phase III Study of Bevacizumab with FOLFOX4 or XELOX versus FOLFOX4 Alone as Adjuvant Treatment for Colon Cancer: Results and Subgroup Analyses from the AVANT Trial[1]

T André, E Van Cutsem, HJ Schmoll, J Tabernero, S Clarke, MJ Moore, D Cunningham, TH Cartwright, JR Hecht, F Rivera, SA Im, G Bodoky, R Salazar, F Maindrault-Goebel, E Shmueli, E Bajetta, M Makrutzki, A Shang, A de Gramont, PM Hoff, AVANT Investigators

Vascular endothelial growth factor (VEGF) has a demonstrated role in colorectal cancer (CRC); increased VEGF expression is associated with tumor invasiveness, vascular density, metastasis, and disease recurrence.[2-5] Bevacizumab—a recombinant, humanized monoclonal antibody directed against VEGF—has been shown to increase progression-free survival (PFS) and/or overall survival (OS) in patients with metastatic CRC (mCRC).[5,7] André and colleagues presented the results and subgroup analyses from the international, multicenter AVANT (Avastin Adjuvant) trial. In this study, patients who underwent surgery for high-risk stage II or stage III CRC were randomized to receive fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX4) alone for 24 weeks, FOLFOX4 plus bevacizumab (5 mg/kg every 2 weeks) for 24 weeks followed by bevacizumab monotherapy (7.5 mg/kg every 3 weeks) for 24 weeks, or capecitabine and oxaliplatin (XELOX) plus bevacizumab (7.5 mg/kg every 3 weeks) for 24 weeks followed by bevacizumab monotherapy (7.5 mg/kg every 3 weeks) for 24 weeks. The study enrolled and randomized 3,451 patients; 2,867 patients had stage III CRC. Patient demographics were similar among treatment arms; 51–55% of patients were male, and the median age was 58 years. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 (86–87%), almost 20% of patients had a primary T4 tumor, and 39–40% of patients had a nodal status of N2. The median duration of follow-up was 48 months (range, 0–66 months). The primary endpoint of the study was disease-free survival (DFS) in stage III CRC patients when all patients with stage III disease had completed the 36-month minimum follow-up, or 836 events had occurred. Additional endpoints included OS in stage III CRC patients, safety, and non-inferior DFS and OS (FOLFOX4 + bevacizumab vs XELOX + bevacizumab).

As observed in other studies, treatment with bevacizumab increased grade 3–5 toxicity (FOLFOX4, 9%; FOLFOX4 + bevacizumab, 23%; XELOX + bevacizumab, 18%). In particular, more patients in the bevacizumab treatment groups experienced hypertension (FOLFOX4, 1.1%; FOLFOX4 + bevacizumab, 10.6%; XELOX + bevacizumab, 10.1%) and proteinuria (FOLFOX4, 0.1%; FOLFOX4 + bevacizumab, 0.9%; XELOX + bevacizumab, 1.1%). Gastrointestinal perforation occurred in less than 1% of patients (FOLFOX4, 0.1%; FOLFOX4 + bevacizumab, 0.7%; XELOX + bevacizumab, 0.2%). The 60-day mortality rate was 0.2% in the FOLFOX4 group, 0.4% in the FOLFOX4 plus bevacizumab group, and 0.5% in the XELOX plus bevacizumab group.

After 48 months of follow-up, 25% of patients in the FOLFOX4 group, 29% of patients in the FOLFOX4 plus bevacizumab group, and 27% of patients in the XELOX plus bevacizumab group experienced an event. The global hypothesis for DFS found that all arms were not statistically different (P=.2024); thus, all other analyses were exploratory in nature. The 3-year DFS rates were 76% (FOLFOX4), 73% (FOLFOX4 + bevacizumab), and 75% (XELOX + bevacizumab). The hazard ratio (HR) for DFS was 1.17 (95% confidence interval [CI], 0.98–1.39) for FOLFOX4 plus bevacizumab versus FOLFOX4 alone. The HR for DFS was 1.07 (95% CI, 0.90–1.28) for XELOX plus bevacizumab versus FOLFOX4 alone. An analysis of the cumulative HR during the first year favored treatments that included bevacizumab (HR, 0.63 [FOLFOX4 + bevacizumab]; HR, 0.61 [XELOX + bevacizumab]). Thereafter, the cumulative HRs were above 1.

Tumor recurrence occurred in 23% of patients in the FOLFOX4 arm, 26% of patients in the FOLFOX4 plus bevacizumab arm, and 23% of patients in the XELOX plus bevacizumab arm. The sites of recurrence and the number of involved sites were comparable in all treatment arms.

An interim analysis of OS was performed at a 48-month median follow-up. Patients in the FOLFOX4 group had improved survival relative to the other treatment arms; 12% of patients died in the FOLFOX4 group, 16% in the FOLFOX4 plus bevacizumab group (HR, 1.31; 95% CI, 1.03–1.67), and 15% in the XELOX plus bevacizumab group (HR, 1.27; 95% CI, 0.99–1.62). There was a nonsignificant difference among the 3 treatment arms in the time from recurrence/new occurrence to death (HR, 1.23 [FOLFOX4 + bevacizumab]; HR, 1.10 [XELOX + bevacizumab]).

The investigators conducted a subgroup analysis (age, sex, race, T stage, number of lymph nodes analyzed, and N stage) to determine if certain patients would benefit from treatment with bevacizumab. In comparisons of FOLFOX4 plus bevacizumab to FOLFOX4 alone or XELOX plus bevacizumab to FOLFOX4 alone, all HRs were proximal to 1 in favor of FOLFOX4.

The study investigators concluded that the addition of bevacizumab to FOLFOX4 or XELOX did not prolong DFS in the adjuvant treatment of stage III CRC. A transient positive effect of bevacizumab treatment was observed during the first year. Interim OS analyses suggest that treatment with bevacizumab may negatively affect OS, but follow-up is ongoing and will continue for at least 5 years. The researchers proposed that bevacizumab may be inducing dormancy, and during dormancy, tumor cells may become resistant to chemotherapy. In addition, induction of the prosurvival pathway can induce resistance. Alternatively, the transient favorable effect observed in the AVANT trial may be associated with bevacizumab's effect on undetectable macrometastases.

3508 Overall Survival (OS) and Updated Disease-Free Survival (DFS) Results of the NSABP C-08 Trial Assessing Bevacizumab in Stage II and III Colon Cancer[8]

CJ Allegra, GA Yothers, MJ O'Connell, S Sharif, NJ Petrelli, LH Colangelo, N Wolmark

The development of adjuvant therapy is a multistep process. This process begins with an evaluation of safety, followed by an analysis of activity in advanced disease, and then an assessment of efficacy in advanced disease. Agents successful in these stages will move on to testing in an adjuvant study. Two randomized controlled trials provided the foundation for the use of bevacizumab plus oxaliplatin for the treatment of advanced CRC in the adjuvant setting. In study E320,[9] 577 previously treated patients were randomized to receive FOLFOX with or without bevacizumab. The addition of bevacizumab significantly increased overall response rate ([ORR], 22.7% vs 8.6%; *P*<.0001), PFS (7.3 months vs 4.7 months; *P*<.0001), and OS (12.9 months vs 10.8 months; *P*=.001) compared to FOLFOX alone. In study NO16966,[7] 1,401 previously untreated patients were randomized to receive XELOX/FOLFOX with or without bevacizumab. PFS (9.4 vs 8.0 months; *P*=.0023) was significantly improved with the addition of bevacizumab, but there was no difference in ORR (38% vs 38%; *P*=.99) and no significant difference in OS (21.3 months vs 19.9 months; *P*=.077).

The NSABP C-08 trial conducted by Allegra and coworkers evaluated the addition of bevacizumab to a modified FOLFOX6 (mFOLFOX6; 5-FU, leucovorin, and oxaliplatin on day 1, followed by an infusion of 5-FU every 2 weeks for 6 months) treatment regimen in patients with stage II and stage III CRC. Patients were stratified according to the number of nodes, then randomized to receive either mFOLFOX6 for 6 months or mFOLFOX6 for 6 months plus bevacizumab (5 mg/kg IV every 2 weeks) for 1 year. The study accrued 1,338 patients in each arm; approximately 58% of patients were less than 60 years of age and 49% of patients were male. The disease status of the patients varied; 24% of patients had stage II disease (0), 45% of patients had stage III disease (1–3), and 29% of patients had stage III disease (4+).

Toxicities of at least grade 3 were increased with the addition of bevacizumab. These included hypertension (mFOLFOX6, 1.8% vs mFOLFOX6 + bevacizumab, 12%; *P*<.0001), pain (6.3% vs 11.1%, respectively; *P*<.0001), proteinuria (0.8% vs 2.7%, respectively; *P*<.001), and wound complications (0.3% vs 1.7% respectively; *P*<.0001). The authors noted that the majority of these toxicities were minor. In order to assess toxicity that may be associated with prior bevacizumab therapy, the investigators evaluated toxicities during a 9-month period that began 3 months after the completion of therapy. During this treatment-free phase, there were no significant differences in toxicities of grade 3 or higher, such as hypertension (mFOLFOX6, 0.6% vs mFOLFOX6 + bevacizumab, 0.7%), pain (1.1% vs 1.1%, respectively), proteinuria (0.1% vs no patients, respectively), venous thrombotic events ([VTE], 0.4% vs 0.2%, respectively), and hemorrhage (0.3% vs 0.3%, respectively). There was a slight increase in arterial thrombotic events (ATEs) with the addition of bevacizumab, but the difference was not significant (0.1% vs 0.5%, respectively).

The primary efficacy endpoint in this study was DFS. After a median follow-up of 56 months, there was a minimal early advantage in treatment with bevacizumab, but this difference was attenuated over time. The HR

favored bevacizumab-including treatment, but overall there was no significant difference in DFS (HR, 0.93; 95% CI, 0.81–1.08; *P*=.34). There was a significant time-treatment interaction (*P*<.0001), with a significant benefit in DFS for patients treated with bevacizumab up to the 1.25-year landmark. Beyond 1.25 years, there was a borderline significant decrease in DFS for the FOLFOX6 plus bevacizumab group, thus accounting for an overall insignificant difference in DFS between the 2 treatment arms. In an analysis of OS at 56 months, there was no significant difference between treatment arms (HR, 0.96; 95% CI, 0.79–1.15; *P*=.64). There was also no difference in OS between treatment arms when colon cancer–specific survival (HR, 0.96; 95% CI, 0.78–1.18; *P*=.71) or stage III disease (HR, 1.02; 95% CI, 0.83–1.24; *P*=.88) was analyzed. The investigators also assessed OS after recurrence and found that there was a nonsignificant decrease in survival for those patients who received bevacizumab (HR, 1.16; 95% CI, 0.94–1.43; *P*=.17). Several explanations for this finding were proposed. Bevacizumab may change the biology of CRC to a more aggressive phenotype; however, a change in OS would be expected if this occurred. Alternatively, bevacizumab is less effective or used less frequently in patients previously exposed to bevacizumab at the time of relapse (but once again, there would be an expected change in OS that was not observed). A third possibility proposed by Allegra and colleagues was that treatment with bevacizumab impaired the ability to detect a recurrence until a later time, since computed tomography (CT) scans depend upon differences in tumor vascularity and permeability.

The investigators concluded that the time-varying effect of bevacizumab on recurrence remained evident at 56 months of follow-up. Treatment with bevacizumab delayed recurrence, but did not prevent it, and may interfere with relapse detection. They found no evidence of a negative effect of bevacizumab on DFS, time to recurrence, OS, or colon cancer–specific survival.

3526 A Randomized Phase III Trial on Maintenance Treatment with Bevacizumab (Bev) Alone or in Combination with Erlotinib (erlo) After Chemotherapy and Bevacizumab in Metastatic Colorectal Cancer (mCRC)[10]

A Johnsson, J-E Frödin, Å Berglund, H Hagman, J Sundberg, D Bergström, RD Christensen, N Keldsen, K-L Spindler, Å Jakobsen

Bevacizumab is currently under investigation for use in maintenance therapy; however, erlotinib may work synergistically with bevacizumab. Johnsson and associates sought to determine if maintenance therapy with bevacizumab plus erlotinib improved efficacy over bevacizumab alone. Previously untreated mCRC patients received doublet chemotherapy plus bevacizumab (2.5 mg/kg) during the induction phase; 162 patients with complete remission (CR), partial remission (PR), or stable disease (SD) were randomized to receive either bevacizumab alone (7.5 mg/kg once every 3 weeks; 80 patients) or bevacizumab (7.5 mg/kg once every 3 weeks; 82 patients) plus erlotinib (150 mg every day) during the maintenance phase.

Induction therapy with chemotherapy plus bevacizumab followed by maintenance therapy with erlotinib plus bevacizumab led to increased median PFS (bevacizumab, 4.2 months vs erlotinib + bevacizumab, 5.9 months; HR, 0.81; 95% CI, 0.57–1.15; *P*=.24). There was an increase in grade 3/4 toxicities during maintenance treatment with erlotinib plus bevacizumab (51%, 40 patients) versus bevacizumab alone (14%, 11 patients), but the majority of these side effects were manageable. Reasons for maintenance discontinuation in the bevacizumab alone and bevacizumab plus erlotinib arms, respectively, included progressive disease (82% vs 66%), toxicity (4% vs 15%), curative surgery (3% vs 6%), and other (10% in each arm). Identification of patient subgroups that would benefit most from the addition of erlotinib to bevacizumab maintenance therapy is currently under investigation. In addition, tumor and blood samples are being analyzed for predictive markers of efficacy.

3565 A Randomized Two-Arm Phase III Study to Investigate Bevacizumab in Combination with Capecitabine Plus Oxaliplatin (CAPOX) versus CAPOX Alone in Post Radical Resection of Patients with Liver Metastases of Colorectal Cancer[11]

EE Voest, N Snoeren, SB Schouten, AM Bergman, O Dalesio, HM Verheul, RA Tollenaar, EJ Hesselink, JM Smit, JR van der Sijp, A Cats, TJM Ruers, IH Borel Rinkes, R van Hillegersberg

Patients with colorectal liver metastases often develop recurrences after surgery. Patient outcome may be improved with the addition of adjuvant chemotherapy. Bevacizumab improves DFS and the chemotherapy response rate in patients with metastatic disease. In a phase III comparative efficacy and safety study (known as the HEPATICA trial), Voest and coworkers evaluated whether the addition of bevacizumab to the capecitabine plus oxaliplatin (CAPOX) chemotherapy regimen would improve DFS in patients following surgery to remove colorectal liver metastases.

Table 1. CAPOX Plus Bevacizumab Versus CAPOX Alone: Toxicities of Grade 3 or Higher[11]

	Arm A 49% (36 pts)	Arm B 51% (38 pts)	Total 74 pts
Hypertension	22.2% (8 pts)	15.8% (6 pts)	18.9% (14 pts)
Diarrhea	11.1% (4 pts)	21.2% (8 pts)	16.2% (12 pts)
Thrombosis/ embolism	11.1% (4 pts)	5.3% (2 pts)	8.1% (6 pts)
Other GI symptoms	2.8% (1 pt)	7.9% (3 pts)	5.4% (4 pts)
Hand-foot syndrome	5.6% (2 pts)	2.6% (1 pt)	4.1% (3 pts)
Abdominal pain/cramping	2.8% (1 pt)	2.6% (1 pt)	2.7% (2 pts)
Febrile neutropenia	0% (0 pts)	5.3% (2 pts)	2.7% (2 pts)
Mucositis/ stomatitis	0% (0 pts)	2.6% (1 pt)	1.4% (1 pt)
Nausea	2.8% (1 pt)	0% (0 pts)	1.4% (1 pt)
Vomiting	0% (0 pts)	2.6% (1 pt)	1.4% (1 pt)
Hemorrhage/ bleeding	0% (0 pts)	2.6% (1 pt)	1.4% (1 pt)
Cardiac ischemia	0% (0 pts)	0% (0 pts)	0% (0 pts)

Arm A=CAPOX plus bevacizumab.
Arm B=CAPOX alone.

CAPOX=capecitabine plus oxaliplatin; GI=gastrointestinal; CI=confidence interval; HR=hazard ratio; OR=odds ratio; ORR= overall response rate; OS=overall survival; PFS=progression-free survival.

Eligible patients were older than 18 years of age, with a complete resection with or without radiofrequency ablation, and an ECOG performance status score of 1 or lower. Exclusion criteria included extrahepatic disease, previous noncolorectal malignancies, and prior chemotherapy for metastatic disease. The study was amended in 2009 to include patients who received a maximum of 3 cycles of CAPOX prior to resection. A total of 79 patients (67% male) were enrolled before premature closure in October 2010 due to the slow accrual rate. The majority of patients had no prior adjuvant therapy (91%) and no prior neoadjuvant therapy (97%). Between 4 and 8 weeks after radical resection/radiofrequency ablation, patients were randomized to receive either 8 cycles of CAPOX plus 16 cycles of bevacizumab (40 patients) or 8 cycles of CAPOX alone (39 patients).

The 2-year DFS rate was 70% in the CAPOX plus bevacizumab arm versus 52% in the CAPOX alone arm (*P*=.072). Toxicity data were available for 74 patients; no significant differences in toxicity between the 2 arms were detected (Table 1). Toxicities of at least grade 3 that occurred in the CAPOX plus bevacizumab arm and CAPOX alone arm, respectively, were hypertension (22.2% vs 15.8%), diarrhea (11.1% vs 21.2%), thrombosis/embolism (11.1% vs 5.3%), other gastrointestinal symptoms (2.8% vs 7.9%), hand-foot syndrome (5.6% vs 2.6%), abdominal pain/cramping (2.8% vs 2.6%), febrile neutropenia (0% vs 5.3%), mucositis/stomatitis (0% vs 2.6%), nausea (2.8% vs 0%), vomiting (0% vs 2.6%), and hemorrhage/bleeding (0% vs 2.6%). The researchers concluded that the addition of bevacizumab to CAPOX therapy following resection of colorectal liver metastases resulted in a nonsignificant increase in DFS.

3578 Phase II Trial of Chemotherapy with High-Dose FOLFIRI Plus Bevacizumab in the Front-Line Treatment of Patients with Metastatic Colorectal Cancer (mCRC) and Genotype UGT1A1*1/ UGT1A1*1 or UGT1A1*1/ UGT1A1*28 (FFCD 0504 trial): Final Results[12]

E Mitry, O Bouché, JF Seitz, PL Etienne, JL Legoux, T Aparicio, G Breysacher, C Lecaille, T Lecomte, JL Jouve

Mitry and colleagues assessed the use of high-dose irinotecan (260 mg/m^2) with 5-FU and leucovorin (HD-FOLFIRI) plus bevacizumab (5 mg/kg IV day 1) in a phase II study of mCRC patients. Their study focused on patients with a UGT1A1 polymorphism that is associated with an increased toxicity to irinotecan.[13] The study enrolled patients with previously untreated mCRC with UGT1A1*1/UGT1A1*1 (group 1) or UGT1A1*1/ UGT1A1*28 (group 2) genotypes. The study design required 54 patients in each group, and a planned interim analysis after the 17th patient in group 1 had a 6-month follow-up. The trial was closed at the interim analysis due to unacceptable toxicity according to the initial study design (≥3 more patients with severe toxicity). The overall response rate (ORR) was 52.9% in group 1 and 58.8% in group 2. Defined toxicity was observed in 41.2% of patients in group 1 (grade 4 neutropenia, 2 patients; febrile neutropenia, 2 patients; grade 3 diarrhea, 4 patients) and 18.8% of patients in group 2 (grade 4 neutropenia, no patients, febrile neutropenia, 2 patients; grade 3 diarrhea, 2 patients). There were no instances of toxic death or grade 4 diarrhea. The authors of the

study suggested that the defined toxicity criteria might have been too strict, as the toxicity was manageable and patients continued on therapy with dose modification. However, there was no clear clinical benefit for adding bevacizumab to HD-FOLFIRI therapy in patients with the UGT1A1 polymorphism.

3598 Determination of Genomic Profile to Predict Clinical Response to FOLFOX Plus Bevacizumab in Metastatic Colorectal Cancer[14]

TJ George Jr, H Liu, LV Duckworth, JE Sullivan, J Dong, C Liu, LH Dang, K Slentz-Kesler, CJ Allegra

George and associates sought to identify a genetic signature to predict clinical response to FOLFOX plus bevacizumab therapy. The study included formalin-fixed paraffin-embedded (FFPE) tumor samples from mCRC patients treated with first-line FOLFOX plus bevacizumab. RNA was extracted from the tumor sample and hybridized to a CRC-specific microarray. Gene expression differences between responders and nonresponders were determined by bioinformatic analysis. Genomic relationships among responders, nonresponders, primary tumors, and metastases were determined by principal component analysis and hierarchical clustering.

CRC microarray was successfully performed on FFPE samples less than 72 months old; 48 different tumor specimens had adequate RNA for analysis. There were 79 liver genes, 205 lung genes, and 117 ovary genes that had significant gene expression differences between the primary tumor and metastases. In the metastases, there were no differences between the responders and nonresponders in the metastatic site, Ki67, or microvessel density. In the primary tumors, there were no significant differences in microvessel density, but Ki67 was significantly higher in responders than in nonresponders (66% vs 35%; P=.05). Hierarchical clustering found a stringent gene listing for responders versus nonresponders in both metastases (>2-fold change; P<.01) and primary tumors (>2-fold change; P<.01). Gene expression products and ontology pathways identified in this study are still under investigation.

3625 Effectiveness and Safety of First- or Second-Line Bevacizumab Treatment in Elderly Patients with Metastatic Colorectal Cancer (mCRC) in ARIES, an Observational Cohort Study (OCS)[15]

M Kozloff, T Bekaii-Saab, JC Bendell, AL Cohn, H Hurwitz, N Roach, H Tezcan, S Fish, ED Flick, Y Mun, D Dalal, A Grothey

In ARIES, an ongoing, multicenter, observational cohort study, Kozloff and associates assessed the safety and efficacy of bevacizumab plus chemotherapy for first- or second-line treatment of mCRC in patients less than

Table 2. Bevacizumab Plus Chemotherapy for First-Line or Second-Line Treatment in mCRC[15]

	First-Line		Second-Line	
	<70 yrs (n=1,126)	≥70 yrs (n=424)	<70 yrs (n=336)	≥70 yrs (n=146)
Median age (range)	58.0 (18–69)	75.0 (70–92)	58.0 (24–69)	76.0 (70–96)
Sex, male, %	56.7	57.3	54.8	61.0
Race, % – White – Black – Other	 79.3 13.6 7.1	 84.4 10.8 4.8	 82.1 11.6 6.3	 83.6 8.9 7.5
Median follow-up (range, mths)	22.2 (1.1–48.2)	18.7 (0.3–48.1)	17.2 (1.2–45.5)	15.8 (0.6–45.5)
Survival characteristics (95% CI)				
Median PFS	10.3 (9.8–10.9)	9.9 (8.9–10.4)	7.9 (7.2–8.3)	7.9 (6.7–9.2)
HR Univariate Multivariate	 1 1	 1.11 (0.99–1.25) 1.11 (0.98–1.25)	 1 1	 0.94 (0.77–1.15) 0.96 (0.78–1.19)
Median OS	25.1 (23.1–26.9)	19.6 (18.1–21.6)	18.7 (17.0–21.4)	17.0 (13.4–21.8)
HR – Univariate – Multivariate	 1 1	 1.29 (1.13–1.48) 1.23 (1.06–1.42)	 1 1	 1.10 (0.88–1.37) 1.17 (0.93–1.48)

CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

70 years of age, 70–79 years of age, and at least 80 years of age. The study enrolled 1,550 first-line patients and 482 second-line patients with metastatic or locally advanced and unresectable CRC treated with bevacizumab plus chemotherapy or bevacizumab plus chemotherapy and a biologic agent.

At the time of study presentation, the median follow-up time was 20.7 months in the first-line group and 16.9 months in the second-line group. In the first-line group, 76.3% of patients had progressive disease and 68.1% of patients had died. In the second-line treatment group, 81.1% had progressive disease and 79.3% had died. The median PFS was similar across all age groups in both cohorts (Table 2). The OS was significantly lower for first-line patients 70 years or older compared to those patients younger than 70 years of age. However, there was no detectable difference in OS by age in the second-line cohorts. A similar risk profile for PFS across all age subgroups was observed. There was an increased risk of all-cause mortality in patients 80 years of age and older when compared with patients younger than 70 years. There was a similar risk of all-cause mortality in patients 70–79 years of age and patients under 70 years of age in both first- and second-line treatment cohorts. The incidence of targeted adverse events (AEs) and serious AEs occurred within 6 months of starting bevacizumab and decreased over time in the first 9 months. Although the incidence patterns of targeted and serious AEs were similar across the age subgroups, there was a higher incidence of targeted and serious AEs in patients 80 years of age and older in the second-line cohort. Based upon the preliminary results from this study, the researchers concluded that mCRC treatment with first- or second-line bevacizumab in patients older than 70 years of age may not be associated with greater safety concerns or poorer clinical outcomes compared with treatment in patients younger than 70 years of age.

6083 Clinical Outcome of Advanced Colorectal Cancer Patients Pre- and Post-Bevacizumab Therapy Using the SEER Database[16]

M Choi, G Dyson, PA Philip, AF Sheilds

Although CRC is associated with poor clinical outcomes, the introduction of new biologic agents such as bevacizumab, cetuximab, and panitumumab, along with active chemotherapy agents, such as oxaliplatin and irinotecan, has improved OS in patients with CRC. Choi and colleagues evaluated the impact of bevacizumab—which was approved by the Food and Drug Administration for advanced CRC in 2004—on the survival of patients with stage IV CRC. The Surveillance, Epidemiology, and End Results (SEER) database was used to compare clinical outcome data from 2003 (pre-biologic) and clinical outcome data from 2005 (post-biologic) to determine the impact of bevacizumab on OS. The analysis included 4,895 patients (15% African American) from 2003 and 5,123 patients (16% African American) from 2005. The mean age of the patients from 2003 was 69 (range, 58–78 years) and 49% were female. The mean age of the patients from 2005 was 68 years (range, 57–78 years), and 49% were female. The median OS was 9 months (95% CI, 8–9) in 2003 and 11 months (95% CI, 10–11) in 2005 (P<.001). For African Americans, the median OS was 9 months in both 2003 (95% CI, 8–11) and 2005 (95% CI, 7–10; P=.665). For European Americans, the median OS was 9 months (95% CI, 8–9) in 2003 and 11 months (95% CI, 10–11) in 2005 (P<.001). There was a slight increased risk of death for African American patients compared to European American patients (HR, 1.23; P<.001). There was also a slight increased risk of death for patients diagnosed in 2003 compared to those diagnosed in 2005 (HR, 1.12; P<.001).

The study authors concluded that there was a minor improvement in the clinical outcome of patients with advanced CRC upon the introduction of bevacizumab, but this improvement did not extend to the African American patient population. In addition, the authors noted that the SEER database has limited information available on the therapeutic agents used. Therefore, the definitive impact of bevacizumab on OS in advanced CRC patients cannot be determined using this database.

Standard Management of Stage IV Colorectal Cancer: Start and Stop, Maintenance, Bevacizumab Beyond Progression? (eQuestions Session)[17]

A Grothey

Bevacizumab targets VEGF-A, which mainly interacts with the VEGF-receptor 2 on the surface of endothelial cells. Signaling through this receptor is associated with cell proliferation, survival, and permeability. VEGF-A can also associate with VEGF receptor-1, which activates signaling pathways involved in cell migration, invasion, and survival. By binding VEGF-A, bevacizumab prevents receptor activation and the associated downstream signaling pathways and products. The anti-VEGF monoclonal antibody has minimal single-agent activity, but is consistently associated with increased PFS when combined with chemotherapy.

At this year's American Society of Clinical Oncology (ASCO) meeting, Dr. Grothey posed the question,

"Is there a rationale to continue bevacizumab beyond progression?" On the pro side of the discussion, bevacizumab targets genetically stable endothelial cells. This is in contrast to anti-epidermal growth factor receptor (EGFR) agents such as cetuximab and panitumumab that target genetically unstable tumor cells, which can develop resistance mechanisms. In addition, increased interstitial pressure resulting from VEGF inhibition can lead to a higher concentration of chemotherapeutic agents.[18] Bevacizumab may also lead to the normalization of vasculature and better oxygenation, which has been proposed to enhance the cytotoxic properties of chemotherapy. In preclinical data, anti-VEGF therapy results in tumor vessel "pruning," normalization of blood vessel architecture, and an antiangiogenic effect that creates a window during which the efficacy of chemotherapy might be increased.[19,20] According to Grothey, the most important pro argument for the continuation of bevacizumab is that a rapid regrowth of blood vessels has been observed after the withdrawal of VEGF inhibitors in experimental models.[21] On the con side of the discussion, there are pathways other than those involving VEGF that activate angiogenesis, such as angiopoietin, fibroblast growth factors, and platelet-derived growth factor. In addition, pericyte activation and proliferation occur in tumors during chronic VEGF blockade.[22] Other cons include the genetic instability of some endothelial cells that can serve as cancer stem cells, the toxicity associated with bevacizumab, the availability of treatment alternatives, and the high cost of bevacizumab therapy.

There is an absence of prospectively randomized clinical data; however, some information can be garnered from observational cohort studies. The BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) registry followed mCRC patients who received either no treatment, bevacizumab, or other treatment following disease progression.[23] Surprisingly, the median OS was approximately 1 year longer for patients who received bevacizumab beyond progression compared to those patients who did not receive bevacizumab in their post-progression treatment (31.8 months vs 19.9 months, respectively; HR, 0.48; *P*<.001). In non-randomized studies, confounding factors can influence results. However, a multivariate analysis of pre- and post-treatment variables on survival revealed that bevacizumab beyond progression was still associated with improved survival (HR, 0.48; 95% CI, 0.41–0.57; *P*<.001). ARIES, another prospective, non-randomized observational study, also followed patients with mCRC who received first-line chemotherapy plus bevacizumab, followed by either no treatment, treatment other than bevacizumab, or bevacizumab at first disease progression.[24] There was an almost 10-month increase in median OS with bevacizumab beyond progression (no bevacizumab in post-progression treatment, 18.7 months vs bevacizumab in post-progression treatment, 27.5 months; HR, 0.52; 95% CI, 0.42–0.63; *P*<.001). Although there are limitations to observational cohort studies, these data provide the foundation for a much-needed randomized controlled trial of bevacizumab beyond disease progression.

A randomized clinical trial is currently under way in Europe (AIO 0504/Roche ML18147). This study is evaluating patients who received any oxaliplatin-containing regimen plus bevacizumab or any irinotecan-containing regimen plus bevacizumab as first-line therapy. Upon disease progression, the patients who were treated with oxaliplatin plus bevacizumab were randomized to receive irinotecan with or without bevacizumab and patients who were treated with irinotecan plus bevacizumab were randomized to receive oxaliplatin with or without bevacizumab. The primary endpoint of this study is OS. Initial data will likely be available by the end of 2011. Two ongoing randomized trials may also shed light on the use of bevacizumab beyond progression. In the VELOUR (Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen) trial, approximately 30% of the patients had prior therapy with bevacizumab. Study results were presented in June at the European Society for Medical Oncology (ESMO) 13th World Conference on Gastrointestinal Cancer in Barcelona. The median OS was 13.5 months for patients treated with aflibercept and 12.06 months for placebo (*P*=.0032). Secondary endpoints also favored aflibercept; PFS was 6.90 versus 4.67 months, respectively (*P*=.00007), with an ORR of 19.8% versus 11.1%, respectively (*P*=.0001). A second ongoing, randomized phase III trial (14T-MC-JVBB) is investigating second-line treatment of patients with mCRC after progression following oxaliplatin and a fluoropyrimidine plus bevacizumab. These patients were randomized to receive FOLFIRI with or without ramucirumab (anti-VEGF receptor-2 antibody). This study should provide further data regarding VEGF inhibition beyond disease progression.

In any discussion of bevacizumab beyond progression, it is important to discuss the side effects of anti-VEGF therapy. The most pertinent side effects are hypertension, gastrointestinal perforation, bleeding, delayed wound healing, and proteinuria. All of these serious AEs most often occur early in the treatment course. From the start of bevacizumab treatment, the incidence of targeted AEs or gastrointestinal perforation was highest in the first 6 months of therapy.[25] This observation is consistent among observational cohort studies and randomized clinical trials. Interestingly, there was no increase in the rates of targeted AEs, bleeding, or gastrointestinal perforation in

patients who continued bevacizumab beyond progression; the longer the patients were treated, the less likely they were to have these AEs.[23]

In the future, it will be important to consider not only bevacizumab beyond progression, but also VEGF inhibition beyond progression, as more multikinase inhibitors and other VEGF inhibitors are added to the clinical arsenal. The continuation of bevacizumab beyond progression has preclinical rationale, including support from observational cohort studies. However, prospective evaluation in randomized phase III trials is needed before bevacizumab or VEGF inhibition beyond progression could become the standard of care.

3510 Final Results from PRIME: Randomized Phase III Study of Panitumumab (pmab) with FOLFOX4 for First-Line Metastatic Colorectal Cancer (mCRC)[26]

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Panitumumab is a human monoclonal antibody that targets EGFR. This agent is approved as a monotherapy for patients with mCRC and wild-type KRAS tumor status who are refractory to chemotherapy. In the Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) study, the safety and efficacy of panitumumab plus FOLFOX4 was compared to FOLFOX4 alone as a first-line treatment of mCRC in patients with wild-type KRAS tumors. The primary analysis of this study found that the addition of panitumumab significantly improved PFS in patients with wild-type KRAS mCRC.[27] Dr. Douillard presented the final descriptive analysis of PFS and OS in the PRIME study, approximately 30 months after the last patient was enrolled.

Inclusion criteria were metastatic adenocarcinoma of the colon or rectum without prior treatment for mCRC. Prior adjuvant 5-FU-based chemotherapy was allowed if the disease recurred more than 6 months after completion of treatment, but prior oxaliplatin or anti-EGFR therapy was not allowed. Available tissue samples, an ECOG performance status of 0–2, and sufficient hematologic, renal, and hepatic function were also required. In the final analysis, there were 656 mCRC patients with wild-type KRAS tumors (panitumumab + FOLFOX4, 325 patients; FOLFOX4 alone, 331 patients) and 440 mCRC patients with mutant KRAS tumors (panitumumab + FOLFOX4, 221 patients; FOLFOX4 alone, 219 patients). Most of the patients were male (58–67%, depending on the treatment arm) and Caucasian (approximately 90%), with a median age of 62 years. The investigators noted that there was a low incidence of liver-only disease (<20%). The median follow-up times were 22.5 months (wild-type KRAS, panitumumab + FOLFOX4), 17 months (wild-type KRAS, FOLFOX4), 14.1 months (mutant KRAS, panitumumab + FOLFOX4), and 16.1 months (mutant KRAS, FOLFOX4).

In patients with wild-type KRAS, the addition of panitumumab to FOLFOX4 improved PFS compared to FOLFOX4 alone (10 months vs 8.6 months, respec-

Table 3. Panitumumab Plus FOLFOX Versus FOLFOX Alone in mCRC Patients With Wild-Type KRAS Tumors[26]

	Primary Analysis		Final Analysis	
	Panitumumab + FOLFOX4 (n=325)	**FOLFOX4 (n=331)**	**Panitumumab + FOLFOX4 (n=325)**	**FOLFOX4 (n=331)**
Median PFS (months)	9.6	8.0	10	8.6
PFS hazard ratio (95% CI)	0.80 (0.66–0.97) *P*=.02		0.80 (0.67–0.97) *P*=.01	
Median OS (months)	23.9	19.7	23.9	19.7
OS hazard ratio (95% CI)	0.83 (0.67–1.02) *P*=.07		0.88 (0.73–1.06) *P*=.17	
ORR ORR *P* Value	55% *P*=.07	48%	57% *P*=.02	48%
Subsequent EGFR Use	8%	18%	13%	25%

CI=confidence interval; EGFR=epidermal growth factor receptor; FOLFOX4=leucovorin, fluorouracil, and oxaliplatin; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). *[See Warnings and Precautions (5.8).]*

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2%] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a]Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 5%] in IFL + Avastin vs. IFL)

	Arm 1 IFL + Placebo (n = 98)	Arm 2 IFL + Avastin (n = 102)	Arm 3 5-FU/LV + Avastin (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥ 2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/ pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Metastatic Breast Cancer (MBC)

Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in Study 5. Grade 3–4 adverse events occurring at a higher incidence (≥2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/ desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).

Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2).

Avastin is not approved for use in combination with capecitabine or for use in second or third line treatment of MBC. The data below are presented to provide information on the overall safety profile of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in which all adverse events were collected for all patients. All patients in Study 6 received prior anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1– 4 events which occurred at a higher incidence (≥5%) in patients receiving capecitabine plus Avastin compared to the capecitabine alone arm are presented in Table 3.

Table 3
NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher Incidence [≥5%] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n = 215)	Capecitabine + Avastin (n = 229)
Body as a Whole		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
Cardiovascular		
Hypertension	2%	24%
Digestive		
Stomatitis	19%	25%
Metabolic/Nutrition		
Weight loss	4%	9%
Musculoskeletal		
Myalgia	8%	14%
Respiratory		
Dyspnea	18%	27%
Epistaxis	1%	16%
Skin/Appendages		
Exfoliative dermatitis	75%	84%
Urogenital		
Albuminuria	7%	22%

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/ hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal

hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 4.

Table 4
NCI-CTC Grades 1–5 Adverse Events in Study 9
(Occuring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/ Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Avastin (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a]Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 4: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (reported from unapproved use for treatment of various ocular disorders): Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual disturbances; Ocular hyperemia; Ocular pain and/or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 9, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. *[See Nonclinical Toxicology (13.3).]*

Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. *[See Clinical Pharmacology (12.3).]*

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥ 65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. *[See Warnings and Precautions (5.8).]*

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). *[See Warnings and Precautions (5.5).]*

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

Genentech

A Member of the Roche Group

Avastin® (bevacizumab)

Manufactured by:
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10127309
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tively), with a 20% reduction in the risk of progression (HR, 0.80; 95% CI, 0.67–0.95; *P*=.01; Table 3). In contrast, panitumumab plus FOLFOX4 had a detrimental effect on PFS in patients with mutant KRAS compared to FOLFOX4 alone (7.4 months vs 9.2 months, respectively). This corresponded to a 27% increase in the risk of disease progression (HR, 1.27; 95% CI, 1.04–1.55; *P*=.02). In the on-treatment analysis of PFS according to KRAS status, similar results were observed. The on-treatment PFS was 8.9 months (panitumumab + FOLFOX4) versus 8 months (FOLFOX4) with an HR of 0.77 (95% CI, 0.63–0.92) in patients with wild-type KRAS, and 7.3 months (panitumumab + FOLFOX4) versus 8.9 months (FOLFOX4) with an HR of 1.32 (95% CI, 1.05–1.65; *P*=.016) in patients with mutant KRAS.

In terms of OS, patients with wild-type KRAS who were treated with panitumumab plus FOLFOX4 had a longer median survival than wild-type KRAS patients treated with FOLFOX4 alone (23.9 months vs 19.7 months, respectively; HR, 0.89; 95% CI, 0.73–1.06; *P*=.17). In patients with mutant KRAS, treatment with panitumumab plus FOLFOX4 resulted in a shorter median survival than treatment with FOLFOX4 alone (15.5 months vs 19.2 months, respectively; HR, 1.17; 95% CI, 0.95–1.45; *P*=.15). Dr. Douillard highlighted the fact that the absence of significant improvements in OS despite improved PFS may be due to post-protocol treatment. In patients with wild-type KRAS, 13% of patients in the panitumumab plus FOLFOX4 arm received second-line anti-EGFR therapy compared with 25% of patients in the FOLFOX4 arm; patients in the FOLFOX4 arm received this treatment earlier than did patients in the panitumumab plus FOLFOX4 arm (15.6 months vs 21.5 months, respectively). Similarly, more patients with mutant KRAS in the FOLFOX4 arm received anti-EGFR therapy than did patients in the panitumumab plus FOLFOX4 arm (16% vs 7%, respectively). Thus, there were a number of patients in the FOLFOX4 alone treatment arm who received panitumumab during second-line treatment.

In the wild-type KRAS patients, the ORR was 57% in the panitumumab plus FOLFOX4 arm versus 48% in the FOLFOX4 arm (odds ratio [OR], 1.47; 95% CI, 1.07–2.04; *P*=.02). In the mutant KRAS patients, the ORR was 40% in the panitumumab plus FOLFOX4 arm versus 41% in the FOLFOX4 arm (OR, 0.98; 95% CI, 0.65–1.47; *P*=.92). The increase in ORR with panitumumab plus FOLFOX treatment in patients with wild-type KRAS was associated with a higher complete resection in the liver. In wild-type KRAS patients with liver-limited disease (<20% of patients), 17 patients (28%) in the panitumumab plus FOLFOX4 group and 10 patients (18%) in the FOLFOX4 group had complete liver resection. The OS curve was improved for patients with complete liver resection (median OS not yet reached) compared to patients without complete liver resection (median OS, 23.6 months; 95% CI, 19.4–30.9) independent of the treatment they received.

The grade 3/4 toxicity profile in the final analysis was similar to what was observed during the primary analysis. Adding panitumumab to FOLFOX4 increased skin toxicity (wild-type KRAS panitumumab + FOLFOX4, 37%; mutant KRAS panitumumab + FOLFOX4, 31% vs wild-type KRAS FOLFOX4, 2%; mutant KRAS FOLFOX4, 1%), diarrhea (18%; 20% vs 10%; 10%, respectively), hypokalemia (10%; 9% vs 5%; 4%, respectively), fatigue (10%; 7% vs 3%; 5%, respectively), mucositis (9%; 6% vs <1%; 3%, respectively), and hypomagnesemia (7%; <1% vs 6%; <1%, respectively). Infusion reactions to panitumumab were very low (<1%). When outcomes were analyzed according to skin toxicity in patients with wild-type KRAS tumors treated with panitumumab regimens, grade 2–4 skin toxicities were associated with improved PFS (grade 2–4, 11.3 months vs grade 0–1, 6.1 months; HR, 0.66; *P*=.002), OS (27.7 months vs 11.5 months; HR, 0.63; *P*=.0001), and ORR (63% vs 41%; *P*=.003) compared to skin toxicities of grade 1 or lower.

The investigators concluded that the addition of panitumumab to FOLFOX4 in the first-line treatment of wild-type KRAS mCRC significantly improved PFS and ORR, with a trend toward improved OS. In addition, grade 2–4 skin toxicity was associated with improved PFS, OS, and ORR and may be an important indicator of clinical outcome during treatment. In patients with mutant KRAS mCRC, panitumumab had a detrimental effect on PFS and OS, indicating that panitumumab should not be used in these patients.

3567 Randomized Phase 3 Study of Panitumumab with FOLFOX4 Compared with FOLFOX4 Alone as First-Line Treatment for Metastatic Colorectal Cancer (mCRC): Results by Eastern Cooperative Oncology Group (ECOG) Performance Status[28]

S Siena, J Cassidy, J Tabernero, R Burkes, ME Bargel, Y Humblet, D Cunningham, F Xu, K Krishnan, JY Douillard

Siena and colleagues extended the primary analysis of the phase III PRIME study[27] by assessing the predictive and prognostic value of the ECOG performance status score. Of the 93% of patients for whom KRAS biomarker data were available, 60% (656 patients) had wild-type KRAS. Of these patients, 616 (94%) had an ECOG performance status score of 0–1 and 40 (6%) had an ECOG performance status score of 2, which were divided equally

Table 4. Panitumumab With FOLFOX4 Versus FOLFOX4 Alone: Predictive and Prognostic Value of the Eastern Cooperative Oncology Group Performance Score[28]

Wild-Type KRAS ECOG 0/1 (n=616)	**Arm 1 (n=305)**	**Arm 2 (n=311)**	**HR (95% CI)**	**Descriptive *P* value**
Median PFS, months (95% CI)	10.4 (9.4–11.3)	8.0 (7.5–9.3)	0.74 (0.60–0.91)	*P*=.004
Median OS, months (95% CI)	25.8 (21.7 – Not estimable)	20.7 (18.2–23.2)	0.77 (0.62–0.95)	*P*=.018
Wild-Type KRAS ECOG 2 (n=40)	**Arm 1 (n=20)**	**Arm 2 (n=20)**	**HR (95% CI)**	**Descriptive *P* value**
Median PFS, months (95% CI)	4.8 (2.7–5.3)	7.6 (5.3–11.1)	2.30 (1.08–4.89)	*P*=.030
Median OS, months (95% CI)	7.0 (4.6–11.7)	11.7 (8.0–15.7)	1.83 (0.90–3.75)	*P*=.097

CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

between the 2 treatment arms. Compared to treatment with FOLFOX4 alone, panitumumab plus FOLFOX4 significantly improved PFS in patients with wild-type KRAS tumors (8 months vs 9.6 months, respectively; HR, 0.80; *P*=.02; Table 4). In patients with wild-type KRAS tumors and an ECOG performance status score of 0–1, PFS (10.4 months vs 8 months, respectively; HR, 0.74; *P*=.004), OS (25.8 months vs 20.7 months, respectively; HR, 0.77; *P*=.018), and ORR (58% vs 48%, respectively) were improved with panitumumab plus FOLFOX4 treatment compared to FOLFOX alone. Patients with wild-type KRAS and an ECOG performance status score of 0–1 had a higher ORR than did patients with wild-type KRAS and an ECOG performance status score of 2 when treated with panitumumab plus FOLFOX4 (58% vs 20%, respectively). In addition, patients with wild-type KRAS and an ECOG performance status score of 2 who were treated with panitumumab experienced an increased number of serious and fatal AEs. Although there were only 20 patients in the wild-type KRAS and ECOG performance status score of 2 subgroup, these results suggest that the addition of panitumumab may increase patient risk without increased efficacy in this patient population.

3574 Evaluation of Panitumumab (pmab) Plus Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) After First-Line Bevacizumab in Patients with Metastatic Colorectal Cancer (mCRC): A Subgroup Analysis of Study 181[29]

M Peeters, T Price, A Strickland, TE Ciuleanu, W Scheithauer, S O'Reilly, M Keane, D Spigel, Y Tian, K Krishnan

Second-line treatment with panitumumab plus FOLFIRI results in a significant improvement in PFS for patients with wild-type KRAS mCRC.[30] Peeters and associates presented a subgroup analysis of a randomized, controlled, phase III study (20050181)[30] that assessed the safety and efficacy of panitumumab plus FOLFIRI versus FOLFIRI alone in patients with wild-type KRAS mCRC who received prior fluoropyrimidine therapy. Their analysis focused on those patients who received bevacizumab as part of first-line treatment (115 patients).

Table 5. Median Survival and Overall Response Rates in Patients Receiving Panitumumab Plus FOLFIRI Versus FOLFIRI Alone[29]

	Panitumumab + FOLFIRI	**FOLFIRI**	**Measure of risk**
All patients (N)	55	60	
Median PFS, months (95% CI)	5.8 (5.2–6.7)	3.7 (3.5–5.3)	HR=0.712 (0.447–1.133)
Median OS, months (95% CI)	15.7 (12.6–23.8)	12.5 (9.2–16.1)	HR=0.680 (0.432–1.069)
Patients with lesions (n)*	53	57	
ORR (95% CI)	30.19% (18.34–44.34)	1.75% (0.04–9.39)	OR=24.22 (3.40–1033.11)

*Patients who had measurable lesions per central radiology review were included in the analysis of ORR.

CI=confidence interval; FOLFIRI=leucovorin, fluorouracil, and irinotecan; HR=hazard ratio; OR=odds ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

The addition of panitumumab to FOLFIRI increased both PFS (panitumumab + FOLFIRI, 5.8 months vs FOLFIRI alone, 3.7 months; HR, 0.71; 95% CI, 0.45–1.13; *P*=.150) and OS (15.7 vs 12.5 months; HR, 0.68; 95% CI, 0.43–1.07; *P*=.093) compared to FOLFIRI alone in patients who had received prior bevacizumab treatment (Table 5). The ORR was significantly higher in the panitumumab plus FOLFIRI arm compared with the FOLFIRI alone arm (30.19% vs 1.75%; odds ratio, 24.22; 95% CI, 3.40–1,033.11 [months]; *P*<.0001). Prior bevacizumab treatment did not alter the efficacy of panitumumab. In patients who had prior bevacizumab treatment, the rates of AEs of interest were comparable to the rates observed in previous panitumumab trials.[27,30,31] The most common grade 3/4 AEs of interest were skin-related toxicity (panitumumab + FOLFIRI, 35%; FOLFIRI alone, 5%), diarrhea (9% vs 8%, respectively), eye toxicity (7% vs 0%, respectively) stomatitis/oral mucositis (7% vs 2%, respectively), nail toxicity (5% vs 0%, respectively), and vascular toxicity (2% vs 15%, respectively). The authors concluded that second-line therapy with panitumumab plus FOLFIRI might be a useful treatment option for patients with wild-type KRAS mCRC who have progressed while receiving bevacizumab as part of first-line therapy.

3575 FOLFIRI Plus Cetuximab versus FOLFIRI Plus Bevacizumab as First-Line Treatment for Patients with Metastatic Colorectal Cancer (mCRC): Analysis of Patients with KRAS-Mutated Tumors in the Randomized German AIO Study KRK-0306[32]

S Stintzing, A Jung, J Neumann, L Fischer von Weikersthal, T Decker, U Vehling-Kaiser, E Jaeger, T Heintges, C Stoll, DP Modest, T Kirchner, W Scheithauer, V Heinemann

The randomized, phase III, German AIO study KRK-0306 is investigating the safety and efficacy of cetuximab (400 mg/m^2 on day 1, followed by 250 mg/m^2 weekly) plus FOLFIRI versus bevacizumab (5 mg/kg every 2 weeks) plus FOLFIRI as first-line treatments for mCRC. Stintzing and colleagues presented the results of a subgroup analysis of patients with the KRAS mutation. KRAS mutations were identified in 96 patients, with 87 patients evaluable (KRAS codon 12, 77 patients; KRAS codon 13, 19 patients). The median age of the patients was 65 years, and 64.4% were male. There were 41 mCRC KRAS mutation patients in the cetuximab plus FOLFIRI arm and 46 mCRC KRAS mutation patients in the bevacizumab plus FOLFIRI arm. The median follow-up time was 21.1 months. There were no significant differences in ORR (cetuximab + FOLFIRI, 43.9%; bevacizumab + FOLFIRI, 47.8%), PFS (7.5 months vs 8.9 months, respectively), or OS (22.7 months vs 18.7 months, respectively) between the 2 treatment arms (HR, 0.86). There were no significant differences in grade 3/4 hematologic toxicities including anemia (cetuximab + FOLFIRI, 2%; bevacizumab + FOLFIRI, 4.3%), leucopenia (18% vs 8.7%, respectively), and neutropenia (28% vs 17.4%, respectively). The most common grade 3/4 nonhematologic toxicities for the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI arms, respectively, were exanthema (20% vs 0%; *P*<.01) and hypertension (8% vs 21.7%; *P*=.08). Thromboembolic events occurred in 8% of patients in the cetuximab plus FOLFIRI arm versus 17.4% of patients in the bevacizumab plus FOLFIRI arm (*P*=.22). The authors concluded that there was no difference in efficacy or survival for mCRC patients with KRAS-mutated tumors treated with cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI.

3576 Efficacy of Chemotherapy Plus Cetuximab According to Metastatic Site in KRAS Wild-type Metastatic Colorectal Cancer (mCRC): Analysis of CRYSTAL and OPUS Studies[33]

C-H Köhne, C Bokemeyer, S Heeger, U Sartorius, P Rougier, E Van Cutsem

The addition of cetuximab to FOLFIRI (CRYSTAL study)[34,35] or FOLFOX4 (OPUS study)[36,37] as first-line treatment in patients with wild-type KRAS mCRC improved clinical outcomes. Köhne and colleagues performed a subgroup analysis of these studies to evaluate patients with liver-limited disease (LLD) or extrahepatic disease (non-LLD). The analysis included 666 patients in the CRYSTAL study with wild-type KRAS tumors (LLD, 140 patients; non-LLD, 526 patients) and 179 patients in the OPUS study with wild-type KRAS tumors (LLD, 48 patients; non-LLD, 131 patients). Treatment with cetuximab plus FOLFIRI significantly improved all efficacy endpoints compared to FOLFIRI alone (ORR, 57.3% vs 39.7%; *P*<.001; PFS, 9.9 months vs 8.4 months; *P*=.001; OS, 23.5 months vs 20 months; *P*=.009). Treatment with cetuximab plus FOLFOX4 versus FOLFOX4 alone significantly improved ORR and PFS (ORR, 57.3% vs 34.0%; *P*<.003; PFS, 8.3 months vs 7.2 months; *P*=.006).

When patients were grouped by metastatic site, treatment with cetuximab plus chemotherapy significantly improved the ORR of patients with LLD (cetuximab + FOLFIRI, 70.6% vs FOLFIRI alone, 44.4%; *P*<.001; cetuximab + FOLFOX4, 76% vs FOLFOX4 alone, 39.1%; *P*=.016) and resulted in high complete resec-

Table 6. Efficacy According to Treatment Arm for Patients With Wild-Type KRAS Tumors Grouped by Metastatic Site[33]

	All patients		LLD		Non-LLD	
	CT	CT + Cetuximab	CT	CT + Cetuximab	CT	CT + Cetuximab
CRYSTAL, n	350	316	72	68	278	248
RR, %	39.7	57.3	44.4	70.6	38.5	53.6
R0R, %	2.0	5.1	5.6	13.2	1.1	2.8
Median PFS, months	8.4	9.9	9.2	11.8	8.1	9.5
Median OS, months	20.0	23.5	27.7	27.8	17.4	22.5
OPUS, n	97	82	23	25	74	57
RR, %	34.0	57.3	39.1	76.0	32.4	49.1
R0R, %	3.1	7.3	4.3	16.0	2.7	3.5
Median PFS, months	7.2	8.3	7.9	11.9	6.0	7.6
Median OS, months	18.5	22.8	23.9	26.3	16.4	19.8

CT=chemotherapy; LLD=liver-limited disease; OS=overall survival; PFS=progression-free survival; RR=response rate; R0R=R0 resection rate.

tion rates (Table 6). PFS was significantly prolonged in patients with LLD when treated with cetuximab (cetuximab + FOLFIRI, 11.8 months vs FOLFIRI alone, 9.2 months [*P*=.035]; cetuximab + FOLFOX4, 11.9 months vs FOLFOX4 alone, 7.9 months [*P*=.039]). PFS was also significantly improved in patients with non-LLD (cetuximab + FOLFIRI, 9.5 months vs FOLFIRI alone, 8.1 months; *P*=.012; cetuximab + FOLFOX4, 7.6 months vs FOLFOX4 alone, 6.0 months; *P*=.023), and OS was significantly improved in patients with non-LLD when treated with cetuximab plus FOLFIRI (cetuximab + FOLFIRI, 22.5 months vs FOLFIRI alone, 17.4 months; *P*=.013). The authors of the study concluded that first-line treatment with cetuximab plus chemotherapy improves clinical outcome in both LLD and non-LLD wild-type KRAS mCRC patients.

3617 Evaluating the Relationship Between Progression-Free Survival (PFS) and Overall Survival (OS) in Clinical Trials of Patients with Metastatic Colorectal Cancer (mCRC)[38]

R Sidhu, A Rong, S Dahlberg

Improvements in PFS have been correlated with improvements in OS in mCRC patients treated with chemotherapy, but it was unknown if treatment with targeted agents would result in a similar correlation. Therefore, Sidhu and colleagues analyzed data from published clinical trials of targeted agents in combination with chemotherapy in mCRC patients to determine if there was a correlation between PFS and OS. Their analysis included 22 studies published between 2000 and 2010, with over 17,000 patients; 11 targeted therapy studies (panitumumab, cetuximab, and bevacizumab), 4 historical studies (fluoropyrimidine alone), 11 validation studies (oxaliplatin and irinotecan-based regimens), and 8 EGFR therapy studies. For all trials included in the analysis, the observed correlation coefficient between PFS and OS was 0.79. This result is similar to what was observed in studies of mCRC patients treated with cytotoxic chemotherapy. The observed correlation coefficient between PFS and OS in trials with targeted agents plus oxaliplatin or irinotecan was 0.88; in first-line phase III trials of targeted agents, this correlation coefficient was 0.89. In an analysis of treatment effect, an HR of 0.80 for PFS appeared to predict a 10% reduction in the risk of death. The authors concluded that PFS and OS are highly correlated. Furthermore, the results are consistent with the proposal that PFS can be a valid surrogate endpoint for OS in clinical trials of mCRC patients treated with targeted therapies.

3569 Initial Change in Tumor Size as a Potent Surrogate of Response and Survival in Metastatic Colorectal Cancer (mCRC) Patients Treated with First-Line Irinotecan and 5-FU Combination Chemotherapy[39]

C Suzuki, L Blomqvist, A Sundin, H Jacobsson, P Byström, A Berglund, P Nygren, B Glimelius

Suzuki and associates evaluated whether the first change in tumor size correlated with OS in mCRC patients, and if outcome could be predicted from the second

change and continued changes at the second follow-up. The authors performed a retrospective analysis of 506 patients (mean age, 61 years) enrolled in the phase III Nordic VI study.[40] Patients received irinotecan with either Nordic bolus 5-FU and folinic acid (FLIRI) or the de Gramont schedule (Lv5-FU2-IRI) every 2 weeks. At baseline, 8 weeks, and 16 weeks, CT scans were performed and change in tumor size was calculated. Cox proportional hazards multiple regression models were used to show that the first change correlated with OS. Although an increase of at least 20% was considered progressive disease by Response Evaluation Criteria in Solid Tumors Group (RECIST) guidelines, it was not associated with impaired OS. A decrease in tumor size of more than 10% but less than 30% was considered stable disease by RECIST, but was predicted to have improved OS in this analysis. A significant difference in OS according to first change values was found in patients with a new lesion/unequivocal nontarget lesion progression, a decrease in tumor size of at least 10% but less than 50%, or a decrease of at least 50% in tumor size; a similar difference in OS was detected using RECIST. Although the second change provided prognostic information, the first change was more informative. The authors concluded that the first change in tumor size correlated with OS and PFS in mCRC. They suggest that cytotoxic treatments in clinical trials can be compared more rapidly with the first change approach versus waiting for the maximal response using RECIST.

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AVASTIN® (bevacizumab)

Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. ***[See Dosage and Administration (2.4), Warnings and Precautions (5.1).]***

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. ***[See Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).]***

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. ***[See Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).]***

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

1.2 Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

1.3 Metastatic Breast Cancer (MBC)

Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.3).]*

Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

1.4 Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent.

The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.4).]*

1.5 Metastatic Renal Cell Carcinoma (mRCC)

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. *[See Adverse Reactions (6.1).]*

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.2 Surgery and Wound Healing Complications

Avastin impairs wound healing in animal models. *[See Nonclinical Toxicology (13.2).]* In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%. *[See Adverse Reactions (6.1).]*

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal

hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. *[See Adverse Reactions (6.1).]*

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer Avastin to patients with recent history of hemoptysis of ≥1/2 teaspoon of red blood. Discontinue Avastin in patients with hemorrhage. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.4 Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤0.3% in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

Discontinue Avastin in patients with fistula formation involving an internal organ. *[See Dosage and Administration (2.4).]*

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. *[See Use in Specific Populations (8.5).]*

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Discontinue Avastin in patients who experience a severe ATE. *[See Dosage and Administration (2.4).]*

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.

Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. *[See Dosage and Administration (2.4).]*

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of <0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known. *[See Dosage and Administration (2.4).]*

5.8 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. *[See Adverse Reactions (6.1).]* In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2 + or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is <2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). *[See Use in Specific Populations (8.5).]* The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. *[See Dosage and Administration (2.4).]*

5.9 Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy. *[See Dosage and Administration (2.4).]*

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6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Gastrointestinal Perforations *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).]*
- Surgery and Wound Healing Complications *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*
- Hemorrhage *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*
- Non-Gastrointestinal Fistula Formation *[See Dosage and Administration (2.4), Warnings and Precautions (5.4).]*
- Arterial Thromboembolic Events *[See Dosage and Administration (2.4), Warnings and Precautions (5.5).]*
- Hypertensive Crisis *[See Dosage and Administration (2.4), Warnings and Precautions (5.6).]*
- Reversible Posterior Leukoencephalopathy Syndrome *[See Dosage and Administration (2.4), Warnings and Precautions (5.7).]*
- Proteinuria *[See Dosage and Administration (2.4), Warnings and Precautions (5.8).]*

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Avastin in 2661 patients with mCRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. *[See Clinical Studies (14).]* The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*

Venous Thromboembolic Events

The incidence of Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Neutropenia and Infection

The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

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In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). *[See Warnings and Precautions (5.8).]*

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2%] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a]Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 5%] in IFL + Avastin vs. IFL)

	Arm 1 IFL + Placebo (n = 98)	Arm 2 IFL + Avastin (n = 102)	Arm 3 5-FU/LV + Avastin (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥ 2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/ pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Metastatic Breast Cancer (MBC)

Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in Study 5. Grade 3–4 adverse events occurring at a higher incidence (≥2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/ desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).

Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2).

Avastin is not approved for use in combination with capecitabine or for use in second or third line treatment of MBC. The data below are presented to provide information on the overall safety profile of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in which all adverse events were collected for all patients. All patients in Study 6 received prior anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1– 4 events which occurred at a higher incidence (≥5%) in patients receiving capecitabine plus Avastin compared to the capecitabine alone arm are presented in Table 3.

Table 3
NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher Incidence [≥5%] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n = 215)	Capecitabine + Avastin (n = 229)
Body as a Whole		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
Cardiovascular		
Hypertension	2%	24%
Digestive		
Stomatitis	19%	25%
Metabolic/Nutrition		
Weight loss	4%	9%
Musculoskeletal		
Myalgia	8%	14%
Respiratory		
Dyspnea	18%	27%
Epistaxis	1%	16%
Skin/Appendages		
Exfoliative dermatitis	75%	84%
Urogenital		
Albuminuria	7%	22%

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/ hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 4.

Table 4
NCI-CTC Grades 1–5 Adverse Events in Study 9
(Occuring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/ Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Avastin (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a]Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 4: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (reported from unapproved use for treatment of various ocular disorders): Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual disturbances; Ocular hyperemia; Ocular pain and/or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 9, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. *[See Nonclinical Toxicology (13.3).]*

Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

AVASTIN® (bevacizumab)

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. *[See Clinical Pharmacology (12.3).]*

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥ 65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. *[See Warnings and Precautions (5.8).]*

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). *[See Warnings and Precautions (5.5).]*

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

Genentech
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Avastin® (bevacizumab)

Manufactured by:
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South San Francisco, CA
94080-4990

02/11 AVA0000306800
10127309
Initial U.S.Approval: February 2004
Code Revision Date: February 2011

In combination with
IV 5-FU–containing chemotherapy in first- and second-line MCRC…

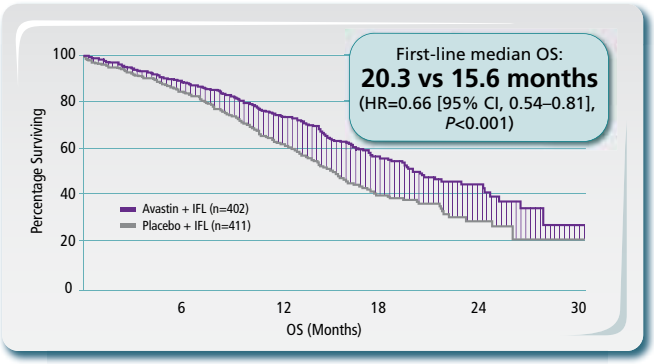
Think Avastin

Because overall survival matters

IV=intravenous; 5-FU=5-fluorouracil; MCRC=metastatic colorectal cancer; IFL=5-FU/leucovorin (LV)/irinotecan; HR=hazard ratio; CI=confidence interval; FOLFOX4=5-FU/LV/oxaliplatin.

The only FDA-approved biologic with significant overall survival (OS) benefits in first- and second-line MCRC[1-4]

4.7-month increase in median OS with Avastin plus IFL in pivotal first-line Study 2107[2,4]



OS in second-line Study E3200:
13.0 months with Avastin plus FOLFOX4 vs 10.8 months with FOLFOX4 alone (HR=0.75 [95% CI, 0.63–0.89], *P*=0.001)[1,3]

Indication

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

Boxed WARNINGS and additional important safety information

- **Gastrointestinal (GI) perforation:** Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies. Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications:** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound dehiscence requiring medical intervention
- **Hemorrhage:** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood). Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)
- Additional serious and sometimes fatal adverse events for which the incidence was increased in the Avastin-treated arm vs control included non-GI fistula formation (≤0.3%), arterial thromboembolic events (grade ≥3, 2.4%), and proteinuria including nephrotic syndrome (<1%). Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs control included hypertension (grade 3–4, 5%–18%) and reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%). Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- The most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions
- Based on animal data, Avastin may cause fetal harm and may impair fertility. Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin. For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother
- The most common grade 3–4 events in Study 2107, which occurred at a ≥2% higher incidence in the Avastin plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)
- The most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the Avastin plus FOLFOX4 vs FOLFOX4 groups, were diarrhea (18% vs 13%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), ileus (4% vs 1%), neuropathy–sensory (17% vs 9%), neurologic–other (5% vs 3%), fatigue (19% vs 13%), abdominal pain (8% vs 5%), headache (3% vs 0%), hypertension (9% vs 2%), and hemorrhage (5% vs 1%)

Please see accompanying brief summary of Prescribing Information, including **Boxed WARNINGS**, for additional important safety information.

References: 1. Avastin Prescribing Information. Genentech, Inc. February 2011. **2.** Hurwitz H, Fehrenbacher L, Novotny W, et al. *N Engl J Med*. 2004;350:2335-2342. **3.** Giantonio BJ, Catalano PJ, Meropol NJ, et al. *J Clin Oncol*. 2007;25:1539-1544. **4.** Data on file. Genentech, Inc.

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