Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

July 2012 | A SPECIAL MEETING REVIEW EDITION | Volume 10, Issue 7, Supplement 9

# Highlights in Metastatic Colorectal Cancer From the 2012 American Society of Clinical Oncology Annual Meeting

## June 1–5, 2012 • Chicago, Illinois

### Special Reporting on:

- Bevacizumab (BEV) Plus Chemotherapy (CT) Continued Beyond First Progression in Patients With Metastatic Colorectal Cancer (mCRC) Previously Treated With BEV Plus CT: Results of a Randomized Phase III Intergroup Study (TML Study)
- Bevacizumab (Bev) With or Without Erlotinib as Maintenance Therapy, Following Induction First-Line Chemotherapy Plus Bev, in Patients (Pts) With Metastatic Colorectal Cancer (MCRC): Efficacy and Safety Results of the International GERCOR DREAM Phase III Trial
- Results of the X-PECT Study: A Phase III Randomized Double-Blind, Placebo-Controlled Study of Perifosine Plus Capecitabine (P-CAP) Versus Placebo Plus Capecitabine (CAP) in Patients (Pts) With Refractory Metastatic Colorectal Cancer (mCRC)
- Phase III CORRECT Trial of Regorafenib in Metastatic Colorectal Cancer (mCRC)
- Final Analysis of the Phase III Randomized Trial of Cetuximab (CET) Plus Either Brivanib Alaninate (BRIV) or Placebo in Patients (pts) With Chemotherapy Refractory, K-RAS Wild-Type (WT), Metastatic Colorectal Carcinoma (mCRC): The NCIC Clinical Trials Group and AGITG CO.20 trial
- Effects of Prior Bevacizumab (B) Use on Outcomes From the VELOUR study: A Phase III Study of Aflibercept (Afl) and FOLFIRI in Patients (pts) With Metastatic Colorectal Cancer (mCRC) After Failure of an Oxaliplatin Regimen
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**PLUS Meeting Abstract Summaries**

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# Bevacizumab (BEV) Plus Chemotherapy (CT) Continued Beyond First Progression in Patients With Metastatic Colorectal Cancer (mCRC) Previously Treated With BEV Plus CT: Results of a Randomized Phase III Intergroup Study (TML Study)

For patients with metastatic colorectal cancer (CRC) who develop disease progression after first-line bevacizumab plus fluoropyrimidine-based chemotherapy, continuing bevacizumab with the second-line chemotherapy regimen appears to provide a significant survival benefit, according to the randomized, phase III, intergroup TML study presented by Dirk Arnold, MD.[1] Dr. Arnold noted that the addition of bevacizumab to fluoropyrimidine-based chemotherapy is standard in the first-line treatment of metastatic CRC or in the second-line setting for bevacizumab-naïve patients. The use of bevacizumab in both the first-line and second-line therapies had not previously been evaluated in a phase III trial. However, there is a scientific rationale for continued bevacizumab; in preclinical studies, sustained vascular endothelial growth factor (VEGF) inhibition has been shown to achieve and maintain tumor regression.[2,3]

Moreover, several observational cohort studies have demonstrated a benefit with continuing bevacizumab beyond first progression. In the BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) study, continuing bevacizumab beyond first progression was independently associated with improved survival (hazard ratio [HR], 0.48; $P<.001$).[4] These findings were confirmed in the ARIES (Avastin [bevacizumab] Regimens: Investigation of Treatment Effects and Safety) observational cohort study, which showed a significant independent improvement in the duration of survival beyond first progression with continued bevacizumab (HR, 0.41; $P<.001$).[5]

Based on these observations, Arnold and colleagues designed the randomized, phase III TML trial to evaluate the efficacy and safety of continuing bevacizumab with standard second-line chemotherapy in patients with metastatic CRC who have progressed after bevacizumab plus standard first-line chemotherapy. The trial enrolled 820 patients with metastatic CRC who had received first-line bevacizumab plus either oxaliplatin-based or irinotecan-based chemotherapy and had documented progressive disease within 4 weeks of starting the study treatment.

Patients had to have received bevacizumab within the past 3 months, reflecting a maximum duration of bevacizumab interruption of 3 months. Moreover, the duration of progression-free survival (PFS) in first-line treatment was required to be at least 3 months. Finally, patients were required to have received first-line bevacizumab for at least 3 months.

For the study treatment, patients were switched to an opposite chemotherapy regimen (oxaliplatin-based or irinotecan-based) and were randomly assigned to receive chemotherapy plus bevacizumab 2.5 mg/kg/week (409 patients) or chemotherapy alone (411 patients). The exact regimen used was at the investigators' discretion. Patients were stratified based on the first-line chemotherapy regimen (oxaliplatin-based vs irinotecan-based), duration of initial PFS (≤9 months vs >9 months), duration from last bevacizumab dose (≤42 days vs >42 days), and Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0–1 vs 2). The study accrued patients between February 2006 and June 2010 at 200 study centers in Europe and Saudi Arabia. The demographic and baseline characteristics were balanced between the arms. The median age was 63 years; approximately 56% of patients had a first-line PFS at or within 9 months; approximately 58% had received irinotecan-based chemotherapy in the first-line setting; and 77% had received their last bevacizumab dose within 42 days.

### Randomized Phase III Study of Adjuvant Chemotherapy With Oral Uracil and Tegafur Plus Leucovorin Versus Intravenous Fluorouracil and Levofolinate in Patients (pts) With Stage III Colon Cancer (CC): Final Results of Japan Clinical Oncology Group Study (JCOG0205)

For patients with stage III CRC cancer, postoperative adjuvant chemotherapy with oral uracil-tegafur plus leucovorin appears to be noninferior to intravenous 5-FU plus levofolinate, according to the final results of the randomized, phase III Japan Clinical Oncology Group Study 0205 (Abstract 3524). In the trial, 1,101 patients aged 20–75 years with stage III CRC were randomly assigned to postoperative uracil-tegafur (300 mg/m$^2$/day) plus leucovorin (75 mg/day) on Days 1–28 every 5 weeks for 5 courses (551 patients) or 5-FU (500 mg/m$^2$) plus levofolinate (250 mg/m$^2$) on Days 1, 8, 15, 22, 29, and 36 every 8 weeks for 3 courses (550 patients). After a median follow-up of 72 months, oral uracil-tegafur demonstrated noninferiority to 5-FU plus levofolinate (HR, 1.02; *P*=.0236). Overall disease-free survival rates were 78.6% at 3 years and 74% at 5 years. The 5-year OS rate was high at 87.9%; the investigators suggested the use of D3 dissection and upstaging with careful lymph node examination as potential explanations. The most common grade 3/4 adverse events were diarrhea (8.5% with uracil-tegafur plus leucovorin vs 9.6% with 5-FU plus levofolinate), ALT elevation (8.7% vs 0.7%), and neutropenia (1.5% vs 8.4%).

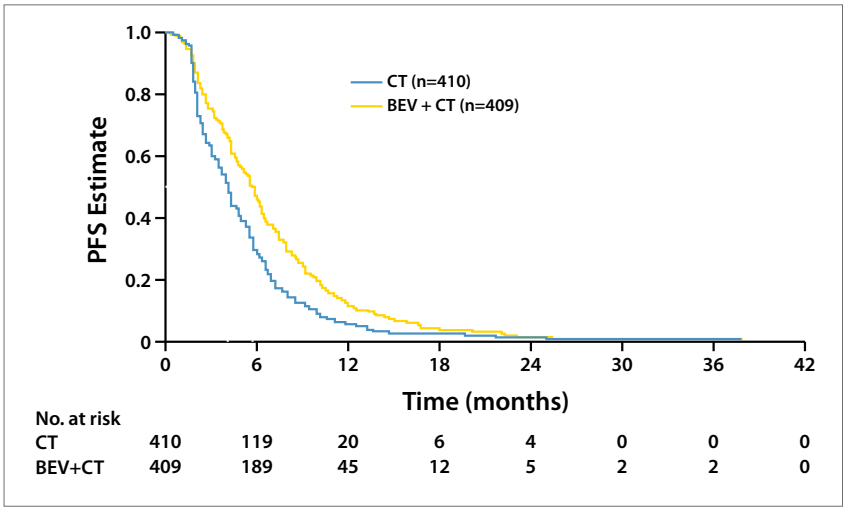


**Figure 1.** Progression-free survival (PFS) in the TML study. BEV=bevacizumab; CT=chemotherapy. Data from Arnold D et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract CRA3503.

The second-line chemotherapy regimen used in the study was oxaliplatin-based in approximately 58% of patients and irinotecan-based in approximately 42%, reflecting the switch from first-line therapy. The most common second-line chemotherapy regimens used in the study were oxaliplatin, 5-fluorouracil (5-FU), leucovorin (FOLFOX) 4/modified FOLFOX4 (18–19%); leucovorin, 5-FU, and irinotecan (FOLFIRI) (14–16%); FOLFOX6 (13–16%); capecitabine/oxaliplatin (11–14%); and capecitabine/irinotecan (12%). Dr. Arnold commented that the variety of regimens used in the study reflect the daily practice patterns in Europe.

In an intent-to-treat analysis, the addition of bevacizumab to second-line chemotherapy was associated with a significant improvement in OS compared with chemotherapy alone, with a median OS of 11.1 months and 9.6 months, respectively (unstratified HR, 0.81; *P*=.0062). Outcomes were similar in a stratified analysis, yielding a HR of 0.83 (*P*=.0211). Prespecified subgroup analyses showed a similar OS benefit with bevacizumab across subgroups. Although there was no significant benefit with bevacizumab in female patients, a treatment-sex interaction test showed no significant interaction between the benefit of bevacizumab and sex. Approximately 68% of patients went on to receive at least 1 subsequent anticancer therapy; there were no notable differences between the 2 arms in the frequency of subsequent therapies or the types of therapies used.

Bevacizumab plus chemotherapy was also more effective than chemotherapy alone in regard to median PFS (5.7 vs 4.1 months; unstratified HR, 0.68; *P*<.0001; Figure 1). There was no significant difference in overall response rate between arms (5.4% and 3.9%, respectively). However, bevacizumab plus chemotherapy was associated with a significant improvement in disease control rate versus chemotherapy alone (68% vs 54%; *P*<.0001).

The investigators reported no significant difference in the incidence of serious adverse events between arms; 3% of patients in each arm died due to adverse events. The incidence of discontinuation due to adverse events was higher with bevacizumab plus chemotherapy versus chemotherapy alone (16% vs 9%) although these were largely discontinuations due to chemotherapy.

The addition of bevacizumab to chemotherapy did not appear to increase the incidence of grade 3–5 chemotherapy-related adverse events. Bevacizumab-specific adverse events were, as expected, based on previous trials. The most frequent bevacizumab-related adverse event was bleeding/hemorrhage, reported in 26% of patients (2% grade 3–5), followed by hypertension (12%; 2% grade 3–5).

Dr. Arnold concluded that, for patients with disease progression following first-line chemotherapy plus bevacizumab, continuing bevacizumab with an altered chemotherapy regimen provided a survival benefit and may be considered as a new second-line treatment option.

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# Bevacizumab (Bev) With or Without Erlotinib as Maintenance Therapy, Following Induction First-Line Chemotherapy Plus Bev, in Patients (Pts) With Metastatic Colorectal Cancer (MCRC): Efficacy and Safety Results of the International GERCOR DREAM Phase III Trial

For patients with previously untreated metastatic CRC without disease progression after induction therapy with chemotherapy plus bevacizumab, maintenance bevacizumab plus erlotinib appears to provide a significant improvement in PFS over bevacizumab alone. These first results of the international, randomized, phase III GERCOR (Groupe Cooperateur Multidisciplinaire en Oncologie) DREAM (Double Inhibition Reintroduction Erlotinib Avastin Metastatic Colorectal Cancer) trial were presented by Christophe Tournigand, MD.[1]

Individual targeted therapies have previously demonstrated a significant survival benefit in metastatic CRC. Inhibition of VEGF with bevacizumab has been shown to extend survival when used in combination with oxaliplatin-based or irinotecan-based chemotherapy in both treatment-naïve and previously treated patients.[2-4] Inhibition of the epidermal growth factor receptor (EGFR) using cetuximab or panitumumab has been shown to extend survival in patients with *KRAS* wild-type tumors.[4-7]

Based on the demonstrated benefit of the individual agents and a scientific rationale suggesting interactions between the 2 pathways, a combination strategy of targeting both EGFR and VEGF was evaluated. In phase III trials, however, administering anti-EGFR and anti-VEGF monoclonal antibodies in combination with chemotherapy was not beneficial, and was actually detrimental.[8,9] Preclinical data suggest that a combination of tyrosine kinase inhibitors (TKIs) targeting VEGFR and EGFR is synergistic, and that the combination of bevacizumab and the EGFR-targeted TKI erlotinib is active.[10,11]

Based on these studies, Tournigand and colleagues developed the OPTIMOX3–DREAM protocol to evaluate the efficacy and safety of bevacizumab plus erlotinib in patients with metastatic CRC following first-line induction therapy. The trial enrolled 700 patients with previously untreated metastatic CRC. The induction therapy regimen of chemotherapy plus bevacizumab was selected at the investigators' discretion; regimens included modified FOLFOX7 (oxaliplatin 100 mg/m$^2$ on Day 1 for 6 cycles, 5-FU 2.4 g/m$^2$ on Days 1–2, folinic acid 400 mg/m$^2$ on Day 1) plus bevacizumab 5 mg/kg on Day 1, every 2 weeks, for 6–12 cycles; XELOX2 (oxaliplatin 100 mg/m$^2$ on Day 1 for 6 cycles, capecitabine 1.25–1.5 g/m$^2$ twice daily on Days 1–8) plus bevacizumab 5 mg/kg on Day 1, every 2 weeks, for 6–12 cycles; or FOLFIRI (irinotecan 180 mg/m$^2$ on Day 1, 5-FU 2.4 mg/m$^2$ on Days 1–2, folinic acid 400 mg/m$^2$ on Day 1) plus bevacizumab 5 mg/kg on Day 1, every 2 weeks, for 12 cycles.

A total of 446 patients without progressive disease after induction therapy were randomly assigned to maintenance therapy with bevacizumab 7.5 mg/kg every 3 weeks either alone (224 patients) or with erlotinib 150 mg/day (222 patients). Patients were required to have an alkaline phosphatase less than 3–5 times the upper limit of normal (ULN) and bilirubin less than 1.5 times the ULN. Adjuvant therapy had to have been given at least 6 months prior to the diagnosis of metastatic disease, or at least 2 years if adjuvant oxaliplatin was used. Patients were 18–80 years of age.

Approximately 26% of patients were age 70 or older; 10% had received prior adjuvant chemotherapy. The most commonly used induction regimen was FOLFOX plus bevacizumab (59%), followed by XELOX plus bevacizumab (30%) and FOLFIRI plus bevacizumab (10%).

After a median follow-up of 31 months, bevacizumab plus erlotinib was associated with a significant

### Randomized Phase II Open-Label Study of mFOLFOX6 in Combination With Linifanib or Bevacizumab for Metastatic Colorectal Cancer

The investigational VEGF and platelet-derived growth factor receptor TKI linifanib does not appear to be more effective than bevacizumab when added to modified FOLFOX6 in the second-line treatment of metastatic CRC, according to results of a multicenter, randomized, phase II, active-control trial (Abstract 3532). In the study, 148 patients with recurrent or metastatic unresectable CRC were randomly assigned to mFOLFOX6 plus linifanib 12.5 mg (n=49), mFOLFOX6 plus linifanib 7.5 mg (n=50), or mFOLFOX6 plus bevacizumab 10 mg/kg (n=49). The median PFS in these 3 arms was 7.7 months, 6.6 months, and 9.0 months, respectively. The median OS was 16.4 months, 12.0 months, and 16.5 months, respectively, indicating better outcomes with high-dose linifanib and bevacizumab compared with low-dose linifanib. The investigators also found no benefit with high-dose or low-dose linifanib versus bevacizumab in regard to ORR (22.4%, 24.0%, and 34.7%, respectively) or median duration of response (5.7 months, 5.7 months, and 7.4 months, respectively). No subgroup was identified that preferentially benefited from linifanib. Some adverse events were significantly ($P$<.05) more frequent with high-dose linifanib versus bevacizumab, including hand-foot syndrome (any grade, 36.7% vs 14.6%; grade 3/4, 16.3% vs 0%), hypothyroidism (12.2% vs 0%), hyperbilirubinemia (12.2% vs 0%), and thrombocytopenia (34.7% vs 14.6%).

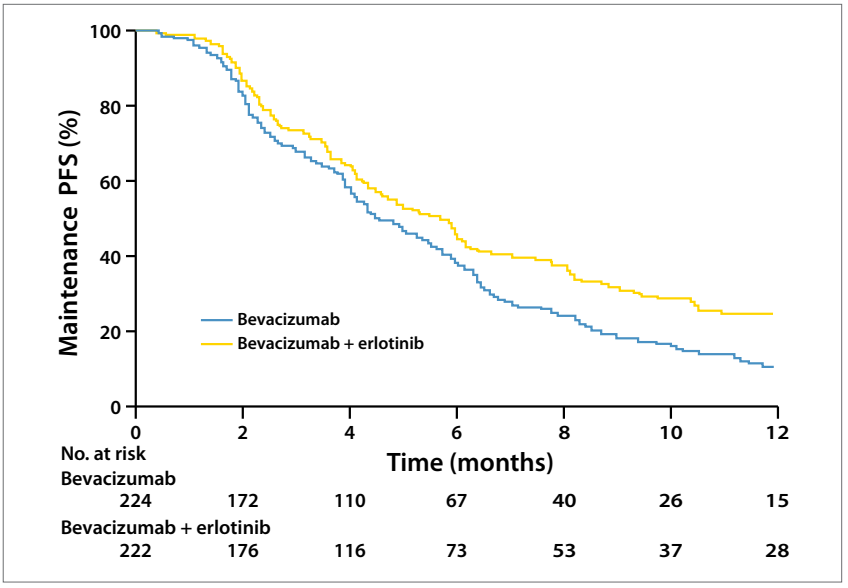


**Figure 2.** Progression-free survival in the GERCOR DREAM trial. GERCOR=Groupe Cooperateur Multidisciplinaire en Oncologie; DREAM=Double Inhibition Reintroduction Erlotinib Avastin Metastatic Colorectal Cancer. Data from Tournigand C, et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract LBA3500.

improvement in median PFS compared with bevacizumab alone (5.75 vs 4.57 months; HR, 0.73; $P$=.0050; Figure 2), with PFS measured starting at the time of randomization to maintenance therapy. An analysis of PFS in the randomized cohort starting from the time of registration, prior to induction therapy, showed a similar improvement in median PFS with bevacizumab plus erlotinib versus bevacizumab alone (10.22 vs 9.23 months; HR, 0.73; $P$=.0045). OS was not yet evaluable for the 446 patients in the randomized portion of the trial. The median OS among the entire enrolled population of 700 patients was 25.4 months.

Although the combination of bevacizumab and erlotinib was generally well tolerated, erlotinib was associated with a substantial increase in the incidence of diarrhea and skin toxicity. The overall incidence of diarrhea was 58% with bevacizumab plus erlotinib versus 13% with bevacizumab alone (grade 3/4: 9% vs 1%). Skin toxicity of any severity developed in 85% of patients receiving bevacizumab plus erlotinib versus 8% of patients receiving bevacizumab alone (grade 3/4: 20% vs 0%). Erlotinib dose reductions were required in approximately 24% of cycles, primarily due to toxicity. Overall, patients in the combination arm received a median of 8 cycles of bevacizumab and 7 cycles of erlotinib; patients in the bevacizumab arm received a median of 7 cycles of therapy. The investigators noted that *KRAS* analyses, as well as OS analyses, are ongoing.

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# Results of the X-PECT Study: A Phase III Randomized Double-Blind, Placebo-Controlled Study of Perifosine Plus Capecitabine (P-CAP) Versus Placebo Plus Capecitabine (CAP) in Patients (Pts) With Refractory Metastatic Colorectal Cancer (mCRC)

The combination of perifosine and capecitabine does not appear to have a benefit in patients with refractory CRC, according to results of the randomized, phase III, double-blind, placebo-controlled X-PECT (Xeloda + Perifosine Evaluation in Colorectal Cancer Treatment) trial presented by Johanna C. Bendell, MD.[1] The treatment of refractory metastatic CRC is a significant unmet need in cancer care. The median PFS in these patients is 2 months, and the median OS is 4–6 months. Capecitabine is approved for use in the first-line setting, though it is often administered to patients with previously treated disease. The phosphatidylinositol-3 kinase (PI3K)/AKT pathway has been identified as a new potential therapeutic target for metastatic CRC, as up to 40% of CRCs contain PI3 kinase mutations and up to 20% contain mutations or deletions in PTEN, a suppressor of the PI3 kinase pathway. Moreover, the mitogen-activated protein (MAP) kinase pathway is dysregulated in approximately 60% of CRCs.

Perifosine is an oral alkylphospholipid that inhibits the AKT/protein kinase B pathway.[2] Perifosine also suppresses nuclear factor-κB (NF-κB), stimulates the proapoptotic molecule Janus kinase (JNK), and promotes cell cycle arrest through its effects on p21.[3] Mechanistic studies have suggested a scientific rationale for combining perifosine and capecitabine. This relates primarily to the ability of perifosine to inhibit NF-κB, as expression of NF-κB is upregulated in fluorouracil-resistant cells.[4] Dr. Bendell noted that inhibition of the NF-κB pathway using other agents, such as proteasome inhibitors or mammalian target of rapamycin (mTOR) inhibitors, has

### Final Results of Study 20050181: A Randomized Phase III Study of FOLFIRI With or Without Panitumumab (pmab) for the Second-Line Treatment (tx) of Metastatic Colorectal Cancer (mCRC)

The benefit of adding panitumumab to FOLFIRI in the second-line treatment of *KRAS* wild-type metastatic CRC was confirmed in a planned final analysis of the randomized, controlled study 20050181 (Abstract 3535). The trial compared the safety and efficacy of panitumumab plus FOLFIRI in patients with metastatic CRC and an ECOG performance status of 0–2 who had received 1 prior fluoropyrimidine-based chemotherapy regimen. A total of 1,186 patients were enrolled in the trial, and *KRAS* status was determined in 91% of patients. Of the 597 patients with *KRAS* wild-type tumors, 303 patients were randomly assigned to panitumumab 6.0 mg/kg every 2 weeks plus FOLFIRI, and 294 patients were assigned to FOLFIRI alone. In the current analysis, conducted 30 months after enrollment of the last patient, the addition of panitumumab to FOLFIRI in patients with *KRAS* wild-type tumors was associated with a significant improvement over FOLFIRI alone in regard to median PFS (6.7 vs 4.9 months; HR, 0.82; *P*=.023) and ORR (36% vs 10%; odds ratio, 5.50; *P*<.0001) and a trend toward an improvement in median OS (14.5 vs 12.5 months; HR, 0.92; *P*=.366). The investigators suggested that post-study anti-EGFR treatment (used in 12.5% of patients in the panitumumab-containing arm and in 34.4% of patients in the control arm) may have confounded differences in OS between arms. As expected, there was no significant difference between arms among patients with *KRAS*-mutant tumors.

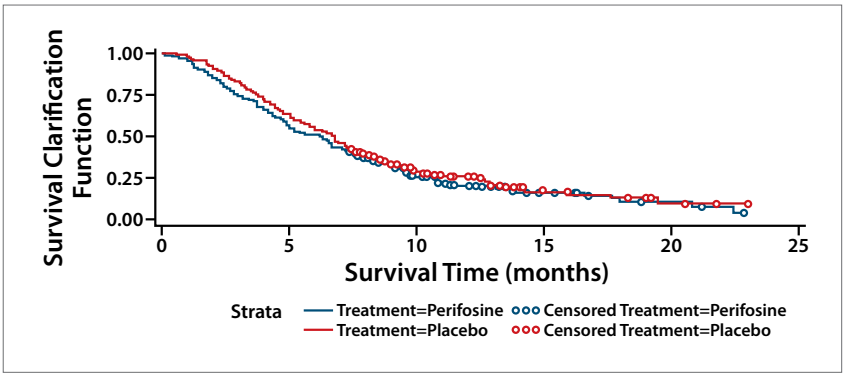


**Figure 3.** Overall survival in the X-PECT trial. X-PECT=Xeloda + Perifosine Evaluation in Colorectal Cancer Treatment. Data from Bendell JC et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract LBA3501.

been shown to augment the antitumor activity of fluorouracil. Moreover, preclinical studies in CRC cell lines have also suggested synergy with a combination of perifosine and capecitabine.

Subsequently, a randomized, phase II study was undertaken evaluating capecitabine, administered at 825 mg/m$^2$ twice daily on Days 1–14 of every 21-day cycle, with perifosine 50 mg once daily or with placebo, in 38 patients with metastatic CRC previously treated with 5-FU or a 5-FU-containing regimen.[5] Patients had received 1 or 2 prior lines of therapy and could not have received prior capecitabine for metastatic disease. In this study, perifosine plus capecitabine was associated with a significant improvement over capecitabine alone in median time to progression (TTP) (27.5 vs 10.1 weeks; *P*<.001) and median OS (17.7 vs 7.6 months; *P*=.0052).

Based on these outcomes, Bendell and colleagues conducted the double-blind, placebo-controlled, randomized phase III X-PECT trial, which compared capecitabine, administered at 1,000 mg/m$^2$ twice daily on Days 1–14 of an every 21-day cycle, plus perifosine 50 mg once daily or placebo, in patients with refractory metastatic CRC. The study was open to patients with recurrent or metastatic CRC who had failed available therapy for the treatment of advanced CRC. Patients were required to have developed progressive disease during, or within 6 months after, fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, and, for patients with *KRAS* wild-type disease, anti-EGFR mAb-containing therapies. Other definitions of treatment failure for oxaliplatin-based therapy included progression within 12 months of adjuvant therapy and discontinuation of oxaliplatin due to toxicity. Patients could not have received prior capecitabine in the metastatic setting, with the exception of radiosensitizing therapy. Other eligibility criteria included an ECOG performance status greater than 2, age 18 years or older, and adequate organ function.

Between March 2010 and August 2011, the trial enrolled 468 patients at 66 sites in the United States; 234 patients were assigned to each arm. Patients were stratified based on *KRAS* status (wild-type vs mutant) and based on the reason for oxaliplatin discontinuation (toxicity vs progression). Baseline characteristics were well matched between groups. Overall, 62% of patients were younger than age 65, 55% were male, and 58% had an ECOG performance status of 1. Approximately 50% of patients had mutant *KRAS*, and 73% of patients had received at least 4 prior therapies. The majority of patients (63%) had discontinued oxaliplatin due to progression.

In an intent-to-treat analysis, there were no significant differences between capecitabine plus perifosine and capecitabine alone as assessed by median OS (6.4 vs 6.9 months; *P*=.315; Figure 3) or median PFS (10.9 vs 11.4 weeks; *P*=.752). Response rates were under 5% in each arm.

Subgroup analyses also showed no significant difference between arms in OS or PFS according to *KRAS* mutation status. However, a preplanned analysis did suggest a benefit with perifosine in the subgroup of patients with *KRAS* wild-type tumors who had discontinued oxaliplatin secondary to toxicity. Among these 86 patients, the median PFS was 18.1 weeks with perifosine plus capecitabine versus 6.6 weeks with placebo plus capecitabine (HR, 0.514; *P*=.003). The median OS was 8 months and 6.2 months, respectively (*P*=.280).

In regard to safety, treatment-related adverse events were generally similar between arms; however, several adverse events occurred more frequently with perifosine versus placebo, including fatigue (55% vs 41%), nausea (43% vs 33%), diarrhea (46% vs 36%), decreased appetite (30% vs 21%), vomiting (30% vs 22%), and grade 1/2 anemia (21% vs 13%).

Correlative studies are ongoing to identify biomarkers associated with differential responses to perifosine. Analyses are being performed on baseline paraffin samples, which were obtained from 75% of patients, and on peripheral blood mononuclear cells, blood, and biopsy samples collected from a subset of patients who participated in a biomarker cohort.

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# Phase III CORRECT Trial of Regorafenib in Metastatic Colorectal Cancer (mCRC)

The oral multikinase inhibitor regorafenib is associated with a significant survival benefit in patients with metastatic CRC previously treated with all available standard therapies, according to results of the randomized, placebo-controlled, phase III CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial, presented by Eric Van Cutsem, MD, PhD.[1] In his presentation, Dr. Van Cutsem noted that many patients with refractory metastatic CRC have a good performance status and would be candidates for additional therapy, again highlighting the need for more effective therapies in this disease setting.[2,3]

Regorafenib is an oral multikinase inhibitor that targets multiple mediators that contribute to cancer growth and development, including KIT, PDGFR, RET, FGFR, VEGFR1-3, and TIE2.[4-6] Through its effects on these kinases, regorafenib inhibits proliferation, blocks signaling in the tumor microenvironment, and inhibits neoangiogenesis.[4-6] A phase I study was undertaken to evaluate the safety and activity of regorafenib in patients with metastatic CRC.[5,6] In the dose-escalation phase, 15 patients received regorafenib at doses ranging from 60 to 220 mg/day on a 3-weeks-on, 1-week-off schedule. In the expansion phase, 23 patients received regorafenib at the recommended dose of 160 mg/day on the same schedule. A safety analysis showed no grade 4 adverse events aside from 1 case of grade 4 thrombocytopenia. The most frequently occurring adverse events were hand-foot skin reaction, skin rash, diarrhea, fatigue, and voice change. In the 27 patients evaluable for response, regorafenib was associated with a disease control rate of 74%, reflecting 1 partial response (4%) and 19 patients (70%) with stable disease. The median PFS was 107 days.

The randomized, double-blind, placebo-controlled phase III CORRECT trial was designed to further evaluate the efficacy and safety of regorafenib in patients with metastatic CRC who had already received standard therapy. Eligible patients had disease progression during, or within 3 months of, approved standard therapies including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, in the case of patients with *KRAS* wild-type tumors, an anti-EGFR mAb. Intolerance to these approved standard therapies was also acceptable. Patients were required to have an ECOG performance status less than 2, a life expectancy of 3 months or longer, no recent major surgery, no cardiovascular dysfunction, and no thrombotic or embolic events in the past 6 months.

### A Randomized, Double-Blind, Phase (Ph) III Study of the Irinotecan-Based Chemotherapy FOLFIRI Plus Ramucirumab (RAM) or Placebo (PL) in Patients (pts) With Metastatic Colorectal Carcinoma (mCRC) Progressive During or Following First-Line Therapy With Bevacizumab (BEV), Oxaliplatin (OXALI), and a Fluoropyrimidine (FP) (RAISE) (NCT01183780)

Ramucirumab is a fully human IgG1 mAb that selectively and potently blocks the human VEGFR-2 receptor. In laboratory studies of human endothelial cells, ramucirumab has been shown to neutralize VEGF-induced mitogenesis. Ramucirumab may also induce antibody-dependent cellular cytotoxicity. An open-label, phase II study showed the activity and safety of ramucirumab in combination with mFOLFOX6 in the first-line treatment of patients with metastatic CRC (Garcia-Carbonero R et al. 2012 ASCO GI Cancers Symposium; Abstract 533), with a median PFS of 11.5 months and an ORR of 58%. The most frequent ramucirumab-related grade 3 adverse event was hypertension (15%). No grade 4 events occurred in more than 1 patient. Based on these results, a randomized, multicenter, double-blind, phase III trial was designed to compare the efficacy and safety of ramucirumab plus FOLFIRI vs placebo plus FOLFIRI in patients with metastatic CRC who have had disease progression during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (Abstract TPS3634). The primary endpoint of the trial is OS; secondary endpoints include PFS, ORR, patient-reported outcomes, safety, and biomarker analyses. The trial plans to recruit 1,050 patients from countries throughout North America, South America, Europe, and Asia. As of May 2012, 419 patients have enrolled and assigned to a treatment arm.

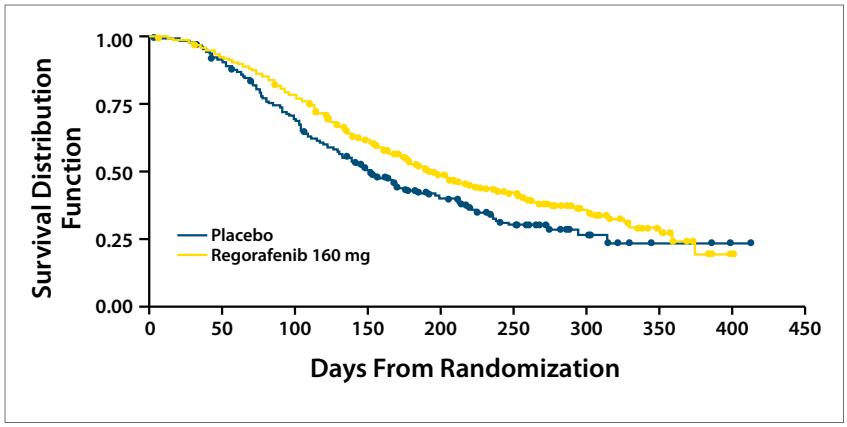


**Figure 4.** Overall survival in the CORRECT trial. CORRECT=Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Data from Van Cutsem E et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30:Abstract 3502.

Between May 2010 and March 2011, this global trial screened 1,052 patients at 114 study centers located in 16 different countries. Patients were stratified according to prior anti-VEGF therapy, time from diagnosis of metastatic disease, and geographical region. A total of 760 patients were ultimately randomly assigned 2:1 to regorafenib 160 mg orally once daily for 3 weeks on/1 week off (505 patients) or placebo for 3 weeks on/1 week off (255 patients), each in addition to best supportive care. The treatment was continued until disease progression, severe toxicity, or patient refusal.

The baseline characteristics were balanced between arms; the median age was 61 years (range, 22–85 years); 61% were male; and 78% were white. The majority of patients (83%) were in North America, Western Europe, Israel, and Australia, followed by Asia (14%) and Eastern Europe (3%). More than half of patients (54% in the regorafenib arm; 62% in the placebo arm) had *KRAS*-mutant tumors, and 48% of patients had received at least 4 prior lines of therapy for metastatic disease.

Dr. Van Cutsem reported that in this trial, regorafenib was associated with a significant improvement in OS compared with placebo, with a median OS of 6.4 months and 5.0 months, respectively (HR, 0.77; 1-sided *P*=.0052; Figure 4). With this outcome, the primary endpoint met the prespecified stopping criteria. The benefit of regorafenib was observed across all prespecified subgroups, including patient demographics, time from diagnosis of metastatic disease, and prior number of therapies. Regorafenib was also effective regardless of *KRAS* mutation status; in this trial, *KRAS* mutation status was not of prognostic value, nor was it predictive of responses to regorafenib.

The median PFS was also significantly longer with regorafenib versus placebo (1.9 vs 1.7 months; HR, 0.49; *P*<.000001). The PFS benefit was also achieved across specified subgroups. There were few objective responses observed in either arm (1.0% with regorafenib vs 0.4% with placebo), though regorafenib was associated with an improvement over placebo in the disease control rate (41.0% vs 14.9%; *P*<.000001).

The most common drug-related adverse events observed with regorafenib were hand-foot skin reaction (any grade, 46.6%; grade 3, 16.6%), fatigue (47.4%; 9.2%), hypertension (27.8%; 7.2%), diarrhea (33.8%; 7.0%), and rash or desquamation (26.0%; 5.8%). There were very few grade 4 adverse events; 5 patients (1%) in the regorafenib arm died from drug-related adverse events. Quality of life analysis using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EQ-5D index, and EQ-5D visual analog scale showed no significant differences in health-related quality of life with regorafenib versus placebo. With its demonstrated survival benefit and manageable adverse event profile, Dr. Van Cutsem called regorafenib a new potential standard of care for patients with chemorefractory metastatic CRC.

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# Final Analysis of the Phase III Randomized Trial of Cetuximab (CET) Plus Either Brivanib Alaninate (BRIV) or Placebo in Patients (pts) With Chemotherapy Refractory, K-RAS Wild-Type (WT), Metastatic Colorectal Carcinoma (mCRC): The NCIC Clinical Trials Group and AGITG CO.20 trial

The combination of cetuximab and brivanib does not appear to improve OS over cetuximab alone in patients with chemotherapy-refractory, *KRAS* wild-type metastatic CRC, according to the final results of the randomized, placebo-controlled, phase III National Institute of Canada (NCIC) Clinical Trials Group and Australasian Gastro-Intestinal Trials Group (AGITG) CO.20 trial presented by Lillian L. Siu, MD.[1] However, the regimen was associated with a significant improvement in PFS and response rate.

Brivanib is an oral inhibitor of the VEGFR and EGFR pathways that has demonstrated antiangiogenic and antitumor activity in a phase I study in patients with advanced or metastatic solid tumors.[2] It was hypothesized that the antiangiogenic activity of brivanib alaninate may synergize with the EGFR-inhibiting activity of cetuximab. Preclinical data using xenograft models provided additional evidence for this combination. A phase I dose-escalation study of brivanib alaninate plus full-dose cetuximab demonstrated the clinical activity of the combination in patients with advanced gastrointestinal malignancies who had failed prior therapy.[3]

In the phase III trial NCIC Clinical Trials Group CO.17, a retrospective analysis showed that the benefit of cetuximab in patients with metastatic CRC was restricted to patients with *KRAS* wild-type tumors.[4] Similarly, in the phase I/II trial of cetuximab plus brivanib, the activity of the regimen was observed primarily in the subset of patients with *KRAS* wild-type tumors.[5] The median PFS associated with brivanib plus cetuximab was 7.2 months among the 25 patients with *KRAS* wild-type tumors and 10.9 months among the 15 patients with *KRAS* wild-type tumors who had no prior anti-EGFR therapy.[5]

Based on these findings, Siu and colleagues developed the randomized, phase III trial of brivanib plus cetuximab versus cetuximab alone in patients with *KRAS* wild-type metastatic CRC previously treated with combination chemotherapy. Patients were required to have received a prior thymidylate synthase inhibitor and were intolerant to, or refractory to, irinotecan and oxaliplatin. Patients could not have received prior anti-EGFR therapy; and 1 prior anti-VEGF or anti-VEGFR therapy was allowed.

A total of 750 patients enrolled on the trial between February 2008 and February 2011. Patients were stratified by study center and by ECOG performance status (0–1 vs 2) and were randomly assigned to cetuximab (400 mg/m$^2$ loading dose on Day 1 followed

### Effect of Bevacizumab on Rate of Oxaliplatin-Induced Thrombocytopenia and Splenomegaly

Oxaliplatin is associated with the development of hepatic sinusoidal injury, which can lead to portal hypertension, splenomegaly, and thrombocytopenia. Previous evidence has suggested that bevacizumab confers a protective effect on oxaliplatin-associated hepatic sinusoidal injury and thrombocytopenia (Klinger M et al. *Eur J Surg Oncol.* 2009;35:515-520.) In the current analysis, Raghav and colleagues evaluated spleen volumes and platelet counts in 184 patients with metastatic CRC who received at least 3 months of first-line FOLFOX with bevacizumab (n=138) or without bevacizumab (n=46) (Abstract 3544). There were no significant differences between the 2 groups at baseline in regard to age, number of oxaliplatin cycles, total oxaliplatin dose, spleen size, or platelet count. Splenomegaly, defined as a spleen volume increase of 30% or more, was significantly more common in patients who received FOLFOX alone than in patients who received bevacizumab plus FOLFOX (48% vs 32%; *P*=.013). The median time to documented splenomegaly was also significantly shorter in patients not receiving bevacizumab (5.5 vs 7.6 months; *P*=.023). Splenomegaly correlated with thrombocytopenia at 3 months (40% vs 16%; *P*=.0005) and beyond (*P*<.0001). The researchers concluded that the addition of bevacizumab to FOLFOX in patients with metastatic CRC provided clinically relevant reductions in oxaliplatin-induced hepatic sinusoidal injury, as evidenced by reductions in splenomegaly and thrombocytopenia.

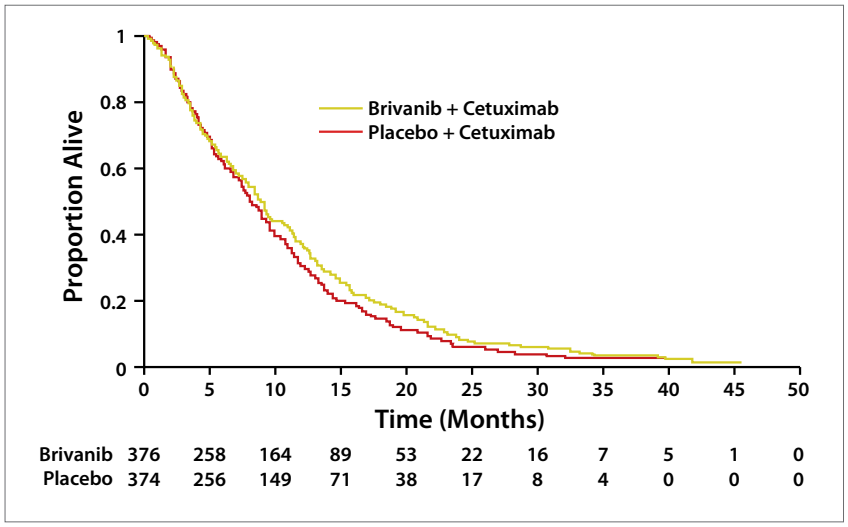


**Figure 5.** Overall survival in the NCIC Clinical Trials Group and AGITG CO.20 trial. NCIC=National Institute of Canada; AGITG=Australasian Gastro-Intestinal Trials Group. Data from Siu LL et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract 3504.

by 250 mg/m$^2$ weekly) plus either brivanib (800 mg once daily) (376 patients) or placebo (374 patients).

Patient characteristics were well balanced between arms. The median age was 64 years; approximately 10% of patients had an ECOG performance status of 2 and more than 90% of patients had received at least 4 prior lines of therapy. Approximately 40% of patients had received prior antiangiogenic therapy.

At the 2012 Gastrointestinal Cancer Symposium, Dr. Siu presented outcomes from the protocol-specified final analysis with a median follow-up of 19 months.[6] At that time, there was no significant difference in OS with brivanib plus cetuximab versus cetuximab alone, with a median OS of 8.8 months and 8.1 months, respectively (HR, 0.88; *P*=.12).

At the 2012 ASCO Annual Meeting, Dr. Siu presented the final analysis of the trial.[1] After a median follow-up of 34 months, there continued to be no significant difference in OS between the 2 arms, with a median OS of 8.9 months with brivanib plus cetuximab versus 8.2 months with placebo plus cetuximab (HR, 0.89; *P*=.13; Figure 5). Subgroup analyses revealed no patient group in which brivanib plus cetuximab provided a significant OS benefit.

The combination of brivanib and cetuximab did appear to provide a PFS benefit over cetuximab alone. At the 19-month analysis, the median PFS was 5.0 months with brivanib plus cetuximab versus 3.4 months with placebo plus cetuximab (HR, 0.72; *P*<.0001).[6] The updated analysis confirmed this benefit, with a median PFS of 4.8 months and 3.4 months, respectively (HR, 0.74; *P*<.0001).[1] The PFS benefit with brivanib was observed across subgroups except for patients with ECOG performance status of 2, although patient numbers were small in this group.

Brivanib plus cetuximab was also associated with a significant improvement in response rate versus cetuximab alone, with an ORR of 14% and 7%, respectively (*P*=.002). The median duration of response was similar between arms, at 5.8 months and 5.4 months, respectively.

In regard to safety, brivanib plus cetuximab was associated with a significant increase in the overall rate of grade 3 or higher adverse events compared with cetuximab (81% vs 54%; *P*<.05). Multiple grade 3 or higher adverse events occurred significantly more frequently (*P*<.05) with brivanib plus cetuximab versus cetuximab alone; the most frequent were fatigue (27% vs 11%), hypertension (11% vs 1%), rash (10% vs 5%), and abdominal pain (10% vs 5%). Increased grade 3 or higher laboratory abnormalities included aspartate transaminase (AST) elevation (17% vs 6%), alanine transaminase (ALT) elevation (22% vs 5%), hyponatremia (15% vs 8%), and thyroid-stimulating hormone (TSH) elevation (25% vs 4%).

Dose reductions and omissions were more common in patients in the combination arm versus the cetuximab-only arm, including reductions and omissions of both cetuximab and brivanib. Overall, 48% of patients in the combination arm received at least 90% of the planned intensity for cetuximab, compared with 72% of patients in the cetuximab monotherapy arm. Fewer than 10% of patients in either arm discontinued cetuximab due to adverse events, whereas 23% of patients in the combination arm discontinued brivanib due to adverse events. The most common reasons for discontinuation in the combination arm were fatigue (5%), ALT elevations (2%), AST elevations (2%), and dyspnea (2%). There was 1 death in the investigational arm considered possibly related to the study drug. A previously presented quality-of-life analysis significantly favored placebo over brivanib in regard to deterioration of global health and physical function.[7]

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# Effects of Prior Bevacizumab (B) Use on Outcomes From the VELOUR Study: A Phase III Study of Aflibercept (Afl) and FOLFIRI in Patients (pts) With Metastatic Colorectal Cancer (mCRC) After Failure of an Oxaliplatin Regimen

In patients with metastatic CRC with disease progression following an oxaliplatin-based regimen, prior bevacizumab did not appear to affect the efficacy or safety of aflibercept added to FOLFIRI, according to a subgroup analysis from the phase III VELOUR (Aflibercept Versus Placebo in Combination with Irinotecan and 5-FU [FOLFIRI] in the Treatment of Patients with Metastatic Colorectal Cancer after Failure of an Oxaliplatin Based Regimen) trial presented by Carmen Joseph Allegra, MD.[1]

Aflibercept is a VEGF-trap that blocks the VEGF signaling cascade by binding VEGF fusion protein before it can bind to its normal receptors.[2] A fusion protein, aflibercept contains key domains from human VEGF receptors 1 and 2 and human IgG Fc. It binds all VEGF-A isoforms, VEGF-B, and placental growth factor (PIGF).[3] Aflibercept binds VEGF-A with higher affinity than do native VEGF receptors.

The phase III VELOUR trial evaluated the addition of aflibercept to FOLFIRI in the second-line treatment of metastatic CRC in patients previously treated with 1 prior oxaliplatin-containing chemotherapy regimen for metastatic disease. Patients with relapse within 6 months of completing oxaliplatin-based adjuvant chemotherapy were also eligible. A total of 1,200 patients were randomly assigned to FOLFIRI plus either aflibercept 4 mg/kg on Day 1 every 2 weeks (600 patients) or intravenous placebo on Day 1 every 2 weeks (600 patients). Patients were stratified according to ECOG performance status (0–1 vs 2), and prior bevacizumab treatment.

In 2011, Van Cutsem and colleagues reported a significant improvement in efficacy with aflibercept plus FOLFIRI versus FOLFIRI alone in regard to both median OS (13.5 vs 12.1 months; HR, 0.817; *P*=.0032) and median PFS (6.9 vs 4.7 months; HR, 0.76; *P*=.00007).[4]

At the 2012 ASCO meeting, Allegra and colleagues presented a prespecified subgroup analysis evaluating the benefit of aflibercept according to prior bevacizumab exposure. In the aflibercept plus FOLFIRI arm, 186 patients (31%) had received prior bevacizumab and 426 patients had not. The distribution was similar in

**Table 1.** Effect of Prior Bevacizumab Exposure on Treatment Outcomes in the VELOUR Trial

| Outcome | Prior Bevacizumab | | | No Prior Bevacizumab | | | *P* Value for Interaction Between Treatment Arm, Prior Bevacizumab |
|---|---|---|---|---|---|---|---|
| | Aflibercept plus FOLFIRI (n=186) | Placebo plus FOLFIRI (n=187) | Hazard Ratio (95% CI) | Aflibercept plus FOLFIRI (n=426) | Placebo plus FOLFIRI (n=427) | Hazard Ratio (95% CI) | |
| Median OS | 12.5 months | 11.7 months | 0.86 (0.67–1.10) | 13.9 months | 12.4 months | 0.79 (0.70–0.93) | .57 |
| Median PFS | 6.7 months | 3.9 months | 0.66 (0.51–0.85) | 6.9 months | 5.4 months | 0.80 (0.68–0.94) | .2 |
| ORR | 11.7% | 8.4% | N/A | 23.3% | 12.4% | N/A | N/A |

CI=confidence interval; ORR=overall response rate; OS=overall survival; N/A=not available; PFS=progression-free survival; VELOUR=Aflibercept Versus Placebo in Combination with Irinotecan and 5-FU [FOLFIRI] in the Treatment of Patients with Metastatic Colorectal Cancer after Failure of an Oxaliplatin Based Regimen. Data from Allegra CJ et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract TPS4136.

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%)].

In Study 5, 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 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, 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 7). [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 metastatic breast cancer MBC, an indication for which Avastin is not approved, 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.

*Ovarian Failure*

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test)was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84 or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6)*.]

*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% |

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**Table 2 (cont'd)**
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) |
|---|---|---|---|
| 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%).

*Glioblastoma*

All adverse events were collected in 163 patients enrolled in Study 5 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 7. 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 3.

**Table 3**
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring 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% |

AVASTIN® (bevacizumab)

**Table 3 (cont'd)**
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring 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) |
|---|---|---|
| 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 3: 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 (from unapproved intravitreal use for treatment of various ocular disorders):* Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

*Gastrointestinal:* Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

*Hemic and lymphatic:* Pancytopenia

*Musculoskeletal:* Osteonecrosis of the jaw

*Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)

*Respiratory:* Nasal septum perforation, dysphonia

*Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders):* Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

## 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 7, 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 adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated 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)*.]

Because of the observed teratogenic effects of bevacizumab in animals and of other 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. Human IgG is excreted in human milk, but 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)*.]

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)*.]

### 8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1)*.]

## 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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01/12 AVA0000764701
10127309
Initial U.S.Approval: February 2004
Code Revision Date: December 2011

### Bevacizumab (BEV) Plus Capecitabine as Maintenance Therapy After Initial Treatment With BEV Plus XELOX in Previously Untreated Patients (pts) With Metastatic Colorectal Cancer (mCRC): Mature Data From STOP and GO, a Phase III, Randomized, Multicenter Study

In patients with metastatic CRC receiving first-line bevacizumab plus capecitabine/oxaliplatin (XELOX), maintenance therapy with bevacizumab plus capecitabine appears to be at least as effective as continuing bevacizumab plus XELOX until disease progression, according to an updated analysis of a multicenter, randomized, phase III trial conducted by the Turkish Oncology Group (Abstract 3565). The trial enrolled 123 patients with previously untreated metastatic CRC who were randomly assigned to 6 cycles of XELOX plus bevacizumab followed by maintenance therapy with capecitabine plus bevacizumab (61 patients) or continuous XELOX plus bevacizumab (62 patients). In both arms, treatment was continued until disease progression, severe toxicity, or withdrawal of consent. In the current analysis, capecitabine plus bevacizumab was significantly more effective than XELOX plus bevacizumab as assessed by median PFS (11.0 vs 8.3 months; *P*=.002) but not by median OS (23.8 vs 20.2 months; *P*=.100) or ORR (66.7% vs 59.0%; *P*=.86). In regard to safety, many grade 3/4 events occurred less frequently with capecitabine plus bevacizumab versus XELOX plus bevacizumab, including fatigue (6.6% vs 16.1%), diarrhea (3.3% vs 11.3%), anorexia (3.3% vs 11.3%), neuropathy (1.6% vs 8.1%), neutropenia (1.6% vs 6.5%), nausea (1.6% vs 4.8%), and anemia (1.6% vs 4.8%).

the placebo plus FOLFIRI arm, with 30% of patients having received prior bevacizumab. Demographic factors were similar between bevacizumab-exposed and bevacizumab-naïve patients. However, the relative frequency of prior bevacizumab use was higher among patients enrolled in North America than in Europe. The median duration of bevacizumab use was 6 months (range, 0–29 months), and the median interval between last bevacizumab exposure and study entry was 2 months (range, 1–33 months).

In their subgroup analysis, the investigators found no significant interaction between treatment and prior bevacizumab use for either OS or PFS (Table 1). The *P* values of 1 or greater indicate no significant difference in the PFS or OS benefit with aflibercept based on prior bevacizumab exposure.

The addition of aflibercept to FOLFIRI was associated with an expected increase in several anti-VEGF—associated grade 3/4 adverse events, including proteinuria, hypertension, hemorrhage, headache, and thromboembolic events. Aflibercept was also associated with an increased incidence of chemotherapy-associated adverse events; the overall serious adverse event rates with aflibercept plus FOLFIRI and FOLFIRI alone were 47% and 33%, respectively, in patients without prior bevacizumab and 52% and 32%, respectively, in patients with prior bevacizumab. Grade 3/4 adverse events more frequent in aflibercept-treated patients included neutropenia, diarrhea, asthenic conditions, infections/infestations, and stomatitis. Prior bevacizumab therapy did not appear to alter the incidence of anti-VEGF–associated or chemotherapy-associated adverse events. Discontinuation rates due to adverse events were higher in aflibercept-treated patients but did not appear to be affected by prior bevacizumab. Moreover, no single adverse event predominated as a cause of discontinuation.

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# FOLFOX4 (12 cycles) Versus Sequential Dose-Dense FOLFOX7 (6 cycles) Followed by FOLFIRI (6 cycles) in Patients With Initially Resectable Metastatic Colorectal Cancer: A GERCOR Randomized Phase III Study (MIROX)

For patients with resectable metastatic CRC, dose-dense FOLFOX7 followed by FOLFIRI does not appear to provide any benefit over the standard FOLFOX4 regimen. According to the phase III GERCOR MIROX (Metastatic Irinotecan plus Oxaliplatin) trial presented by Mohamed Hebbar, MD, PhD, the 2 regimens demonstrated similar outcomes after a median follow-up exceeding 4 years.[1] Dr. Hebbar noted that the liver is the primary site of metastatic disease in patients with CRC, and that 15–20% of metastases are initially resectable. For these patients with resectable metastases, perioperative FOLFOX4 (6 cycles before surgery and 6 cycles after surgery) has demonstrated a significant PFS benefit over surgery alone, and is considered standard therapy for these patients.[2] Another phase III trial compared FOLFIRI versus 5-FU/FA administered after complete resection of liver metastases, and found no statistically significant difference between the 2 regimens.[3]

The GERCOR investigators hypothesized that the combination of FOLFOX and FOLFIRI may be preferable to FOLFOX alone, as it may reduce oxaliplatin-associated neuropathy and could enhance efficacy. The investigators also proposed that patients should be allowed to receive either perioperative or postoperative chemotherapy, which could limit selection bias and allow a more personalized treatment strategy.

A phase II study evaluated this strategy in 47 patients with resectable CRC metastases.[4] The chemotherapy regimen consisted of 6 cycles of FOLFOX7 (leucovorin 400 mg/m$^2$ and oxaliplatin 130 mg/m$^2$ in a 120-minute infusion and FU 2,400 mg/m$^2$ in a 46-hour infusion, every 2 weeks) followed by 6 cycles of FOLFIRI (leucovorin 400 mg/m$^2$, irinotecan 180 mg/m$^2$ in a 90-minute infusion plus bolus FU 400 mg/m$^2$ and FU 2,400 mg/m$^2$ as a 46-hour infusion, every 2 weeks). Chemotherapy was administered perioperatively in 22 patients and postoperatively in 25 patients. The regimen was associated with a 2-year disease-free survival rate of 47% and a 2-year OS rate of 89%. The primary toxicities were grade 3/4 neutropenia (13%) and thrombocytopenia (11%).

Based on these outcomes, the GERCOR investigators developed the phase III MIROX trial. Between May 2004 and June 2010, the trial enrolled 284 patients ages 18–75 years with resectable or resected CRC metastasis. Patients who had received prior adjuvant FOLFOX after resection of the primary tumor could enroll if more than 12 months had passed since adjuvant therapy.

Patients were randomly assigned to 6 cycles of FOLFOX7 followed by 6 cycles of FOLFIRI (142 patients) or 12 cycles of FOLFOX4 (142 patients). It was recommended that patients received 4–6 cycles of therapy prior to surgery. Stratification was based on timing of chemotherapy (perioperative vs postoperative), use of radiofrequency ablation, and Blumgart's prognostic score (0–1 vs 2–3 vs 4–5), which accounts for disease-free interval (<12 vs ≥12 months), primary tumor (N+ vs N0), number of metastases (≥1 vs 1), size of largest metastasis (>5 vs ≤5 cm), and preoperative carcinoembryonic antigen level (>200 vs ≤200).[5]

Baseline characteristics were well balanced between the arms. Although patients could have only 1 metastatic site, nearly half of patients had more than 1 metastasis; the liver was the site of metastasis in approximately 83%

### FOLFOXIRI Plus Bevacizumab as First-Line Treatment of BRAF Mutant Metastatic Colorectal Cancer Patients

The *BRAF* V600E mutation is associated with poor outcomes in patients with metastatic CRC, with a median PFS of 6 months or less with standard therapy. A retrospective analysis suggested that an intensive first-line regimen with bevacizumab plus FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) may improve outcomes in these patients. Salvatore and colleagues therefore conducted a small study to prospectively evaluate this intensive strategy (Abstract 3585). A total of 15 patients with previously untreated *BRAF*-mutant metastatic CRC received bevacizumab plus FOLFOXIRI. At 6 months, 11 of 15 patients (73%) remained progression-free. After a median follow-up of 21.6 months, the median PFS was 9.2 months and the median OS had not been reached. In a pooled analysis of these 15 patients and 24 of the 25 patients in the initial retrospective cohort, the regimen was associated with an ORR of 72%, including 1 CR. The median PFS in this cohort was 11.8 months, and the median OS was 23.8 months.

### Phase II Study Of Preoperative Radiation With Concurrent Capecitabine, Oxaliplatin, and Bevacizumab Followed by Surgery and Postoperative 5-FU, Leucovorin, Oxaliplatin (FOLFOX), and Bevacizumab in Patients With Locally Advanced Rectal Cancer: A Trial of the Eastern Cooperative Oncology Group (E3204)

Single-agent fluoropyrimidine plus radiation therapy is a standard preoperative therapy for patients with stage II/III rectal cancer. A phase II study was undertaken to evaluate an alternative preoperative strategy of capecitabine, oxaliplatin, and bevacizumab plus radiotherapy in patients with locally advanced T3 or T4 rectal cancer (Abstract 3605). After 6–8 weeks of rest, patients underwent surgery; within 12 weeks of surgery, patients started a postoperative regimen of FOLFOX plus bevacizumab. The study enrolled 54 patients with a median age of 54 years (range, 26–83 years). At baseline, 50 patients (93%) had T3 disease and 4 patients had T4 disease. The preoperative regimen resulted in downstaging in the majority of patients; restaging yielded T0 in 11 patients, T1 in 3 patients, T2 in 15 patients, and T3 in 19 patients. However, the pathological CR rate was 17% (9 patients), which the investigators noted was not an improvement over historical controls. Moreover, the combination was associated with higher-than-expected rates of acute and postsurgical complications. Early complications included wound infections (9 patients), dehiscence (6 patients) and abscess (1 patient). Late complications included non-healing wounds (23 patients), dehiscence (12 patients), bowel obstruction/ileus (5 patients) and abscess (2 patients). Two patients died from adverse events during chemoradiotherapy.

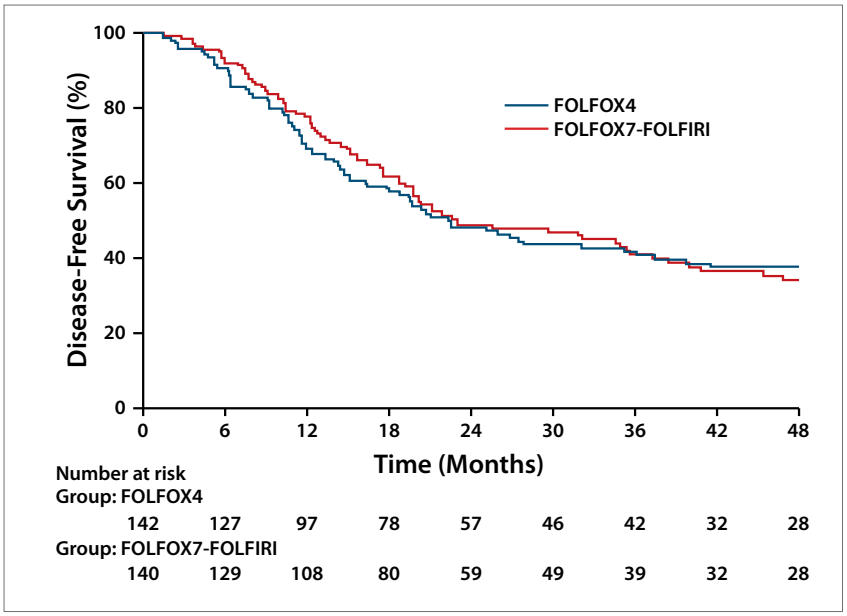


**Figure 6.** Disease-free survival in the GERCOR MIROX trial. GERCOR=Groupe Cooperateur Multidisciplinaire en Oncologie; MIROX=Metastatic Irinotecan plus Oxaliplatin. Data from Hebbar M et al. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract 3506.

of patients. Metastases were synchronous in 55–59% of patients, and in approximately 85% of patients, the largest metastasis was less than 5 cm.

After a median follow-up of 50 months, there was no significant difference between FOLFOX7-FOLFIRI and FOLFOX4 in median disease-free survival (DFS) (23.0 vs 22.4 months; HR, 0.97; *P*=.86; Figure 6) or median OS (not reached in either arm; HR, 1.07; *P*=.76). The 2-year disease-free survival rates were 48% and 49%, respectively, and 2-year OS rates were 90% and 88%, respectively. The estimated 4-year OS exceeded 70%, which Dr. Hebbar commented was better than expected.

An exploratory subgroup analysis of chemotherapy chronology suggested better outcomes in patients who had received postoperative chemotherapy versus perioperative chemotherapy (median DFS, 39.9 vs 23.0 months), however the rates of synchronous metastases were substantially different between arms (40% and 66%, respectively), indicating a substantial difference between the 2 patient groups. The investigators plan to conduct a multivariate analysis evaluating the effect of chemotherapy chronology in the context of known prognostic factors.

Safety analyses revealed some difference between arms. Compared with FOLFOX4, FOLFOX7-FOLFIRI was associated with lower rates of grade 3/4 neutropenia (22% vs 33%) and neurotoxicity (16% vs 24%), and higher rates of diarrhea (21% vs 10%), thrombocytopenia (9% vs 5%), and nausea (9% vs 3%).

The median oxaliplatin dose was 1,218 mg in the FOLFOX7-FOLFIRI arm and 1,385 mg in the FOLFOX4 arm. The median number of oxaliplatin- or irinotecan-based cycles was 12 and 9, respectively. Among the 59% of patients who received perioperative chemotherapy, FOLFOX7-FOLFIRI and FOLFOX4 yielded similar response outcomes, including response rate after preoperative chemotherapy (50% and 49%, respectively), completion of surgery after preoperative chemotherapy (88% and 80%, respectively), and R0 resection rate after preoperative chemotherapy (84% and 90%, respectively).

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# Commentary


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## Introduction

For many years, palliative care in advanced colorectal cancer had lagged in terms of drug development. Recently, 2 new agents have shown survival benefit and clear efficacy in this setting. Aflibercept is an inhibitor of vascular endothelial growth factor (VEGF) that binds to VEGF-A, VEGF-B, and placental growth factor. It is being used as second-line therapy in combination with a regimen of irinotecan, fluorouracil (5-FU), and folinic acid (FOLFIRI). In 2011, Van Cutsem and colleagues reported results from the VELOUR (Aflibercept Versus Placebo in Combination with Irinotecan and 5-FU [FOLFIRI] in the Treatment of Patients with Metastatic Colorectal Cancer after Failure of an Oxaliplatin Based Regimen) trial, which showed that aflibercept plus FOLFIRI improved survival over FOLFIRI alone in second-line treatment of metastatic colorectal cancer.[1] Survival benefits were seen in patients who had previously progressed on oxaliplatin-based therapy.

The field has been enriched by a new agent, regorafenib, an oral multikinase inhibitor currently in clinical trials. At the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, I reported results from the CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) study, a phase III trial that aimed to establish a new standard of care.[2] Regorafenib improved overall survival (OS) in patients who experienced progressive disease or intolerability on all available standard treatment options, including 5-FU/capecitabine, irinotecan, oxaliplatin, bevacizumab, and epidermal growth factor receptor (EGFR) antibodies (in patients with *KRAS* wild-type tumors). There was a 23% reduction in deaths (hazard ratio [HR], .77) in the regorafenib arm. For progression-free survival (PFS), the HR was .49, meaning there was a 50% reduction of progressive events in the study, which was highly statistically significant. The PFS curve highlighted that only a subgroup of patients benefited from regorafenib. It is our next goal to identify those patients who are most likely to benefit.

Updated data regarding both aflibercept and regorafenib were presented at the 2012 ASCO Annual Meeting. Studies also reported on perifosine plus capecitabine, a sequential approach of oxaliplatin, 5-FU, and leucovorin (FOLFOX) followed by FOLFIRI, and perioperative chemotherapy with FOLFOX in patients with resectable liver metastases.

## ASCO Abstracts

It was a good year at ASCO for colorectal cancer. There were exciting developments and some interesting, surprising findings.

A subgroup analysis of the phase III VELOUR trial focused on patients who had previously received bevacizumab as first-line therapy, a common regimen in the United States.[3] Even in these patients, continuation of VEGF inhibition with aflibercept beyond progression showed survival benefit. This observation is important because many patients in the United States are treated with bevacizumab-containing therapy in the first-line setting. These data were confirmed by the TML study, a European trial that looked at bevacizumab beyond progression.[4] Patients who had been treated with bevacizumab in first-line therapy were crossed over to a different chemotherapy regimen but either did or did not continue bevacizumab beyond progression. The incremental benefit reflected that achieved with aflibercept in the VELOUR trial, with a median difference in OS of 1.4 months and a HR of .81, meaning a 19% reduction of death events with the use of bevacizumab beyond progression.

We now have 2 trials that support the principle that continued VEGF inhibition beyond progression is

### Efficacy and Safety of Bevacizumab in Metastatic Colorectal Cancer (mCRC): Pooled Analysis From Randomized Controlled Trials (RCTs)

Multiple meta-analyses have established the efficacy and safety of adding bevacizumab to chemotherapy in patients with metastatic CRC. However, as Tebbutt and colleagues noted, these meta-analyses were conducted primarily from published data, precluding the completion of extensive subgroup analyses (Abstract 3614). To better define the effect of bevacizumab in different patient groups, Tebbutt and colleagues conducted a meta-analysis based on the clinical databases of 7 phase II or III randomized, controlled trials. Individual patient data were pooled from 6 first-line trials (AVF2017, NO16966, ARTIST, AVF2192, AVF0780, and AGITG MAX) and the second-line ECOG E3200 trial. In the overall population, bevacizumab plus chemotherapy was significantly more effective than chemotherapy alone in regard to median OS (18.7 vs 16.1 months; HR, 0.80; *P*=.0003) and median PFS (8.8 vs 6.4 month; HR, 0.57; *P*<.0001). Subgroup analysis confirmed the benefit of bevacizumab across subgroups, including in patients receiving single-agent chemotherapy, doublet chemotherapy, an irinotecan-based regimen, or an oxaliplatin-based regimen, and was not affected by *KRAS* status. The benefit of bevacizumab remained statistically significant across all subgroups for PFS and did not reach significance for OS among patients with *KRAS*-mutant tumors and those receiving single-agent chemotherapy. Safety analyses confirmed the increased incidence of known anti-VEGF–related adverse events with the addition of bevacizumab.

beneficial for patients. How this finding will be incorporated into clinical practice is uncertain. The incremental differences were not as large as might have been expected. Although the survival benefit is statistically significant, it may not lead to a worldwide change of practice because the threshold for adopting new treatment approaches differs based on the financial capabilities of each country's healthcare system. The demonstration of prolonged VEGF inhibition beyond progression is descriptive of tumor biology and perhaps also suggests how to interpret resistance to therapy and progression based on the Response Evaluation Criteria In Solid Tumors (RECIST), which might be less clinically relevant than previously believed.

An updated analysis from the CORRECT trial was presented by Eric Van Cutsem, MD.[5] Regorafenib was associated with a significant improvement in OS compared with placebo, with a median OS of 6.4 months and 5.0 months, respectively (HR, .77; 1-sided *P*=.0052). Regorafenib is currently under review by the US Food and Drug Administration (FDA). If approved, it will be used mainly in the established therapy setting of refractory colon cancer. Future trials might target patients in the maintenance therapy setting, perhaps using this oral agent as maintenance therapy after prior induction treatment or as an option before EGFR inhibitors are used as last-line therapy.

The GERCOR (Groupe Cooperateur Multidisciplinaire en Oncologie) DREAM (Double Inhibition Reintroduction Erlotinib Avastin Metastatic Colorectal Cancer) trial examining bevacizumab with or without erlotinib as maintenance therapy was an interesting trial that generated surprising results.[6] This trial used an induction chemotherapy approach with an oxaliplatin-based regimen plus bevacizumab. After a certain number of cycles, patients were randomized to continue bevacizumab as a single agent or to receive bevacizumab plus erlotinib. The addition of erlotinib to bevacizumab as maintenance therapy improved PFS, with a HR of .73. No survival difference was seen, which was expected, although follow-up continues. An intriguing aspect to this study is that for a long time, the idea of using a VEGF inhibitor plus an EGFR inhibitor had been disregarded based on negative data from first-line trials that showed detrimental effects when this approach was used in combination with chemotherapy. It may now be time to revisit the idea of using EGFR inhibitors and bevacizumab. In 2007, Saltz and coworkers reported results of the BOND 2 (Bowel Oncology With Cetuximab Antibody) trial, which investigated the use of bevacizumab/cetuximab with or without irinotecan as last-line therapy in patients with irinotecan-refractory colorectal cancer.[7] The addition of irinotecan improved the overall response rate (37% with irinotecan vs 20% without), time to tumor progression (7.3 months with irinotecan vs 4.9 months without), and OS (14.5 months with irinotecan vs 11.4 months without). Although I do not expect erlotinib to become the standard of care in the treatment algorithms of colorectal cancer, the DREAM trial provides proof of principle and opens the door for future research of EGFR inhibition and bevacizumab.

The X-PECT (Xeloda + Perifosine Evaluation in Colorectal Cancer Treatment) study investigated perifosine plus capecitabine versus placebo plus capecitabine in patients who had pretreated colorectal cancer or were refractory to treatment.[8] Johanna C. Bendell, MD, presented the data. This phase III trial was initiated after intriguing phase II data showed a large spread in survival curves with the use of perifosine in this patient population.[9] It should be noted that these phase II data were generated with approximately 20 patients, and the probability of statistical error was high. The phase III data were absolutely negative, which has ended the evaluation of perifosine in colorectal cancer and might have further implications for this drug in other malig-

### EORTC Liver Metastases Intergroup Randomized Phase III Study 40983: Long-Term Survival Results

Previous data from the European Organisation for Research and Treatment of Cancer (EORTC) 40983 study showed that treatment with FOLFOX4 improved PFS in colorectal patients with resectable liver metastases (Nordlinger B et al. *Lancet*. 2008;371:1007-1016). OS data, gathered after a median of 8.5 years, were reported at the ASCO 2012 meeting (Abstract 3508). Patients (N=364) were randomized to receive perioperative FOLFOX4 (oxaliplatin 85 mg/m$^2$ and 5-FU/leucovorin), 6 cycles before and 6 cycles after surgery, or surgery alone. PFS, the primary endpoint, was improved at 3 years in the FOLFOX4 group as compared with the surgery alone group (36.2% vs 38.1%). The median OS was 5 months longer in the FOLFOX4 group than in the surgery alone group (63.7 months vs 55 months), although this difference was not statistically significant. The study was not powered to detect differences in OS, and the investigators proposed that a potential benefit in this outcome may have been diminished by second-line treatment lines and more deaths unrelated to cancer in the FOLFOX4 arm.

nancies. The negative data from this study also highlight the fact that we should not trust very small phase II trials in which the magnitude of benefit is unrealistically large.

The European Organisation for Research and Treatment of Cancer (EORTC) 40983 study examined perioperative chemotherapy with FOLFOX in patients with resectable liver metastases.[10] Previous data from this study have shown statistically significant differences in PFS with the FOLFOX regimen in this setting.[11] The follow-up analysis of this trial examined OS in 364 patients. The OS data were negative from a statistical perspective, but there was a difference in median OS of approximately 5 months. The statistically negative data in OS should not preclude the use of FOLFOX or chemotherapy in the context of liver resection because this trial was clearly underpowered to show a survival benefit. These data represent a statistical phenomenon. In addition, OS is impacted by many factors that cannot be controlled within the study design.

An interesting study from Salvatore and colleagues focused on patients with *BRAF*-mutant metastatic colorectal cancer, who have very poor prognosis.[12] Approximately 8% of patients with metastatic colorectal cancer are *BRAF* mutant, and these patients have only recently been included in clinical, prospective trials that have mainly focused on single-agent combinations with PI3 kinase inhibitors, MEK inhibitors, and *BRAF* inhibitors. This study examined a "kitchen sink" regimen of irinotecan, oxaliplatin, fluorouracil, and folinate (FOLFOXFIRI) plus bevacizumab, an approach that is similar to the one being used in aggressive pancreatic cancer. This study showed intriguingly positive outcomes, including rates of PFS and OS that are unprecedented. It should be noted that this study included only 15 patients, but the results are so intriguing that, outside of a clinical trial, this regimen may represent a standard of care for the treatment of *BRAF*-mutant tumors. Prospective validation by another group would be welcomed.

The phase III GERCOR MIROX (Metastatic Irinotecan plus Oxaliplatin) study examined a sequential approach of FOLFOX followed by FOLFIRI versus FOLFOX alone in patients with metastatic colorectal cancer who were potential candidates for liver resection.[13] The idea behind this study was to use all available agents that have activity in colorectal cancer more or less sequentially to maximize exposure of the tumor cells to all active chemotherapy agents that are available. Interestingly, this study showed no difference in the use of FOLFOX alone compared to FOLFOX and FOLFIRI. Therefore, integration of a FOLFIRI regimen into this perioperative setting in patients with resectable liver metastasis is not worthwhile.

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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), 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), 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 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 (14.3)*.]

**1.4 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 2.6% compared to 0.8% 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).*]

**5.10 Ovarian Failure**

The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. [See *Adverse Reactions (6.1), Use in Specific Populations (8.6).*]

## 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).*]
- Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

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 3795 patients with CRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled, single arm (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14).*] Data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, an indication for which Avastin is not approved. The population was aged 18-88 years (median 59), 43.2% male and 85.3% white. The population included 1783 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin, 480 first-line metastatic NSCLC patients who 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 5, 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 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, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs. 19 patients ) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants was evaluated in two randomized studies. 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 (VTE). 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.

In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and Administration (2.4).*]

*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%)].

In Study 5, 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 7. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 7, 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 7). [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 metastatic breast cancer MBC, an indication for which Avastin is not approved, 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.

*Ovarian Failure*

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test)was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84 or with Avastin (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

*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% |

**Table 2 (cont'd)**
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) |
|---|---|---|---|
| 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%).

*Glioblastoma*

All adverse events were collected in 163 patients enrolled in Study 5 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 7. 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 3.

**Table 3**
NCI-CTC Grades 1–5 Adverse Events in Study 7
(Occurring 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 3: 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 (from unapproved intravitreal use for treatment of various ocular disorders)*: Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

*Gastrointestinal:* Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

*Hemic and lymphatic:* Pancytopenia

*Musculoskeletal:* Osteonecrosis of the jaw

*Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)

*Respiratory:* Nasal septum perforation, dysphonia

*Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders):* Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

## 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 7, 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 adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated 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)*.]

Because of the observed teratogenic effects of bevacizumab in animals and of other 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. Human IgG is excreted in human milk, but 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)*.]

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)*.]

### 8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See *Warnings and Precautions (5.10), Adverse Reactions (6.1)*.]

## 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.

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01/12 AVA0000759202
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Initial U.S.Approval: February 2004
Code Revision Date: December 2011

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

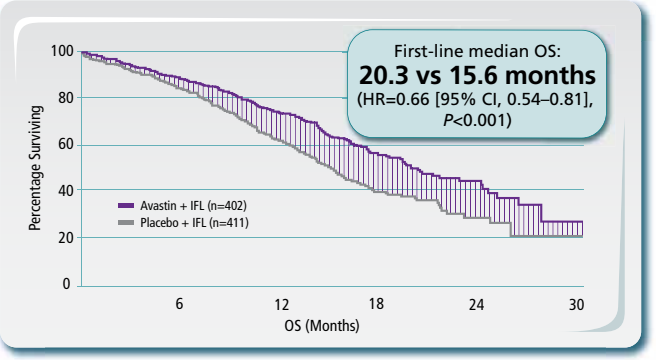
# Think Avastin

## 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[1,2,4]




**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
- **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 healing complications 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 adverse events
- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.4%)
  - — Proteinuria including nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — 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
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

### Most common adverse events
- 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
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

### Pregnancy warning
- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- 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. September 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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 AVA0000455301 Printed in USA. (11/11)

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