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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Colorectal Cancer From the 2013 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

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Special Reporting on:

- Bevacizumab (bev) in Combination With Capecitabine (cape) for the First-Line Treatment of Elderly Patients With Metastatic Colorectal Cancer (mCRC): Results of a Randomized International Phase III Trial (AVEX)
- Induction Treatment in First-Line With Chemotherapy + Bevacizumab (bev) in Metastatic Colorectal Cancer: Results From the gercor-DREAM Phase III Study
- A Molecular Profile of Colorectal Cancer to Guide Prognosis and Therapy After Resection of Primary or Metastatic Disease
- FOLFOXIRI Plus Bevacizumab (bev) Versus FOLFIRI Plus Bev as First-Line Treatment of Metastatic Colorectal Cancer (MCRC): Results of the Phase III Randomized TRIBE Trial
- Bevacizumab (Bev) With or Without Erlotinib as Maintenance Therapy, in Patients (Pts) With Metastatic Colorectal Cancer (mCRC): Exploratory Analysis According to KRAS Status in the gercor DREAM Phase III Trial
- PEAK (Study 20070509): A Randomized Phase II Study of mFOLFOX6 With Either Panitumumab (Pmab) or Bevacizumab (bev) as First-Line Treatment (tx) in Patients (pts) With Unresectable Wild-Type (WT) KRAS Metastatic Colorectal Cancer (mCRC)

PLUS Meeting Abstract Summaries

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Bevacizumab (bev) in Combination With Capecitabine (cape) for the First-Line Treatment of Elderly Patients With Metastatic Colorectal Cancer (mCRC): Results of a Randomized International Phase III Trial (AVEX)

David Cunningham, MD, and colleagues presented results from the prospective, international, phase III AVEX (Avastin With Xeloda in the Elderly) trial, which was the first phase III trial to prospectively investigate a biologic in elderly patients with metastatic colorectal cancer (CRC).[1] Despite a median age of 69 years for patients with metastatic CRC, older patients remain undertreated.[2] Although the optimal treatment approach for this patient population remains to be determined, studies have suggested that elderly patients benefit from the combination of chemotherapy plus bevacizumab, an anti-angiogenic antibody that binds to vascular endothelial growth factor (VEGF).[3-5] To provide insights regarding optimal therapy in elderly patients, the AVEX trial enrolled 280 patients ages 70 years or older with treatment-naïve metastatic CRC and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients were not optimal candidates for irinotecan- or oxaliplatin-based chemotherapy. Prior adjuvant chemotherapy, excluding anti-VEGF therapy, was allowed if completed at least 6 months prior to inclusion. Patients with clinically significant cardiovascular disease and those recently using anticoagulant or antithrombolytic agents were excluded.

Patients were stratified based on ECOG PS and geographic locations; they were then randomized equally to receive capecitabine (1,000 mg/m^2 twice daily on days 1–14) with or without standard bevacizumab (7.5 mg/kg on day 1) in 21-day cycles. The trial's primary endpoint was progression-free survival (PFS) with secondary endpoints of overall response rate (ORR), time to response (TTR), duration of response (DOR), overall survival (OS), and safety. The trial was designed to detect a 31% reduction in the risk of progression with the addition of bevacizumab and required 232 events to achieve 80% via a 2-sided test with an alpha level of 5%. Patient characteristics were generally well balanced, including median age of 76–77 years (range, 70–87 years) and ECOG PS of 0–1 in more than 90% of patients. Metastasis was observed in the liver (62.9–67.9%), lung (35.7–40.7%), or another site (22.9–35.0%), and the liver was the only site of metastasis in approximately 37–39% of patients. In the combination versus monotherapy arms, the majority of patients had a history of prior surgical resection (73.6% vs 63.6%, respectively), and a greater proportion of patients who received antibody treatment had received prior adjuvant therapy (32.1% vs 18.6%).

A significant difference in median PFS was observed for patients who received bevacizumab plus capecitabine, reflecting a 47% risk reduction (9.1 months vs 5.1 months; hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.41–069; P<.001; Figure 1).

Results of a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Pegfilgrastim (PEG) in Patients (pts) Receiving First-Line FOLFOX or FOLFIRI and Bevacizumab (B) for Colorectal Cancer (CRC)

Tamas Pinter, MD, and colleagues presented results from the randomized, double-blind, phase III PAVES (Pegfilgrastim and Anti-VEGF Evaluation) study (Abstract LBA445). Febrile neutropenia is a known complication in patients receiving biological therapy in combination with chemotherapy. The PAVES study evaluated the efficacy of pegfilgrastim in reducing the incidence of febrile neutropenia in treatment-naïve patients with locally advanced or metastatic CRC during treatment with bevacizumab plus FOLFOX (FOLFOX-bev) or FOLFIRI (FOLFIRI-bev). Patients had measurable, unresectable CRC based on RECIST 1.1 criteria. Chemotherapy plus bevacizumab was administered in 2-week cycles for 4 weeks during the study; however, patients were allowed to continue their assigned regimen until disease progression. The primary endpoint was the incidence of febrile neutropenia, with secondary endpoints of ORR, PFS, and OS. Following stratification based on region (North America vs the rest of the world), stage (locally advanced vs metastatic), and type of chemotherapy (FOLFOX vs FOLFIRI), 845 patients were randomized 1:1 to receive either 6 mg pegfilgrastim or placebo at least 24 hours after each treatment with FOLFOX-bev or FOLFIRI-bev. Patients were a median age of 61 years, 512 (61%) were male, 819 (97%) had metastatic disease, and 414 (49%) received FOLFOX. Four cycles of treatment were completed by 783 patients. The incidence of grade 3/4 febrile neutropenia observed during the first 4 cycles of treatment for the pegfilgrastim arm versus the placebo arm was 2.4% versus 5.7%, respectively (odds ratio, 0.41; P=.014). Median PFS, median OS, and ORR were not significantly different for patients who received pegfilgrastim versus placebo.

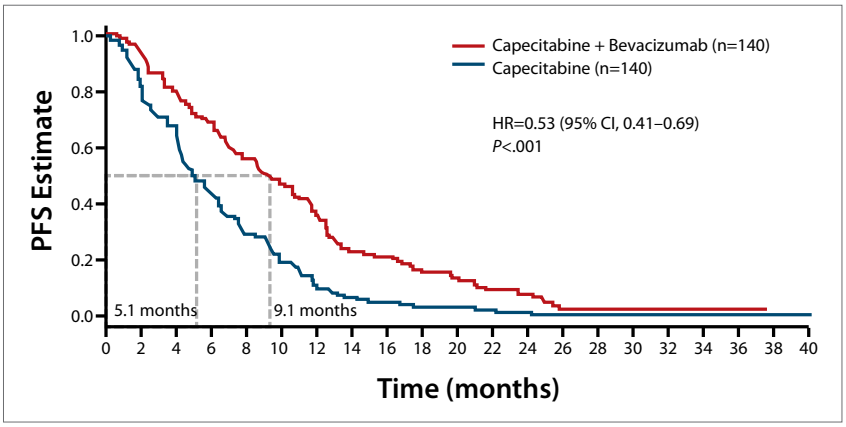

Figure 1. In the phase III AVEX trial, there was a significant difference in median PFS for patients who received bevacizumab plus capecitabine compared with those who received capecitabine alone.

AVEX=Avastin With Xeloda in the Elderly; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival. Data from Cunningham D et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 337.

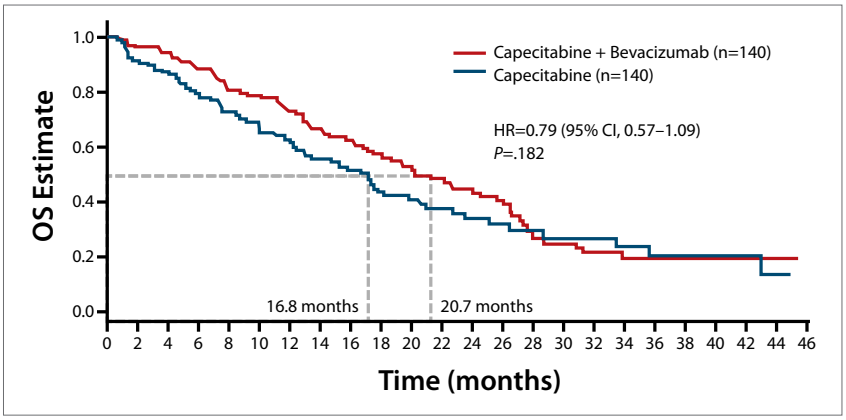

Figure 2. In the phase III AVEX trial, there was no significant difference for median OS when bevacizumab was added to capecitabine. There was a trend toward improved OS for patients receiving the combination treatment.

AVEX=Avastin With Xeloda in the Elderly; CI=confidence interval; HR=hazard ratio; OS=overall survival. Data from Cunningham D et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 337.

Subset analyses showed improvement in median PFS in virtually all subgroups examined, including those based on sex, age, ECOG PS, metastatic site, and location of primary disease. No significant difference was observed for median OS for the combination treatment versus capecitabine monotherapy (20.7 months vs 16.8 months; HR, 0.79; 95% CI, 0.57–1.09; *P*=.182); however, the speaker noted a trend toward improved OS for patients receiving the combination treatment (Figure 2). Thirty-seven percent of patients received second-line therapy after the trial, with the treatment types distributed similarly in both arms. The addition of bevacizumab also elicited an improvement in ORR, comprising patients with a complete response (CR) or partial response (PR; 19.3% vs 10.0%; *P*=.042) and in the disease control rate, which included patients with stable disease (SD; 74.3% vs 57.9%; *P*=.005). The duration of drug exposure was shorter than the PFS for both arms, consistent with the likelihood that some patients who showed a response but ceased study treatment subsequently received capecitabine with or without bevacizumab.

The safety profile for patients treated with bevacizumab was generally consistent with previously reported data. Patients in the combination arm were more likely to experience an adverse event (AE) that resulted in drug discontinuation (25.4% vs 14.0%). AEs of any grade that are known to be associated with bevacizumab treatment were generally more frequent in the combination arm, and those observed in at least 5% of patients in the combination versus monotherapy arm included bleeding and/or hemorrhage (25.4% vs 6.6%), hypertension (19.4% vs 5.1%), venous thrombolic events (11.9% vs 5.1%), and proteinuria (7.5% vs 0.7%). AEs of grade 3 or higher that are related to chemotherapy and occurred in at least 5% of patients in the combination arm included hand-foot syndrome (14.9% vs 6.6%), diarrhea (6.7% vs 6.6%), asthenia (5.2% vs 4.4%), in the combination versus monotherapy arms, respectively. The authors concluded that the combination of bevacizumab plus capecitabine is effective and well tolerated in metastatic CRC patients ages 70 years and older.

References

1. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab (bev) in combination with capecitabine (cape) for the first-line treatment of elderly patients with metastatic colorectal cancer (mCRC): results of a randomized international phase III trial (AVEX). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 337.
2. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2009_pops09. Accessed March 17, 2013.
3. Cassidy J, Saltz LB, Giantonio BJ, Kabbinavar FF, Hurwitz HI, Rohr UP. Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. *J Cancer Res Clin Oncol*. 2010;136:737-743.
4. Kozloff MF, Berlin J, Flynn PJ et al. Clinical outcomes in elderly patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy: results from the BRiTE observational cohort study. *Oncology*. 2010;78:329-339.
5. Price TJ, Zannino D, Wilson K, et al. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of capecitabine, bevacizumab and mitomycin C. *Ann Oncol*. 2012;23:1531-1536.

Induction Treatment in First-Line With Chemotherapy + Bevacizumab (bev) in Metastatic Colorectal Cancer: Results From the gercor-DREAM Phase III Study

Christophe Tournigand, MD, and colleagues presented safety and efficacy data from the phase III DREAM (Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer) study, conducted by the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR).[1] The trial enrolled 700 patients with treatment-naïve, unresectable, metastatic CRC and World Health Organization (WHO) PS of 0–2 for treatment every 2 weeks with a modified regimen of folinic acid (leucovorin), oxaliplatin, and fluorouracil (5-FU) (mFOLFOX7) plus bevacizumab (n=429); modified capecitabine and oxaliplatin (mXELOX) plus bevacizumab (n=204); or folinic acid (leucovorin), and 5-FU, irinotecan (FOLFIRI) plus bevacizumab (n=67), based on the investigator's choice (Table 1).[2] Each treatment was administered in a 2-week cycle. mFOLFOX plus bevacizumab and mXELOX plus bevacizumab were administered for 3 months; FOLFIRI plus bevacizumab was administered for 6 months. Oxaliplatin was administered for a maximum of 6 cycles. Patients who did not progress on initial treatment were pooled and stratified based on ECOG PS, number of metastatic sites (1 vs >1), prior adjuvant chemotherapy, and baseline alkaline phosphatase levels. They were then randomized to receive maintenance treatment with bevacizumab (7.5 mg/kg every 3 weeks) either as monotherapy or in combination with erlotinib (150 mg/day) until disease progression. Patient baseline characteristics were similar among the 3 arms, with a median age of 63 years (range, 26–80) for the entire study population. Approximately three-fourths of patients were younger than 70 years of age, 59–61% were male, and 55–61% had an ECOG PS of 0. The colon was the primary tumor site in approximately three-fourths of patients, 45–51% of patients had a single metastatic site, 78–87% of patients had synchronous disease, 8–10% of patients had received prior adjuvant therapy, and 46–51% of patients had normal levels of alkaline phosphatase.

The 3 induction treatments yielded similar efficacies, with a median PFS of 8.6 months for mFOLFOX7 plus bevacizumab, 9.0 months for mXELOX plus bevacizumab (HR, 0.99; 95% CI, 0.81–1.23; *P*=.964), and 9.0 months for FOLFIRI plus bevacizumab (HR, 0.94; 95% CI, 0.69–1.29; *P*=.723; Figure 3). ORRs were 48%, 50%, and 63%, respectively. The authors previously reported PFS findings based on maintenance treatment after a median follow-up of 31.0 months and the occurrence of 327 PFS events; the addition of erlotinib significantly prolonged PFS during the maintenance treatment, with a median PFS of 5.8 months for the combination versus 4.6 months for bevacizumab alone (HR, 0.73; 95% CI, 0.59–0.91; *P*=.005).[3] During the maintenance portion of the trial, the main differences in AEs for combination treatment versus bevacizumab alone were grade 3/4 diarrhea (9% vs <1%, respectively) and grade 3 skin toxicity (19% vs 0%, respectively).

The investigators noted grade 3/4 AEs of interest based on differences among the 3 induction treatment regimens (Table 2). FOLFIRI plus

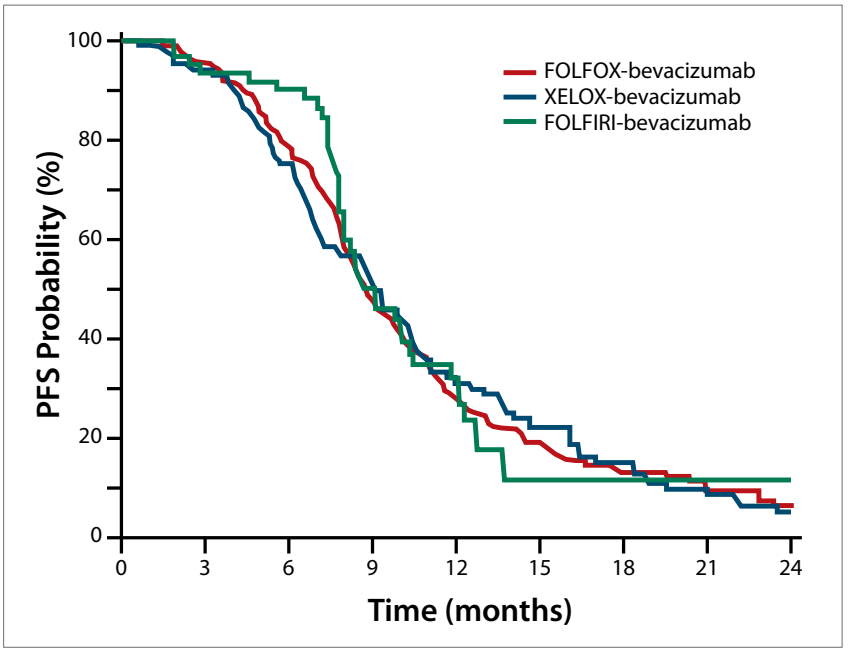

Figure 3. In the phase III DREAM trial, PFS did not significantly differ among the 3 treatment arms: mFOLFOX7 plus bevacizumab, mXELOX plus bevacizumab, and FOLFIRI plus bevacizumab.

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; FOLFIRI=folinic acid (leucovorin), fluorouracil, and irinotecan; mFOLFOX7=modified regimen of folinic acid (leucovorin), oxaliplatin, and fluorouracil; mXELOX=modified capecitabine and oxaliplatin; PFS=progression-free survival. Data from Tournigand C et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.

Table 1. Treatment Regimens Administered During the GERCOR-DREAM Trial

mFOLFOX7-Bevacizumab	mXELOX-Bevacizumab	FOLFIRI-Bevacizumab
Bevacizumab (5 mg/kg) Folinic acid (400 mg/m^2) Oxaliplatin (100 mg/m^2) 5-FU infusion (2,400 mg/m^2)	Bevacizumab (5 mg/kg) Oxaliplatin (100 mg/m^2) Capecitabine (1,250 mg/m^2)*	Bevacizumab (5 mg/kg) Folinic acid (400 mg/m^2) Irinotecan (180 mg/m^2) 5-FU bolus (400 mg/m^2) 5-FU infusion (2,400 mg/m^2)

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; 5-FU=5-fluorouracil; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie.
*Twice daily on days 1–7.
Data from Tournigand C et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.

Table 2. Select Grade 3/4 Adverse Events With Higher Incidence in 1 Treatment Arm in the GERCOR-DREAM Trial

	mFOLFOX7-Bevacizumab (%)	mXELOX-Bevacizumab (%)	FOLFIRI-Bevacizumab (%)
Neutropenia	7	2	18
Diarrhea	5	17	12
Hand-foot syndrome	<1	5	3
Neuropathy	7	1	0

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie; mFOLFIRI=modified folinic acid (leucovorin), fluorouracil, and irinotecan; mFOLFOX7=modified regimen of folinic acid (leucovorin), oxaliplatin, and fluorouracil; mXELOX=modified capecitabine and oxaliplatin. Data from Tournigand C et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.

bevacizumab was associated with higher rates of grade 3/4 neutropenia (18%) and diarrhea (12%). Modified XELOX plus bevacizumab showed higher rates of hand-foot syndrome (5%) and diarrhea (17%), and mFOLFOX7 plus bevacizumab showed a higher rate of neuropathy (7%). The authors concluded that modified XELOX plus bevacizumab administered every 2 weeks provides efficacy results similar to those achieved by mFOLFOX7 or FOLFIRI combined with bevacizumab as first-line induction therapy in this patient population.

References

1. Tournigand C, Scheithauer W, Samson B, et al. Induction treatment in first-line with chemotherapy + bevacizumab (bev) in metastatic colorectal cancer: results from the gercor-DREAM phase III study. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.
2. Benson AB, Cartwright TH. Gastrointestinal Cancers. Clinical Care Options. http://www.clinicaloptions.com/Oncology/Conference%20Coverage/GI%202013/Gastrointestinal%20Cancers/Downloadable%20slideset.aspx. Accessed April 3, 2013.
3. Tournigand C, Samson B, Scheithauer W, et al. 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. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30(suppl 18): Abstract LBA3500.

A Phase II Trial of Salvage Treatment With Gemcitabine and S-1 Combination in Heavily Pretreated Patients With Metastatic Colorectal Cancer

Sun Jin Sym, MD, and colleagues presented results from a phase II trial of gemcitabine plus the oral fluoropyrimidine S-1 in heavily pretreated patients with unresectable, metastatic CRC (Abstract 488). In areas outside of the United States, including Korea, the cost of targeted therapies is often prohibitive. In addition, the presence of a *KRAS* mutation predicts a negative response to EGFR-targeted agents such as cetuximab and panitumumab. The current study was undertaken to expand treatment options after standard therapies have failed. Enrolled patients had unresectable, metastatic CRC and had progressed following treatment with 5-FU, oxaliplatin, and irinotecan. The 36 patients were a median age of 58 years (range, 28–72 years), and 30 (83%) patients had an ECOG PS of 0–1. Approximately half of the patients were male. Patients received S-1 (30 mg/m^2) orally twice daily for 14 consecutive days with gemcitabine (1,000 mg/m^2) administered in a 30-minute infusion on days 1 and 8 in 21-day cycles for a maximum of 9 cycles. The study's primary objective was ORR. Patients received a median 5 cycles of treatment (range, 1–9). The ORR was 16.7% (95% CI, 4.5–28.9%). The disease control rate was 61.1% (95% CI, 45.2–77.0%) and included 6 PRs and 16 SDs. Median duration of disease control was 61.1 months (95% CI, 45.2–77.0 months). Median DOR was 10.3 months (95% CI, 6.1–14.5 months). Median PFS was 3.7 months (95% CI, 2.2–5.2 months), and median OS was 10.0 months (95% CI, 7.4–12.7 months). Neutropenia (12%) was the most common grade 3/4 toxicity. Grade 3/4 AEs were uncommon, and no dose reductions were required. The authors concluded that the combination of gemcitabine plus S-1 was well tolerated and may serve as a therapeutic option for patients with good PS and no further treatment options.

A Molecular Profile of Colorectal Cancer to Guide Prognosis and Therapy After Resection of Primary or Metastatic Disease

Joshua M. Uronis, PhD, and colleagues presented the development of a gene expression profile to classify patients with CRC into molecular subgroups of colorectal cancer with the goal of guiding prognosis and therapy following resection of primary or metastatic disease.[1] Currently used biomarkers for identifying patients at high risk of recurrence after surgical resection of CRC have poor predictive value and are not applicable to metastatic disease. As one of the most common cancer types in both men and women, CRC is diagnosed in more than 140,000 people each year and is the third leading cause of cancer mortality in the United States, causing approximately 50,000 estimated deaths per year.[2] Surgical resection can be curative for patients with early-stage CRC, as well as for a subset of patients with stage IV disease. However, current biomarkers cannot predict which patients are at high risk for recurrence; moreover, the use of adjuvant therapy is controversial. Thus the development of a panel of predictive and prognostic biomarkers is urgently needed to guide this treatment decision.

Wang and coworkers published the first study in which gene expression was used as a prognostic marker in patients with Duke's B CRC.[3] The study followed 74 patients, among whom 31 relapsed within 3 years and 43 remained disease-free. Gene expression profiling using the patients' RNA identified a 23-gene signature that predicted disease recurrence with an overall performance accuracy of 78%. Subsequently, numerous studies have attempted to define prognostic biomarkers, but most have been limited, primarily due to low sample numbers.

The current biomarker analysis used an unsupervised analysis approach, in which raw differences in gene expression are compared among tumor samples. Four data sets available to the public with gene expression data were mined and yielded 850 patients with primary CRC as the predominant disease.[4] After pooling the information from these patients into a single data set, consensus cluster analysis yielded 6 molecular subgroups of colorectal cancer with similar expression levels for several genes. Analysis of the recurrence-free survival for the 6 groups showed a significant difference for each (P=.0009), as determined by log-rank sum test. However, the biomarker set was considered prognostic and not truly predictive of response to treatment.

In order to devise a truly predictive biomarker, the investigators next used pathway-based mixture modeling, in which patient samples within a single group are classified into subgroups based on the probability that oncogenic pathways are either active or inactive. Nineteen different oncogenic pathways were chosen based on their influence on basic oncogenic events, such as cell-cell interactions, apoptosis, cell growth and metabolism, or mediation of the cell cycle. Gene expression signatures were examined to determine the probability of pathway activation in specific cancer cell lines, and these predictions were then tested by probing the same cell lines with targeted drugs, with the expectation that the targeted drugs would be more active in cell lines with activated target genes.

SPIRITT (Study 20060141): A Randomized Phase II Study of FOLFIRI With Either Panitumumab (pmab) or Bevacizumab (bev) as Second-Line Treatment (tx) in Patients (pts) With Wild-Type (WT) *KRAS* Metastatic Colorectal Cancer (mCRC)

J. Randolph Hecht, MD, and colleagues presented results from the multicenter, randomized, phase II SPIRITT (Second-Line Panitumumab-Irinotecan Treatment Trial) study, which compared the addition of panitumumab or bevacizumab to second-line chemotherapy in patients with metastatic CRC characterized by wild-type *KRAS* (Abstract 454). In a phase III trial, panitumumab added to second-line FOLFIRI demonstrated significant improvement in PFS in metastatic CRC patients with the wild-type *KRAS* gene (Peeters M et al. *J Clin Oncol.* 2010;28:4706-4713). The SPIRITT study randomized 182 patients equally to receive FOLFIRI plus either panitumumab (arm A; 6.0 mg/kg) or bevacizumab (arm B; 5.0 mg/kg or 10.0 mg/kg, based on institutional standard) in 2-week cycles. The primary endpoint was median PFS, with secondary endpoints of median OS, ORR, time to progression, safety, and exploratory biomarker analysis. Median PFS for the panitumumab arm (7.7 months; 95% CI, 5.7–11.8 months) and the bevacizumab arm (9.2 months; 95% CI, 7.8–10.6 months) did not significantly differ (HR, 1.01; 95% CI, 0.68–1.50). Median OS for FOLFIRI plus panitumumab (18.0 months; 95% CI, 13.5–21.7 months) and FOLFIRI plus bevacizumab (21.4 months; 95% CI, 16.5–24.6 months) was also similar (HR, 1.06; 95% CI, 0.75–1.49). No differences in treatment outcomes were revealed for PFS or OS via subgroup analysis. The ORRs were 32% (95% CI, 23–43%) with panitumumab and 19% (95% CI, 11–29%) with bevacizumab. Post-study treatment for the 2 arms was imbalanced, with 26% of patients in arm A versus 54% of patients in arm B receiving anti-EGFR therapy. In arm A, 78% of patients had an AE of worst grade 3 or 4 versus 65% of patients in arm B. Grade 5 AEs were reported for 7% of patients in each arm. Rates of treatment discontinuation were similar in arms A and B (29% vs 25%, respectively).

This approach showed that, as the predicted probability of pathway activation increased, so did the sensitivity of the cell lines to drugs that specifically target these pathways. Examples of this correlation include inhibition of phosphoinositide 3-kinase (PI3K) by a specific inhibitor (P<.001) and epidermal growth factor receptor (EGFR) inhibition by gefitinib (P=.0011).[5] Correlations were also demonstrated between IC_{50} values for the drugs lapatinib, erlotinib, and rapamycin and activation of their respective molecular targets of HER2 (P<.0001), EGFR (P<.0001), and mTOR (P<.024) based on gene expression analysis. Similarly, the cell lines were grouped based on their predicted probabilities of sensitivity to inhibition of specific pathways (P>.5 vs P<.5). Significant differences in IC_{50} values were obtained for the 2 groups based on treatment with lapatinib (P<.0001), erlotinib (P<.0001), or dasatinib (P=.07), but not for rapamycin (P=.87).

The data set representing 850 CRC patients was then analyzed to predict the probability of dysregulation of the 19 oncogenic pathways of interest. The tumors were initially grouped based on unique patterns of *KRAS* pathway dysregulation. Again, 6 molecular subgroups of colorectal cancer were obtained, and a significant difference in recurrence-free survival was demonstrated (P=.0004). The model was then applied to a data set of 133 metastatic CRC samples, from 39 primary and 94 metastatic lesions, obtained via surgical resection and compiled at Duke University. Tumors were initially examined histologically to confirm tissue integrity. Purified tumor RNA was then used to obtain gene expression profiles from genomic microarrays. Six molecular subgroups were again obtained with significant differences in recurrence-free survival (P=.046).

There is a current need for patient-derived CRC explants (PDCCEs) to facilitate genetic, histological, and drug-sensitivity studies. Therefore, the investigators have developed a murine model in which patient CRC explants are injected subcutaneously into mice and are subsequently reinjected until the sample shows a 100% uptake rate. Histological evaluation of the injected tissues showed that the tissue and cancer architecture were generally conserved, even as late as 11 generations after the initial injection.[6] In contrast, clonal cell lines obtained from commercial sources did not replicate tumor or tissue architecture. Two PDCCEs were then selected based on predicted sensitivity or insensitivity to an mTOR inhibitor. As predicted, RAD-001, a known mTOR inhibitor, elicited a response that was comparable to that of vehicle control in the PDCCE-resistant sample. However, a clear response was observed for treatment with RAD-001 relative to vehicle control in the PDCCE-sensitive cells. These in vivo explants will be used to validate drug predictions based on gene expression analysis. The authors concluded that the combination of unsupervised gene expression cluster analysis with in vivo explant analysis will offer a unique ability to define predictive gene expression biomarkers for CRC.

References

1. Uronis JM, VanDeusen JB, Datto MB, et al. A molecular profile of colorectal cancer to guide prognosis and therapy after resection of primary or metastatic disease. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 339.
2. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2009_pops09. Accessed March 17, 2013.
3. Wang Y, Jatkoe T, Zhang Y, et al. Gene expression profiles and molecular markers to predict recurrence of Dukes' B colon cancer. *J Clin Oncol*. 2004;22:1564-71.
4. National Center for Biotechnology Information. Gene Expression Omnibus. http://www.ncbi.nlm.nih.gov/geo. Accessed March 18, 2013.
5. Bild AH, Yao G, Chang JT, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature*. 2006;439:353-357.
6. Uronis JM, Osada T, McCall S, et al. Histological and molecular evaluation of patient-derived colorectal cancer explants. *PLoS One*. 2012;7:e38422.

Panitumumab (pmab) in Patients (pts) With Chemorefractory Metastatic Colorectal Cancer (mCRC): Final Analysis From a Community-Based, Observational Study (VECTOR) in Germany

Christian A. Lerchenmüller, MD, and colleagues presented results from the prospective, observational, non-interventional VECTOR study, which was conducted to determine the efficacy and safety of panitumumab in routine clinical practice in Germany (Abstract 550). In previous trials of patients with relapsed or refractory metastatic CRC who have the wild-type *KRAS* gene, panitumumab monotherapy improved PFS compared with best supportive care (Van Cutsem E et al. *J Clin Oncol*. 2007;25:1658-1664; Amado RG et al. *J Clin Oncol*. 2008;26:1626-1634). In this study, eligibility criteria were largely unrestricted in order to ensure a representative population sample. Predefined endpoints included ORR and skin toxicity. The patients (N=428) were a median age of 69 years (range, 22–89 years), and 93% had undergone prior surgery. Patients had received a median 18 cycles (range, 1–144) of prior chemotherapy, most commonly consisting of FOLFIRI (27%) or FOLFOX (21%) with or without antibody therapy, and given with palliative (65%), curative/palliative (35%), or curative (3%) intent. Sixty-four percent of patients had received 3 or more prior regimens. The median panitumumab dose was 6 mg/kg (range, 2.4–7.2 mg/kg) every 2 weeks for a median 8 cycles (range, 2–45 cycles), and 143 (33%) patients received more than 10 cycles. The ORR during panitumumab treatment was 20%, including 2% PRs. SD was reported in a further 40% of patients. The most common skin reactions associated with panitumumab therapy, observed in at least 5% of patients, were skin rash (53%), dry skin (10%), and pruritus (6%). Over half of patients (52%) experienced a skin reaction of grade 2 or greater. Other toxicities were reported for 21% of patients, with the most common being diarrhea (5%), nausea (5%), pain (3%), fatigue (2%), and vomiting (1%). Three serious adverse drug reactions and 2 grade 1 infusion reactions were reported.

FOLFOXIRI Plus Bevacizumab (bev) Versus FOLFIRI Plus Bev as First-Line Treatment of Metastatic Colorectal Cancer (MCRC): Results of the Phase III Randomized TRIBE Trial

Fotios Loupakis, MD, and colleagues presented data from the phase III TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) trial, conducted by the Gruppo Oncologico Nord Ovest (GONO) group.[1] Bevacizumab plus doublet chemotherapy is the current standard of care for metastatic CRC.[2,3] In a previous phase III trial, the GONO group compared the combination of 5-FU by continuous infusion, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) versus FOLFIRI.[4] This trial enrolled 244 patients with unresectable, metastatic CRC and randomized them to either treatment arm. Grade 2/3 peripheral neurotoxicity was increased in the FOLFOXIRI arm (19% vs 0%; *P*<.001), as was grade 3/4 neutropenia (50% vs 28%; *P*<.001). Although toxicity increased with FOLFOXIRI, this regimen was superior based on ORR (66% vs 41%; *P*=.0002), median PFS (9.8 months vs 6.9 months; *P*=.0006), and median OS (22.6 months vs 16.7 months; *P*=.032). More recently, the group published results from a randomized phase II study exploring the combination of FOLFOXIRI plus bevacizumab as first-line therapy for metastatic CRC, followed by maintenance treatment with bevacizumab monotherapy.[5] The study enrolled 57 patients with metastatic CRC. At a median follow-up of 28.8 months, PFS at 10 months was 74% (95% CI, 62–85%). No new safety signals were observed.

The current trial compared FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment in patients with unresectable, metastatic CRC. The trial's primary endpoint was PFS, with secondary endpoints of OS, safety, R0 resection, and biomarkers.[6] The trial design required 379 events and assumed a median PFS for FOLFIRI-bevacizumab of 11 months to detect an HR for PFS of 0.75 in favor of FOLFOXIRI-bevacizumab with a 2-sided type 1 error of 0.05 and 80% power.[7,8] Key eligibility criteria included histologically proven adenocarcinoma; unresectable, metastatic disease; at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria; age 18–75 years; ECOG PS of 0–2, or 0 for patients ages 71–75 years; and no prior chemotherapy for advanced disease. Prior to 1:1 randomization, patients were stratified by treatment center, ECOG PS of 0 versus 1–2, and prior adjuvant treatment.

A Cost-Effectiveness Analysis of Bevacizumab (BV) Plus Chemotherapy (CT) Versus Aflibercept (AFLI) Plus CT in Patients With Metastatic Colorectal Cancer (mCRC) Previously Treated With BV

Robert Morlock, PhD, and colleagues presented results from an analysis comparing the cost-effectiveness of 2 anti-VEGF therapies, aflibercept and bevacizumab, in the treatment of patients with metastatic CRC previously treated with bevacizumab (Abstract 417). Ziv-aflibercept, an anti-angiogenic agent, is a soluble fusion protein that includes a portion of the extracellular domains of the human VEGF receptors. The current study evaluated the efficacy and costs of adding bevacizumab or ziv-aflibercept to an existing second-line chemotherapy regimen that includes oxaliplatin or irinotecan. An illness-death Markov model was modified to include 3 clinical stages of CRC: PFS, progressed disease, and death. Clinical outcomes included PFS, OS, and quality-adjusted life-years (QALYs) gained. Cost outcomes included direct costs and incremental cost-effectiveness ratios. The Bucher method was used to compare results from the TML (Treatment Across Multiple Lines) and VELOUR (Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen) trials, which investigated the 2 treatments of interest (Arnold D et al. *J Clin Oncol* [ASCO Annual Meeting Abstracts]. 2012;30. Abstract CRA3503; Van Cutsem E et al. *J Clin Oncol*. 2012;30:3499-3506). Only direct costs for patients were considered. Drug costs were based on wholesale acquisition costs, and Medicare reimbursement costs were used to determine the costs of treating AEs. The analysis showed similar efficacies for the 2 treatments. When comparing the addition of bevacizumab versus aflibercept to chemotherapy, the adjusted indirect HR for OS was 0.94 (95% CI, 0.702–1.258) and for PFS was 1.03 (0.769–1.357). Bevacizumab and aflibercept treatment added 0.498 and 0.479 QALYs, respectively. The costs for bevacizumab versus aflibercept were $5.97/mg versus $16.00/mg, $2,473/cycle versus $5,031/cycle, and $4,946/month and $10,068/month, respectively. Patients in the aflibercept arm generally had higher rates of grade 3/4 AEs, including neutropenia (20% vs 16.2%), diarrhea (19% vs 10.0%), and hypertension (16.4% vs 1.7%). The study estimated that aflibercept treatment cost $39,104 more per patient than treatment with bevacizumab.

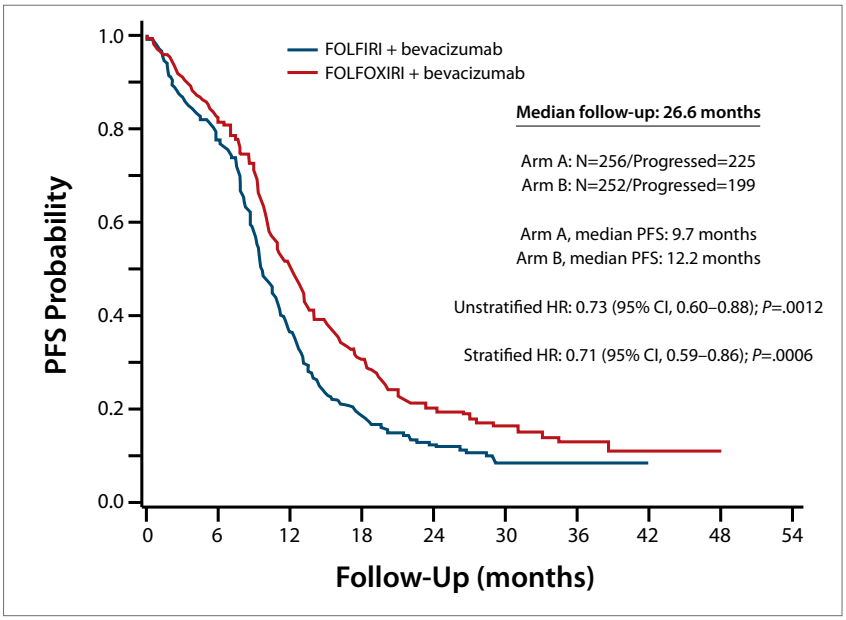

Figure 4. In the phase III TRIBE trial, median PFS was higher in patients who received FOLFOXIRI plus bevacizumab as compared with those who received FOLFIRI plus bevacizumab.

FOLFIRI=folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; FOLFOXIRI=fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan; PFS=progression-free survival; TRIBE=Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer. Data from Loupakis F et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 336.

Patients in arm A (n=256) received a FOLFIRI plus bevacizumab regimen consisting of bevacizumab (5 mg/kg), irinotecan (180 mg/m^2), l-leucovorin (200 mg/m^2), 5-FU bolus (400 mg/m^2), plus 5-FU infusion (2,400 mg/m^2 over 48 hours). Patients in arm B (n=252) received a FOLFOXIRI plus bevacizumab regimen consisting of bevacizumab (5 mg/kg), irinotecan (165 mg/m^2), oxaliplatin (85 mg/m^2), l-leucovorin (200 mg/m^2), and 5-FU infusion (3,200 mg/m^2 over 48 hours). Treatments were given every 2 weeks, with a maximum of 12 cycles, followed by maintenance therapy with bevacizumab and 5-FU until disease progression.

Randomization of 508 patients at 35 Italian treatment centers occurred from July 2008 to May 2011. Patient baseline demographics were well balanced between both arms. Most patients were male (60–61%). The median age was 60–61 years (range, 29–75 years), and most patients (89–90%) had an ECOG PS of 0. Patient baseline disease characteristics of interest included synchronous metastases (79–81%), prior adjuvant chemotherapy (12%), more than 1 metastatic site (69–76%), and metastasis to the liver only (18–23%). At a median follow-up of 26.6 months, 225 patients had progressed in arm A and 199 in arm B. Median PFS was 9.7 months for patients in arm A versus 12.2 months for patients in arm B (unstratified HR, 0.73; 95% CI, 0.60–0.88; *P*=.0012; Figure 4), meeting the study's primary endpoint. The response rate was also significantly higher among the patients who received FOLFOXIRI-bevacizumab (65% vs 53%; *P*=.006). Subgroup analysis generally showed equivalence for the 2 treatments; however, the control regimen appeared better for those who had received prior adjuvant treatment (n=61; *P*=.072) whereas FOLFOXIRI-bevacizumab was superior for patients who had not (n=447).

Safety analysis of arms A and B showed similar rates of serious AEs (19.7% vs 20.5%), fatal AEs (1.6% vs 2.4%), treatment-related deaths (1.6% vs 2.4%), and deaths within 60 days of randomization (2.7% vs 3.6%), all respectively. No unexpected toxicities emerged. Grade 3/4 AEs with significantly different incidences in arm A versus arm B included diarrhea (11% vs 19%; *P*=.012), stomatitis (4% vs 9%; *P*=.048), neutropenia (20% vs 50%; *P*<.001), and neurotoxicity (0% vs 5%; *P*<.001), respectively. Notably, the incidence of febrile neutropenia was similar for the control and experimental treatments (6% vs 9%, respectively; *P*=.315). Patients received a median 12 induction cycles (range, 1–25) in arm A versus 11 (range, 1–21) in arm B. Patients in arm A had fewer delayed cycles (6% vs 16%) and fewer cycles with dose reduction (8% vs 21%). The relative dose intensities were higher for patients in arm A for 5-FU (83% vs 73%) and for irinotecan (84% vs 74%). For patients receiving FOLFOXIRI-bevacizumab, the relative dose intensity of oxaliplatin was 75%.

References

1. Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (MCRC): results of the phase III randomized TRIBE trial. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 336.
2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335-2342.
3. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26:2013-2019.
4. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670-1676.
5. Masi G, Loupakis F, Salvatore L, et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol*. 2010;11:845-852.
6. Benson AB, Cartwright TH. Gastrointestinal Cancers. Clinical Care Options. http://www.clinicaloptions.com/Oncology/Conference%20Coverage/GI%202013/Gastrointestinal%20Cancers/Downloadable%20slideset.aspx. Accessed April 3, 2013.
7. Kozloff M, Yood MU, Berlin J, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. *Oncologist*. 2009;14:862-870.
8. Sobrero A, Ackland S, Clarke S, et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. *Oncology*. 2009;77:113-119.

Bevacizumab (Bev) With or Without Erlotinib as Maintenance Therapy, in Patients (Pts) With Metastatic Colorectal Cancer (mCRC): Exploratory Analysis According to *KRAS* Status in the gercor DREAM Phase III Trial

Benoît Samson, MD, and colleagues presented results from an exploratory analysis of the influence of *KRAS* status on erlotinib efficacy in patients from the GERCOR-DREAM trial.[1] As previously described, patients in arm A received bevacizumab monotherapy for maintenance treatment and patients in arm B received erlotinib plus bevacizumab.[2] *KRAS* status was available for 403 of the 452 patients who were randomized for maintenance treatment. The *KRAS* gene was wild-type in 234 patients (58%) and mutated in 169 patients (42%).

Among patients with the wild-type *KRAS* gene, maintenance treatment consisted of bevacizumab monotherapy for 106 patients and of bevacizumab plus erlotinib for 128 patients. Among the patients with mutated *KRAS*, 92 patients received bevacizumab alone and 77 patients received the combination for maintenance therapy. Patient baseline characteristics—such as age 70 years or older (25–29%), evidence of metachronous disease (11–19%), presence of a single metastatic site (44–51%) and WHO PS of 0 (57–64%)—were well balanced among patients with wild-type *KRAS* versus mutated *KRAS* and randomized to either treatment. Approximately one-fourth of patients in each group had platelet counts greater than 400,000/μL, 42–58% of patients had lactate dehydrogenase (LDH) greater than the upper limit of normal, and approximately one-half of patients had alkaline phosphatase levels above the upper limit of normal. The majority of patients (57–63%) received the mFOLFOX-bevacizumab regimen, 26–31% of patients received mXELOX plus bevacizumab, and 11–12% of patients received FOLFIRI as induction therapy. Approximately 40–45% of patients throughout the 4 groups had a time to maintenance therapy of 3 months, with the remainder having a time to maintenance therapy of 6 months.

For the entire group of patients included in this study (n=452), median PFS from inclusion was 9.33 months for maintenance with bevacizumab alone versus 10.55 months for maintenance with bevacizumab plus erlotinib (HR, 0.76; 95% CI, 0.61–0.94; *P*=.393). As shown in Table 3, no significant difference in median PFS was discerned based on *KRAS* mutational status for maintenance therapy with either bevacizumab only or the combination regimen. Median PFS was similar during the entire study period as well as during the maintenance period only.

The investigators also examined the possible correlation of PFS and skin toxicity among patients who received erlotinib as part of their maintenance therapy. Agents that target EGFR, including erlotinib, are often associated with skin reactions.[3] Moreover, skin toxicities, particularly acneiform rash, have been correlated with improved outcomes in patients with non–small cell lung cancer. In patients from the GERCOR-DREAM study with wild-type *KRAS*, severity of skin toxicity (grade 0–1 vs 2–4) was not correlated with median PFS (*P*=.106; Figure 5). In contrast, for patients with mutated *KRAS*, median PFS was prolonged among those who experienced a higher

Table 3. PFS for Patients With Known *KRAS* Mutation Status From the GERCOR-DREAM Study

	***KRAS* Wild-Type**		***KRAS* Mutated**	
Arm	**A**	**B**	**A**	**B**
From Study Inclusion				
Median PFS (months)	9.7	10.9	9.8	9.8
HR (95% CI)	0.80 (0.59–1.08)		0.86 (0.61–1.22)	
P Value	.141		.393	
Maintenance Period Only				
Median PFS (months)	5.7	6.0	4.5	4.7
HR (95% CI)	0.83 (0.61–1.12)		0.82 (0.58–1.16)	
P Value	.213		.255	

CI=confidence interval; DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie; HR=hazard ratio; PFS=progression-free survival.

Samson B et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstract). 2012;30(suppl 34): Abstract 448.

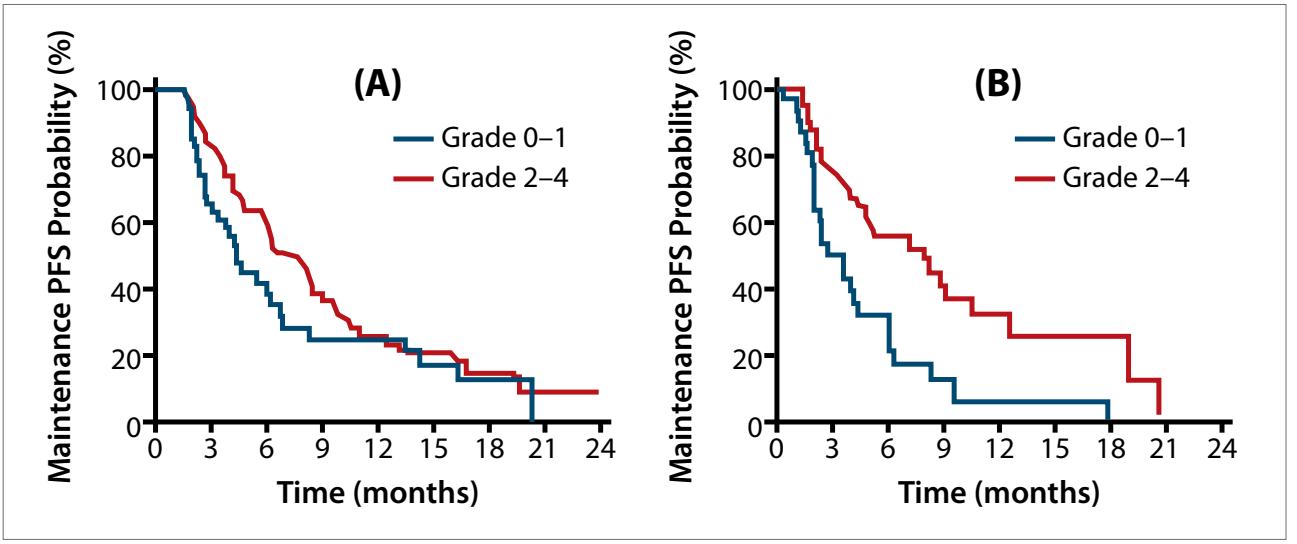

Figure 5. In patients from the phase III GERCOR-DREAM study, severity of skin toxicity did not correlate with median PFS in patients with wild-type *KRAS* (A). Among patients with mutated *KRAS*, there was a significant association between severity of skin toxicity and median PFS (B).

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie; PFS=progression-free survival. Data from Samson B et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 448.

grade severe skin reaction (7.8 months vs 3.6 months; HR, 0.43; 95% CI, 0.24–0.77; *P*=.001). The authors concluded that, in contrast to the addition of anti-EGFR antibodies, the addition of erlotinib to bevacizumab did not appear to be detrimental in patients with mutated *KRAS*. They suggested that a lack of statistical power might have contributed to the outcomes in this exploratory analysis.

References

1. Samson B, Tournigand C, Scheithauer W, et al. Bevacizumab (Bev) with or without erlotinib as maintenance therapy, in patients (pts) with metastatic colorectal cancer (mCRC): exploratory analysis according to *KRAS* status in the gercor DREAM phase III trial. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 448.
2. Tournigand C, Scheithauer W, Samson B, et al. Induction treatment in first-line with chemotherapy + bevacizumab (bev) in metastatic colorectal cancer: Results from the gercor-DREAM phase III study. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.
3. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. *Lung Cancer*. 2012;78:8-15.

Multicenter Phase II Study of FOLFOX or Biweekly XELOX and Cetuximab as First-Line Treatment in Patients With Wild-Type KRAS/BRAF Metastatic Colorectal Cancer (mCRC) (FLEET Study)

Dr. Ho Min Kim and colleagues presented results of the multicenter, phase II FLEET study (Abstract 463). The phase III COIN (Continuous Chemotherapy Plus Cetuximab, or Intermittent Chemotherapy With Standard Continuous Palliative Combination Chemotherapy With Oxaliplatin and a Fluoropyrimidine in First-Line Treatment of Metastatic Colorectal Cancer) study, conducted by the Medical Research Council, examined the addition of cetuximab to first-line, oxaliplatin-based chemotherapy and failed to detect a significant difference in PFS or OS relative to chemotherapy alone in patients with metastatic CRC who have the wild-type *KRAS* gene (Maughan TS et al. *Lancet*. 2011;377:2103–2114). However, a randomized phase II study suggested that the addition of cetuximab to XELOX improved outcomes relative to XELOX alone (Borner M et al. *Ann Oncol*. 2008;19:1288-1292). The current study enrolled patients with treatment-naïve, metastatic CRC with tumors that were confirmed as EGFR-positive and wild-type for *KRAS* and *BRAF*. Patients received cetuximab (500 mg/m^2) plus the investigator's choice of either mFOLFOX6 (n=37; oxaliplatin [85 mg/m^2], 1-LV [200 mg/m^2], 5-FU bolus [400 mg/m^2], plus 5-FU infusion [2,400 mg/m^2]) or XELOX (n=25; oxaliplatin [85 mg/m^2] plus capecitabine (2,000 mg/m^2]) every 2 weeks. Patient characteristics included 34 men, median age of 65.9 years (range, 34–83 years), 55% with PS of 0, and 47% with liver metastasis. Rates of grade 3/4 AEs were similar for both treatments and were mostly grade 3, with the exception of 1 patient (2.7%) with grade 4 hypomagnesemia and 5 patients (13.5%) with grade 4 neutropenia in the mFOLFOX6 plus cetuximab arm. The response rate was 64.9% for mFOLFOX6 plus cetuximab, representing 2 CRs and 22 PRs, versus 72.0% for XELOX plus cetuximab, representing 18 PRs.

PEAK (Study 20070509): A Randomized Phase II Study of mFOLFOX6 With Either Panitumumab (Pmab) or Bevacizumab (bev) as First-Line Treatment (tx) in Patients (pts) With Unresectable Wild-Type (WT) KRAS Metastatic Colorectal Cancer (mCRC)

Lee Schwartzberg, MD, and colleagues presented results from the PEAK (A Phase 2 Study of Panitumumab Plus mFOLFOX6 vs Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Subjects With Wild-Type *KRAS* Tumors) study.[1] Panitumumab is a fully human antibody against EGFR. A multicenter, phase III trial of 1,183 patients with treatment-naïve, metastatic CRC randomized patients 1:1 to receive FOLFOX4 with or without panitumumab.[2] In patients with wild-type *KRAS*, chemotherapy plus panitumumab significantly prolonged median PFS relative to control (9.6 months vs 8.0 months; HR, 0.80; 95% CI, 0.66–0.97; *P*=.02). In contrast, the inclusion of panitumumab was deleterious for patients with mutated *KRAS*, as shown by a reduced median PFS relative to control (*P*=.02) and reduced OS (15.5 months vs 19.3 months; HR, 1.24; 95% CI, 1.04–1.62; *P*=.068).

A current standard of care for patients with treatment-naïve CRC includes an oxaliplatin-based regimen plus bevacizumab; however, the role for EGFR inhibition in treating metastatic CRC remains unclear. The PEAK trial was designed to compare the inhibition of EGFR versus inhibition of VEGF in combination with standard chemotherapy in metastatic CRC patients with wild-type *KRAS*. Key eligibility criteria included metastatic cancer of the colon or rectum; no prior chemotherapy, anti-VEGF, or anti-EGFR treatment for metastatic CRC; measurable disease; wild-type *KRAS* tumor status; and ECOG PS of 0 or 1. The study's primary objective was PFS, with secondary objectives of OS, ORR, resection rate, safety, and exploratory biomarker analysis. All patients received mFOLFOX6, consisting of oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), 5-FU (400 mg/m^2), all on day 1, plus 5-FU infusion (2,400 mg/m^2) administered throughout 46 hours. In addition, patients randomized to arm A received panitumumab (6.0 mg/kg) and patients in arm B received bevacizumab (5.0 mg/kg). Treatment was given in 2-week cycles for a maximum of 12 cycles. No formal hypothesis was tested in this study; however, the overall goal was to determine the HR for PFS with panitumumab versus bevacizumab.

Two hundred eighty-five patients with wild-type *KRAS* tumors were randomized, and 278 patients received treatment. Patient baseline characteristics were well balanced between the 2 arms, including median age of 61–63 years (range, 23–82 years), ECOG PS of 0 (63–64%), primary tumor location in the colon (64–68%), and presence of a

Is There a Role for Chemotherapy in Metastatic Colorectal Cancer Patients With a Poor Performance Status?

Hui-Li Wong, MBBS, FRACP, and colleagues presented results from an analysis of treatment outcomes in routine clinical care for metastatic CRC patients with poor ECOG PS (Abstract 534). Because these patients are typically excluded from clinical trials, optimal treatment for this patient population is unknown. Using prospectively collected data on treatment-naïve patients with metastatic CRC, the current analysis compared differences in clinical and treatment characteristics of patients with poor ECOG PS (≥2) versus those with good ECOG PS (0–1). Based on data from 864 patients and median follow-up of 11.5 months, 161 patients (18.6%) had an ECOG PS of 2 or greater. Compared with the patients with a good ECOG PS, patients with a poor ECOG PS were significantly more likely to be ages 75 years or older (58.4% vs 28.3%), more likely to have a Charlson index score greater than 1 (57.8% vs 36.4%), less likely to have had primary tumor resection (47.2% vs 30.6%), and more likely to have received treatment with palliative intent only (94.4% vs 64.4%; *P*<.0001 for all). A significantly greater proportion of patients with poor ECOG PS did not receive combination chemotherapy (48.4% vs 12.9%; *P*<.0001) and did not receive bevacizumab treatment (68.7% vs 44.2%; *P*<.0001). Median OS was significantly lower in patients with poor versus good PS (6.6 months vs 29.0 months, respectively; HR, 0.25; 95% CI, 0.19–0.32; *P*<.0001). For patients with poor ECOG PS who received chemotherapy, median OS was prolonged compared with those who received none (9.0 months vs 3.5 months; HR, 0.26; 95% CI, 0.24–0.56; *P*<.0001). The authors noted that the study was limited by the small number of patients with poor ECOG PS and the inability to distinguish between patients with poor PS due to advanced cancer and those with poor PS due to comorbidities or frailty.

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 5, 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 6, 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, 5 and 8. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 8, 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 8). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure (CHF)

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 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.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were significantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

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%
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.

Avastin in Combination with Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin Based Chemotherapy in Second-line mCRC Patients who have Progressed on an Avastin Containing Regimen in First-line mCRC:

No new safety signals were observed in Study 4 when Avastin was administered in second line mCRC patients who progressed on an Avastin containing regimen in first line mCRC. The safety data was consistent with the known safety profile established in first and second line mCRC.

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 5. 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 6 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 8. 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 8
(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 an immune response to Avastin. In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and 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

Hepatobiliary disorders: Gallbladder perforation

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 8, 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 5, 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)

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01/13 AVA0000764704
10136665
Initial U.S. Approval: February 2004
Code Revision Date: January 2013

single metastatic site (37–39%). Median PFS was similar for treatment with panitumumab or bevacizumab (10.9 months vs 10.1 months, respectively; HR, 0.87; 95% CI, 0.85–1.17; *P*=.35; Figure 6). At the time of reporting, median OS had not been reached for panitumumab and was 25.4 months for bevacizumab (HR, 0.72; 95% CI, 0.47–1.11; *P*=.14). Eighty-two patients (58%) in the panitumumab arm and 76 patients (54%) in the bevacizumab arm experienced a CR or PR, and resection rates were 13% and 11%, respectively. Subgroup analysis failed to uncover significant differences for either treatment, with the exception that patients with 3 or more metastatic sites appeared to derive a greater PFS benefit from panitumumab (n=76; HR, 0.52; 95% CI, 0.29–0.95; Figure 7). Subgroup analysis based on OS suggested a potential benefit for patients with baseline LDH of at least 1.5 times the upper limit of normal (0.40; 95% CI, 0.16–0.98) or age younger than 65 years (HR, 0.41; 95% CI, 0.21–0.79).

Both treatment combinations were similar in terms of toxicity and rates of treatment discontinuation, and no new safety signals emerged. Seventeen patients in the panitumumab arm (12%) and 44 patients in the bevacizumab arm (31%) received an anti-EGFR monoclonal antibody after the protocol treatment phase, for median durations of 10.0 and 11.9 months. Anti-VEGF therapy was administered after study treatment to 43 patients in the panitumumab arm (30%) and 32 patients in the bevacizumab arm (22%), for a median duration of 10.9 and 8.4 months, respectively. The most severe AE was grade 3/4 in 116 patients who received chemotherapy plus panitumumab (86%) and in 106 patients who received bevacizumab plus chemotherapy (76%). Serious AEs were observed in 61 patients in the panitumumab arm (44%) versus 53 in the bevacizumab arm (38%). Grade 5 AEs occurred in 7 in the panitumumab arm (5%) versus 9 in the bevacizumab arm (6%). The rate of treatment discontinuation was similar for the 2 arms (24–27%). The most common grade 3/4 AEs that were at least 5% more common with panitumumab than bevacizumab, occurring in at least 2% of patients in 1 arm, included skin disorders (32% vs 1%), fatigue (11% vs 9%), hypokalemia (11% vs 5%), hypomagnesemia (7% vs 0%), mucosal inflammation (7% vs 1%), decreased appetite (5% vs 1%), stomatitis (5% vs <1%), and dehydration (4% vs <1%). The most common grade 3/4 AEs that were at least 5% more common with

Phase II Study to Evaluate Efficacy and Safety of Irinotecan, Capecitabine, and Bevacizumab in Metastatic Colorectal Cancer (mCRC) Patients

Pilar García Alfonso, MD, PhD, and colleagues presented results from a multicenter, open-label, single-arm, phase II clinical trial of bevacizumab added to the XELIRI regimen (Abstract 501). The trial enrolled patients with ECOG PS 0–2 and histologically confirmed, metastatic CRC and measurable disease. Exclusion criteria included previous exposure to bevacizumab and previous chemotherapy, with the exception of adjuvant treatment completed at least 6 months prior to study entry. The XELIRI regimen consisted of irinotecan (175 mg/m^2) on day 1 and oral capecitabine (1,000 mg/m^2) twice daily on days 2–8, plus bevacizumab (5 mg/kg) on day 1 in 2-week cycles. At baseline, the 77 evaluable study patients were a median age of 65.1 years (range, 41.4–81.1 years) and had an ECOG PS of 0–1 (96.1%). Most patients (66.2%) were male. The primary tumor locations included the colon (53.2%), rectum (31.2%), and both (15.6%), and 64.9% of patients had undergone primary tumor resection. Prior adjuvant treatment had been administered to 36.4% of patients. Metastases were present in the liver in 62.3% and in the lungs in 53.2%. *KRAS* status was wild-type in 46.8% of tumor samples, mutated in 45.5%, and unavailable in 7.8%. Mean treatment time was 7.1±4.9 months, with a median 12 treatment cycles (range, 1–43). The ORR was 37.7%, and the disease control rate was 84.4%. The study yielded a PFS of 11.84 months and an OS of 24.80 months. No significant difference was seen for OS, PFS, or ORR based on *KRAS* status. The most common grade 3–5 AEs, occurring in at least 10% of patients, included diarrhea (18.2%), asthenia (16.9%), pulmonary embolism (13.0%), and neutropenia (10.4%).

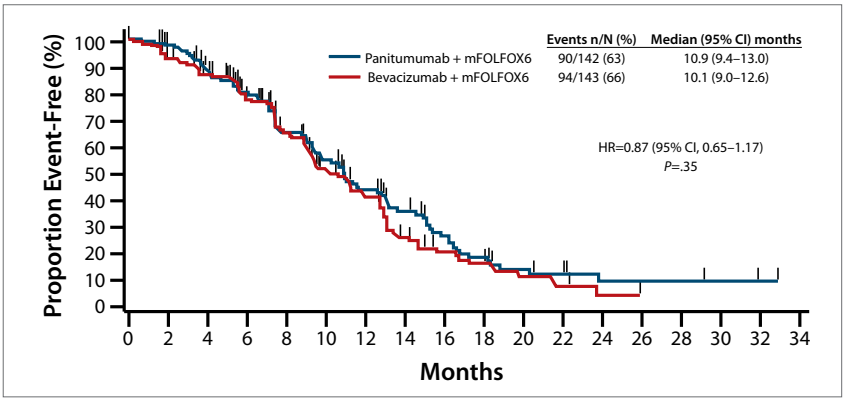
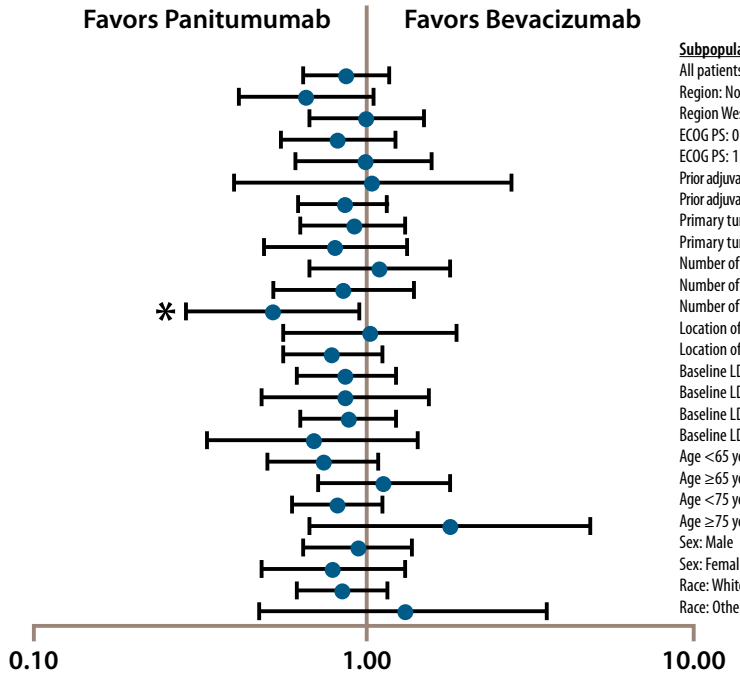


Figure 6. The phase II PEAK trial examined panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 for first-line treatment of metastatic colorectal cancer subjects with wild-type *KRAS* tumors. Median PFS did not significantly differ between the 2 treatment arms.

CI=confidence interval; FOLFOX=folinic acid (leucovorin), oxaliplatin, and fluorouracil; PEAK=A Phase 2 Study of Panitumumab Plus mFOLFOX6 vs. Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Subjects With Wild-Type *KRAS* Tumors; HR=hazard ratio; PFS=progression-free survival. Data from Schwartzberg LS et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 446.



Subpopulation	N	HR	95% CI
All patients	285	0.87	0.65–1.17
Region: North America	124	0.66	0.42–1.04
Region Western Europe	161	1	0.68–1.47
ECOG PS: 0	180	0.81	0.56–1.18
ECOG PS: 1	104	0.99	0.62–1.57
Prior adjuvant oxaliplatin therapy: Yes	30	1.05	0.40–2.73
Prior adjuvant oxaliplatin therapy: No	255	0.86	0.63–1.16
Primary tumor: Colon	188	0.91	0.64–1.31
Primary tumor: Rectal	97	0.81	0.49–1.33
Number of sites: 1	109	1.1	0.68–1.77
Number of sites: 2	99	0.85	0.52–1.38
Number of sites: ≥3	76	0.52	0.29–0.95
Location of site: Liver	76	1.03	0.57–1.86
Location of site: Other	208	0.79	0.56–1.10
Baseline LDH: <1.5 × ULN	208	0.87	0.61–1.22
Baseline LDH: ≥1.5 × ULN	67	0.87	0.48–1.56
Baseline LDH: <2 × ULN	228	0.89	0.64–1.23
Baseline LDH: ≥2 × ULN	47	0.69	0.33–1.43
Age <65 years	170	0.74	0.51–1.08
Age ≥65 years	115	1.13	0.72–1.79
Age <75 years	259	0.82	0.60–1.11
Age ≥75 years	26	1.8	0.68–4.74
Sex: Male	182	0.95	0.66–1.36
Sex: Female	103	0.79	0.48–1.30
Race: White/Caucasian	258	0.84	0.62–1.15
Race: Other	27	1.3	0.48–3.50

Figure 7. In the phase II PEAK trial, which compared panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 for first-line treatment of metastatic colorectal cancer subjects with wild-type *KRAS* tumors, subgroup analysis failed to identify significant differences in PDF between patients receiving panitumumab plus mFOLFOX6 or bevacizumab plus mFOLFOX6, with the exception that patients with 3 or more metastatic sites appeared to derive benefit from panitumumab. CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HR=hazard ratio; ULN=upper limit of normal.

*Hazard ratio where the upper bound of the 95% confidence interval ≤1.00. Data from Schwartzberg LS et al. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 446.

bevacizumab, occurring in at least 2% of patients in 1 arm, included hypertension (7% vs 0%). Patients in both arms received a median 12 cycles of antibody therapy, 11 cycles of oxaliplatin, and 12–13 cycles of 5-FU bolus or 5-FU infusion. Median relative dose intensities for chemotherapeutic agents were similar for both arms (86% for panitumumab and 92% for bevacizumab).

References

1. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK (study 20070509): a randomized phase II study of mFOLFOX6 with either panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) in patients (pts) with unresectable wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 446.
2. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28:4697-4705.

Safety and Efficacy During First Line With Cetuximab in KRAS Wild-Type Metastatic Colorectal Cancer (mCRC): Results of a Large Prospective Multicenter Cohort Carried Out by the Premium French Observational Study

Laurent Mineur, MD, and colleagues presented results from a prospective, multicenter, observational cohort study to determine the safety and efficacy of cetuximab added to first-line chemotherapy for treating patients with wild-type *KRAS*, metastatic CRC in daily practice in France (Abstract 555). The study prospectively enrolled patients with at least 1 measurable lesion who received first-line treatment with cetuximab plus chemotherapy. Of the 496 patients, the mean age was 65.7 years, 63% were male, and 12% had an ECOG PS of 2 or 3. The primary tumor site was the colon in 69.5% of patients and the rectum in 30.5%, and 66% had undergone primary tumor resection. Metastasis was restricted to the liver in 44% of patients. Chemotherapy consisted of FOLFIRI (51.8%), FOLFOX4 (36.5%), or other (11.7%). Cetuximab was administered weekly or every 2 weeks in 20.2% and 79.8% of patients, respectively. The responses included 4.6% CR, 44.9% PR, 24.0% SD, and 16.5% progressive disease, yielding an ORR of 49.5%. Reasons for cetuximab treatment discontinuation in 207 patients included progressive disease (35.3%), therapeutic break (23.2%), surgery recruitment (20.0%), allergic reaction (8.7%), cutaneous toxicity (7.2%), patient request (2.9%), and others (2.7%). The most common grade 3/4 AEs occurring in at least 2% of patients included neutropenia (7.9%), diarrhea (5.3%), folliculitis (3.0%), vomiting (2.2%), and xerosis (2.0%).

Commentary

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Several important studies from the 2013 American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Cancers Symposium focused on how to best integrate targeted agents, particularly bevacizumab and the epidermal growth factor receptor (EGFR) antibodies, into the management of patients with colorectal cancer. Dr. Fotios Loupakis presented an interesting phase III study from Italy, the TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) trial.[1] The TRIBE trial aimed to demonstrate the effects of intensified chemotherapy plus bevacizumab as first-line therapy for patients with unresectable metastatic colorectal cancer. The trial randomized 508 patients to either folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (FOLFIRI) plus bevacizumab, which is one of the standards of care, or the combination of 5-FU by continuous infusion, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab. The Italian FOLFOXIRI/bevacizumab regimen does not contain bolus 5-FU, and irinotecan is administered at a dose of 165 mg/m^2. This regimen also uses a high dose of continued-infusion 5-FU of 3.2 gm throughout 48 hours. Progression-free survival was the primary endpoint of the study, with approximately 250 patients in each treatment arm. Progression-free survival was 9.7 months for the FOLFIRI/bevacizumab arm versus 12.2 months for the FOLFOXIRI/bevacizumab arm; the hazard ratio (HR) was 0.71, which is clinically meaningful. The concern with FOLFOXIRI/bevacizumab is that it uses up all of the chemotherapy backbones in first-line therapy, raising the question of what agents should be used later.

The response rate, as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, is also important in this study. It is possible that the aggressive FOLFOXIRI/bevacizumab arm could convert patients with liver metastasis from unresectable to resectable. FOLFOXIRI/bevacizumab had a response rate of 65%, as compared to 53% with FOLFIRI/bevacizumab. Although this 12% difference was statistically significant, it is a bit underwhelming in terms of what could be expected in order to convert many patients from unresectable to resectable disease. Reassuringly, however, there was no increase in fatal or serious adverse events with the more intense FOLFOXIRI/bevacizumab regimen. There were increases in diarrhea, stomatitis, and neutropenia, but not in febrile neutropenia, which is important. The FOLFOXIRI/bevacizumab regimen appears safe, but the question remains regarding whether this intense regimen is needed as upfront therapy. I believe that it will be useful in only a select number of patients with a high tumor load, when a rapid response is needed, and perhaps in patients with *BRAF*-mutated cancer who have a very poor prognosis with limited ability to undergo a more sequential approach toward metastatic disease.

A different approach to treatment was examined in the phase III, randomized AVEX (Avastin With Xeloda in the Elderly) trial, presented by Dr. David Cunningham.[2] This trial reduced the intensity of first-line chemotherapy. The study had an interesting design. It compared

Phase II Trial of Combined Chemotherapy With Irinotecan, S-1, and Bevacizumab (IRIS/Bev) in Patients With Metastatic Colorectal Cancer (mCRC): Final Analysis—Hokkaido Gastrointestinal Cancer Study Group (HGCSG) Trial

Satoshi Yuki, MD, and colleagues presented final results from a single-arm, phase II study investigating bevacizumab plus irinotecan and S-1 as first-line treatment in 52 patients with metastatic CRC (IRIS-bev; Abstract 460; Komatsu Y et al. *Acta Oncol*. 2012;51:867-872). The study's primary endpoints included safety, with secondary endpoints of response rate, OS, PFS, and completion of protocol treatment. Patient characteristics included median age of 63.5 years (range, 48–82 years) and ECOG PS of 0 (100%). The colon or rectum was the primary tumor site in 67.3% and 32.7% of patients, respectively. Metastasis was observed in the liver (67.3%), lung (44.2%), lymph node (44.2%), and peritoneum (13.5%). Treatment consisted of S-1, a combination of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and oxonic acid (40–60 mg, depending on body surface area) by mouth twice daily on days 1–14, irinotecan (100 mg/m^2) on days 1 and 15, and bevacizumab (5 mg/kg) on days 1 and 15 in a 4-week cycle. After a median follow-up of 54.9 months, the most common grade 3/4 AEs occurring in at least 10% of patients were neutropenia (27%), hypertension (21%), diarrhea (17%), and anemia (12%). No life-threatening AEs were reported. Dose intensities were 92% (range, 61–100%) for S-1, 92% (range, 29–100%) for irinotecan, and 90% (range, 41–100%) for bevacizumab. The ORR was 63.5% (95% CI, 50.4–76.5%), which included 5.8% CRs and 57.7% PRs. An additional 30.7% of patients had SD, yielding a disease control rate of 94.2%. Median PFS was 17.0 months (95% CI, 14.2–19.8 months), and median OS was 39.6 months (95% CI, 34.1–45.0 months). A randomized trial (TRICOLORE) comparing IRIS-bev with mFOLFOX6 or XELOX plus bevacizumab is under way.

capecitabine versus capecitabine plus bevacizumab in 280 patients older than 70 years; the median age of the patient population was 76 years. The age of the patient population is important because colorectal cancer is a disease of the elderly. The AVEX trial aimed to clarify what can be achieved with less intense chemotherapy when bevacizumab is added to a fluoropyrimidine single-agent backbone. This study used a standard dose and schedule of capecitabine, 1,000 mg/m^2 twice daily for 2 weeks on, 1 week off. Bevacizumab was administered at 7.5 mg/kg every 3 weeks. Progression-free survival was the primary endpoint. The results were quite astounding. Median progression-free survival was 4 months longer in the capecitabine/bevacizumab arm versus the capecitabine-only arm (9.1 months vs 5.1 months, respectively). The HR was 0.53, which is very strong, highly statistically significant, and clinically meaningful. These results highlight the strong synergistic interaction between fluoropyrimidine and bevacizumab. They raise the question of whether oxaliplatin or irinotecan are really needed as part of first-line therapy with a fluoropyrimidine-plus-bevacizumab backbone. Unfortunately, a US trial that tried to address this question in an elderly patient population was closed due to poor accrual.[3] In the AVEX trial, all predefined subgroups benefited from the addition of bevacizumab to capecitabine. Overall survival was not the primary endpoint of the study, and the limited number of patients—280—makes it almost impossible to achieve significant differences here. However, overall survival was longer by a median of 4 months in the capecitabine/bevacizumab arm; among patients in the capecitabine/bevacizumab arm, overall survival was 20.7 months versus 16.8 months in the capecitabine-only arm (HR, 0.79; 95% confidence interval [CI], 0.57–1.09; *P*=.182). The median overall survival of 20.7 months in an elderly patient population was remarkable, in particular since only approximately one-third of patients received subsequent lines of therapy after first-line treatment with capecitabine/bevacizumab or capecitabine alone. In addition, response rate nearly doubled from 10% to 19.3% with the addition of bevacizumab to capecitabine. Although this endpoint has limited clinical meaning, it is an interesting finding. The results of AVEX support the idea that a fluoropyrimidine plus bevacizumab has a strong synergism in terms of efficacy. A fluoropyrimidine plus bevacizumab is commonly used as maintenance therapy after induction treatment with FOLFOX plus bevacizumab to avoid the cumulative neurotoxicity related to oxaliplatin. The idea of an induction maintenance therapy approach has recently gained traction in colorectal cancer. The results of prospective trials investigating maintenance therapy with a fluoropyrimidine/bevacizumab combination will be presented at the 2013 ASCO meeting.

In colorectal cancer, the question is what can be used as maintenance therapy beyond standard fluoropyrimidine-based chemotherapy. Among the more provocative data presented at the 2012 ASCO meeting were results from the phase III DREAM (Double Inhibition Reintroduction Erlotinib Avastin) trial.[4] In this study, patients received induction chemotherapy with an oxaliplatin-based regimen and bevacizumab followed by maintenance therapy with either bevacizumab or bevacizumab with erlotinib, a small-molecule EGFR inhibitor. As a single agent, erlotinib has not been thought to be active in colorectal cancer. When erlotinib was added to bevacizumab, however, patients experienced a prolonged progression-free survival compared to bevacizumab alone, with an HR of 0.7.[4] Although this result did not

XELOX With Bevacizumab in Elderly Patients Age 75 or Older With Metastatic Colorectal Cancer: Results of a Planned Interim Analysis for Multicenter Phase II ASCA Study

Keiichiro Ishibashi, MD, and colleagues presented results from a planned interim analysis of an open-label, multicenter, phase II study of XELOX plus bevacizumab in patients ages 75 years or older with metastatic CRC (Abstract 502). The study's primary endpoint was PFS, with secondary endpoints of safety, ORR, time to treatment failure, and OS. Of the 36 enrolled patients, the median age was 78 years (range, 75–86 years), 58.3% were male, and ECOG PS was 0 (83.3%) or 1 (16.7%). The primary tumor site was the colon (66.7%) or rectum (33.3%), and 63.9% of patients had undergone primary tumor resection. The most common metastatic sites were the liver (58.3%), lung (36.1%), and lymph nodes (38.9%). The median creatinine clearance was 60.8 mL/min (range, 32.6–84.6 mL/min). Patients received bevacizumab (7.5 mg/kg) and oxaliplatin (130 mg/m^2) on day 1 plus capecitabine (1,000 mg/m^2) orally twice daily for 14 days in a 3-week cycle. With a median follow-up of 250 days, the study reported an ORR of 55.6%, including 1 patient (2.8%) with CR, and a disease control rate of 91.7%. The time to treatment failure was 209 days (95% CI, 141–329 days). The most common non-hematologic grade 3 or higher AEs occurring in at least 5% of patients were sensory neuropathy (13.9%), hypertension (11.1%), fatigue (8.3%), hand-foot syndrome (8.3%), and bleeding, diarrhea, and anorexia, each occurring in 5.5% of patients. The incidence of grade 3 or higher AEs was significantly greater in patients with low creatinine clearance (<64 mL/min) versus those with a high creatinine clearance (77.7% vs 22.2%; *P*<.001) and was observed for hematologic (*P*=.003) and non-hematologic (*P*=.020) AEs.

change the standard of care, it showed that erlotinib might work synergistically with bevacizumab, which had not necessarily been expected. Presentations at the 2013 ASCO GI meeting included a subgroup analysis of *KRAS* mutation status on the effect of erlotinib plus bevacizumab as maintenance therapy.[5] *KRAS* mutation status serves as a predictive marker for whether patients have a chance to benefit from EGFR monoclonal antibodies. In the DREAM subgroup analysis, surprisingly, there was no difference between the *KRAS*–wild-type and *KRAS*-mutant populations with regard to the effect of erlotinib on progression-free survival. In *KRAS*-mutant patients, the addition of erlotinib to bevacizumab did not appear to be antagonistic, in contrast to previous reports of combination therapy with EGFR antibodies and bevacizumab, which routinely show antagonism. The effects of erlotinib as a small molecule appear to differ from those of monoclonal antibodies targeting the EGFR.

A critical question is whether *KRAS* wild-type patients will benefit from treatment with bevacizumab or EGFR antibodies as first-line or second-line therapy. There are 2 definitive phase III studies undergoing data analysis, which will be presented soon. The FIRE-3 (5-FU, Folinic Acid and Irinotecan [FOLFIRI] Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First Line Treatment Colorectal Cancer [CRC]) study was a randomized, head-to-head comparison between FOLFIRI/cetuximab and FOLFIRI/bevacizumab as first-line therapy in 520 colorectal cancer patients with *KRAS* wild-type tumors.[6] The primary endpoint is response rate. These data will be presented at the 2013 ASCO meeting. A larger study from the Cancer and Leukemia Group B and the Southwest Oncology Group, CALGB/SWOG 80405, allowed investigators to select either FOLFOX or FOLFIRI, and then compared head-to-head cetuximab and bevacizumab in approximately 1,100 patients with *KRAS* wild-type tumor.[7] The primary endpoint is overall survival, and data are expected next year. Results of these studies are eagerly awaited.

Some preliminary phase II data regarding treatment of *KRAS* wild-type patients were presented at the ASCO GI meeting. The PEAK (A Phase 2 Study of Panitumumab Plus mFOLFOX6 vs. Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Subjects With Wild-Type *KRAS* Tumors) study compared FOLFOX with panitumumab, an EGFR antibody, and bevacizumab as first-line therapy in 280 patients with wild-type *KRAS* colorectal cancer.[8] Interestingly, there were no substantial differences in progression-free survival in this population. Response rates were also similar (58% in the panitumumab arm and 54% in the bevacizumab arm). This study was decently powered, and the results confirm that we cannot necessarily assume that one treatment approach—meaning EGFR antibody first-line or bevacizumab first-line—would be superior in any of these parameters in *KRAS* wild-type colorectal cancer. For overall survival, there was no difference in the HR, although follow-up was limited. Median overall survival had not been reached for panitumumab and was 25.4 months for bevacizumab (HR, 0.72; 95% CI, 0.47–1.11; *P*=.14). Many patients were censored along the way, and the overall survival results are not yet mature.

The SPIRITT (Second-Line Panitumumab-Irinotecan Treatment Trial) study compared FOLFIRI/panitumumab and FOLFIRI/bevacizumab in the second-line setting.[9] All patients in this study had received first-line therapy with bevacizumab and an oxaliplatin-based regimen. Results were similar to those in the first-line PEAK study.[8] There were no apparent differences in progression-free survival or overall survival. Response rates, however, appeared to differ in the second-line setting. In the SPIRITT trial, approximately 32%

FOLFOXIRI Plus Bevacizumab (BEV) in Patients (pts) With Previously Untreated Metastatic Colorectal Cancer (mCRC): Preliminary Safety Results From the OPAL Study

Alexander Stein, MD, and colleagues presented safety results from the OPAL (Study of Avastin [Bevacizumab] in Combination With FOLFOXIRI in Patients With Previously Untreated Metastatic Colorectal Cancer) study (Abstract 515). The open-label, single-arm, phase II study's primary endpoint was PFS, with secondary endpoints of OS, ORR, the proportion of patients achieving resectability, and safety. Patients received up to 12 cycles of FOLFOXIRI plus bevacizumab (5 mg/kg) every 2 weeks in the induction phase followed by up to 40 cycles of 5-FU infusion (3,200 mg/m^2) on day 1 plus folinic acid (200 mg/m^2) on day 1 every 2 weeks in the maintenance phase. The 90 patients in the safety population were a median age of 58 years (range, 29–71 years). Most (71%) were male, and 54% had an ECOG PS of 0. Thirty-nine percent of patients had a primary rectal tumor, 57% had multiple metastatic sites, and 39% had metastasis to the liver only. The relative dose intensities were 86%±14% for bevacizumab, 85%±16% for oxaliplatin, 84%±16% for irinotecan, and 81%±16% for 5-FU. No new safety signals emerged. Grade 3/4 AEs occurring in at least 5% of patients during the induction phase included leukopenia/neutropenia (24%), diarrhea (10%), vomiting (8%), nausea (7%), and neurotoxicity (7%) during induction. Grade 3/4 AEs of interest due to bevacizumab included venous thromboembolism (6%) and hypertension (3%) during induction plus abscesses/fistulae (1%) and wound-healing complications (1%) during maintenance. At the time of reporting, resection of metastases had occurred in 23% of patients, including curative resection in 13% of patients.

of patients had a response with panitumumab compared to 19% of patients receiving bevacizumab. The SPIRITT trial was not meant to be a formal comparison between the 2 regimens; it was more of a benchmarking trial for both arms. The meaning of the difference in response rates is unclear. In the second-line setting, the primary goal of medical therapy is prolonging time to tumor progression and improving survival, not increasing response.

These studies are interesting because they show that active treatment approaches in the first-line and second-line settings include EGFR antibodies or bevacizumab, which is now also used beyond progression from first-line to second-line therapy. In the end, it is always good to have options so that we can tailor our approach toward different patient populations. Results of the larger studies are necessary to allow a definitive comparison between EGFR antibodies and bevacizumab, particularly in first-line therapy. Thus far, data suggest that there is no important difference in terms of outcomes for the major parameters between EGFR antibodies and bevacizumab in *KRAS* wild-type tumors.

The benefits seen with the addition of novel agents (eg, aflibercept, regorafenib) and approaches (the use of bevacizumab beyond progression) have been incremental at best, increasing overall survival by approximately 1.5 months with each new attempt. It is generally agreed that future treatment approaches will involve the targeting of patient subpopulations based on molecular profiles. Currently, much international effort is focused on characterizing these different subpopulations based on factors such as gene expression profiling, genetic analysis, mutation analysis, and deep sequencing. The goal is to no longer manage colorectal cancer as if it were one entity but to subcharacterize patients based on their molecular profile. An interesting study presented at ASCO by Dr. Joshua Uronis aimed to establish a molecular profile of colorectal cancer based on a molecular subgroup analysis, which eventually characterized 6 different groups of patients.[10] This study also examined the prognostic implications of these groups and offered predictive implications for how they would response to certain targeted agents. In another study presented at ASCO GI, colorectal cancer patients were subcharacterized using similar technologies into 3 different groups.[11] The actual molecular profile characteristics and the number of subgroups identified remain to be seen, in particular with regard to therapeutic implications. These molecular profiling data are still preliminary, but they highlight that in the future it should be possible to subcharacterize colorectal cancer patients and target them with specific interventions that will, hopefully, increase the benefits seen in the experimental arms of clinical trials. The question is how do we best get there, and, in particular, how should clinical trials be conducted so that the results are strong enough to convince regulatory agencies to approve drugs for subgroups of patients.

The regimens FOLFOX4 and modified FOLFOX6 are widely used in first-line therapy of colorectal cancer as an adjuvant therapy. These regimens are associated with risk of neutropenia and febrile neutropenia. Dr. Tamas Pinter presented results from the randomized, double-blind, phase III PAVES (Pegfilgrastim and Anti-VEGF Evaluation) study, which examined whether the prophylactic use of the growth factor pegfilgrastim can prevent febrile neutropenia, which is potentially life-threatening.[12] This large study randomized 845 patients to either FOLFOX plus pegfilgrastim or FOLFOX plus placebo. An interesting finding is that throughout the first 4 cycles of FOLFOX, the incidence of febrile neutropenia was a very low 5.7%, even in the absence of the growth factor. The prophylactic addition of the growth factor reduced the rate of febrile neutropenia even further, to 2.4%. This difference was statistically significant, but it has not influenced my clinical practice. The incidence of febrile neutropenia associated with FOLFOX was too low to justify the addition of pegfilgrastim as a prophylactic agent.

A Phase II Study on Third-Line Chemotherapy Combined Bevacizumab With S-1 for Metastatic Colorectal Cancer With Mutated KRAS: SAVIOR Study

Akinori Takagane, MD, and colleagues presented results from the phase II SAVIOR study, which investigated third-line S-1 chemotherapy plus bevacizumab in patients with mutated *KRAS*, metastatic CRC (Abstract 552). The 29 evaluated patients were a median age of 67 years (range, 38–78), and 93% of patients had an ECOG PS of 0–1. The primary tumor was located in the colon (55%), rectum (35%) or cecum (10%), and 83% of patients had undergone surgery for their primary tumor. Metastasis was reported in the liver (76%), lung (35%), abdominal lymph node (10%), or other site (28%). Patients received S-1 (80–120 mg, based on body surface area) for 4 weeks followed by 2 weeks' rest, plus bevacizumab (5 mg/kg) on days 1, 15, and 29. The primary endpoint was the disease control rate, with secondary endpoints of response rate, median PFS, median OS, and safety. Median dose intensities were 83.3% (range, 37.1–100%) for S-1 and 66.7% (range, 33.3–100%) for bevacizumab. After a median follow-up of 273 days, the disease control rate was 69.0%, with no CRs or PRs. Median PFS was 3.7 months (95% CI, 2.1–6.6 months), median OS was 9.0 months (95% CI, 7.0–12.0 months), and median time to treatment failure was 3.0 months (95% CI, 1.8–4.3 months). AEs of grade 3 or higher occurring in at least 10% of patients included anorexia (20%), anemia (17%), and diarrhea (10%).

Overall, this was an interesting year for colorectal cancer at ASCO GI. There were some important data on the integration of targeted agents into the treatment algorithm, as well as on the prospective use of molecular subprofiling, which will change the treatment landscape and our approach to patients in the future.

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References

1. Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (MCRC): results of the phase III randomized TRIBE trial. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 336.
2. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab (bev) in combination with capecitabine (cape) for the first-line treatment of elderly patients with metastatic colorectal cancer (mCRC): results of a randomized international phase III trial (AVEX). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 337.
3. Puthillath A, Mashtare T Jr, Wilding G, et al. A phase II study of first-line biweekly capecitabine and bevacizumab in elderly patients with metastatic colorectal cancer. *Crit Rev Oncol Hematol*. 2009;71:242-248.
4. Tournigand C, Scheithauer W, Samson B, et al. Induction treatment in first-line with chemotherapy + bevacizumab (bev) in metastatic colorectal cancer: results from the gercor-DREAM phase III study. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 457.
5. Tournigand C, Samson B, Scheithauer W, et al. 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. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30(suppl 18): Abstract LBA3500.
6. ClinicalTrials.gov. 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab versus FOLFIRI plus bevacizumab in first line treatment colorectal cancer (CRC). http://clinicaltrials.gov/ct2/show/NCT00433927. Identifier: NCT00433927. Accessed April 3, 2013.
7. Venook AP, Blanke CD, Goldberg RM, et al. Assessing the combination of FOLFOX or FOLFIRI with bevacizumab, cetuximab, or both in metastatic colorectal cancer. *Commun Oncol*. 2006a;3:593-593.
8. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK (study 20070509): a randomized phase II study of mFOLFOX6 with either panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) in patients (pts) with unresectable wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 446.
9. Hecht JR, Cohn AL, Dakhil SR, et al. SPIRITT (Study 20060141): a randomized phase II study of FOLFIRI with either panitumumab (pmab) or bevacizumab (bev) as second-line treatment (tx) in patients (pts) with wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 454.
10. Uronis JM, VanDeusen JB, Datto MB, et al. A molecular profile of colorectal cancer to guide prognosis and therapy after resection of primary or metastatic disease. *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 339.
11. Simon I, Roepman P, Schlicker A, et al. Association of colorectal cancer intrinsic subtypes with prognosis, chemotherapy response, deficient mismatch repair, and epithelial to mesenchymal transition (EMT). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract 333.
12. Pinter T, Abella S, Cesas A, et al. Results of a phase III, randomized, double-blind, placebo-controlled trial of pegfilgrastim (PEG) in patients (pts) receiving first-line FOLFOX or FOLFIRI and bevacizumab (B) for colorectal cancer (CRC). *J Clin Oncol* (ASCO Gastrointestinal Cancers Symposium Abstracts). 2012;30(suppl 34): Abstract LBA445.

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 4599 patients with CRC, non-squamous NSCLC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, 5 and 8) or uncontrolled, single arm (Study 6) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14)*.] The population was aged 18-89 years (median 60 years), 45.4% male and 85.8% (3729/4345) White. The population included 2184 first- and second-line mCRC patients who received a median of 10 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. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin and exposure to Avastin in 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

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 6, 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 5, 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 6, 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, 5 and 8. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 8, 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 8). [See *Warnings and Precautions (5.8)*.]

Congestive Heart Failure (CHF)

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 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.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were significantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

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%
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.

Avastin in Combination with Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin Based Chemotherapy in Second-line mCRC Patients who have Progressed on an Avastin Containing Regimen in First-line mCRC:

No new safety signals were observed in Study 4 when Avastin was administered in second line mCRC patients who progressed on an Avastin containing regimen in first line mCRC. The safety data was consistent with the known safety profile established in first and second line mCRC.

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 5. 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 6 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 8. 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 8
(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 an immune response to Avastin. In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and 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

Hepatobiliary disorders: Gallbladder perforation

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 8, 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 5, 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.

AVASTIN® (bevacizumab)

Manufactured by:
Genentech, Inc.

A Member of the Roche Group
1 DNA Way
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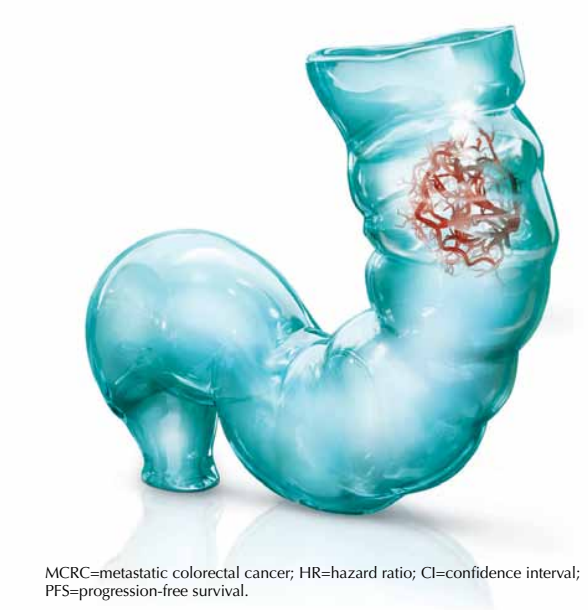
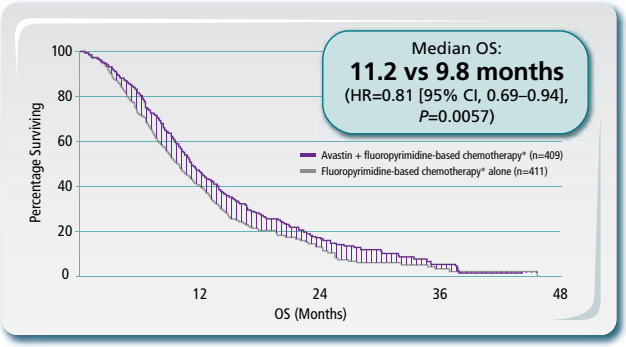


MCRC=metastatic colorectal cancer; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival.

The only biologic to prospectively demonstrate significant overall survival (OS) in a Phase III MCRC trial after treatment with a first-line Avastin-containing regimen[1]



*Chemotherapy combinations included both irinotecan- and oxaliplatin-containing regimens. At first progression, chemotherapy was switched: oxaliplatin→irinotecan or irinotecan→oxaliplatin.[1]

- 1.7-month increase in median PFS beyond first progression with Avastin plus fluoropyrimidine-based chemotherapy*: 5.7 vs 4.0 months with fluoropyrimidine-based chemotherapy* alone (HR=0.68 [95% CI, 0.59–0.78], *P*<0.0001)[1]
- There was no significant difference in response rate[1]

Indications

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.

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

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, 2.6%)
  - — Proteinuria (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

- Across all studies, the most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - — Epistaxis
  - — Headache
  - — Hypertension
  - — Rhinitis
  - — Proteinuria
  - — Taste alteration
  - — Dry skin
  - — Rectal hemorrhage
  - — Lacrimation disorder
  - — Back pain
  - — 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

Indication-specific adverse events

- When continued beyond first progression in MCRC, no new safety signals were observed in Study ML18147 when Avastin was administered in second-line MCRC patients who progressed on an Avastin-containing regimen in first-line MCRC. The safety data was consistent with the known safety profile established in first- and second-line MCRC

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to Genentech at (888) 835-2555.

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

Reference: 1. Avastin Prescribing Information. Genentech, Inc. January 2013.

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