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). Despite a median age of 69 years for patients with metastatic CRC, older patients remain undertreated. 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). 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 stratified based on ECOG PS and geographic locations; arm 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], 0.41–0.69; P<.001; Figure 1).
for patients who received bevacizumab plus capecitabine compared with those who survived. Data from Cunningham D et al. AVEX=Avastin With Xeloda in the Elderly; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.

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.

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.

 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 thrombotic 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
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). The trial enrolled 700 patients with treatment-naive, 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) (mFOLFIRI) plus bevacizumab (n=67); modified capcitabine and oxaliplatin (mXELOX) plus bevacizumab (n=204); or folinic acid (leucovorin), oxaliplatin, and fluorouracil (5-FU) (mFOLFOX7) plus bevacizumab (n=67), based on the investigator’s choice (Table 1). Each treatment was administered in a 2-week cycle. mFOLFIRI 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 mFOLFIRI 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). 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 bevacizumab was associated with a significantly lower incidence of grade 3/4 diarrhea compared with mFOLFIRI plus bevacizumab (9% vs 15%, respectively; P=.0006). Grade 3/4 neutropenia was similar across all arms, however.-grade 3/4 thrombocytopenia was more common with mFOLFIRI plus bevacizumab (9% vs 0%, respectively; P=.0012). Unstratified HR: 0.73 (95% CI, 0.60–0.88; P=.005).

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


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

<table>
<thead>
<tr>
<th></th>
<th>mFOLFOX7-Bevacizumab (%)</th>
<th>mXELOX-Bevacizumab (%)</th>
<th>FOLFIRI-Bevacizumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (5 mg/kg)</td>
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<tr>
<td>Folinic acid (400 mg/m²)</td>
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<tr>
<td>Oxaliplatin (100 mg/m²)</td>
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<tr>
<td>5-FU infusion (2,400 mg/m²)</td>
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<tr>
<td>Bevacizumab (5 mg/kg)</td>
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<tr>
<td>Oxaliplatin (100 mg/m²)</td>
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<td></td>
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<tr>
<td>Capecitabine (1,250 mg/m²)*</td>
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</table>

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; 5-FU=5-fluorouracil; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie; mFOLFOX7=modified regimen of folinic acid (leucovorin), oxaliplatin, and fluorouracil; mXELOX=modified capecitabine and oxaliplatin.

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

<table>
<thead>
<tr>
<th></th>
<th>mFOLFOX7-Bevacizumab (%)</th>
<th>mXELOX-Bevacizumab (%)</th>
<th>FOLFIRI-Bevacizumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>&lt;1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Neutropathy</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

DREAM=Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer; GERCOR=Groupe Coopérateur Multidisciplinaire en Oncologie; mFOLFOX7=modified folinic acid (leucovorin), oxaliplatin, and fluorouracil; 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.

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/m²) orally twice daily for 14 consecutive days with gemcitabine (1,000 mg/m²) 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. 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. 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. 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. 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 (19.4 months; 95% CI, 16.3–24.6 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). Correlations were also demonstrated between IC₅₀ 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 IC₅₀ 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 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 reinfected 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. 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**


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**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 S50). 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. Bevacizumab plus doublet chemotherapy is the current standard of care for metastatic CRC. 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. 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%; \( P < 0.001 \)), as was grade 3/4 neutropenia (50% vs 28%; \( P < 0.001 \)). Although toxicity increased with FOLFOXIRI, this regimen was superior based on ORR (66% vs 41%; \( P = 0.0002 \)), median PFS (9.8 months vs 6.9 months; \( P = 0.0066 \)), and median OS (22.6 months vs 16.7 months; \( P = 0.032 \)). 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. 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. 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. 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 Afiblercept (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, afiblercept and bevacizumab, in the treatment of patients with metastatic CRC previously treated with bevacizumab (Abstract 417). Ziv-afiblercept, 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-afiblercept 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 (Afiblercept 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 afiblercept 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 afiblercept treatment added 0.498 and 0.479 QALYs, respectively. The costs for bevacizumab versus afiblercept 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 afiblercept 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 afiblercept treatment cost $39,104 more per patient than treatment with bevacizumab.
Patients in arm A (n=256) received a FOLFIRI plus bevacizumab regimen consisting of bevacizumab (5 mg/kg), irinotecan (180 mg/m²), leucovorin (200 mg/m²), 5-FU bolus (400 mg/m²), plus 5-FU infusion (2,400 mg/m² over 48 hours). Patients in arm B (n=252) received a FOLFOXIRI plus bevacizumab regimen consisting of bevacizumab (5 mg/kg), irinotecan (165 mg/m²), oxaliplatin (85 mg/m²), leucovorin (200 mg/m²), and 5-FU infusion (3,200 mg/m² 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
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

Benoit 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. As previously described, patients in arm A received bevacizumab monotherapy for maintenance treatment and patients in arm B received erlotinib plus bevacizumab. 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 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. 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 severity of skin toxicity (grade 0–1 vs 2–4).

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.

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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
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. 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. 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/m²), leucovorin (400 mg/m²), 5-FU (400 mg/m²), all on day 1, plus 5-FU infusion (2,400 mg/m²) 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
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the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving Avastin plus FOLFIRI (27%) compared to patients receiving FOLFIRI alone (5%) in Study 8. In Study 7, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26%) compared to patients receiving PC plus placebo (17%). Beta-blocker use was also increased in the PC plus Avastin vs. placebo arm (18% vs. 14%). There were 19 (4.5%) infections with Grade 0–2 in the PC plus Avastin arm of which 3 (0.7%) were considered possibly related to Avastin. In patients receiving Avastin alone, there was a higher incidence (9%) of infections 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 2

<table>
<thead>
<tr>
<th>Grade 3–4 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm</th>
<th>IFN-α + Placebo</th>
<th>IFN-α + Avastin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>47%</td>
<td>52%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td>Constipation</td>
<td>29%</td>
<td>40%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>GI Hemorrhage</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omar’, cerebrovascular</td>
<td>20%</td>
<td>26%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29%</td>
<td>40%</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>0.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine retention</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0%</td>
<td>5%</td>
</tr>
</tbody>
</table>

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), the incidence of Grade 3 or 4 neutropenia was increased in the Avastin arm (20%) compared to 0.6% for patients receiving paclitaxel alone.

Recovery of ovarian function is defined as resumption of menses, or 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 not well characterized in populations of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

A post-treatment semen sample was collected on Days 1 and 21 of each cycle. Clinical laboratories were collected on Days 1 and 21 of each cycle. A 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not reported in Table 2: hypoglycemia (1% vs. 0.1%), 3rd trimester (0.1% vs. 0.0%), urinary tract infection (0.4% vs. 0.0%), and arterial thromboembolic event (3%, vs. 0%); infection (0.3% vs. 0.1%). In patients receiving Avastin alone, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients administered in combination with Avastin when compared to interferon alfa alone. In these 14 patients, three tested positive for neutralizing antibodies against Avastin before the start of the study, and five tested positive at the end of the study. The clinical significance of these anti-product antibody responses to bevacizumab is uncertain.

Immunochemistry 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, comparisons of the incidence of antibodies to Avastin with the incidence of antibodies to other therapeutic monoclonal antibodies are not meaningful.

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

Blood

Cardiovascular

Abdominal Pain

Vascular disorders

Digestive

Nausea

Hemic/Lymphatic

Abnormal Involuntary Movements

Musculoskeletal and connective tissue disorders

Metastatic Renal Cell Carcinoma

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin chemotherapy plus Avastin 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 in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus etoposide were tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal rejections. (See Nonclinical Toxicology (13.9).)
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Because of the observed teratogenic effects of bevacizumab in animals and of other inhibition 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 secreted 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 the 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 (12.6).]

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 anemia, sepsis, deep thromboembolism, hypertension, hypotension, myocardial infarction, congestive heart failure, diabetes, constipation, anemia, leukopenia, anemia, dehydration, hypokalemia, and hypoglycemia. 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 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 (8%) 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, anemia, 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%) 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%). Abrupt discontinuation of Avastin and chemotherapy recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See Warnings and Precautions (5.16) Adverse Reactions (6.5).]

10 OVERDOSAGE

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

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Code Revision Date: January 2013

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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 and 32 patients in the bevacizumab 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/m²) on day 1 and oral capecitabine (1,000 mg/m²) 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.

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: Other</td>
<td>0.48</td>
<td>0.27–0.86</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race: White/Caucasian</td>
<td>0.84</td>
<td>0.62–1.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>0.79</td>
<td>0.48–1.30</td>
<td>.02</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1.8</td>
<td>0.68–4.74</td>
<td>.003</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>0.82</td>
<td>0.60–1.11</td>
<td>.24</td>
</tr>
<tr>
<td>Baseline LDH: &lt;2 × ULN</td>
<td>0.89</td>
<td>0.64–1.23</td>
<td>.37</td>
</tr>
<tr>
<td>Baseline LDH: &lt;1.5 × ULN</td>
<td>0.87</td>
<td>0.61–1.22</td>
<td>.35</td>
</tr>
<tr>
<td>Location of site: Liver</td>
<td>1.03</td>
<td>0.57–1.86</td>
<td>1.00</td>
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<tr>
<td>All patients</td>
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<td>0.65–1.17</td>
<td>.35</td>
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</tbody>
</table>

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.
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**


**Commentary**

Axel Grothey, MD  
Professor of Oncology  
Mayo Clinic  
Rochester, Minnesota

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. 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/m². This regimen also uses a high dose of continuous-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. This trial reduced the intensity of first-line chemotherapy. The study had an interesting design. It compared...
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/m² 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 oxalaplatin 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

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**XEOLOX 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/m²) on day 1 plus capecitabine (1,000 mg/m²) 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 recently 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.\(^9\) 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%
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 and 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. This study also examined the prognostic implications of these groups and offered predictive implications for how they would respond to certain targeted agents. In another study presented at ASCO GI, colorectal cancer patients were subcharacterized using similar technologies into 3 different groups. 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. 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.

Acknowledgment
The Mayo Clinic Foundation has received funding for research conducted by Dr. Grothey from Genentech, Bayer, Datichi, and Eisai.

References
9. Hecht JR, Cohn AL, Dalal 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.
Avastin® (bevacizumab)

6 ADVERSE REACTIONS

The following common 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 (5.7)].
- Surgery and wound healing [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 (5.2)].
- Non-Gastrointestinal Fistula Formation [See Dosage and Administration (2.4), Warnings and Precautions (5.4)].
- Hypertensive crisis [See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.5)].
- 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 (5.6)].

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 first dose of Avastin were evaluated with serial CNS imaging, showing Grade 2 CNS hemorrhage in documented in one of 83 Avastin-treated patients (1.2%), 9% CI 0.06%–3.89%.

In a clinical study in patients with squamous cell histology and two of 53 (3.8%) patients receiving Avastin developed venous thromboembolism (VTE) which consisted of deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the incidence of grade ≥3 adverse events between PC alone and FOLFOX+Avastin in this population. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had evidence of venous thromboembolism including DVT during chemotherapy and 1 patient had VTE after completing chemotherapy. In a study of 661 patients treated with Avastin, 6 were reported with confirmed DVT and 12 with PE.

In a randomized study in 1097 patients treated with Avastin in combination with chemotherapy, the risk of developing VTE was increased in patients receiving Avastin compared with an equal placebo arm (13.5% vs. 6.9%, 9% CI 0.4%–24.7%)

The incidence of severe hypertension is increased in patients receiving Avastin. The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients has not been established. There is insufficient information on the use of Avastin. Because these reactions are reported voluntarily from a population of patients treated with Avastin, it is not possible to reliably estimate the incidence of reports of these events and therefore also the underestimation of the true frequency with which these and other serious adverse reactions occurring in nursing infants from bevacizumab, a decision should be made whether to continue Avastin therapy in the infant with caution and under medical supervision. In patients who have developed proteinuria during Avastin treatment and who continue Avastin therapy, monitoring of proteinuria is recommended.

The incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving Avastin in combination with FOLFOX chemotherapy compared to FOLFOX chemotherapy alone (144). In Study 7, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving pacitaxel/carboplatin (PC) plus Avastin (26.4%) compared with patients receiving PC alone (7.2%). Neutropenic fever was also increased in the PC plus Avastin arm (18.4%) vs. 1.8% for PC alone were there. 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 infections in patients receiving PC alone, of which 2 were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, pyelectasia, neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm (13.6%) compared to the PC alone arm (9.2%) patients (6.6%).

In study 1, one fatal event of neutropenic infection occurred in a patient with pneumonia, and neutropenia, catheter infection and wound infection. In clinical studies, the most common adverse reactions were headache, thirst, fatigue and hypertension. 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 first dose of Avastin were evaluated with serial CNS imaging, showing Grade 2 CNS hemorrhage in documented in one of 83 Avastin-treated patients (1.2%), 9% CI 0.06%–3.89%.

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

Table 1

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<th>Event</th>
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<td>2%</td>
<td>3%</td>
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<tr>
<td>Adverse events due to Avastin</td>
<td>3%</td>
<td>3%</td>
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Adverse events other than those noted in Table 1 and reported in ≥5% of patients in any arm were as follows:

- Fever
- Rash
- Chills
- Pruritus
- Hypotension
- Hypertension
- Hypokalemia
- Hypocalcemia
- Urticaria
- Eosinophilia
- Eosinophils
- Neutrophilia
- Neutrophilia
- Neutropenia
- Leukopenia

AVASTIN® (bevacizumab) and hypertension, and hemorrhage (3% to 0.3%); including episitis, small intestinal hemorrhage, aneurysm rupture, gastric ulcer hemorrhage, gingival bleeding, subcutaneous hemorrhage, intracranial large vessel hemorrhage, respiratory tract hemorrhage, and thrombocytopenia.

Grade 1–5 adverse events occurring at a higher incidence (>5%) in patients receiving IFX plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%); including hypertension

AVASTIN® (bevacizumab) approximately 1 to 12 times the recommended dose of bevacizumab demonstrated synergistic efficacy, 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 resections. (See Nonclinical Toxicology (14.9).

Because of the observed toxic effects of bevacizumab in animals and of other inhibitors of angiogenesis in human, 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 breast milk to a significant extent 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 the drug, taking into account the half-life of the bevacizumab (approximately 20 days) and the importance of the drug to the mother. (See Clinical Pharmacology (12.1).)

8.4 Gastrointestinal Use

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

Anti-tumor 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 cromoblastomatus monkeys with open growth plates exhibited physical 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 physical dysplasia was dose-related and were related primarily 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 and older as compared to younger patients were atrial fibrillation, deep-venous thrombosis, hemorrhage, hypertension, myocardial infarction, congestive heart failure, diabetes, constipation, anorexia, leukopenia, anemia, hypertension, and hypokalemia. The frequency of adverse events on Avastin was similar in elderly patients as compared to younger patients.

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

In Study 2, patients aged 65 years and older receiving AVASTIN had a greater relative risk for granulocytopenia as compared to younger patients. (See Warnings and Precautions (5.8).)

The rate of severe and non-fatal 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 was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (21.5% vs. 14.1%). (See Warnings and Precautions (5.9).)

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.

In a prospectively designed subset of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure in the chemotherapy-alone arm (23%) was significantly less compared to the control arm (32%). 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 was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (21.5% vs. 14.1%). (See Warnings and Precautions (5.9).)

10 OVERDOSAGE

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

AVASTIN® (bevacizumab)

Manufactured by: Genentech, Inc.

A Member of the Roche Group

Genentech

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Initial U.S. Approval: February 2004

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NOW APPROVED: Avastin continued beyond first progression in MCRC

In combination with fluoropyrimidine-based chemotherapy following a first-line Avastin-containing regimen...

Think Avastin

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
- Surgery and wound healing complications
- Hemorrhage
- Additional serious adverse events

Most common adverse events
- Across all studies, the most common adverse events observed in Avastin patients at a rate >10% and at least twice the control arm rate were:
  - Epistaxis
  - Proteinuria
  - Lacrimation disorder
  - Hypertension
  - Dry skin
  - Exfoliative dermatitis
  - Rhinitis
  - Rectal hemorrhage

Pregnancy warning
- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- Advise pregnant 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.

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

Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included:
- Hypertension (grade 3–4, 5%–18%)
- 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.

Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included:
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- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin.


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

Continuing to deliver proven overall survival

Median OS: 11.2 vs 9.8 months
(HR=0.81 [95% CI, 0.69–0.94], P=0.0057)

1. 1-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)
2. There was no significant difference in response rate

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


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Avastin® bevacizumab