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APPROVAL PACKAGE FOR:

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Medical Review(s)

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Primary Clinical Review

Cover Sheet

Submission Type Biologic Licensing Application
Submission Number STN 125085

Letter Date
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Established Name Bevacizumab
Trade Name or Proposed Trade Name Avastin
Therapeutic Class Monoclonal Antibody
Sponsor Genentech

Priority Designation (S or P) P

Sponsor's Proposed:
- Formulation Sterile Liquid
- Dosing Regimen 5 mg/kg IV every Two Weeks
- Indication Metastatic Colorectal Cancer
- Intended Population Initial Treatment of Metastatic Colorectal Cancer

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APPEARS THIS WAY
ON ORIGINAL

1.0 Executive Summary

1.1 Recommendation on Clinical Approvability

Approval is recommended for the use of bevacizumab in combination with an intravenous 5-fluorouracil based regimen in the treatment of metastatic colorectal cancer.

This recommendation is based on the highly statistically significant improvement in overall survival seen with the addition of bevacizumab to the combination of irinotecan, 5-fluorouracil, and leucovorin.

1.2 Recommendation on Postmarketing Actions

The following clinical post-marketing commitments are recommended.

1. To obtain preliminary safety and activity data and to characterize the pharmacokinetics of Bevacizumab in pediatric patients in Study AVF2117s, a Phase 1, dose-escalation trial, enrolling up to 24 children with relapsed or refractory solid tumors to be conducted by the Children's Oncology Group (COG). Safety data will include an assessment of the effect of Bevacizumab on growth and development, including fertility. Patient accrual will be completed by December 31, 2005, the study will be completed by March 31, 2006, and the final study report submitted by December 31, 2006.

2. To collect data and conduct analyses within study NO16966 that will characterize the clinical consequences of both full-dose and low-dose anticoagulation therapy and assess the role of the international normalization ratio (INR) as a predictor of subsequent hemorrhage and/or thrombosis in patients treated with Bevacizumab. This will be evaluated in a subset of 1320 subjects, enrolled in the amended study NO16966, 50 percent of whom will be randomized to receive Bevacizumab. The final protocol will be submitted by March 31, 2004, patient accrual will be completed by June 30, 2005, the study will be completed by March 30, 2007, and the final study report submitted by September 28, 2007.

3. To conduct analyses to characterize the comparative incidence of proteinuria, risk factors associated with proteinuria, and the clinical course of proteinuria (including time to resolution) using available data from ongoing trials AVF2107g, AVF2192g, and AVF2119g. Collection of data under these studies will be completed by June 30, 2004, an analysis post-last patient observed will be submitted by December 31, 2004, the one year follow-up period will be completed by June 30, 2005, and an analysis post-one year follow-up will be submitted by December 30, 2005.

4. To assess for risk factors associated with proteinuria by prospectively collecting and analyzing data to characterize the incidence and clinical course (including duration) of proteinuria in patients during treatment with Bevacizumab and following the discontinuation of Bevacizumab and in concurrent control patients. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

5. To explore patient factors associated with the risk of development of proteinuria, characterize the clinical course of proteinuria, and assess screening strategies that more accurately identify patients at increased risk of high-grade proteinuria and nephrotic syndrome in 100 patients treated with Bevacizumab alone or in combination with erlotinib in study AVF2938g. The data will be analyzed by overall study population and by treatment arm. The final protocol will be submitted by March 31, 2004, patient accrual will be completed by March 31, 2005, the study will be completed by March 31, 2006, and the final study report submitted by September 29, 2006.

6. To conduct analyses to characterize the comparative incidence of hypertension in patients treated with Bevacizumab to those not receiving Bevacizumab, risk factors associated with hypertension, and the clinical course of hypertension (including time to resolution), using available data from studies AVF2107g, AVF2192g, and AVF2119g. Collection of data under these studies will be completed by June 30, 2004, an analysis post-last patient observed will be submitted by December 31, 2004, the one year follow-up period will be completed by June 30, 2005, and an analysis post-one year follow-up will be submitted by December 30, 2005.

7. To prospectively collect and analyze data characterizing the incidence and clinical course (including duration and medical management) of hypertension in patients during treatment and following the discontinuation of Bevacizumab and in concurrent control patients. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

8. To provide narrative descriptions of each vascular adverse event (myocardial infarction, cerebrovascular accident, peripheral arterial event,

vascular aneurysm or other vessel wall abnormalities, and venous thromboembolic events) for patients enrolled in study AVF2540g and to provide descriptive statistics of the incidence of vascular events (overall and each subtype). Patient accrual will be completed by June 30, 2004, the study will be completed by December 31, 2004, and the final study report submitted by June 30, 2005.

9. To collect data and conduct analyses of the comparative incidence of delayed vascular events (myocardial infarction, cerebrovascular accident, peripheral arterial event, vascular aneurysm or other vessel wall abnormalities, and venous thromboembolic events) in Bevacizumab-treated patients following the discontinuation of Bevacizumab (from 12 to 24 months after initiation of treatment) and in concurrently enrolled control patients (over the same time interval-12 to 24 months after initiation of treatment) in NSABP study C-08. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, this portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

10. To assess the relative impact on fertility and gonadal function of Bevacizumab in combination with chemotherapy, as compared to patients receiving chemotherapy alone. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the portion of the study will be completed by December 31, 2007, and the final report for this portion of the study submitted by June 30, 2008.

11. To examine the long-term impact of Bevacizumab on pregnancy outcome. This will be evaluated through inclusion of a special section in the periodic adverse experience report (PAER) containing a thorough and cumulative evaluation of pregnancy, spontaneous abortion, and fetal malformation. The PAER will be submitted at quarterly intervals for three years from the date of approval. This commitment will be fulfilled by submission of a final PAER by February 28, 2007.

12. To directly assess the pharmacokinetic interactions between irinotecan and Bevacizumab in a single-arm, cross-over study in approximately 32 evaluable subjects. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 30, 2005, the study will be completed by March 31, 2006, and the final study report submitted by September 29, 2006.

13. To assess the pharmacokinetic profile of Bevacizumab in a rodent model of hepatic dysfunction. The final protocol will be submitted by March 31,

2004, the study will be initiated by June 30, 2004, completed by September 30, 2004, and the final study report submitted by December 31, 2004.

14. To perform additional analyses of clinical pharmacokinetic data from studies AVF0780g and AVF2107g in order to provide a comparison of clearance in patients with hepatic dysfunction. The results of these additional analyses will be submitted by June 30, 2004.

15. To obtain further information on the pharmacokinetics of Bevacizumab by assessing Bevacizumab drug levels at 3 and 6 months post-treatment in NSABP study C-08. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the pharmacokinetic evaluation will be completed by June 30, 2008, and the population pharmacokinetics final study report submitted by December 31, 2008.

16. To develop a standardized approach to the collection of data and generation of narrative descriptions of selected adverse events (gastrointestinal perforation, intra-abdominal abscess, fistula, wound dehiscence) that will include description of the event, surgical operative and pathology reports, and outcome/resolution information, for all such patients enrolled in studies NO16966 and NSABP study C-08. The summary report for this data will be submitted by June 30, 2008.

17. To provide the final study report for study E3200, examining the comparative safety and effectiveness of single agent Bevacizumab, Bevacizumab in combination with the FOLFOX4 regimen, and FOLFOX4 alone. The study will be completed by September 30, 2005 and the final study report submitted by March 31, 2006.

18. To provide the study report for study AVF2192g examining the comparative efficacy and safety of 5-fluorouracil and leucovorin with and without Bevacizumab in patients with newly diagnosed metastatic colorectal cancer who are unable to tolerate irinotecan- based therapy. The final study report will be submitted by September 30, 2004.

19. To develop a validated, sensitive and accurate assay for the detection of an immune response (binding and neutralizing antibodies) to Bevacizumab, including procedures for accurate detection of antibodies to Bevacizumab in the presence of serum containing Bevacizumab and vascular endothelial growth factor. The assay methodology and validation report will be submitted by September 30, 2004.

20. To more accurately characterize the immune response to Bevacizumab in NSABP study C-08 using the more sensitive, validated assay described

above. The final protocol will be submitted by June 30, 2004, patient accrual will be completed by December 29, 2006, the study will be completed by June 30, 2008, and the final study report submitted by December 31, 2008.

1.3 Summary of Clinical Findings

1.3.1 Overview of Clinical Review

1.3.2 Efficacy

A single primary efficacy study, AVF2107g, was conducted. Protocol AVF2107g was a randomized, placebo-controlled, active-therapy, multicenter trial conducted in patients receiving initial therapy for metastatic colorectal cancer. Protocol AVF2107g randomized 923 patients to one of three treatment arms:

1. ARM 1: Irinotecan, 5-Fluorouracil, and Leucovorin plus Placebo
2. ARM 2: Irinotecan, 5-Fluorouracil, and Leucovorin plus Bevacizumab
3. ARM 3: 5-Fluorouracil, Leucovorin, and Bevacizumab

Following a pre-planned analysis of safety, enrollment to the 5-fluorouracil, leucovorin and bevacizumab arm (Arm 3 above) was discontinued. Enrollment continued in the remaining arms. Comparisons of efficacy endpoints were conducted between Arms 1 and 2 above.

The findings of this study were:

1. Statistically significant improvement in the primary endpoint, overall survival, from 20.3 to 15.6 months, $p < 0.001$, favoring the bevacizumab arm. Major protocol violations were presents in 39.9% of patients in Arm 1 and 49.5% of patients in Arm 2. The effect remained statistically significant when patients with major protocol violation were excluded from the analysis.

2. Statistically significant improvement in the secondary efficacy endpoints of progression free survival and response rate, favoring the bevacizumab arm.

The supportive study, AVF0780g, randomized 104 patients undergoing initial treatment of metastatic colorectal cancer to one of three arms:

1. 5-Fluorouracil and Leucovorin
2. 5-Fluorouracil and Leucovorin plus Bevacizumab 5 mg/kg
3. 5-Fluororuacil and Leucovorin plus Bevacizumab 10 mg/kg

The key findings of the study include:

1. A statistically significant improvement (after adjustment for multiplicity) in the co-primary endpoint progression free survival when the patients in the arm receiving 5 mg/kg of bevacizumab are compared to the control group. Progression free survival improved from 5.2 to 9 months, p = 0.005.

2. When the patients receiving 10 mg/kg of bevacizumab were compared to the control population, progression free survival was longer (5.2 vs. 7.2 months). This observed difference was not statistically significant.

3. A higher overall response rate was observed in patients in the 5 mg/kg arm as compared to the control population (40.0% vs. 16.7%). This observed difference was not statistically significant.

4. A higher response rate was observed in patients in the 10 mg/kg arm as compared to the control population (24.2% vs. 16.7%). This observed difference was not statistically significant.

1.3.3 Safety

The safety profile of bevacizumab was assessed and adverse event information obtained in the major efficacy trial (897 patients), the supportive study (102 patients), and in other Genentech-sponsored studies in patients who received bevacizumab (1032 total, 441 non-colorectal cancer patients). Safety information was also obtained from select studies conducted under IND 7921 (National Cancer Institute IND for bevacizumab) and in the National Cancer Institute's AdEERs database of expedited reports.

The most serious adverse events associated with bevacizumab were:

1. Gastrointestinal Perforation and Impaired Wound Healing
2. Life-threatening and Fatal Hemorrhagic Events
3. Hypertensive Crisis
4. Life-threatening Thromboembolic Events
5. Nephrotic Syndrome a
6. Congestive Heart Failure

In the major efficacy trial, intestinal perforation, sometimes complicated by intra-abdominal abscess was seen in one of 396 patients in the irinotecan, 5-fluorouracil, and leucovorin and six of 392 patients in the irinotecan, 5-fluorouracil, and leucovorin plus bevacizumab arm. Four of the 109 patients in the 5-fluorouracil, leucovorin, and bevacizumab arm developed intestinal perforation/intra-abdominal abscess. An increase in the incidence of wound dehiscence was also noted with bevacizumab.

In the major efficacy trial, the incidence of hemorrhage was increased in the bevacizumab arms as compared to control. This was primarily due to a marked increase in grade 1-2 events such as epistaxis and gastrointestinal hemorrhage with only a small increase in the incidence of grade 3-4 hemorrhage in the bevacizumab arms when compared to control. The incidence of epistaxis in the 392 patients receiving irinotecan, 5-fluorouracil, and leucovorin plus bevacizumab was 35% as compared to 10% in the 396 patients receiving irinotecan, 5-fluorouracil, and leucovorin alone. In one study of 98 patients with non-small cell lung cancer randomized to chemotherapy or to chemotherapy plus bevacizumab, the incidence of serious or fatal hemoptysis was 9.1% in bevacizumab treated patients versus 0% in patients receiving chemotherapy alone. In a second study, five patients of approximately 200 patients receiving chemotherapy plus bevacizumab died due to hemoptysis compared to no patients in the chemotherapy alone arm.

Marked increases in blood pressure have been noted with the use of bevacizumab. This includes a two to three fold increase in the number of patients with a blood pressure in which either the systolic is greater than 200 or the diastolic is greater than 110 (2.5% vs. 6.6%). Severe hypertension has been associated with adverse events including subarachnoid hemorrhage, hemorrhagic cerebrovascular accident, and hypertensive encephalopathy.

The incidence of proteinuria is increased with the use of bevacizumab. These data are limited by the lack of a sensitive and specific screening assay for detection of proteinuria, the lack of compliance with 24 hour urine collections, and by the lack of information concerning the adequacy of 24 hour collections. In the major efficacy study, none of the 396 patients in the irinotecan, 5-fluorouracil, and leucovorin group, three of 392 patients receiving irinotecan, 5-flurorouracil, and leucovorin with bevacizumab, and three of the 109 patients receiving 5-fluorouracil, leucovorin, and bevacizumab had a 24 hour collection with greater than 3.5 grams of protein (NCI CTC Grade 3). The highest incidence of moderate and severe proteinuria was observed in a placebo-controlled, dose ranging trial of bevacizumab in patients with metastatic renal cell cancer. In the study, the incidence of proteinuria appears to be dose-related.

The incidence of thromboembolic events was slightly increased in patients receiving bevacizumab plus chemotherapy as compared to those receiving chemotherapy alone. The most notable increase was in the incidence of deep vein thrombosis. However, increased incidence of cerebrovascular events, myocardial infarction, and intra-abdominal thromboembolism was also noted.

The incidence of congestive heart failure (CHF) was not increased in the major efficacy study. However, the incidence of CHF was increased in a randomized study in patients who had received prior anthracycline therapy as compared to controls (11/229 vs. 2/215). A higher than expected incidence of CHF was noted in a single arm study of patients receiving both mitoxantrone and bevacizumab.

Here, six of 44 patients developed congestive heart failure. Four of these were grade 3-4 events.

In the Genentech safety database of 1032 patients, the most common NCI CTC grade 3 and 4 adverse events reported in 875 patients receiving bevacizumab were asthenia, pain, hypertension, diarrhea, and leukopenia. In 157 patients receiving single agent therapy, the most common grade 3-4 events were pain and hypertension. The most common adverse events in 1032 patients, regardless of severity, were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

1.3.4 Dosing, Regimen, and Administration

The major efficacy study administered bevacizumab 5 mg/kg every two weeks for up to 96 weeks. In other studies, dosing has ranged from 3 mg/kg to 20 mg/kg every two weeks and to 15 mg/kg every three weeks. The comparability of various doses and schedules (on a mg/kg/week basis) has not been established. Of note, in the supportive study (AVF0780g) clinical outcomes (PFS, response rate, and overall survival) were better in the 5 mg/kg dose group as compared to the 10 mg/kg dose group. The optimal dose of bevacizumab has not been established.

1.3.5 Drug-Drug Interactions

Formal drug-drug interaction studies have not been performed. The pharmacokinetics of irinotecan and its active metabolite SN-38 were assessed in a subgroup of patients enrolled in the major efficacy study. The average SN-38 levels were 33% higher in patients receiving bevacizumab in combination with irinotecan, 5-fluorouracil, and leucovorin (n = 29) when compared with patients receiving irinotecan, 5-fluorouracil, and leucovorin alone (n = 39). The importance of this finding is unclear. In other studies, SN-38 levels have been noted to vary due to allelic differences in the enzymes that metabolize irinotecan. Further, the clinical consequences of an increase in SN-38 levels are also unclear since there is little information available on the dose response relationship of irinotecan. However, in the major efficacy study both diarrhea and leukopenia were increased in patients receiving chemotherapy plus bevacizumab when compared to those receiving chemotherapy alone.

1.3.6 Special Populations

Gender and race had little effect on the adverse event profile of bevacizumab. There is a slightly higher incidence of hypertension and proteinuria among African-Americans as compared to other racial groups. In those over age 65, the incidence of asthenia, anorexia, dehydration, leukopenia, and sepsis was higher

than in those less than 65 years. An increase in adverse events uniquely associated with bevacizumab such as hypertension, deep vein thrombosis, myocardial infarction, congestive heart failure, and subarachnoid hemorrhage was also observed in the elderly as compared to younger patients.

2.0 Background

2.1 Clinical Context of Application

For many years, 5-fluorouracil and leucovorin were the only available treatment options for patients receiving initial treatment of metastatic colorectal cancer. More recently, agents such as irinotecan and oxaliplatin have build upon this underlying regimen. In a metanalysis, the response rate of 5-fluorouracil and leucovorin (5FU/LV) was 23% with an median overall survival of 11.5 months (JCO 10: 896-903, 1992). Various doses and schedules of 5-fluorouracil and leucovorin have been studied and there was been ongoing debate concerning the value of infusional versus bolus 5-fluorouracil. In a direct comparison of infusional versus bolus 5-fluorouracil, the response rate of the infusional regimen was 37% while that of the bolus regimen was 14%. However, this increase in response rate had little impact on overall survival (14.3 vs. 13.1 months) (JCO 15:808-815, 1997).

The addition of irinotecan to 5-fluorouracil and leucovorin has been directly compared using both bolus and infusional regimens. In a study of bolus 5FU, 231 patients were randomized to irinotecan, 5-fluorouracil, and leucovorin (IFL) and 226 to 5FU/LV. The median time to progression was 7 months in the IFL arm and 4.3 months in the 5FU/LV arm. Overall survival was 14.8 months with IFL and 12.6 months with 5FU/LV (N Engl J Med 343: 905-914, 2000). In a second study of infusional 5FU/LV, 199 patients were randomized to irinotecan, 5-fluorouracil and leucovorin and 188 to 5FU/LV. Both arms of this study used an infusional 5FU regimen and investigators could choose one of two schedules of infusional 5FU. The median time to progression was 6.7 months in the irinotecan group and 4.4 months with 5FU/LV. Overall survival was 17.4 months in the irinotecan group and 14.1 months with 5FU/LV (Lancet 355: 1041-1047, 2000).
More recently, oxaliplatin has been added to infusional 5FU/LV (FOLFOX). In a comparison of FOLFOX and infusional 5FU/LV, the median progression free survival was 9 months in the FOLFOX arm and 6.2 months with 5FU/LV. Median overall survival was 16.2 months with FOLFOX and 14.7 months with 5FU/LV. The difference in overall survival was not statistically significant. However, when overall survival was calculated in patients who did not receive second line irinotecan or oxaliplatin, the difference in overall survival became statistically significant (JCO 18:2938-2947, 2000). A second study compared FOLFOX using infusional 5FU to bolus IFL. This study randomized 267 patients to FOLFOX and 264 to IFL. The median time to progression was 8.7 months in the FOLFOX arm and 6.9 months with IFL. Median overall survival was 19.5 months with FOLFOX

and 15 months with IFL (JCO 22:23-30, 2004). Note that the overall survival with FOLFOX was greater in this study (19.5 months) than that in the original study comparing FOLFOX to 5FU/LV (16.2 months). However, the time to progression/progression free survival on the two studies was similar (8.7 vs. 9 months). The differences in these findings, the lack of a survival benefit versus a significant benefit, may in part be due to differential use of second line chemotherapy and to a large number of protocol violations in the initial study that compared 5FU/LV and FOLFOX.

The control arm of the current study employed a bolus IFL regimen. It is important to compare the toxicity of the IFL regimen in the current study to that seen in the large studies cited above. In the study that compared IFL and 5FU/LV, grade 3-4 diarrhea was seen in 22.7% of patients and grade 3-4 neutropenia in 53.8%. In the study that compared FOLFOX and IFL, 28% of patients experienced grade 3-4 diarrhea and 40% grade 3-4 neutropenia.

In this Biologics Licensing Application, bevacizumab added to IFL has been shown to provide a survival advantage when compared to IFL alone. The median overall survival of IFL plus bevacizumab (20.3 months) is similar to more recent studies using FOLFOX (19.5 months).

Currently, bevacizumab is not available in the United States or in foreign markets. It is the first product in its class to be submitted for licensure.

2.2 Pre-submission Activity

IND 7023 was submitted on January 31, 1997. Eleven studies have been conducted under this IND. A discussion between FDA and Genentech of the development plan for bevacizumab was held in January of 1999. At that time, the sponsor was encouraged to develop a protocol that would study dosing for a fixed period versus continuation of bevacizumab following discontinuation of chemotherapy.

A pre-Phase 3 meeting was held on March 7, 2000 to discuss AVF2107g, the major efficacy study in this application. The following issues arose at this meeting: the selection of an appropriate control arm, the study endpoint, an appropriate level of type 1 error, and the collection of adverse events. Issues unique to bevacizumab included a discussion of the continuation of bevacizumab in patients with a partial response and the timing of the termination visit. Several follow up teleconferences were held. Ultimately, it was decided that IFL would serve as the control arm. Overall survival, which has served as the basis for full approval of non-hormonal first line regimens in patients with metastatic cancer, was chosen as the primary endpoint. In the final version of this study, the sponsor chose to collect grade 1-2 events in the first 211 patients randomized to a bevacizumab containing arm and to continue bevacizumab in patients who had progressed on first line therapy. A separate meeting to discuss Chemistry,

Manufacturing, and Control and facilities issues prior to initiation of the major efficacy trial was held on March 9, 2000.

Multiple additional communications on this development program, by letter and teleconference calls, between FDA and Genentech occurred during 2001-2003.

On May 6, 2003, a meeting was held to discuss [redacted]

The sponsor presented a proposal [redacted]

Ultimately, Genentech decided [redacted] would not be feasible.

A pre-BLA meeting was held on June 27, 2003. The following issues arose at this meeting: submission of safety data obtained in the 1870 patients (32 studies) enrolled under BB-IND 7921 (sponsored by the National Cancer Institute), provision of subject narratives for all patients experiencing serious adverse events, and the inclusion of all analyses discussed in the final statistical analysis plan. A follow up teleconference was held on July 25, 2003. At this meeting the request for safety data obtained under IND 7921 was modified to include a much smaller submission packet. Also, it was agreed that patient narratives for serious adverse events involving nausea, vomiting, diarrhea, dehydration and neutropenia would only be required only for grade 4 events. Several follow up teleconferences were held and agreement was ultimately reached concerning the content of safety data to be included in the BLA.

3.0 Integrated Review of Clinical Data

3.1 Data Sources and Review Method

Data were reviewed from both the Genentech and National Cancer Institute (NCI) database. The Genentech database contained the following studies.

Study #	Phase	Indication	# of Patients	Bevacizumab	Chemotherapy
AVF0737g	1		25	0.1, 0.3, 1, 3, 10 mg/kg d 1, 28, 35, 42	
AVF761g	1		4	3 mg/kg q wk	Doxorubicin 50 mg/M^2
			4	3 mg/kg q wk	Carboplatin AUC 6 Paclitaxel 175 mg/M^2
			4	3 mg/kg q wk	5-Fluorouracil 500 mg/M^2 Leucovorin 20 mg/M^2
[redacted]	2	NSCLC[1]	32		Carboplatin AUC 6 Paclitaxel 200 mg/M^2

			32	7.5 mg/kg q 3 wks	Carboplatin AUC 6 Paclitaxel 200 mg/M^2
			35	15 mg/kg q 3 wks	Carboplatin AUC 6 Paclitaxel 200 mg/M^2
—	2	—	15	10 mg/kg q 2 wks	
—	2	—	18	3 mg/kg q 2 wks	
			41	10 mg/kg q 2 wks	
			16	20 mg/kg q 2 wks	
AVF0780g	2	Colorectal	36		5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
			35	5 mg/kg q 2 wks	5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
			33	10 mg/kg q 2 wks	5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
AVF2192g	2	Colorectal	100		5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
			100	5 mg/kg q 2 wks	5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
AVF2107g	3	Colorectal	411		5-Fluorouracil 500 mg/M^2 Leucovorin 20 mg/M^2 Irinotecan 125 mg/M^2
			402	5 mg/kg q 2 wks	5-Fluorouracil 500 mg/M^2 Leucovorin 20 mg/M^2 Irinotecan 125 mg/M^2
			110	5 mg/kg q 2 wks	5-Fluorouracil 500 mg/M^2 Leucovorin 500 mg/M^2
AVF2119g	3	Breast	230		Capecitabine 2500 mg/M^2
			232	15 mg/kg q 3 wks	Capecitabine 2500 mg/M^2
AVF0778g		Extension	39	Variable	Variable
AVF2540g		Extension	56	Variable	Variable

The major efficacy study, AVF2107g, and the supportive study, AVF780g, were reviewed in detail. Complete reviews of these trials are included in Section 6.1.

Data from the National Cancer Institute database were also reviewed. This included expedited reports from all clinical studies that were reported to the Adverse Events Expedited Reporting System (AdEERs), as well as, information from select individual trials. This information is included in the Summary of Clinical Safety in Section 6.1. The trials for which detailed safety data was provided were:

Genentech Number	NCI Number	Indication	Bevacizumab	Chemotherapy
AVF2380s	E3200	Colorectal	Bevacizumab 10 mg/kg q 2 wks	FOLFOX4
			None	FOLFOX4
			Bevacizumab 10 mg/kg q 2 wks	None

AVF2310s	2490	AML	Bevacizumab 10 mg/kg q 2 wks	Cytarabine Mitoxantrone
AVF2309s	2772	Breast	Bevacizumab 15 mg/kg q 3 wks	Doxorubicin Docetaxel
AVF0890s	T98-0035	Renal	Bevacizumab 3, 10 , 20 mg/kg q 2 wks	
AVF2307s	2722	Breast	Bevacizumab 10 mg/kg q 2 wks	Docetaxel

3.2 Clinical Pharmacology

Please see Clinical Pharmacology review.

3.3 Integrated Review of Efficacy

3.3.1 Approach to Review of the Efficacy

Efficacy was reviewed in the pivotal study, AVF2107g, and in a supportive study, AVF780g. Additionally, summary information obtained from the interim analysis of the NCI-sponsored study E3200 (addressing the single agent activity of bevacizumab in colorectal cancer) was reviewed.

A Phase 3 trial, AVF2119g, which randomized patients with metastatic breast cancer to capecitabine or to capecitabine plus bevacizumab, was also briefly reviewed. Two aspects of this trial were thought to, potentially, be applicable to patients with colorectal cancer. First, the addition of bevacizumab to capecitabine did not improve progression free survival when compared to capecitabine alone. Second, the chemotherapy agent used in this study, capecitabine, is also commonly used in patients with metastatic colorectal cancer.

3.3.2 Review of Trials by Indication

Pivotal Study AVF2107g

A Phase III, Multi-Center, Randomized, Active-Controlled Clinical Trial to Evaluate the Efficacy and Safety of rhuMAb VEGF (Bevacizumab) in Combination with Standard Chemotherapy in Subjects with Metastatic Colorectal Cancer

Study Design

Patients with newly diagnosed metastatic colorectal cancer were randomized to IFL + Placebo, IFL + Bevacizumab 5 mg/kg, or 5FU/LV + Bevacizumab 5 mg/kg. Bevacizumab was given every two weeks. Note that both the IFL + Placebo and IFL + Bevacizumab arms were blinded until first progression. Following a pre-planned analysis of safety, enrollment to the 5FU/LV/Bevacizumab arm was

discontinued. Enrollment continued in the IFL + Placebo and IFL + Bevacizumab arms. The study was initiated in September 2000 and 923 patients were enrolled at 163 centers. The initial BLA submission had a data cutoff of February 2003. The Safety Update covered the period from February 2003 to July 2003.

The primary endpoint of this study was overall survival. Secondary endpoints included progression free survival, response rate, duration of response, time to change in the FACT-C score, and patient safety. Exploratory analyses included the assessment of the efficacy of continued bevacizumab following initial progression.

Study Results

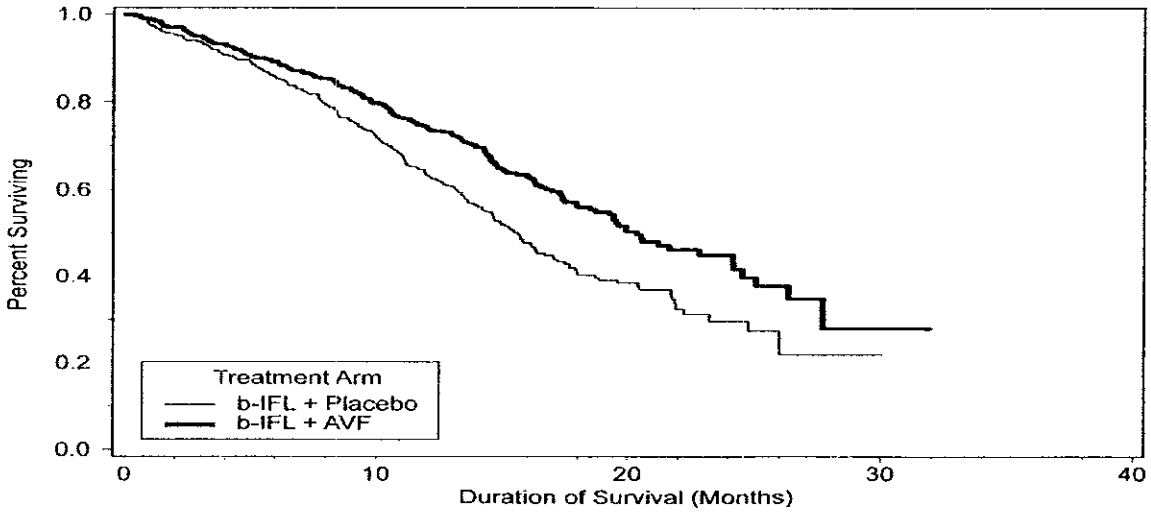
There were a number of issues concerning protocol conduct, specifically eligibility, protocol treatment, and data collection violations. Overall, 39.9% of patients in the IFL + Placebo and 49.5% of patients in the IFL + Bevacizumab arm had a major protocol violation. For additional details please see Sections 6.1 and 4.2.

Patient demographics and other baseline characteristics were well balanced between arms. Information concerning patient demographics, drug delivery, the use of additional therapies following first progression, and the outcome of the various secondary endpoints is discussed in Section 6.1.

Efficacy

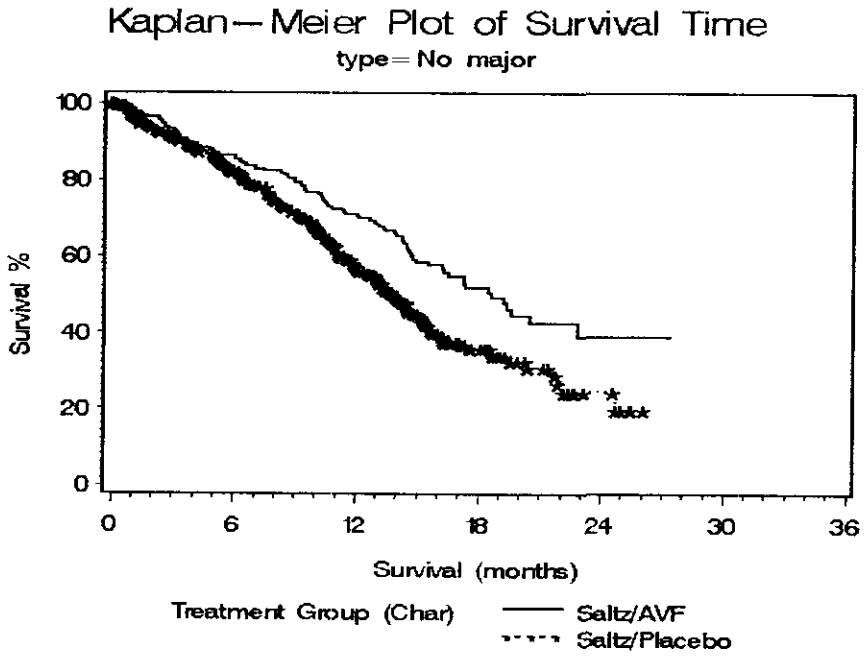
Overall Survival

The addition of bevacizumab to IFL provided a highly statistically significant improvement in survival when compared to IFL alone. A comparison of the two principal arms in the intent to treat population is as follows.



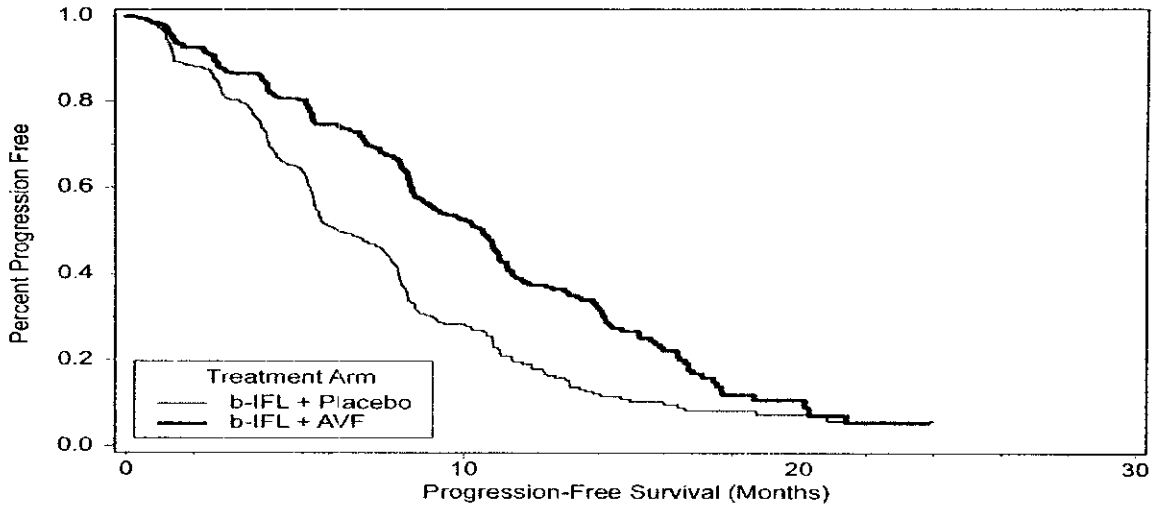
	IFL + Placebo N = 411	IFL + Bevacizumab N = 402
Number of Deaths	225	174
Median Survival	15.6 mo	20.3 mo
Hazard Ratio		0.66
p value (stratified logrank test)		< 0.0001

Given the large number of protocol violations, a sensitivity analysis was performed that excluded patients with major protocol treatment, conduct, and/or major eligibility violations. The figure below illustrates the overall survival of patients without major violations (N = 450). The p value for the comparison of these patients is p = 0.0012.



An additional sensitivity analysis was performed which excluded patients with both major and minor protocol violations. Removal of these patients resulted in a decrease from 813 to 301 patients in the two principal arms. Despite this, the survival advantage remained significant at p = 0.0364.

Progression Free Survival



	IFL + Placebo N = 411	IFL + Bevacizumab N = 402
Number of Progressions/Deaths	284	230
Progression Free Survival (months)	6.2	10.6
Hazard Ratio		0.544
p value (stratified logrank test)		< 0.0001

The addition of bevacizumab to IFL chemotherapy resulted in a significant improvement in progression free survival. The effect of bevacizumab on progression may have been magnified by the schedule of tumor assessment. Tumor assessments were performed every six weeks for the first 24 weeks (6 months) and then every 12 weeks. However, the magnitude of the difference in progression between arms is similar to that seen with overall survival (4.3 versus 4.7 months).

Supportive Study: AVF0780g

Study Design

A Phase II, Multidose, Randomized Multicenter Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Recombinant Humanized Monoclonal Anti-VEGF Antibody (rhuMAb VEGF) Combined with 5-Fluorouracil and Leucovorin Chemotherapy in Subjects with Metastatic Colorectal Cancer

AVF780g was a randomized Phase 2 study that was conducted to establish the activity of bevacizumab in colorectal cancer and to determine the appropriate dose for use in Phase 3 studies. One hundred and four patients with newly diagnosed colorectal cancer were randomized to 5FU/LV, 5FU/LV + bevacizumab 5 mg/kg, or 5FU/LV + bevacizumab 10 mg/kg. Bevacizumab was

given every two weeks. In this small study, an imbalance in important prognostic factors was noted between the arms. In general, these tended to favor the control arm.

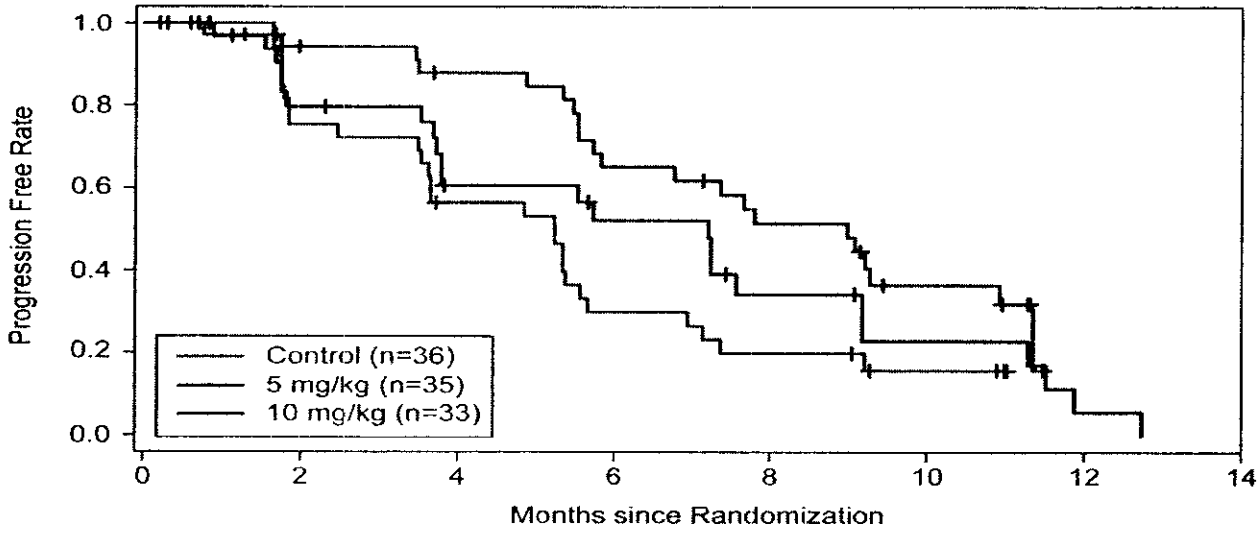
The co-primary endpoints were progression free survival and response rate. Upon first progression, patients in the control arm were able to crossover to bevacizumab 10 mg/kg every two weeks.

Information regarding entry criteria, stratification factors, patient demographics, and drug delivery as well as an analysis of secondary endpoints are detailed in Section 6.1.

Efficacy

The primary endpoints of this study were progression free survival (PFS) and response rate. Based on an amendment to the protocol following initiation, the primary analysis for both progression and response were based upon the findings of an independent radiology facility (IRF). Where scans could not be independently reviewed, investigator assigned response or progression was used. In three patients in the 5 mg/kg and one in the 10 mg/kg arm, the date of progression was determined by the investigator.

Progression Free Survival



	Control N = 36	5 mg/kg N = 35	10 mg/kg N = 33
Number of Progressions	26	22	23
Median PFS (mo)	5.2	9	7.2
Hazard Ratio		0.44[1]	0.691[2]
p value (logrank test)		0.005[1]	0.236[2]

[1]Control compared to 5 mg/kg
[2]Control compared to 10 mg/kg

In calculating this p value, no correction was made for the use of two primary endpoints. If a Bonferroni adjustment is used, the p value of 0.005 for the comparison of the 5 mg/kg arm to control remains significant. The 10 mg/kg arm showed some improvement in progression free survival when compared to control which was not statistically significant and appears to be smaller in magnitude than that seen in the 5 mg/kg arm. Imbalances in patient characteristics between arms do not appear to account for greater efficacy in the lower dose arm.

It should be noted that three patients in the control arm, one in the 5 mg/kg arm, and five in the 10 mg/kg arm discontinued treatment prior to their first assessment. In a small study, early discontinuations could affect study outcome and could result in loss of power. Seven of these nine patients were censored in the analysis of progression free survival. For further information please see the review of study AVF0780g in Section 6.1.

The crossover of patients from the control arm to open-label, single agent bevacizumab, who were not later confirmed to have progressive disease by the independent radiology facility, diminished the number of events and thus the power of the analysis of PFS. In five patients progression was not confirmed by the IRF prior to crossover. In two patients, films were not available for IRF review. In two patients, the IRF determined that stable disease was present at crossover. In one patient who crossed over, both the investigator and IRF determined that the patient had stable disease.

Response Rate

Response rates were based primarily on determinations by the IRF. Investigator assessment of response was used in two patients, one in the 5 mg/kg and one in the 10 mg/kg arm. The response rate was higher in both bevacizumab arms when compared to control. Complete responses were observed only in the 5 mg/kg arm.

IRF/Investigator Response

	5FU/LV N = 36	5FU/LV + 5 mg/kg N = 35	5FU/LV + 10 mg/kg N = 33
Response Rate	6 (16.7%)	14 (40.0%)	8 (24.2%)
p value (χ^2 test)		0.03[1]	0.43[1]
Complete Response	0	2	0
Partial Response	6	12	8

[1] when compared to control

If the Bonferroni method is used to correct for multiplicity, none of these comparisons are statistically significant.

Overall Survival

	5FU/LV	5FU/LV + 5 mg/kg	5FU/LV + 10 mg/kg
Overall Survival (mo)	13.6	17.7	15.2
p value (logrank test)		p = 0.52	p = .978

Although median survival was longer in the bevacizumab arms (with longest median survival in the 5 mg/kg arm), survival was not statistically significantly different across the study arms. Patients with disease progression in the control arm were allowed to crossover to single agent bevacizumab; approximately two-thirds (22/36) of patients in the control arm receiving second-line bevacizumab. Of these 22, approximately one-quarter (5 patients) did not have IRF documentation of progression at the time of crossover.

Among the 22 patients who crossed over, 14 had progressive disease at their first assessment following crossover. In the remaining eight patients, one patient was not assessed. Again among the 22 patients, there were six patients with stable disease and one patient with a partial response (5%) as their best response to second line therapy.

The failure to detect a statistically significant difference in overall survival in the bevacizumab arms as compared to control may be due to the absence of an effect of bevacizumab on survival when used in combination with this chemotherapeutic regimen, the small sample size of this study, and the longer survival in the control arm as a result of survival prolongation with second-line bevacizumab. With regard to the last explanation, overall survival in the control arm of this study is similar to that in the literature, making this an unlikely explanation. Information concerning additional therapies following progression is not available.

Single Agent Activity

The single agent activity of bevacizumab has been studied in the Phase 2 and 3 setting in patients renal cell, non-small cell lung cancer, and colorectal cancer.

In a Phase 2 study of patients bevacizumab 10 mg/kg was administered every two weeks. No objective responses or responses based on were seen.

In a second Phase 2 study of patients who had failed a previous anthracycline and/or taxane based therapy, patients were given 3, 10 or 20 mg/kg of bevacizumab every two weeks. Several of these patients had not failed prior therapy. Despite, this the response rate to single agent

bevacizumab was 6.7%. There was no significant difference in response based on dose.

In a Phase 2 study of patients with metastatic renal cell carcinoma who had progressed after first-line high dose IL-2 therapy or were not considered candidates for high-dose IL-2, 116 patients were randomized to placebo, 3 mg/kg bevacizumab, or 10 mg/kg bevacizumab every two weeks. Eight of these 116 patients had not received high dose IL-2. Four of 39 patients in the 10 mg/kg arm had a partial response. There was a significant improvement in time to progression when patients in the 10 mg/kg arm were compared to placebo in an interim analysis. Differences in overall survival were not statistically significant. Given that the trial was conducted at a single center and involved a small number of highly selected patients (those that were able to tolerate high dose IL-2), the effect on PFS should be confirmed in additional studies. If there is single agent activity observed in renal cell carcinoma, this may be a reflection of the dependence of this histologic subtype of cancer on vascular endothelial growth factor.

In a Phase 2 study of patients with stage IIIB or IV non-small cell lung cancer, patients in the control arm were allowed to crossover to single agent bevacizumab following progression on standard chemotherapy. Nineteen patients crossed over to single agent bevacizumab. No responses were seen.

The a Phase 2 study of patients with metastatic colorectal cancer, patients in the control arm were allowed to crossover to single agent bevacizumab following progression on standard chemotherapy. Twenty-two patients crossed over to single agent bevacizumab. One patient had a response.

In a Phase 3 study of patients with metastatic colorectal cancer who had failed prior irinotecan based therapy, the Data Monitoring Committee closed the bevacizumab alone arm (10 mg/kg every two weeks) to accrual after approximately 250 patients had been entered into each study arm. This was due to a decrease in overall survival in the single agent bevacizumab arm when compared to patients receiving conventional chemotherapy.

AVF2119g

This Phase 3 study randomized 462 patients with metastatic breast cancer who had progressed following treatment with an anthracycline and a taxane based regimen to capecitabine or capecitabine plus bevacizumab 15 mg/kg every three weeks. In this study, there were differences in the incidence of poor prognostic characteristics between the two arms. In aggregate, neither arm was clearly favored. As a measure of tumor burden, the median sum of the longest diameter as determined by the investigator was 5.7 cm in the capecitabine alone arm and 7.6 cm in the capecitabine plus bevacizumab arm. This is compared to median values of 10 and 11 cm in the two principal arms of the major efficacy study AVF2107g. In this open-label study, 15 patients in the capecitabine alone arm

did not receive treatment on study compared to three patients in the capecitabine plus bevacizumab arm. Finally, the dose density of capecitabine was slightly lower in the bevacizumab arm.

Progression free survival was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus bevacizumab group, p = 0.86. The response rate was 9.1% with capecitabine and 19.8% with capecitabine plus bevacizumab, p = 0.001. However, the median duration of response was shorter in the bevacizumab arm and the higher response rate did not translate into an improvement in progression free survival. Median duration of response was 7.6 months in the capecitabine arm (57.1% of responders censored) and 5.0 months (47.8% of responders censored) in the capecitabine plus bevacizumab group. Median overall survival was 14.5 months in the capecitabine arm and 15.0 months in capecitabine plus bevacizumab group. In the capecitabine licensing trials, the response rate of capecitabine alone was 25.6%.

The lack of activity of bevacizumab in this trial remains unexplained. Possible causes of this lack of effect include, the lack of activity of bevacizumab in the treatment of breast cancer or that bevacizumab in not effective in combination with third line therapy.

3.3.3 Clinical Microbiology

Not applicable

3.3.4 Efficacy Conclusions

In 815 patients with newly diagnosed colorectal cancer, the addition of bevacizumab to IFL provided a statistically significant improvement in overall survival when compared to IFL alone. The magnitude of the survival benefit, 4.7 months, is striking. It is supported by a similar improvement in progression free survival, 4.3 months. Interpretation of the level of statistical significance in the analysis of OS and PFS should be viewed in light of the large number of patients with protocol violations of various types. When patients with protocol violations were excluded from the analysis of overall survival, the difference remained highly statistically significant. However, the p value was less robust.

In a three-arm Phase 2 study enrolling 104 patients, the addition of 5 mg/kg of bevacizumab every two weeks to 5FU/LV demonstrated a statistically significant improvement in progression free survival when compared to 5FU/LV alone. Progression free survival was also longer in patients receiving 5FU/LV plus 10 mg/kg of bevacizumab every two weeks when compared to those receiving 5FU/LV. This difference was not statistically significant. Conclusions concerning this study are limited by the size of this study. However, the lower dose of bevacizumab was more effective than the higher dose. Again, it should be noted that the optimal dose of bevacizumab has not yet been established.

3.4 Integrated Review of Safety

3.4.1 Approach to Review of Safety

Please see Section 3.1 for information concerning the trials reviewed.

Safety was reviewed in the major efficacy trial (AVF2107g) and in the supportive trial (AVF0780g). Safety was also reviewed in all patients who had received bevacizumab in other Genentech sponsored studies; a total of 1032 patients received bevacizumab in these studies. In some instances, safety was also reviewed for patients participating in the control arms of the other Genentech sponsored studies.

Safety was also reviewed in select studies conducted under BB-IND 7921 (held by the NCI) and in the NCI AdEERs database of expedited reports. The data cutoff date for these reports was May 30, 2003 and as of that date1870 patients had been enrolled under this IND.

In interpreting the Genentech database, it should be noted that in the major efficacy study only grade 3-4 events and grade 1-4 thrombembolism, hypertension and proteinuria were collected in 298 of 396 patients in the IFL + Placebo and 290 of 392 patients in the IFL + Bevacizumab arm. Grade 1-4 adverse events were obtained in 309 patients concurrently enrolled to Arms 1-3 of this study.

An additional issue is the collection of adverse events during Treatment Periods 1 and 2. Treatment Period 1 includes the time from randomization to first progression. Following first progression, patients could choose to be unblinded and to receive additional therapy on or off study. If patients in the IFL + Bevacizumab and 5FU/LV/Bevacizumab arms remained on study, they could continue to receive bevacizumab. There was no crossover permitted for placebo patients. This is referred to as Treatment Period 2. The tables below, except where clearly stated, contain only information from Treatment Period 1.

In the Summary of Clinical Safety, the sponsor has grouped patients into the following Treatment/Disease groups.

Group	Disease	Contributing Patients
Colorectal Studies		N = 568
AVF2107g	Colorectal	N = 501
AVF780g	Colorectal	N = 67
Other Combination Studies		N = 307
AVF2119g	Breast	N = 229
—	Non-Small Cell Lung	N = 66
AVF761g	Solid Tumors	N = 12
Single Agent Therapy		N = 157

AVF737g	Solid Tumors	N = 25
—	—	N = 15
—	—	N = 75
AVF780g	Crossover Colorectal	N = 22
—	Crossover Non-Small Cell Lung	N = 19
AVF780g	Extension Colorectal	N = 1
Total		N = 1032

Note that the Colorectal Studies group includes the 290 patients for whom only grade 3-4 events were collected. The majority of analyses include these patients. This may, in some instances, decrease the percentage of patients experiencing an adverse event of lesser severity since these patients remain in the denominator, but no grade 1-2 events were collected. This may be offset in comparisons of these 290 patients in the bevacizumab arm to 298 patients in the control arm in AVF2107g in whom adverse events were collected in a similar manner. In addition, adverse events of any severity are presented in a summary table that omits these 290 patients.

3.4.2 Safety Findings

3.4.2.1 Exposure

Major Efficacy Study: AVF2107g

In the pivotal study, total dose intensity was calculated as the total dose received by the patient divided by the expected total dose. The expected total dose was calculated as the dose that the patient should have received between the day zero and the date of progression.

Total Dose Density

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Study Drug			
Mean	96.3%	94.3%	94.8%
Median	99%	97%	97%
25-75	94-101	90-100	90-100
5-Fluorouracil			
Mean	79.3%	74.3%	87.5%
Median	80%	73%	91%
25-75	66-96	61-89	80-98
Irinotecan			
Mean	78.4%	72.7%	-
Median	81%	73%	-
25-75	65-96	58-89	-

This analysis is notable for the high levels of study drug administered. In part, this is related to the dose modification criteria for bevacizumab. Bevacizumab was held for high-grade toxicities, but was not given at a reduced dose for lesser toxicities. These analyses are also remarkable for the nearly equal dose intensities of 5-fluorouracil and irinotecan. It is interesting to note that despite the controversy surrounding irinotecan, the median dose reduction of irinotecan and 5-fluorouracil are nearly identical.

Length of Exposure

	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Duration (months)		
Mean	9.1	8.5
Median (25-75)	8 (4-14)	7 (3-12)
≤ 12 Months	69.6%	76.1%
> 12 Months	30.4%	23.9%

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Both the duration of bevacizumab exposure and the exposure by dose were examined in all patients receiving bevacizumab on Genentech sponsored studies.

Duration of Bevacizumab Administration

	Colorectal Studies	Other Combination	Single Agent	Total
Duration (months)				
Mean	10.5	6.4	3.6	8.2
Median (25-75)	9 (4-16)	5 (2-9)	2 (1-4)	6 (2-13)
≤ 12 Months	60.7%	85%	94.3%	73.1%
> 12 Months	39.3%	15%	5.7%	26.9%

Exposure by Dose

Several doses of bevacizumab were studied in the development period. The sponsor presents the following table in the discussion of the dose.

Study	1.5 mg/kg/wk	2.5 mg/kg/wk	5 mg/kg/wk	10 mg/kg/wk
—	0	32	34	0
—	0	0	15	0
—	18	0	41	16
AVF780g	0	35	32	0
AVF2119g	0	0	229	0
AVF2107g	0	501	0	0
Total	18	568	351	16

Given the small numbers of patients in other groups, targeted adverse events by dose were analyzed only in the 2.5 and 5 mg/kg/wk groups.

3.4.2.2 Deaths

Major Efficacy Study: AVF2107g

	IFL + Placebo N = 411	IFL + Bevacizumab N = 402	5FU/LV/Bevacizumab N = 110
All Deaths (% Patients)	246 (59.8%)	207 (51.5%)	78 (70.9%)
Cause of Death (% of Deaths)			
Colorectal Cancer	225 (91.5%)	192 (92.8%)	68 (87.2%)
Other (% of Deaths)	21 (8.5%)	15 (7.2%)	10 (12.8%)
Cardio-respiratory	6 (2.4%)	2 (1.0%)	3 (3.8%)
Sepsis	8 (3.3%)	5 (2.4%)	3 (3.8%)
Thromboembolism	3 (1.2%)	2 (1.0%)	1 (1.3%)
Hemorrhage	0	1 (0.5%)	0
Other/Unknown	4 (1.6%)	5 (2.4%)	3 (3.8%)

The higher rate of deaths in the 5FU/LV/Bevacizumab arm is a reflection of the greater maturity of the data (enrollment in this cohort was suspended earlier and thus patients in this cohort have longer follow up). The majority of deaths in all arms are reported to be due to colorectal cancer.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Total	309 (54.4%)	195 (63.5%)	72 (45.9%)	576 (55.8%)
Cause of Death (% of Deaths)				
Progressive Disease	282 (91.3%)	177 (90.8%)	72 (100%)	531 (92.2%)
Bleeding	1 (0.3%)	3 (1.5%)	0	4 (0.7%)
Cardiac	5 (1.6%)	0	0	5 (0.9%)
Infection	7 (2.3%)	2 (1.0%)	0	9 (1.6%)
Pulmonary Embolism	3 (1.0%)	0	0	3 (0.5%)
Ischemic Bowel	1 (0.3%)	0	0	1 (0.2%)
Other	5 (1.6%)	8 (4.1%)	0	13 (2.3%)
Unknown	5 (1.6%)	5 (2.6%)	0	10 (1.7%)

The majority of deaths in the three groups are due to progressive disease. Deaths due to causes other than progressive disease are not reported among patients receiving single agent therapy.

3.4.2.3 Other Serious Adverse Events

Major Efficacy Study: AVF2107g

The following table illustrates the number and type of serious adverse events that occurred in more than 2% of patients on either of the two principal arms of AVF2107g during first line therapy. Serious adverse events are those that required medical intervention (including hospitalization) to prevent more serious outcomes or resulted in permanent disability or death. This incidence of serious adverse events was similar in the two study arms for each category with the exception of deep venous thrombosis which was reported in 8.7% of patients in the IFL + Bevacizumab arm as compared to 4.8% of patients in the IFL arm.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall	171 (43.2%)	200 (51.0%)
Body as a Whole		
Abdominal Pain	8 (2.0%)	14 (3.6%)
Fever	13 (3.3%)	6 (1.5%)
Sepsis	10 (2.5%)	9 (2.3%)
Pain[1]	3 (0.8%)	10 (2.6%)
Cardiovascular		
Deep Vein Thrombosis	19 (4.8%)	34 (8.7%)
Pulmonary Embolus	20 (5.1%)	16 (4.1%)
Intra-Abdominal Thrombosis	7 (1.8%)	14 (3.6%)
Line Related Thrombosis	9 (2.3%)	6 (1.5%)
Digestive		
Diarrhea[2]	41 (10.4%)	41 (10.5%)
Ileus[3]	20 (5.0%)	16 (4.1%)
Vomiting	15 (3.8%)	14 (3.6%)
Nausea	8 (2.0%)	5 (1.3%)
Hemic/Lymphatic		
Leukopenia	18 (4.5%)	24 (6.1%)
Metabolic/Nutrition		
Dehydration	14 (3.5%)	16 (4.1%)

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

In the 1032 patients treated with bevacizumab on Genentech sponsored studies, the following serious adverse events occurred in at least 2% of patients.

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	311 (54.8%)	102 (33.2%)	37 (23.6%)	450 (43.6%)
Body as a Whole				
Abdominal Pain	27 (4.8%)	4 (1.3%)	2 (1.3%)	33 (3.2%)
Sepsis	19 (3.3%)	5 (1.6%)	1 (0.6%)	25 (2.4%)
Fever	14 (2.5%)	5 (1.6%)	0	19 (1.8%)
Cardiovascular				
Deep Vein Thrombosis	46 (8.1%)	8 (2.6%)	3 (1.9%)	57 (5.5%)
Pulmonary Embolus	19 (3.3%)	4 (1.3%)	0	23 (2.2%)
Thrombophlebitis	13 (2.3%)	2 (0.7%)	0	15 (1.4%)
Myocardial Infarction	12 (2.1%)	0	1 (0.6%)	13 (1.3%)
Hypertension	6 (1.1%)	1 (0.3%)	5 (3.2%)	12 (1.2%)
Digestive				
Diarrhea	69 (12.0%)	9 (2.9%)	1 (0.6%)	79 (7.7%)
Ileus	34 (6.0%)	2 (0.7%)	0	36 (3.5%)
Vomiting	20 (3.5%)	3 (1.0%)	1 (0.6%)	24 (2.3%)
Hemic/Lymphatic				
Leukopenia	32 (5.6%)	8 (2.6%)	0	40 (3.9%)
Metabolic/Nutrition				
Dehydration	22 (3.9%)	0	0	22 (2.1%)
Respiratory				
Dyspnea	6 (1.1%)	7 (2.3%)	1 (0.6%)	14 (1.4%)
Pneumonia	6 (1.1%)	2 (0.7%)	5 (3.2%)	13 (1.3%)

An interesting finding is the increased incidence of serious adverse events categorized as deep venous thrombosis in patients with colorectal cancer compared to patients with other cancers. Another is that the incidence of hypertension as a serious adverse event is actually higher with single agent therapy than in patients receiving combination treatment. Single agent studies were performed earlier in the drug development process and it may be that earlier in the development program patients were more likely to be hospitalized for the very high blood pressure readings seen with bevacizumab.

3.4.2.4 Dropouts and Other Significant Adverse Events

Major Efficacy Study: AVF2107g

In the IFL + Placebo arm, 7.1% of patients discontinued due to an adverse event during Treatment Period 1. Adverse events leading to discontinuation that

occurred in more than 1% of patients included asthenia, pulmonary embolism, and diarrhea. In the IFL + Bevacizumab arm, 8.7% of patients discontinued during Treatment Period 1. Adverse events leading to discontinuation that occurred in more than 1% of patients also included asthenia and diarrhea. In the 5FU/LV/Bevacizumab arm, 9.2% of patients discontinued due to an adverse event during Treatment Period 1. Events that occurred in more than 1% of patients included deep vein thrombosis and myocardial infarction.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Across all Genentech sponsored studies, 12.0% of patients treated on Colorectal Studies, 17.9% in the Other Combination group, and 12.1% of patients receiving Single Agent therapy discontinued due to an adverse event. In patients participating in Colorectal Studies, adverse events leading to discontinuation in more than 1% of patients include asthenia and diarrhea. In the Other Combination group, asthenia, deep vein thrombosis, and hypertension led to discontinuation in more than 1% of patients. In the Single Agent group, asthenia, deep vein thrombosis, and hypercalcemia led to discontinuation in more than 1% of patients.

3.4.2.5 Other Search Strategies Applied to Clinical Safety Database

The search strategies included a review of adverse event listings, laboratory values (both local and central laboratory), vital signs, and patient narratives.

3.4.2.6 Common Adverse Events

Grade 3-4 Events

Major Efficacy Study: AVF2107g

Selected grade 3-4 adverse events during first line therapy in the pivotal study are shown in the table below. Only those that occurred at a higher incidence in one study arm (i.e. differ incidence by at least 2% between the two principal arms) are included. Note that several of these tables reference footnotes. Footnotes are included in Section 6.1.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Gr 3 or 4 Adverse Events	295 (74.5%)	340 (86.7%)
Gr 3	279 (70.4%)	331 (84.4%)
Gr 4	86 (21.7%)	121 (30.9%)
Body as a Whole		
Asthenia[1]	28 (7.0%)	38 (9.7%)
Abdominal Pain	20 (5.0%)	32 (8.2%)
Pain[2]	21 (5.3%)	30 (7.6%)

Cardiovascular		
Deep Vein Thrombosis	19 (4.8%)	34 (8.7%)
Hypertension	10 (2.5%)	46 (11.7%)
Intra-Abdominal Thrombosis	5 (1.3%)	13 (3.3%)
Syncope	4 (1.0%)	11 (2.8%)
Digestive		
Diarrhea[3]	99 (25.0%)	133 (33.9%)
Vomiting	42 (10.6%)	30 (7.6%)
Nausea	37 (9.3%)	26 (6.6%)
Constipation	9 (2.3%)	14 (3.6%)
Hemic/Lymphatic		
Leukopenia	122 (30.8%)	145 (37.0%)
Metabolic/Nutrition		
Hyperglycemia	17 (4.3%)	9 (2.3%)

The overall incidence of grade 3 and 4 events is increased in the bevacizumab arm. This is primarily due to an increase in hypertension, diarrhea, and leukopenia. Another striking finding in this table is the high overall incidence of grade 4 events, 21.7% and 30.9%. Nausea, vomiting, and hyperglycemia occurred at a higher incidence in the control arm; all other grade 3 and 4 adverse events were more common in the bevacizumab arm.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Grade 3-4 events, which occurred in at least 5% of patients in any Treatment/Disease group, included in the Summary of Clinical Safety are shown in the table below.

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	500 (88.0%)	240 (78.2%)	73 (46.5%)	813 (78.8%)
Body as a Whole				
Asthenia[1]	72 (12.7%)	31 (10.1%)	14 (8.9%)	117 (11.3%)
Abdominal Pain	61 (10.7%)	8 (2.6%)	6 (3.8%)	75 (7.3%)
Pain[2]	56 (9.9%)	34 (11.1%)	20 (12.7%)	110 (10.7%)
Cardiovascular				
Hypertension	94 (16.5%)	56 (18.2%)	21 (13.4%)	171 (16.6%)
Deep Vein Thrombosis	50 (8.8%)	13 (4.2%)	3 (1.9%)	66 (6.4%)
Digestive				
Diarrhea[3]	216 (38.0%)	36 (11.7%)	3 (1.9%)	255 (24.7%)
Vomiting	48 (8.5%)	10 (3.3%)	1 (0.6%)	59 (5.7%)
Nausea	41 (7.2%)	15 (4.9%)	1 (0.6%)	57 (5.7%)
Ileus[4]	38 (6.7%)	4 (1.3%)	0	42 (4.1%)
Hemic/Lymphatic				

Leukopenia	172 (30.3%)	51 (16.6%)	0	223 (21.8%)
Metabolic/Nutrition				
Dehydration	48 (8.5%)	6 (2.0%)	0	54 (5.2%)
Hypokalemia	33 (5.8%)	6 (2.0%)	1 (0.6%)	40 (3.9%)
Respiratory				
Dyspnea	23 (4.0%)	34 (11.1%)	11 (7.0%)	68 (6.6%)
Skin				
Exfoliative Dermatitis	9 (1.6%)	66 (21.5%)	0	75 (7.3%)

Here, 46.5% of patients receiving single agent bevacizumab had grade 3-4 adverse events. Approximately half of these events were categorized as hypertension or pain. The percentage of patients with deep vein thrombosis was higher in patients with colorectal cancer than with other tumors.

Grade 1-4 Events

Major Efficacy Study: AVF2107g

This table illustrates selected grade 1-4 adverse events that occurred during first line therapy in the 309 patients concurrently enrolled and treated on Arms 1-3 of the major efficacy study. Individual adverse events are included in the table if there was a difference in incidence between arms of at least 5%.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Total			
Gr 1	96 (98.0%)	99 (97.1%)	108 (99.1%)
Gr 2	95 (96.9%)	97 (95.1%)	96 (88.1%)
Gr 3	74 (75.5%)	93 (91.2%)	80 (73.4%)
Gr 4	23 (23.5%)	33 (32.4%)	23 (21.1%)
Body as a Whole			
Pain[1]	54 (55.1%)	62 (60.8%)	67 (61.5%)
Abdominal Pain	54 (55.1%)	62 (60.8%)	55 (50.5%)
Headache/Migraine	19 (19.4%)	27 (26.5%)	30 (25.7%)
Accidental Injury	9 (9.2%)	13 (12.7%)	6 (5.5%)
Abdominal Distension	5 (5.1%)	0	5 (5.5%)
Cardiovascular			
Hypertension	14 (14.3%)	23 (22.6%)	37 (33.9%)
Hypotension/Postural Hypotension	7 (7.1%)	15 (14.7%)	8 (7.3%)
Flushing	6 (6.1%)	2 (2.0%)	8 (7.3%)
Deep Vein Thrombosis	3 (3.1%)	9 (8.8%)	6 (5.5%)
Digestive			
Nausea	68 (69.4%)	73 (71.6%)	72 (66.1%)
Vomiting	46 (46.9%)	53 (52.0%)	51 (46.8%)
Anorexia/Cachexia	29 (29.6%)	44 (43.1%)	38 (34.9%)

Constipation	28 (28.6%)	41 (40.2%)	32 (29.4%)
Stomatitis/Mucositis	18 (18.4%)	33 (32.4%)	33 (30.3%)
Dyspepsia	15 (15.3%)	25 (24.5%)	19 (17.4%)
Weight Loss	10 (10.2%)	15 (14.7%)	18 (16.5%)
Flatulence	10 (10.2%)	11 (10.8%)	21 (19.3%)
GI Hemorrhage[2]	6 (6.1%)	25 (24.5%)	21 (19.3%)
Gastroesophageal Reflux	5 (5.1%)	8 (7.8%)	1 (0.9%)
Hemic/Lymphatic			
Leukopenia	53 (54.1%)	58 (56.9%)	12 (11.0%)
Anemia/Hypochromic Anemia	30 (30.6%)	36 (35.3%)	27 (24.8%)
Metabolic/Nutrition			
Dehydration/Hypovolemia	21 (21.4%)	23 (22.5%)	17 (15.6%)
Hypokalemia	11 (11.2%)	12 (11.8%)	18 (16.5%)
Bilirubinemia	0	1 (1.0%)	7 (6.4%)
Musculoskeletal			
Myalgia[3]	7 (7.1%)	8 (7.8%)	16 (14.7%)
Nervous			
Dizziness	20 (20.4%)	27 (26.5%)	21 (19.3%)
Depression	18 (18.4%)	13 (12.8%)	15 (13.8%)
Anxiety and agitation	16 (16.3%)	11 (10.8%)	8 (7.3%)
Respiratory			
Upper Respiratory Infection[4]	38 (38.8%)	48 (47.1%)	44 (40.4%)
Dyspnea	15 (15.3%)	26 (25.5%)	27 (24.8%)
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Singultus	8 (8.2%)	5 (4.9%)	1 (0.9%)
Voice Alteration/Laryngitis	2 (2.0%)	9 (8.8%)	6 (5.5%)
Skin/Appendages			
Alopecia	25 (25.5%)	33 (32.3%)	6 (5.5%)
Sweating	15 (15.3%)	14 (13.7%)	10 (9.2%)
Dry Skin	7 (7.1%)	7 (6.9%)	22 (20.2%)
Exfoliative Dermatitis	3 (3.1%)	3 (2.9%)	21 (19.3%)
Nail disorder	3 (3.1%)	2 (2.0%)	9 (8.3%)
Skin discoloration	3 (3.1%)	2 (2.0%)	17 (15.6%)
Skin Ulcer	1 (1.0%)	6 (5.9%)	7 (6.4%)
Special Senses			
Taste Loss/Perversion	9 (9.2%)	14 (13.7%)	23 (21.1%)
Excess Lacrimation	2 (2.0%)	6 (5.9%)	20 (18.3%)
Urogenital			
Proteinuria	24 (24.5%)	37 (36.3%)	39 (35.8%)
Urinary Retention/Impairment	0	6 (5.9%)	2 (1.8%)

When all grades of adverse events are examined, several additional adverse events that occur more frequently in bevacizumab-treated patients as compared to those receiving chemotherapy alone become prominent. These include headache, gastrointestinal hemorrhage, epistaxis, and proteinuria.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

The applicant was asked to provide a table of adverse events which included only patients in which grade 1-4 events were collected. In study AVF2107g, only grade 3-4 events (with the exception of proteinuria, thromboembolism and hypertension) were collected in 290 patients enrolled in the IFL + Bevacizumab arm. These patients are omitted from the table below. Adverse events that occurred in at least 10% of patients in any Treatment/Disease group are included in the table below.

	Colorectal Studies N = 278	Other Combination N = 307	Single Agent N = 157	Total N = 742
Body as a Whole				
Asthenia[1]	217 (78.1%)	198 (64.5%)	109 (69.4%)	524 (70.6%)
Pain[2]	168 (60.4%)	176 (57.3%)	108 (68.8%)	452 (60.9%)
Abdominal Pain	149 (53.6%)	64 (20.8%)	35 (22.3%)	307 (41.4%)
Headache/Migraine	82 (29.5%)	110 (35.8%)	64 (40.8%)	256 (34.5%)
Fever	86 (30.9%)	55 (17.9%)	29 (18.5%)	183 (24.7%)
Chills	40 (14.4%)	20 (6.5%)	8 (5.1%)	68 (9.2%)
Accidental Injury	28 (10.1%)	24 (7.8%)	13 (8.3%)	65 (8.8%)
Cardiovascular				
Hypertension	88 (31.7%)	82 (26.7%)	30 (19.1%)	200 (27.0%)
Flushing	13 (4.7%)	24 (7.8%)	17 (10.8%)	54 (7.3%)
Digestive				
Diarrhea[3]	245 (88.1%)	161 (52.4%)	50 (31.8%)	456 (61.5%)
Nausea	195 (70.1%)	155 (50.5%)	69 (43.9%)	419 (56.5%)
Vomiting	135 (48.6%)	91 (29.6%)	48 (30.6%)	274 (36.9%)
Anorexia/Cachexia	110 (39.6%)	92 (30.0%)	50 (31.8%)	252 (34.0%)
Stomatitis/Mucositis	101 (36.3%)	125 (40.7%)	25 (15.9%)	251 (33.8%)
Constipation	95 (34.2%)	72 (23.5%)	45 (28.7%)	212 (28.6%)
GI Hemorrhage[4]	72 (26.0%)	22 (7.2%)	4 (2.5%)	98 (13.2%)
Dyspepsia	59 (21.2%)	40 (13.0%)	25 (15.9%)	124 (16.7%)
Flatulence	42 (15.1%)	19 (6.2%)	8 (5.1%)	69 (9.3%)
Hemic/Lymphatic				
Leukopenia	85 (30.6%)	79 (25.7%)	4 (2.5%)	168 (22.6%)
Anemia	70 (25.2%)	52 (16.9%)	25 (15.9%)	147 (19.8%)
Metabolic/Nutrition				
Edema	65 (23.4%)	55 (17.9%)	28 (17.8%)	148 (19.9%)
Dehydration	51 (18.3%)	21 (6.8%)	4 (2.5%)	76 (10.2%)
Weight Loss	46 (16.5%)	34 (11.1%)	23 (14.6%)	103 (13.9%)
Hypokalemia	40 (14.4 %)	14 (4.6%)	6 (3.8%)	60 (8.1%)
Musculoskeletal				
Arthralgia/Arthritis	32 (11.5%)	58 (18.9%)	49 (31.2%)	139 (18.7%)
Myalgia	31 (11.2%)	58 (18.9%)	31 (19.7%)	120 (16.2%)

Nervous				
Dizziness	67 (24.1%)	41 (13.4%)	26 (16.6%)	134 (18.1%)
Insomnia	61 (21.9%)	42 (13.7%)	20 (12.7%)	123 (16.6%)
Depression	35 (12.6%)	36 (11.7%)	18 (11.5%)	89 (12.0%)
Neuropathy	43 (7.6%)	87 (28.3%)	53 (33.8%)	183 (17.7%)
Hyperesthesia	3 (1.1%)	11 (3.6%)	17 (10.8%)	31 (4.2%)
Respiratory				
Upper Respiratory Infection	138 (49.6%)	144 (46.9%)	84 (53.5%)	366 (49.3%)
Epistaxis	104 (37.4%)	67 (21.8%)	20 (12.7%)	191 (25.7%)
Dyspnea	72 (25.9%)	102 (33.2%)	49 (31.2%)	223 (30.1%)
Cough Increased	63 (22.7%)	70 (22.8%)	46 (29.3%)	179 (24.1%)
Skin				
Rash/Maculopapular Rash	69 (24.8%)	55 (17.9%)	24 (15.3%)	148 (20.0%)
Alopecia	46 (16.5%)	57 (18.6%)	15 (9.6%)	118 (15.9%)
Dry Skin	39 (14.0%)	14 (4.6%)	9 (5.7%)	62 (8.4%)
Exfoliative Dermatitis	34 (12.2%)	193 (62.9%)	1 (0.6%)	228 (30.7%)
Sweating	31 (11.2%)	20 (6.5%)	6 (3.8%)	57 (7.7%)
Pruritis	25 (9.0%)	18 (5.9%)	22 (14.0%)	65 (8.8%)
Special Senses				
Taste Disorder	46 (16.5%)	17 (5.5%)	5 (3.2%)	68 (9.2%)
Excess Tearing	40 (14.4%)	17 (5.5%)	0	57 (7.7%)
Urogenital				
Proteinuria	92 (33.1%)	84 (27.4%)	8 (5.1%)	184 (24.8%)
Urinary Tract Infection	38 (13.7%)	19 (6.2%)	11 (7.0%)	68 (9.2%)

Several adverse events of mild or moderate severity (grade 1-2 events) were not identified in the table of grade 3-4 events above. These common adverse events include headache, stomatitis, gastrointestinal hemorrhage, edema, epistaxis, rash, and proteinuria.

Note that the incidence of epistaxis with single agent use is slightly lower than with combination therapy. Headache occurred at a higher incidence in patients receiving single agent therapy as compared to those receiving bevacizumab plus chemotherapy. This may be due to the use of, in general, higher doses with single agent therapy. The incidence of proteinuria was lower in patients receiving single agent treatment as compared to combination therapy. See Section 6.1 for additional discussion concerning the frequency with which urine dipsticks were collected on the various studies.

3.4.2.7 Less Common Adverse Events

Major Efficacy Study: AVF2107g

Adverse events of any severity that differ by at least 5% and grade 3 and 4 events which differ by at least 2% between arms are included in Section 3.4.2.6.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Adverse events of any severity that occurred in at least 10% of patients and grade 3 and 4 events which occurred in at least 5% of patients are included in Section 3.4.2.6.

3.4.2.8 Laboratory Findings

Leukopenia

Major Efficacy Study: AVF2107g

Incidence of Leukopenia Coded as an Adverse Event

A slightly higher incidence of the adverse event grade 3-4 leukopenia was noted in patients receiving IFL + Bevacizumab.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Leukopenia		
Gr 3	92 (23.2%)	98 (25.0%)
Gr 4	30 (7.6%)	47 (12.0%)

This is not consistent with the lower dose density in the IFL + Bevacizumab arm, but could be due to an increased time on study. Alternatively, the increase in leukopenia may be related to increases in SN-38 levels in the bevacizumab arm. For additional details, please see Clinical Pharmacology review. Another important consideration is the low incidence of grade 3-4 leukopenia in the IFL arm of this study compared to other studies in the literature cited above in which the incidence of grade 3-4 leukopenia ranged from 40-53.8%.

Despite the increase in the incidence of leukopenia, an increase in sepsis was not seen. The incidence of grade 3-4 sepsis was 2.5% in the IFL + Placebo and 3.1% in the IFL + Bevacizumab arm.

Neutropenia Based on Laboratory Data

Complete blood counts were to be collected on days one and 21 of each cycle and analyzed at a central laboratory. No data are available for one-quarter to one-third of patients beyond the baseline CBC. Therefore, the incidence of neutropenia was calculated in terms of the number of patients with a value obtained beyond screening or cycle 1 day 0.

	IFL + Placebo N = 303	IFL + Bevacizumab N = 276
Neutropenia		
Gr 3	35 (11.5%)	49 (17.8%)
Gr 4	6 (2.0%)	9 (3.3%)

The incidence of thrombocytopenia among patients with central laboratories was also examined. Grade 3 thrombocytopenia occurred in one patient in the IFL + Placebo and one in the IFL + Bevacizumab arm.

Due to differences in the doses and schedules of chemotherapy, the incidences of leukopenia, neutropenia, and thrombocytopenia were not examined in patients receiving bevacizumab across all Genentech sponsored studies. The adverse event grade 3-4 leukopenia was reported in two of 157 patients in the Single Agent group. One of these patients was miscoded. The episode of leukopenia actually occurred during treatment with chemotherapy on the control arm prior to crossover to single agent therapy. In the second patient, this event occurred during treatment on the extension study. This patient was treated on AVF0776g with single agent bevacizumab and later received bevacizumab plus chemotherapy on the extension study.

Proteinuria

AVF2107g

Proteinuria Based on Results of Serial Urine Dipsticks

Overall, 40.2% of patients in the IFL + Placebo arm, 49.7% in the IFL + Bevacizumab arm, and 53.2% of those receiving 5FU/LV/Bevacizumab had a dipstick reading 1+ or greater during first line therapy. This table includes the number of patients with a positive urine dipstick during first line therapy. Patients are listed only once, at their highest level recorded.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 394	5FU/LV/Bevacizumab N = 109
Urine Dipsticks			
1+	104 (26.3%)	130 (33.0%)	27 (24.8%)
2+	41 (10.4%)	42 (10.7%)	15 (13.8%)
3+	9 (2.3%)	18 (4.6%)	12 (11.0%)
4+	5 (1.3%)	6 (1.5%)	4 (3.7%)

The protocol stated that patients with $\geq$ 1+ proteinuria should undergo a 24 hour collection. Analyses of the incidence of proteinuria using 24 hour collections are confounded by the lack of correlation between screening urine dipsticks and 24 hour collections and the lack of information on the adequacy of the 24 hour collections. However, even when 24 hour collections with a creatinine clearance

(not required per protocol) within the expected range are examined, the lack of correlation between 24 hour collections and urine dipsticks remains evident. Both falsely high and falsely low dipstick values (based on comparison to 24 hour urinary protein levels) were seen.

24 Hour Collections

Urine dipsticks greater than 1+ occurred in 413 patients and 24 hour urine collections were obtained in 326 patients (78.9%) during first line therapy. However, it is not clear that these 326 urine collections were obtained as specified in the protocol. See Section 6.1 for further discussion of protocol-required collection. These results are examined in terms of the highest value recorded per patient during first line therapy.

24 Hour Collections by Absolute Value

	IFL + Placebo N = 118	IFL + Bevacizumab N = 159	5FU/LV/Bevacizumab N = 50
≤ 150 mg	53	68	17
151-1000 mg	59	82	21
1000-1999 mg	5	6	5
2000-2999 mg	1		4
3000-3999 mg			1
4000-4999 mg			1
≥ 5000 mg		3	1

No patient in the placebo group, three (1.9%) in the IFL + Bevacizumab arm, and three (6.0%) in the 5FU/LV/Bevacizumab arm had a 24 hour collection with greater than 3.5 grams of proteinuria. This table suggests an overall trend an increased incidence of more severe proteinuria with the use of bevacizumab. The overall incidence and the incidence of severe proteinuria appears to be increased in the 5FU/LV/Bevacizumab arm when compared to the IFL + Bevacizumab group.

Continued Dosing and Retreatment

Limited information is available on the effect of retreatment following the development of proteinuria more than 2 grams of proteinuria (two patients). Given the small number of patients and the timing of dosing and urine collection, conclusions cannot be drawn from this experience. For additional details please see Section 6.1.

Resolution of Proteinuria

The time to resolution of proteinuria can also be examined only in a limited number of patients due to inadequate follow up. Data is available on seven

patients in the 5FU/LV/ Bevacizumab arm. No patient had a normal 24 hour collection on follow up. However, decreases in the 24 hour collection were noted one to four months after completion of therapy in the three patients with multiple 24 hour urine collections following termination.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Conclusions concerning the incidence and severity of proteinuria using the entire Genentech database are difficult since the frequency of urinalysis varied from one to eight weeks in various studies. Please see Section 6.1 for additional details. Evidence of a possible dose effect, risk factors for the development of proteinuria, and significant adverse events related to proteinuria are discussed below.

Dose Effect

In a trial of patients with metastatic renal cell carcinoma were randomized to 10 mg/kg of bevacizumab, 3 mg/kg of bevacizumab, or placebo there is a suggestion of a dose effect with regard to the incidence of proteinuria. Patients in the placebo arm could crossover on progression to bevacizumab 3 mg/kg and results in this group are presented separately. Results of 24 hour collections are shown below. Data from this study should be interpreted with caution since 24 hour urines were not collected in a protocol specified schedule.

24 Hour Collections

				Crossover from Placebo Arm	
	10 mg/kg N = 19	3 mg/kg N = 14	Placebo N = 15	3 mg/kg N = 7	3 mg/kg + Thalidomide N = 5
< 1 gm	10	12	12	7	5
1 to < 2 g	2		1		
2 to < 3 g	3		1		
3 to < 4 g			1		
4 to < 5 g	1	2			
≥ 5 g	3				

There appears to be a relationship between dose and the incidence of more severe proteinuria in this study conducted in patients with metastatic renal cell carcinoma. However, since these patients have underlying renal cell carcinoma, caution must be used in the interpretation of this data.

Risk Factors

The applicant provided a post hoc analysis of risk factors for the development of proteinuria using the entire Genentech database. The relationship between adverse events coded as proteinuria and those coded as hypertension was of

interest. Among the 264 patients with hypertension, 103 (39.0%) also had proteinuria. While among the 768 patients without hypertension, 136 (17.7%) also had proteinuria.

Serious Adverse Events Related to Proteinuria

Five patients in the Genentech database developed nephrotic syndrome and an additional eight patients significant proteinuria. Significant proteinuria, in general, refers to greater than 2 grams of proteinuria. See Summary of Clinical Safety for additional details. One patient with proteinuria who was treated with bevacizumab required dialysis and one died shortly after the onset of severe hypertension and proteinuria. Two patients underwent biopsy, one biopsy showed membroproliferative glomerulonephritis and a second focal segmental glomerulosclerosis.

One patient treated under BB-IND 7921 developed nephrotic syndrome.

3.4.2.9 Vital Signs

Hypertension

Bevacizumab can result in clinically significant changes in blood pressure. When blood pressure is examined in terms of the mean and median increase across the entire study population, there is little change both between baseline and post-treatment blood pressure and between patients who received bevacizumab and those who did not. However, there is clearly an increased incidence in patients with markedly elevated blood pressure who receive bevacizumab as compared to those receiving chemotherapy alone.

Major Efficacy Study: AVF2107g

The following table illustrates the number and proportion of patients in each arm during first line therapy with either a systolic or diastolic blood pressure or both a systolic and diastolic blood pressure above those listed.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
> 140/90	261 (65.9%)	310 (79.1%)	89 (81.6%)
> 150/100	169 (42.7%)	234 (59.7%)	73 (67.0%)
> 200/110	10 (2.5%)	26 (6.6%)	11 (10.1%)

Note that there is an increase in the percentage of patients with hypertension defined as a systolic more than 140 and diastolic more than 90. However, there is an even greater increase in incidence between the bevacizumab and placebo arms as higher cutoff values are used.

Since a single reading with either a systolic greater than 200 or diastolic greater than 110 would have less weight than multiple elevated readings, these values where further examined. One of 10 patients in the IFL + Placebo, 11 of 26 in the IFL + Bevacizumab, and five of 11 in the 5FU/LV/Bevacizumab arm had these extreme values recorded on more than one occasion.

Whether these values involved primarily systolic or diastolic hypertension was also examined.

	Both Bevacizumab Arms
# of Patients	37
# Patients SBP > 200 Only	12
# Patients DBP > 110 Only	19
# Patients both SBP/DBP >200/110	6

This table notes that in slightly more than half of these patients extreme blood pressures were predominantly due to diastolic hypertension.

Anti-Hypertensive Medications

Ten patients in the IFL + Placebo and 46 in the IFL + Bevacizumab arm had a grade 3-4 hypertensive event (requiring medication or more intensive therapy). In the IFL + Placebo arm, six of 10 patients were given a new class of drug and in the IFL + Bevacizumab arm, 36 of 46 patients were given a new class of drug. New classes of medication included angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics, and combination medications.

Resolution of Hypertension

Thirty-six patients entered the follow up phase with ongoing hypertension. In eight of 10 patients in the IFL + Placebo arm, hypertension remained ongoing four months after discontinuation of study drug. In 18 of 26 patients in the IFL + Bevacizumab arm, hypertension remained ongoing four months after discontinuation of study drug.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Across all Genentech sponsored studies, the applicant conducted exploratory analyses to assess the risk factors for the development of hypertension, including dose. A descriptive assessment of the sequelae of hypertension was also conducted.

Risk Factors

Post hoc exploratory analyses suggested that age was not clearly associated with the development of hypertension and that a prior history of hypertension was only minimally associated with the development of hypertension on bevacizumab. There appeared to be a relationship between the development of an adverse event coded as proteinuria and as hypertension. Among the 239 patients with proteinuria, 103 (43.1%) also had hypertension. While among the 793 patients without proteinuria, 161 (20.3%) also had hypertension.

Assessment of the relationship of dose and severity of hypertension

Hypertension	2.5 mg/kg/week N = 571	5 mg/kg/week N = 351
Gr 1	44 (7.7%)	13 (3.7%)
Gr 2	25 (4.4%)	7 (2.0%)
Gr 3	69 (12.1%)	62 (17.7%)
Gr 4	0	0

On inspection, there appears to be a slight increase in the incidence of grade 3 hypertension in the 5 mg/kg/week group. However, this is not a randomized comparison and conclusions cannot be drawn.

In an NCI sponsored study in renal cell carcinoma, patients were randomized to placebo, bevacizumab 3 mg/kg every two weeks, or bevacizumab 10 mg/kg every two weeks. In this study, seven patients (17.9%) in the 10 mg/kg group developed grade 3 hypertension. No patients in the 3 mg/kg group, or placebo group developed grade 3 hypertension.

Serious Hypertensive Adverse Events

Four patients on Genentech sponsored studies and two treated under BB-IND 7921 developed hypertensive encephalopathy. Reports of subarachnoid hemorrhage and hemorrhagic stroke in association with either a systolic blood pressure greater than 200 and/or a diastolic pressure greater than 110 have also occurred.

3.4.2.10 ECGs

Not applicable

3.4.2.11 Special Safety Studies

3.4.2.11.1 Targeted Adverse Events

Perforation and Wound Healing

Major Efficacy Study: AVF2107g

An increased incidence of intestinal perforation was noted with the use of bevacizumab in AVF2107g. This is illustrated in the table below.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Perforation	1 (0.2%)	6 (1.5%)	4 (3.7%)
Dehiscence	2 (0.5%)	4 (1.0%)	1 (0.9%)
Fistula	0	3 (0.8%)	0
Abnormal Healing	0	2 (0.5%)	2 (1.8%)
Ischemic Bowel	0	2 (0.5%)	0
Abscess	3 (0.8%)	10 (2.6%)	5 (4.6%)

Events were noted to occur early in treatment.

Please see Drug Safety review of the incidence of intestinal perforation with irinotecan containing regimens in Section 6.3.1.

Post-Operative Complications

The following table provides an overview of post-operative complications.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
# Undergoing Major Surgery	25	39	15
# Procedures	28	45	18
# Post-Operative Complications	1	6	1

The date of last dose of study drug prior to surgery in patients experiencing post operative complications varied from one to 56 days.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Several patients have had post-operative complications or difficulties with wound healing. Two patients who illustrate this difficulty are discussed. One patient received bevacizumab 30 days after her initial surgery. Forty-one days after the initial surgery, she developed wound dehiscence of the skin and fascia. A second patient initiated bevacizumab treatment two months after her initial

surgery. After two additional months on study, the patient developed a clinically evident intra-abdominal abscess associated with an anastomotic dehiscence.

Hemorrhage

Major Efficacy Study: AVF2107g

The overall incidence of grade 3-4 bleeding was relatively low, 2.5% in the IFL + Placebo arm and 3.3% in the IFL + Bevacizumab arm. The majority of these events involved gastrointestinal hemorrhage. Of concern are the patients with significant and unexpected bleeding events such as retroperitoneal or subarachnoid hemorrhage in the bevacizumab arms. Subarachnoid hemorrhage was associated with severe hypertension in one patient and with stroke in two patients. Retroperitoneal hemorrhage was associated with excess anticoagulation.

Grade 1-4 events were collected in the first 309 patients enrolled on Arms 1-3. A striking increase in the incidence of low grade epistaxis and gastrointestinal hemorrhage (typically rectal hemorrhage or bleeding from the stoma) was noted in patients receiving bevacizumab as compared to the placebo arm.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Gr 1	10	35	35
Gr 2	0	0	0
Gr 3	0	1	0
Gastrointestinal Hemorrhage	6 (6.1%)	25 (24.5%)	22 (20.2%)
Gr 1	5	19	16
Gr 2		3	1
Gr 3	1	2	5
Gr 4		1	

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Using the entire Genentech database, a relatively low incidence of hemorrhage has been seen. However, in select studies, the incidence has been much higher.

Hemoptysis

There was an increased incidence of serious or fatal hemoptysis in patients with non-small cell lung cancer treated with bevacizumab. In a randomized Phase 2 study, no patients in the control group and six patients in the bevacizumab arms experienced serious or fatal hemorrhage. This represents an overall incidence of 9.1%. The expected incidence is less than 1% and no patients in the control arm of this study developed serious or fatal hemoptysis. An analysis done at the time

of these events suggested that these events were associated with squamous histology. Three of these events were associated with cavitation.

With this in mind, the Eastern Cooperative Oncology Group initiated E4599. This study randomized patients with newly diagnosed non-small cell lung cancer to carboplatin/paclitaxel or carboplatin/paclitaxel plus 15 mg/kg bevacizumab every three weeks. Patients with squamous cell histology were excluded from this study. Five cases of fatal hemoptysis have been seen on the bevacizumab arm of this study. All of these events were associated with cavitation or necrosis.

Other Serious Hemorrhagic Adverse Events

Additional significant hemorrhagic events have been seen in patients treated with bevacizumab. Two patients participating in the Phase 1 study, AVF737g, developed significant hemorrhagic events. One patient had an occult cerebral metastasis and experienced a central nervous system bleed 14 days after her first infusion of study drug. A second patient developed spontaneous hemorrhage into a necrotic tumor mass in her thigh. Embolization of the mass was required to control the bleeding.

NCI-Sponsored Studies

In the NCI database, hemorrhagic central nervous system events have been seen in seven patients. Gastrointestinal bleeding has also been seen. Events of particular concern include three patients with bleeding from their biliary stents due to erosion into the hepatic artery or in once instance, the portal vein. An additional patient bled into a liver metastasis and developed hematobilia in the absence of a stent.

Thromboembolic Events

Major Efficacy Study: AVF2107g

The overall incidence of thrombosis of any severity during first line therapy in the two principal arms is illustrated in the following table.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall	65 (16.4%)	79 (20.2%)
Cerebrovascular Event	0	4
Myocardial Ischemia	4	6
Pulmonary Embolism	20	16
Deep Venous Thrombosis	19	34
Catheter Related	11	7
Thrombophlebitis	3	3

Intra-abdominal Thromboembolism	7	14
Gr 3-4 Intra-abdominal thrombosis	5	13

While the overall incidence of thromboembolic events is not significantly different between arms, there is an increase in cerebrovascular and myocardial events and some change in the pattern of adverse events between arms. There was an increase in intra-abdominal thrombosis in the bevacizumab arm (see details of events considered intra-abdominal in Section 6.1). While many of these were discovered on routine CT scan, most were considered to be grade 3 events and required anti-coagulation. Also note that this was a blinded study suggesting that there was not an ascertainment bias in the bevacizumab arm.

Thromboembolic Events and the Use of Full Dose Anti-Coagulation

Because of concerns regarding possible potentiation of the risk of hemorrhage, patients were required to discontinue bevacizumab if the use of full dose warfarin was required for treatment of an intercurrent thromboembolic event. Despite this, 83 patients continued to receive bevacizumab, in violation of the protocol while receiving full dose warfarin.

Information on subsequent complications experienced by patients receiving full dose warfarin and blinded study drug are presented in the table below.

	IFL + Placebo	IFL + Bevacizumab
	On Study	On Study
# Patients	30	53
# Thromboembolic Events		
Gr 4	0	4
Gr 3	1	7
# Bleeding Events		
Gr 4	0	1
Gr 3	2	1

While the number of patients experiencing severe or life-threatening hemorrhage was low and similar in both arms, the incidence of additional serious/life-threatening thromboembolic events appears increased in patients receiving bevacizumab (1/30 vs. 11/53).

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Overall incidence of thromboembolic events

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	111 (19.5%)	28 (9.1%)	6 (3.8%)	145 (14.0%)
Pulmonary Embolism	20 (3.5%)	5 (1.6%)	0	25 (2.4%)
Deep Vein Thrombosis	50 (8.8%)	14 (4.6%)	4 (2.5%)	64 (6.2%)
Line Related Thrombosis	11 (1.9%)	2 (0.6%)	1 (0.6%)	10 (9.7%)
Intra-Abdominal Thrombosis	17 (3.0%)	5 (1.6%)	0	22 (2.1%)
Thrombophlebitis	9 (1.6%)	0	1 (0.6%)	27 (2.6%)
Thromboembolism	1 (0.2%)	4 (1.3%)	1 (0.6%)	6 (0.6%)
Myocardial Infarction	13 (2.3%)	0	1 (0.6%)	13 (1.3%)
Angina Pectoris	1 (0.2%)	0	1 (0.6%)	2 (0.2%)
Cerebrovascular Accident	4 (7.0%)	3 (1.0%)	1 (0.6%)	6 (0.6%)
Transient Ischemic Attack	2 (2.3%)	1 (0.3%)	0	5 (0.5%)

The incidence of thromboembolic events is highest in patients in the Colorectal Studies and lowest in patients receiving single agent therapy. An additional point raised by this table is that myocardial infarction was rare in non-colorectal cancer patients, but that cerebrovascular events were seen in all groups.

Serious Thrombotic Events

Three patients in the Genentech database have developed ischemic bowel.

Congestive Heart Failure

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

The incidence of CHF in all patients receiving bevacizumab in Genentech sponsored studies is shown below. Given the difference in the exposure to cardiotoxic agents, the incidence of CHF in patients with metastatic breast cancer is described separately.

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Congestive Heart Failure				22 (2.1%)
Gr 1	0	0		0
Gr 2	0	1 (0.3%)	1 (0.6%)	2 (0.2%)
Gr 3	7 (1.2%)	9 (2.9%)	2 (1.3%)	18 (1.7%)
Gr 4	0	1 (0.3%)	1 (0.6%)	2 (0.2%)

AVF2119g

In AVF2119g, a study that randomized patients with metastatic breast cancer to capecitabine or capecitabine plus bevacizumab, two events were noted in the capecitabine arm and 11 in the bevacizumab arm. All patients with an event had previously been exposed to cardiotoxic agents (12 to an anthracycline and one to trastuzumab). Two patients continued bevacizumab following the event. Specific cardiac follow up information is not available. However, additional adverse events were not reported. A second study in patients with metastatic breast cancer, [redacted] treated patients who had failed anthracycline and/or taxane therapy with 3, 10, or 20 mg/kg of bevacizumab every two weeks. Two of 75 patients developed congestive heart failure. One of these patients continued bevacizumab following the event. One month after the event, her ejection fraction was unchanged.

NCI Sponsored Studies

The National Cancer Institute database was also reviewed for instances of congestive heart failure. Study 2490 treated patients with relapsed/refractory acute myelogenous leukemia with high dose cytarabine, mitoxantrone 40 mg/M^2, and bevacizumab 10 mg/kg. Six of 44 patients in this study (13.6%) developed congestive failure.

Diarrhea

Major Efficacy Study: AVF2107g

The incidence of grade 3 and 4 diarrhea in the two principal arms during first line therapy is shown in the table below.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Diarrhea		
Gr 3	95 (24.0%)	119 (30.4%)
Gr 4	4 (1.0%)	14 (3.6%)

The incidence of grade 3-4 diarrhea was higher in the bevacizumab than in the placebo arm. Possible explanations for this are a longer time on study in the bevacizumab arm, an imbalance between arms in the ability to tolerate chemotherapy, or a lack of appropriate dose reduction in the bevacizumab arm.

In evaluating the time to onset of diarrhea (see Section 6.1) in the two principal arms, it appears that the slope in the time to development of diarrhea is increased between months five and 10 in the bevacizumab containing arms. Given this finding and that few cases occurred late in treatment, the increase in incidence of grade 3-4 diarrhea in the bevacizumab containing arms cannot be

attributed to a longer time on study. Differences in compliance with protocol specified dose modification was considered as a possible explanation. A direct comparison of compliance was not conducted by either the applicant or FDA. However, the median number of dose reductions of 5-fluorouracil or irinotecan among all patients in the IFL + Placebo or IFL + Bevacizumab arm was similar.

To further examine the question of dose, the total dose of 5-fluorouracil and irinotecan in each of the principal arms was examined according to the presence/absence of grade 3-4 diarrhea.

	IFL + Placebo	IFL + Bevacizumab
Total Dose Administered		
5-Fluorouracil		
Grade 3-4 Diarrhea	12140 mg (N = 99)	17375 mg (N = 133)
No Grade 3-4 Diarrhea	15759 mg (N = 297	18048 mg (N = 259)
Irinotecan		
Grade 3-4 Diarrhea	2957 mg (N = 99)	4170 mg (N = 133)
No Grade 3-4 Diarrhea	3879 mg (N = 297)	4384 mg (N = 259)

Patients with grade 3-4 diarrhea received a lower total dose of chemotherapy than those not experiencing severe diarrhea. In patients with and without grade 3-4 diarrhea, the total doses of 5FU and of irinotecan are higher in the bevacizumab arm as compared to the placebo group. The higher overall total dose is felt to be a reflection of the delay in time to progression (and thus the longer time on study treatment) among patients in the bevacizumab arm. However, the gap in dose between patients with and without grade 3-4 diarrhea is smaller in the bevacizumab arm when compared to placebo.

The increase in the incidence of diarrhea may also be related to higher mean levels of SN-38, the active metabolite of irinotecan, in patients receiving bevacizumab. The pharmacokinetics of irinotecan were assess in a subset of patients enrolled in AVF2107g. There were no differences in the pharmacokinetics of irinotecan between patients receiving bevacizumab and those receiving chemotherapy alone. In the pharmacokinetics subset, patients who receiving bevacizumab (N = 39) had higher mean levels of SN-38 as compared to the subset of patients who received chemotherapy alone (N = 29). However, SN-38 levels are variably associated with diarrhea (this is linked more closely with SN-38 glucuronide levels which were not measured). Further, there is typically a great deal of variability in SN-38 levels within a patient population due to allelic differences in the enzymes which metabolize irinotecan. Therefore, it is difficult to draw conclusions concerning the relevance of the increase in SN-38 or its relationship to increased diarrhea. Please see Clinical Pharmacology review for further details.

3.4.2.11.2 Events Unique to Biologic Products

Infusional Toxicity

Major Efficacy Study: AVF2107g

Infusional toxicities observed with intravenous administration of large proteins (including antibodies) are typically more frequent with the first administration. Adverse events occurring within 48 hours of the first administration of study drug were examined in the first 309 patients concurrently enrolled to Arms 1-3. Adverse events experienced by at least 5% of patients and adverse events of interest are listed below.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Overall	47 (48%)	53 (52%)	44 (40%)
Abdominal Pain	10 (10%)	7 (7%)	6 (6%)
Asthenia	7 (7%)	11 (11%)	5 (5%)
Nausea	11 (11%)	22 (21%)	12 (11%)
Diarrhea	9 (9%)	15 (15%)	4 (4%)
Vomiting	5 (5%)	4 (4%)	4 (4%)
Insomnia	5 (5%)	6 (6%)	2 (2%)
Sweating	6 (6%)	1 (1%)	1 (1%)

The incidence of any specific event was low and there was no clear pattern between arms.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

AVF2119g

The incidence of infusional events, identified through analysis of adverse events that occurred within 48 of the first administration, was also examined in a Phase 3 study in patients with metastatic breast cancer, AVF2119g.

	Capecitabine N = 215	Capecitabine + Bevacizumab N = 229
Tachycardia	5 (2.3%)	4 (1.7%)
Myalgia	3 (1.4%)	5 (2.2%)
Dyspnea	2 (0.9%)	4 (1.7%)
Cough Increased	2 (0.9%)	4 (1.7%)
Rhinitis	1 (0.5%)	0
Sinusitis	1 (0.5%)	0
Pruritus	1 (0.5%)	1 (0.4%)
Arthralgia	1 (0.5%)	1 (0.4%)

Vasodilation	0	4 (1.7%)
Fever	0	4 (1.7%)
Urticaria	0	1 (0.4%)

Overall, there was a slight increase in adverse events within 48 hours of the first administration in the bevacizumab arm, but no clear pattern emerged. The one patient with urticaria did not have a recurrence with continued treatment.

Allergic Reactions

Major Efficacy Study: AVF2107g

Adverse event reports coded with the term allergic reaction or related terms were examined. All such adverse reactions were attributable to other agents (contrast dyes, etc.) and not to the use of bevacizumab.

Serious Allergic Events

NCI Sponsored Studies

In the NCI database, nine allergic events are recorded. One is clearly related to the use of bevacizumab and a second is possibly related. One patient developed stridor and wheezing during bevacizumab infusion. The patient responded to epinephrine, diphenhydramine, and steroids and did not require hospitalization. This event occurred with the first dose of bevacizumab. It is unknown if the patient was rechallenged. The second patient received carboplatin/paclitaxel followed by bevacizumab. During the bevacizumab infusion, she developed chills and flushing. The infusion was discontinued and the patient was hospitalized. Shortly after this event, the patient died of massive hemoptysis and was not rechallenged.

Immunogenicity

The assay used in testing was not sufficiently sensitive to allow detection of lower titers. In addition, testing was done shortly after the last administration of bevacizumab. Circulating levels of bevacizumab may interfere with the detection of unbound antibodies.

Major Efficacy Study: AVF2107g

No patients on the pivotal study developed anti-bevacizumab antibodies.

All Patients Treated with Bevacizumab on Genentech Sponsored Studies

Across all Genentech sponsored studies, data is available on 837 patients. None of these patients developed anti-bevacizumab antibodies.

3.4.2.12 Withdrawal Phenomena/Abuse Potential

Bevacizumab has no known abuse potential. A withdrawal phenomenon has not been seen.

3.4.2.13 Human Reproduction and Pregnancy Data

There is no data concerning the use of bevacizumab in human pregnancy or in patients who wish to become pregnant after the use of bevacizumab. In animal studies, bevacizumab has led to fetal loss. Again in animal studies, the use of bevacizumab has led to gonadal changes which improved, but did not fully resolve upon discontinuation. Please see Toxicology review for further details.

3.4.2.14 Overdose Experience

There are no patients who have knowingly received an overdose of bevacizumab. Sixteen patients have received the highest dose tested, 20 mg/kg every two weeks. This was associated with headache in nine of 16 patients and severe headache in three patients.

3.4.2.15 Post-Marketing Experience in U.S. and Foreign Markets

There is no post-marketing experience with bevacizumab.

3.4.3 Adequacy of Safety Exposure and Safety Assessments

A sufficient number of patients have been exposed to bevacizumab to allow the detection of adverse events occurring in at least 5% of patients. Several areas remain in which insufficient information is available. These include the characterization of risk factors associated with intestinal perforation, further definition of the adverse event proteinuria, follow up information concerning the resolution of hypertension and proteinuria, and the development of long term vascular events. These will be addressed in post-marketing commitments.

3.4.4 Safety Conclusions

Serious events associated with the use of bevacizumab include intestinal perforation and abnormal wound healing, thromboembolic events, nephrotic syndrome, and hypertensive crisis/encephalopathy. The incidence of congestive heart failure appears to be increased in patients receiving bevacizumab and concurrent anthracycline therapy and in patients receiving bevacizumab who have a history of prior treatment with cardiotoxic agents. Bleeding is also increased with the use of bevacizumab, but this is largely confined to grade 1-2 events. However, in patients with non-small cell lung cancer, the risk of serious and fatal hemoptysis is significant.

There is insufficient information to draw conclusions concerning the relationship between the appropriate management of patients who develop proteinuria while receiving bevacizumab. There is also insufficient information to describe the clinical course of proteinuria or hypertension in bevacizumab treated patients. There are no data as to the long-term/delayed toxicities of bevacizumab such as the potential for an increased incidence of late vascular events.

The safety profile of this product is unique when compared to other anti-cancer agents. In general, the adverse events profile associated with the use of bevacizumab is less severe that than associated with typical cytotoxic agents. Whether bevacizumab has synergistic toxicity when administered with cytotoxic agents has not been fully explored.

3.5 Other Clinical Issues

3.5.1 Dosing, Regimen and Administration Issues

The pivotal study examined the efficacy of bevacizumab 5 mg/kg every two weeks. In this study, the first dose of bevacizumab was to be given over 90 minutes, the second over 60 minutes and the third over 30 minutes. Subsequent doses were then to be given over 30 minutes. An analysis of compliance with the delivery of bevacizumab over these protocol specified time intervals is provided below.

Cycle	Infusion Duration per Protocol	IFL + Placebo	IFL + Bevacizumab
% Treated per Protocol			
Cycle 1 Day 0	76-115 minutes	85.1%	84.8%
Cycle 1 Day 14	46-75 minutes	79.4%	79.5%
Cycle 1 Day 28	16-45 minutes	79.1%	77.9%

Bevacizumab has been administered at a variety of doses and schedules. The pharmacodynamic equivalence of these doses, in terms of efficacy, is unknown. The toxicity profiles of these different doses and schedules may also be affected by differences in underlying tumor and in the type of chemotherapy received.

Three Phase 2 trials randomized patients with the same underlying disease to different doses and schedules of bevacizumab plus chemotherapy. [redacted] randomized patients with non-small cell lung cancer to chemotherapy or chemotherapy with either 7.5 or 15 mg/kg bevacizumab every three weeks. Median time to progression was 5.9 months in the control, 3.5 months in the 7.5 mg/kg, and 7.0 months in the 15 mg/kg arm. Here, the higher dose appeared more efficacious. However, this may in part be related to the development of severe or fatal bleeding in five of 32 patients in the 7.5 mg/kg arm as compared to one of 34 patients in the 15 mg/kg arm.

— randomized patients with metastatic breast cancer to 3, 10, or 20 mg/kg of bevacizumab every two weeks. The response rate was 5.6% in the 3 mg/kg, 7.3% in the 10 mg/kg, and 6.3% in the 20 mg/kg arm. Response did not appear to be dose related. Grade 3-4 headache occurred in one patient in the 3 mg/kg, one patient in the 10 mg/kg, and 3 patients in the 20 mg/kg arm. Two of the events in the 20 mg/kg group were considered serious.

AVF0780g randomized patients with metastatic colorectal cancer to chemotherapy or to chemotherapy plus either 5 or 10 mg/kg of bevacizumab every two weeks. Median progression free survival was 5.2 months in the control, 9 months in the 5 mg/kg, and 7.2 months in the 10 mg/kg arm. Here, the 5 mg/kg dose appeared to be more active. Deep thrombophlebitis occurred in 4 of 35 patients in the 5 mg/kg arm and in no patients in the 10 mg/kg arm.

3.5.2 Use in Special Populations

3.5.2.1 Demographic Worksheet

The demographic makeup of the 1032 patients treated with bevacizumab in Genentech sponsored studies is included in the table below.

	Total N = 1032
Age	
Median (25-75)	57 (21-88)
Sex	
Male	425 (41.2%)
Female	607 (58.8%)
Race	
White	836 (81.0%)
Black	118 (11.4%)
Hispanic	39 (3.8%)
Asian	19 (2.8%)
Other	10 (1.0%)
Weight (kg)	
Median	74
Performance Status	
0	573 (55.6%)
1	448 (43.5%)
2	10 (1.0%)
Medical History	
Thrombosis	38 (3.7%)
Hypertension	365 (35.4%)
Prior Cancer Treatment	
Yes	898 (87.1%)

No	133 (12.9%)
Tumor Type	
Colon	594 (57.6%)
Breast	310 (30.0%)
Lung	89 (8.6%)
Other	39 (3.8%)

3.5.2.2 Special Considerations based on Race

Of the 1032 patients treated with bevacizumab in the Genentech database, 836 were White, 118 Black, and 78 Hispanic or Other. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., those reported at higher absolute incidence (at least 2% higher) in patients whose race was categorized as Black or Hispanic/Other as compared to White, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Race in ISS Database			
	White N = 836	Black N = 118	Hispanic/Other N = 78
Adverse Event Term	Grade 3-4	Grade 3-4	Grade 3-4
Hypertension	138 (16.5%)	25 (21.2%)	8 (10.3%)
Hypokalemia	30 (3.6%)	7 (5.9%)	3 (3.8%)

Hypertension was reported at a higher incidence in Black patients when compared to Whites or patients characterized as Hispanic/Other.

In the major efficacy study, a subset analysis examined the efficacy of bevacizumab in patients who were considered White versus those considered Non-White. The median survival of Non-White patients in the IFL + Bevacizumab arm had not yet been reached at the time of analysis while the median survival among Whites was 19.6 months. When hazard ratios comparing the median survival in the IFL + Bevacizumab group to that in the IFL + Placebo group by race are generated there is considerable overlap in the 95% confidence intervals surrounding these values.

3.5.2.3 Special Considerations based on Gender

Of the 1032 patients treated with bevacizumab in the Genentech database, 607 were female and 425 male. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., events that differed in absolute incidence by at least 2% between males and females, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Gender in ISS Database		
	Female N = 607	Male N = 425
Grade 3-4 Events		
Body as a Whole		
Asthenia	76 (12.5%)	37 (8.7%)
Pain	37 (6.1%)	16 (3.8%)
Headache	22 (3.6%)	3 (0.7%)
Digestive		
Diarrhea	126 (20.8%)	123 (28.9%)
Skin		
Exfoliative Dermatitis	71 (11.7%)	4 (0.9%)

In general, the incidence of grade 3-4 adverse events was similar in females and males, an exception is exfoliative dermatitis. Modest differences in the incidence of adverse events may be attributed to the underlying cancer type and chemotherapeutic regimen employed. Slightly less than half of the female patients were enrolled in the two studies of patients with metastatic breast cancer, [redacted] and AVF2119g. [redacted] administered single agent bevacizumab while AVF2119g administered capecitabine plus bevacizumab. Exfoliative dermatitis has been reported in association with the use of capecitabine. In AVF2119g, the incidence of exfoliative dermatitis was 75.3% in the capecitabine arm and 84.3% in the capecitabine plus bevacizumab arm.

In the major efficacy study, a subset analysis examined the efficacy of bevacizumab in males versus females. The median survival of males in the IFL + Bevacizumab arm was 21.2 months while the median survival in female patients was 18.0 months. When hazard ratios comparing the median survival in the IFL + Bevacizumab group to that in the IFL + Placebo group by sex are generated there is some overlap in the 95% confidence intervals surrounding these values.

3.5.2.4 Special Considerations based on Age for Adults

Adverse events in the elderly were reviewed both in the pivotal study and in all patients treated on Genentech sponsored studies. In the pivotal study, 392 patients, 266 less than 65 and 126 at least 65, were treated in the IFL + Bevacizumab arm. In both bevacizumab arms of the pivotal study 30 patients were at least 75. Among the 1032 patients treated on Genentech sponsored studies, 297 were at least 65 and 62 were at least 75. Patients greater than 75 were not reviewed separately.

Review of the pivotal study was confined to grade 3-4 events since these were collected throughout the study. Events that differed by at least 2% are included below.

	< 65 N = 266	≥ 65 N = 126
Overall	231 (86.8%)	121 (96.0%)
Body as a Whole		
Asthenia	26 (9.8%)	16 (13.0%)
Abdominal Pain	28 (10.5%)	10 (7.9%)
Sepsis	8 (3.0%)	7 (5.6%)
Cardiovascular		
Hypertension	35 (13.2%)	20 (15.9%)
Deep Vein Thrombosis	23 (8.6%)	15 (11.9%)
Intra-Abdominal Thrombosis	10 (3.8%)	1 (0.8%)
Hypotension	2 (0.8%)	5 (4.0%)
Myocardial Infarction	2 (0.8%)	4 (3.2%)
Congestive Heart Failure	1 (0.3%)	4 (3.2%)
Digestive		
Diarrhea	94 (35.3%)	49 (38.9%)
Vomiting	24 (9.0%)	10 (7.9%)
Constipation	8 (3.0%)	7 (5.6%)
Anorexia/Cachexia	8 (3.0%)	8 (6.3%)
Hemic/Lymphatic		
Leukopenia	94 (35.3%)	59 (46.8%)
Anemia	6 (2.3%)	7 (5.6%)
Metabolic/Nutrition		
Dehydration	17 (6.4%)	20 (15.9%)
Hypokalemia	12 (4.5%)	11 (8.7%)
Hyponatremia	4 (1.5%)	7 (5.6%)

Note that adverse events such as asthenia, anorexia, and dehydration are increased in the elderly. Leukopenia and sepsis are also increased. Further, there is an increase in adverse events uniquely associated with bevacizumab such as hypertension, deep thrombophlebitis, myocardial infarction, and congestive heart failure in elderly as compared to younger patients. Several adverse events of note were not increased in the elderly. These include pulmonary embolism and cerebrovascular accident.

Of the 742 patients who have received bevacizumab on Genentech sponsored trials in which grade 1-4 adverse events were collected, 530 were less than 65 and 212 at least 65 years of age. Forty-three were at least age 75. Adverse events in patients greater than 75 were not assessed. Grade 1-4 adverse events in those less than 65 and those 65 years or greater are included below. The table below includes adverse events that differ by at least 5%.

	< 65 N = 530	≥ 65 N = 212
Overall	529 (99.9%)	211 (99.5%)
Body as a Whole		
Asthenia	357 (67.4%)	155 (73.1%)
Headache	197 (37.2%)	47 (22.2%)
Digestive		
Diarrhea	316 (59.6%)	149 (70.3%)
Anorexia/Cachexia	162 (30.6%)	90 (42.4%)
Dyspepsia	80 (15.1%)	44 (20.8%)
GI Hemorrhage	15 (2.8%)	17 (8.0%)
Hemic/Lymphatic		
Leukopenia	107 (20.2%)	61 (28.8%)
Anemia	83 (15.7%)	48 (22.6%)
Metabolic/Nutrition		
Edema	88 (16.6%)	69 (32.5%)
Respiratory		
Epistaxis	128 (24.2%)	63 (29.7%)
Cough Increased	118 (22.3%)	61 (28.8%)
Voice Alteration	26 (4.9%)	24 (11.3%)
Skin		
Exfoliative dermatitis	201 (37.9%)	27 (12.7%)

When grade 1-4 adverse events are examined, dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration occurred at a higher incidence in the elderly as compared to younger patients. Headache and exfoliative dermatitis were reported at a lower incidence in the elderly as compared to younger patients.

In the major efficacy study, a subset analysis examined the efficacy of bevacizumab in terms of age (less than 40, 40 to 64, and at least 65 years). In the IFL + Bevacizumab arm, the median survival in those less than 40 was 22.8 months. In those 40-64, it was 15.8 months and in those 65 or greater median overall survival was 24.2 months. When hazard ratios comparing the median survival in the IFL + Bevacizumab group to that in the IFL + Placebo group by age are generated there is considerable overlap in the 95% confidence intervals surrounding these values.

3.5.2.5 Special Considerations based on Age for Pediatrics

The safety of bevacizumab in pediatric patients has not been studied. In immature cynomolgous monkeys, the use of bevacizumab was associated with physeal dysplasia and delayed growth plate maturation. For additional information please see toxicology review.

3.5.2.6 Other Special Considerations

Renal Dysfunction

Patients with significant renal dysfunction were excluded from Genentech sponsored studies. Eligibility criteria for the Phase 3 program required patients to have a creatinine less than 2 mg/dL. The eligibility criteria for the Phase 1 and 2 program required patients to have a creatinine of less than 1.5 mg/dL. The one exception to this was —— which required a creatinine less than 1.8 mg/dL.

Of the 1032 patients treated with bevacizumab in the Genentech database, 33 patients had a calculated creatinine clearance of less than 50 mL/min at study entry. Events, which are increased by at least 2% in these patients, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Renal Function in ISS Database		
	With Renal Dysfunction N = 33	Without Renal Dysfunction N = 999
Body as a Whole		
Abdominal Pain	5 (15.2%)	70 (7.0%)
Cardiovascular		
Pulmonary Embolism	3 (9.1%)	21 (2.1%)
Congestive Heart Failure	2 (6.1%)	11 (1.1%)
Digestive		
Diarrhea	9 (27.3%)	240 (24.0%)
Anorexia	2 (6.1%)	23 (2.3%)
GI Hemorrhage	1 (3.0%)	15 (1.5%)
Hemic/Lymphatic		
Anemia	2 (6.1%)	28 (2.8%)
Metabolic/Nutrition		
Hypokalemia	3 (9.1%)	37 (3.7%)
Hypercalcemia	2 (6.1%)	8 (0.8%)
Respiratory		
Dyspnea	3 (9.1%)	65 (6.5%)
Urogenital		
Proteinuria	2 (6.1%)	7 (0.7%)
Urinary Tract Infection	2 (6.1%)	9 (0.9%)

Since the number of patients with an abnormal creatinine clearance is small it is difficult to draw conclusions concerning differences in the adverse event profile of patients with renal dysfunction. However, patients with an abnormal calculated creatinine clearance had a higher incidence of electrolyte abnormalities, diarrhea, pulmonary embolism, CHF and proteinuria. The incidence of hypertension was similar in patients with normal and abnormal renal function and is not included in this table.

Hepatic Dysfunction

Patients with significant hepatic dysfunction (NCI CTC grade 3 or greater) were excluded from Genentech sponsored studies of bevacizumab. Of the 1032 patients treated with bevacizumab in the Genentech database, 333 had abnormal liver function tests at baseline. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., higher absolute incidence of at least 2% in patients abnormal hepatic function, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Hepatic Function in ISS Database		
	With Hepatic Dysfunction N = 334	Without Hepatic Dysfunction N = 698
	Grade 3-4	Grade 3-4
Abdominal Pain	28 (8.4%)	47 (6.7%)
Fever	4 (1.2%)	8 (1.1%)
Stomatitis	4 (1.2%)	4 (0.6%)
Epistaxis	2 (0.6%)	2 (0.3%)
Exfoliative Dermatitis	28 (8.4%)	47 (6.7%)

Approximately half the patients in the ISS database had underlying colorectal cancer. In the pivotal study, AVF2107g, only seven patients in the IFL + Placebo and 10 patients in the IFL + Bevacizumab arm had grade 3-4 hepatic dysfunction during therapy. This number was too small to permit analysis of adverse event profile in patients with severe hepatic dysfunction.

Pregnancy

Bevacizumab has not been studied in pregnancy. In animal models, bevacizumab has been shown to cause fetal loss. For further information please see toxicology review.

3.5.3 Outcome of Advisory Committee Meeting

An Advisory Committee Meeting was not held.

4.0 Mitigating Factors for Interpretation of Clinical Data

4.1 Other Discipline Reviews

4.1.1 CMC

See Chemistry Manufacturing and Control Report.

4.1.2 Pharmacology /Toxicology

See Clinical Pharmacology and Toxicology Reports.

4.2 Auditing Functions

4.2.1 DSI Outcomes

Please see DSI report. Six sites were inspected. These include the

Warning letters issued at two sites, —— ——

4.2.2 Financial Disclosure

In the pivotal study, AVF2107g, financial disclosure information was provided for 98.8% of investigators and 98.8% of sub-investigators. In the supportive study, AVF780g, financial disclosure information was provided for 85.7% of investigators and 49.5% of sub-investigators. Five investigators/subinvestigators on AVF2107g had qualifying disclosures. These include Drs. ——— ——— Dr. —— enrolled 11 patients. The remaining investigators each enrolled smaller numbers of patients. The conclusions regarding safety and efficacy in the pivotal study are not materially affected by exclusion of patients from these investigator sites.

4.3 Other Factors

Several findings noted in the DSI report also became evident during the conduct of AVF2107g, the major efficacy study. These include:

1. Patient eligibility
2. Drug dispensation and record keeping
3. Placing sites that were noted to have difficulties in compliance with Good Clinical Practice on hold without FDA notification
4. The repeated queries of adverse events said to be related to study drug

The issue of patient eligibility is discussed in Sections 3.3.2 and 6.1.

Drug dispensation and record keeping are discussed further in Section 6.1. Briefly, several sites administered the incorrect kit of blinded study drug due to an inaccurate reading of the very long study drug kit number. In many instances, the correct study drug was actually administered. However, 14 patients received the incorrect study drug. Since these were confined to a single event, they were not thought to have affected outcome. These events occurred

over a period of several years. Sites that did not have an error in drug dispensation were not informed of this potential problem.

During the conduct of the study, the FDA placed the IND on partial hold due to irregularities at three sites. The first site came to attention as a result of a call to the FDA. A warning letter was issued at this site. As part of the evaluation of irregularities at this site, it was learned that the applicant had a policy which placed sites on internal hold due to difficulties in compliance with Good Clinical Practice. This occurred at four sites. The issues at these sites had been resolved by the time the FDA became was aware of the issues. A second site was placed on hold due to recurrent drug dispensation errors (discussed above). The third site came to attention during an audit of patients enrolled on another clinical trial at that institution. [redacted]
Patients enrolled at this site were excluded from the analysis of study AVF2107g.

During BLA review, the issue of repeated queries, also noted in the DSI report, became apparent. Sites were frequently asked whether the adverse event was related to study drug despite a clear indication that the event was related in the initial adverse event report. It was also noted that serious adverse events were occasionally reassigned or removed from the database. The applicant was asked to provide further information on this practice.

Forty-three serious adverse events were removed from the database. Of these 43 events, 19 are of concern. Twelve of the 19 occurred in the IFL + Placebo arm, five in the IFL + Bevacizumab, and two in the 5FU/LV/Bevacizumab group. Three of the 19 events were considered non-serious on further query, one occurred 29 days after discontinuation, one involved the removal of deep vein thrombosis in a patient who also had a pulmonary embolism, and 14 were reclassified as due to progressive disease. The applicant was asked about the classification of adverse events that were thought to be due to progressive metastatic colorectal cancer as non-serious. They referred to Section 5.1 of the protocol in which it states:

> For this protocol, an AE is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding) that emerges or worsens relative to pretreatment baseline during the treatment or posttreatment periods, regardless of the suspected cause. Note: Unchanged, chronic conditions or those related to the underlying disease or medical conditions that are consistent with natural disease progression are **NOT** AEs and should not be recorded on AE pages of the CRF, unless there is an exacerbation of a chronic condition.
>
> For example: A pretreatment blood glucose of 280 mg/dL and a

posttreatment blood glucose of 270 mg/dL in a subject with diabetes is an example of a preexisting condition that did not worsen in intensity or frequency and as such, would not be recorded as an AE.

Examples of serious adverse events attributed to progressive disease and removed from the database include: dysphasia, pancreatic cancer, seizure, small bowel obstruction, hematochezia, and cord compression.

There are a large number of issues concerning the conduct of the major efficacy study, AVF2107g. The survival advantage in the IFL + Bevacizumab arm compared to IFL + Placebo remained despite these difficulties in study conduct. It is likely that the conduct of the study under represented the adverse event profile of bevacizumab. However, the occurrence of adverse events did not lead to a diminution in the survival advantage of bevacizumab.

5.0 Summative Assessment

5.1 Conclusion on Available Data

The addition of bevacizumab to IFL chemotherapy provides a highly statistically significant survival advantage when compared to IFL alone. The safety profile of bevacizumab is acceptable. Adverse events associated with bevacizumab include intestinal perforation, impaired wound healing, hypertensive crisis, hemorrhage, thromboembolism, nephrotic syndrome, and congestive heart failure.

5.2 Recommendations for Regulatory Action

Approval is recommended for the use of bevacizumab in combination with an intravenous 5-fluorouracil based regimen in the treatment of metastatic colorectal cancer.

5.3 Review of Labeling

Please refer to Labeling Review.

5.4 Comments to Sponsor

5.4.1 Comments Regarding Labeling

Please refer to labeling review.

5.4.2 Comments Regarding Need for Additional Data

Please see recommendations concerning Post-Marketing Commitments above.

5.4.3 Comments Regarding Other Topics

None

6.0 Individual Trial / Study Reports

6.1 Major Efficacy and Safety Trials

6.1.1 AVF2107g

Pivotal Study: AVF2107g

A Phase III, Multi-Center, Randomized, Active-Controlled Clinical Trial to Evaluate the Efficacy and Safety of rhuMAb VEGF (Bevacizumab) in Combination with Standard Chemotherapy in Subjects with Metastatic Colorectal Cancer

Study Design

Patients with newly diagnosed metastatic colorectal cancer were initially randomized to IFL (irinotecan, 5-fluorouracil, leucovorin) + Placebo, IFL + Bevacizumab, or 5FU/LV (5-fluorouracil + leucovorin) + Bevacizumab. Following a pre-planned analysis of safety, enrollment to the 5FU/LV/Bevacizumab arm was discontinued. Enrollment continued to the IFL + Placebo and IFL + Bevacizumab arms. The study was initiated in September 2000 and 923 patients were enrolled at 163 centers. The initial BLA submission has a data cutoff of February 2003. The Safety Update covered the period from February 2003 to July 2003. The applicant's Objectives and Eligibility Criteria follow.

Study Objectives

Primary Objectives

- To evaluate the efficacy of multiple administrations of rhuMAb VEGF (5 mg/kg every 2 weeks) when combined with chemotherapy versus 5-fluorouracil (5-FU)/leucovorin/irinotecan for treatment of metastatic colorectal cancer, as measured by duration of survival
- To evaluate the safety of multiple administrations of rhuMAb VEGF (5 mg/kg every 2 weeks) when combined with chemotherapy versus 5 FU/leucovorin/irinotecan for treatment of metastatic colorectal cancer

Secondary Objectives

- To evaluate the safety of 5-FU/leucovorin/irinotecan/rhuMAb VEGF when 300 subjects had been randomized versus 5-FU/leucovorin/irinotecan and 5-FU/leucovorin/rhuMAb VEGF
- To evaluate the efficacy of multiple administrations of rhuMAb VEGF (5 mg/kg every 2 weeks) when combined with chemotherapy versus 5-FU/leucovorin/irinotecan for treatment of metastatic colorectal cancer, as

measured by time to disease progression, objective response rate, and duration of objective response
- To determine the plasma pharmacokinetics of irinotecan when administered in combination with 5-FU/leucovorin and rhuMAb VEGF versus 5-FU/leucovorin alone
- To investigate the disposition of rhuMAb VEGF
- To compare changes in quality of life in subjects with metastatic colorectal cancer receiving rhuMAb VEGF (5 mg/kg every 2 weeks) combined with chemotherapy versus 5-FU/leucovorin/irinotecan

Exploratory Objectives
- To evaluate efficacy and safety during second-line therapy
- To compare efficacy and safety between the arm that was discontinued following the interim safety analysis and the 5-FU/leucovorin/irinotecan arm.

Subject Selection

Subjects with previously untreated, histologically confirmed metastatic colorectal cancer were eligible for participation in this study. Resected or biopsied primary tumors or metastatic site served as the basis for histologic confirmation.

Inclusion Criteria

All subjects must meet the following criteria to be eligible for study entry:
- Written informed consent
- Age $\geq$ 18 years
- Histologically confirmed colorectal carcinoma with evidence of metastases (i.e., by radiographic imaging or biopsy)
- Ability to tolerate CT contrast dye (added Amendment 1)
- Bi-dimensionally measurable disease (minimum of two lesions, as defined by the RECIST criteria)
- ECOG performance status of 0 or 1
- Use of an effective means of contraception in women of childbearing potential
- Life expectancy of >3 months
- Willingness and capability to be accessible for follow-up until death or study termination by Genentech

Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for study entry:
Cancer History
- Prior chemotherapy other than adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole
- Administration of adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole completed $\leq$ 12 months prior to Day 0

- Administration of fluoropyrimidines as a radiosensitizer during pelvic radiotherapy for rectal cancer completed ≤ 12 months prior to Day 0 (added Amendment 2)
- Prior radiotherapy to a measurable, metastatic lesion(s) to be used to measure response
- Radiation therapy within 28 days prior to Day 0 (14 days per Amendment 1)
- Prior biotherapy for colorectal cancer
- Evidence of clinically detectable ascites on Day 0
- Other invasive malignancies within 5 years prior to Day 0 (other than basal cell carcinoma of the skin)

rhuMAb VEGF Risk Factors

- History or evidence upon physical examination of CNS disease (e.g., primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of stroke)
- Active infection requiring parenteral antibiotics on Day 0
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 0, or anticipation of need for major surgical procedure during the course of the study; fine needle aspirations within 7 days prior to Day 0
- Current or recent (within the 10 days prior to Day 0) use of full-dose oral or parenteral anticoagulants (except as required to maintain patency of preexisting, permanent indwelling IV catheters) or thrombolytic agent (for subjects receiving warfarin, international normalized ratio [INR] of <1.5; appropriate use of heparin should be discussed with the Medical Monitor)

- Chronic, daily treatment with aspirin (>325 mg/day) or non-steroidal anti-inflammatory medications (of the kind known to inhibit platelet function at doses used to treat chronic inflammatory diseases)
- Pregnancy (positive pregnancy test) or lactation
- Proteinuria at baseline or clinically significant impairment of renal function. Subjects unexpectedly discovered to have ≥ 1+ proteinuria at baseline should undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate <500 mg of protein/24 hr to allow participation in the study.
- Serious, non-healing wound, ulcer, or bone fracture
- Evidence of bleeding diathesis or coagulopathy

General Medical Concerns

- Current or recent (within the 28 days prior to Day 0) participation in another experimental drug study
- Clinically significant cardiovascular disease (e.g., uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or Grade II or greater peripheral vascular disease within 1 year prior to Day 0.

- Screening clinical laboratory values
  - ANC of <1500/μL
  - Platelet count of <75,000/μL
  - INR of ≥ 1.5
  - Total bilirubin of > 2.0 mg/dL (1.6 mg/dL per Amendment 2)
  - AST or ALT ≥ 5 times upper limit of normal for subjects with documented liver metastases; >2.5 times the upper limit of normal for subjects without evidence of liver metastases
  - Serum creatinine of > 2.0 mg/dL
  - Hemoglobin of < 9 gm/dL (may be transfused to maintain or exceed this level)
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications

Stratification Factors

Patients were stratified by ECOG performance status (0 vs. 1), site of primary disease (colon vs. rectum), number of organ sites (1 vs. > 1), and institution. Patients were initially randomized to:

Treatment

1. **Arm 1: IFL + Placebo**
   a. Irinotecan 125 mg/M^2 weekly for 4 weeks in each 6 week cycle
   b. Leucovorin 20 mg/M^2 IVB weekly for 4 weeks in each 6 week cycle
   c. 5-Fluorouracil 500 mg/M^2 IVP weekly for 4 weeks in each 6 week cycle
   d. Placebo every two weeks

2. **Arm 2: IFL + Bevacizumab**
   a. Irinotecan 125 mg/M^2 weekly for 4 weeks in each 6 week cycle
   b. Leucovorin 20 mg/M^2 IVB weekly for 4 weeks in each 6 week cycle
   c. 5-Fluorouracil 500 mg/M^2 IVP weekly for 4 weeks in each 6 week cycle
   d. Bevacizumab 5 mg/kg every two weeks

3. **Arm 3: 5FU/LV/Bevacizumab**
   a. Leucovorin 500 mg/M^2 over 2 h weekly for 6 weeks of each 8 week cycle
   b. 5-Fluorouracil 500 mg/M^2 IVB weekly for 6 weeks of each 8 week cycle
   c. Bevacizumab 5 mg/kg every two weeks

Since there was no prior safety information for the combination of IFL + Bevacizumab, AVF2107g was initially designed as a three arm study. Following enrollment of the first 309 patients, the Data Safety Monitoring Board determined that the IFL + Bevacizumab combination was safe and further enrollment in the 5FU/LV/Bevacizumab arm was discontinued. Patients initially enrolled in this arm continued their assigned treatment.

The study then enrolled an additional 311 patients to IFL + Placebo and 299 patients to IFL + Bevacizumab arm.

Amendment History and Dose Modification

The initial protocol had a complicated dose reduction scheme. This was further complicated by the controversy surrounding the safety of the approved dose of IFL. Several protocol amendments that altered the dose modification criteria of IFL are summarized below.

	Original Protocol	Amendment 2	Amendment 3
ANC/Platelets			
Gr 2	Reduce 1 level	Hold till ≤ gr 1, reduce 1 level	Reduce 1 level
Gr 3/4-1st dose		Hold till gr 0, reduce 2 levels	Removed
Gr 3	Hold till ≤ gr 1, reduce 1 level	Hold till ≤ gr 1, reduce 1 level	Hold till ≤ gr 2, reduce 1 level
Gr 4	Hold till ≤ gr 1, reduce 2 levels	Hold till ≤ gr 1, reduce 2 levels	Hold till ≤ gr 2, reduce 2 levels
Febrile Neutropenia			Hold till resolved, reduce 2 levels
Diarrhea			
Gr 1			Hold till baseline, no anti-diarrheal meds, continue dose
Gr 2	Reduce 1 level	Hold if diarrhea within 24 h dosing, reduce 1 level	Hold till baseline, no anti-diarrheal meds, reduce 1 level
Gr 3/4-1st dose		Hold till gr 0, then reduce 2 levels	Removed
Gr 3	Hold till ≤ gr 1, reduce 1 level	Hold till ≤ gr 1, no diarrhea within 24 h dosing, reduce 1 level	Hold till baseline, no anti-diarrheal meds, reduce 1 level
Gr 4	Hold till ≤ gr 1, reduce 2 levels	Hold till ≤ gr 1, no diarrhea within 24 h dosing, reduce 2 levels	Hold till baseline, no anti-diarrheal meds, reduce 2 levels

Additional protocol modifications were made during the course of the study. Amendment 1 provided dose modification criteria for 5FU and irinotecan for Arms 1 and 2 and for 5FU in Arm 3. Amendment 3 changed the hematologic criteria for cycle initiation to require a platelet count ≥ 100,000/μL and noted that dose reductions for grade 3 and 4 toxicities should be maintained at the start of a new cycle.

Throughout the protocol, dose reductions were made for grade 2 toxicities. However, the continuation of these dose reductions at subsequent cycles was at the discretion of the investigator. Throughout the protocol, doses omitted due to toxicity could be given within the same cycle.

Treatment Periods

Patients continued the assigned treatment regimen until first progression. This is referred to as Treatment Period 1. Following Treatment Period 1, all patients could choose to receive additional investigator selected chemotherapy on or off study. On study, patients randomized to a bevacizumab containing arm could choose to receive investigator selected chemotherapy alone, unblinded therapy with bevacizumab alone, or unblinded therapy with bevacizumab plus investigator selected chemotherapy. Treatment could continue for up to 96 weeks. After 96 weeks, patients originally assigned to the bevacizumab arms could enter an extension study, AVF2540g and receive an additional two years of bevacizumab. Patients in the placebo group could receive treatment with investigator selected chemotherapy on or off study following their first progression, but were not permitted to crossover to bevacizumab. On study treatment following first progression is referred to as Treatment Period 2. Treatment Period 2 did not end with a second progression. Patients were allowed to continue on study with a change in chemotherapy. Patients originally assigned to a bevacizumab containing arm could continue bevacizumab plus additional investigator selected chemotherapy. All patients, regardless of whether they continued to receive additional regimens on study following Treatment Period 1, were followed for overall survival. Information continued to be collected, as possible, in all patients on additional therapies following first progression.

Endpoints and Assessments

The primary endpoint of this study was overall survival. The duration of survival was defined as the time from randomization to death due to any cause. Overall survival was assessed using a stratified logrank test. Stratification factors included performance status, number of organs involved with tumor, and primary site. The population for this test was to exclude patients enrolled at a site under criminal investigation. The applicant assumed a 33% improvement in overall survival from 15 to 20 months. With these assumptions, the study had an 80% power to detect this difference using a two-sided alpha of 0.05. The first interim analysis occurred after 300 patients were randomized and the second after 50% of the expected deaths had occurred. The final analysis was planned when 385 deaths had occurred in the two principal arms.

Secondary endpoints included progression free survival, response rate, duration of response, time to change in the FACT-C score, and patient safety. Pharmacokinetic information was also obtained. Tumor assessments were performed at baseline, every six weeks for the first 24 weeks, and then every 12 weeks. Progression free survival was defined as the time from randomization to disease progression or death due to any cause during first line therapy. Progression free survival was assessed using a stratified logrank test with the stratification factors performance status, number of organs involved with tumor, site of primary tumor, and region in which the patient was enrolled. A two-sided significance level of 0.05 was used. The population for this test was to exclude patients enrolled at a site under criminal investigation and at a second site at which significant irregularities had become apparent prior to unblinding. The applicant did not

agree to remove patients at the second site from this analysis or from the analysis of response rate.

Response rate was defined as confirmed complete or partial response by the RECIST criteria during first line therapy. An independent radiology facility was not used. Response rates were compared using the chi-squared test with a two-sided 0.05 level of significance. The population was to be identical to that for progression free survival, but again the applicant has removed only patients enrolled at the site under criminal investigation. Duration of objection response was to be analyzed in the same population. Only descriptive comparisons would be provided.

The FACT-C questionnaire was administered at baseline, every six weeks for the first 24 weeks, and then every 12 weeks. FACT-C questionnaires were limited to the first 300 patients enrolled. The applicant has agreed that the analysis of the FACT-C questionnaire not be used in labeling information or in promotional materials.

Patient safety was assessed through the collection of adverse events. Grade 1-4 adverse events were collected in 309 patients concurrently enrolled on Arms 1, 2, and 3. Following the discontinuation in enrollment in Arm 3, only grade 3-4 events were collected in the 298 patients subsequently enrolled in Arm 1 and the 290 patients subsequently enrolled in Arm 2. Grade 1-4 adverse events were collected throughout the study in what the applicant refers to as targeted adverse events: proteinuria, hypertension, and thromboembolic events.

Study Results

Study Populations

Two Principal Arms

	IFL + Placebo	IFL + Bevacizumab
Intent to Treat[1]	411	402
Not Treated with Study Drug	15	10
Adverse Event	1	2
Progressive Disease	2	2
Patient/Physician Decision	12	6
Not Treated with Chemotherapy	14	7
Adverse Event	1	0
Progressive Disease	2	1
Patient/Physician Decision	11	6
Safety Population[2]	396	392

[1]Excludes patients enrolled at a site under criminal investigation.
[2]Collection of all Grade 3-4 adverse events and Grade 1-4 thrombosis, proteinuria, and hypertension.

The applicant has excluded patients who did not receive blinded study drug from the safety population. However, the adverse events causing discontinuation in three patients were included in Case Report Tabulations and are included in the analyses below (these patients are not included in the denominator). This includes one patient in

the IFL + Placebo arm who developed infection in the absence of neutropenia and two patients in the IFL + Bevacizumab arm. One patient in the IFL + Bevacizumab arm had a cerebrovascular accident and the second a pulmonary embolism.

There is also a discrepancy between the patients who did not receive blinded study drug and those who did not receive chemotherapy. One patient in the IFL + Placebo arm began chemotherapy, but did not receive study drug. This was due to a positive urine dipstick. This patient later developed diarrhea and dehydration and discontinued the study. The patient is considered to have discontinued due to patient/physician decision rather than to an adverse event. Three patients in the IFL + Bevacizumab arm began chemotherapy, but did not receive study drug. Two of these patients did not begin study drug due to proteinuria. One discontinued due to a cerebrovascular accident and the second due to progressive disease (prior to radiologic assessment). In the third patient, 13241, it is not clear why they did not receive study drug. This patient discontinued due to a pulmonary embolism.

Concurrently Enrolled Arms 1-3

	IFL + Placebo	IFL + Bevacizumab	5FU/LV/Bevacizumab
Intent to Treat[1]	100	103	110
Not Treated with Study Drug	2	1	1
Progressive Disease	1	1	0
Patient/Physician Decision	1	0	1
Not Treated with Chemotherapy	2	1	1
Progressive Disease	1	1	0
Patient/Physician Decision	1	0	1
Safety Population[2]	98	102	109

[1]Excludes patients enrolled at a site under criminal investigation
[2]Grade 1-4 adverse events collected.

Here, four patients did not receive either chemotherapy or blinded study drug prior to discontinuation.

Subject Eligibility

The applicant stated that 18.1% of the patients enrolled were ineligible, categorizing 10.8% of these as major eligibility violations and 9.3% as minor eligibility violations.

Per Applicant

	IFL Placebo	IFL Bevacizumab	5FU/LV Bevacizumab	Total
All Eligibility Violations	83 (20.2%)	63 (15.7%)	21 (19.1%)	167 (18.1%)
Major Violations	48 (11.7%)	42 (10.4%)	10 (9.1%)	100 (10.8%)
No Measurable Lesions	3	0	0	3 (0.7%)

Chemotherapy for Metastases	7	9	3	19 (2.1%)
No Informed Consent	0	1	0	1 (0.2%)
Other Malignancy	7	2	1	10 (1.1%)
Full Dose Warfarin at Entry	5	0	0	5 (0.5%)
CNS Disease	4	6	0	10 (1.1%)
Cardiovascular Disease	0	1	0	1 (0.1%)
24 h Urine Protein > 500 mg	5	2	2	9 (1.0%)
Performance Status > 1	4	3	2	9 (0.8%)
Laboratory Abnormalities[1]	4	3	0	7 (0.8%)
Adjuvant Chemotherapy < 11 Mos of Entry	9	8	4	21 (2.3%)
Major Surgery < 28 d of Entry	4	10	0	14 (1.5%)
Radiotherapy within 14 d of Entry	6	4	1	11 (1.2%)
Minor	45 (10.9%)	27 (6.7%)	14 (12.7%)	86 (9.3%)
One Target Lesion	32	18	10	60 (6.5%)
Laboratory Abnormalities	6	4	2	12 (1.3%)
Adjuvant Chemotherapy 11-12 Mos Prior to Entry	5	3	2	10 (1.1%)
Ascites	3	3		6 (0.7%)

[1]To qualify as a major laboratory abnormality the ANC must by < 1000/μL, platelets < 50,000/μL, INR > 2.0, Bilirubin > 2 mg/dL, AST/ALT > 10xULN with liver metastases or > 5xULN without, Creatinine > 3 mg/dL, Hemoglobin < 8 g/dL

Given the high percentage of ineligible patients identified by the applicant, the eligibility criteria were closely reviewed.

	IFL Placebo N = 411	IFL Bevacizumab N = 402	5FU/LV Bevacizumab N = 110
All Eligibility Violations	147 (35.8%)	135 (33.6%)	34 (30.9%)
Major Violations	112 (27.2%)	100 (24.9%)	26 (23.6%)
Metastatic Adenocarcinoma of the Colon or Rectum	1	1	1
Two Target Lesions Not Identified	34	19	11
Two Targets Not Measurable by RECIST	7	7	6
Prior Chemotherapy for Metastatic Disease	3	5	2
Other Invasive Malignancy	8	2	2
Full Dose Anti-coagulation at Entry	9	3	0
CNS Disease	0	7	0
Uncontrolled HTN-BP > 190/105	6	6	1
24 h Urine Protein > 500 mg	5	1	2
Performance Status > 1	2	3	1
Laboratory Abnormalities[1]	13	7	1
Adjuvant Chemotherapy[2]	8	9	5
Major Surgery within 28 d of Entry	24	28	2
Radiotherapy within 14 d of Entry	1	1	0
Other	2	3	0

Minor	34 (8.3%)	35 (8.7%)	8 (7.3%)
Uncontrolled HTN BP > 160/100	39	35	9
Minor Surgery within 28 d of Entry	3	2	2
Laboratory Abnormalities	6	6	1
Ascites	0	2	0
Other	0	1	0

[1]Defined as AST/ALT > 5xULN, bilirubin > 2 mg/dL, Hgb < 8 g/dL, INR > 1.5
[2]Includes both patients who completed adjuvant chemotherapy < 12 mo prior to entry and those that did not receive fluoropyrimidines alone

There are significant differences between the patients identified as ineligible and violations identified as major versus minor by the applicant and on review. These primarily involve:

- An increase in the number of patients who lack two measurable lesions and a recategorization of these patients as a major eligibility violation.
- Recategorization of patients who had undergone major surgery within 28 days of entry or that had significant laboratory abnormalities with major eligibility violation.
- Inclusion on patients who entered with uncontrolled hypertension.
- One patient listed as having no informed consent by the applicant was not considered ineligible during review. This patient was incorrectly randomized to this study (rather than another Genentech study at the same institution). The error was detected prior to patient treatment.

There were patients with additional violations that were not identified in the FDA review of eligibility violations above. These include:

- Patients who did not complete their screening urine assessments.
- The protocol required that patients have two bi-dimensionally measurable lesions. Several patients had only uni-dimensional measurements. Since the RECIST criteria were used, these patients were not considered ineligible.
- The protocol required that patients with clinically significant cardiovascular disease be excluded from the study. Review of the past medical history noted a significant number of patients with a past history of cardiovascular disease. Seventy patients in IFL + Placebo, 65 in IFL + Bevacizumab, and 17 in the 5FU/LV/Bevacizumab arm had what appears to be clinically significant disease. Due to difficulties in the assessment of clinical significance, these patients are not included in the FDA review.

Given the issues above, failure to adhere to protocol specified treatments were also carefully reviewed.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Total Major and Minor Violations	166 (41.9%)	195 (49.7%)
Major Protocol Violations	75 (18.9%)	130 (33.2%)
Adverse Event of > 42 Days w/o Discontinuation	34	67

Received Full Dose Warfarin	30	50
Study Gap > 42 Days	20	45
Continued Same Therapy > 42 Days Past PD	13	14
Minor Protocol Violations	91 (23.0%)	66 (16.8%)
Adverse Event Lasting 21-42 Days	20	24
Incorrect Study Drug Administered	7	3
Dosing Error	70	42
Delayed IRB Review of Amendment	5	3
Study Gap Between Treatment Periods	0	15

Major deviations from the treatment plan for which patients were not removed from study include grade 3 or 4 adverse events lasting more than 42 days, the use of full dose warfarin, and a gap in study drug administration greater than 42 days. Patients with grade 3 or 4 adverse events lasting 21 days or more were to be removed from study if this was thought to compromise the patient's ability to participate. Given the difficulty in determining whether these adverse events would compromise the patient's ability to continue, a longer cutoff period, 42 days, was used by the FDA in categorizing this as a major violation. The applicant did not consider this a protocol violation since the protocol stated that patients may be removed for a grade 3-4 adverse event lasting more than 21 days. Forty-two days was chosen since this value represents two half-lives of bevacizumab and one cycle of IFL. Adverse events of shorter duration were considered a minor violation. Removal of these patients from the category Major Protocol Violations would decrease the number of major violations to 55 (13.9%) in Arm 1 and 94 (24.0%) in Arm 2.

Given the concerns about hemorrhage and the use of bevacizumab at the time this study was initiated, the use of full dose warfarin was prohibited while on study drug; patient requiring such therapy were to have blinded study drug discontinued. This is, therefore, considered a major protocol violation. While this is primarily a safety concern, there is also reason to be concerned about bias in the selection of patients who remained on study on full dose warfarin and those who discontinued. This is discussed further below.

A gap in study drug administration of greater than 42 days is also considered a major violation. The cause of these gaps is detailed below. Finally, patients who had a response of progressive disease on IFL + Study Drug were considered to have a major protocol violation is they continued on the same chemotherapy regimen for greater than 42 days. Here, 42 days was chosen because it represents continuation of the same regimen at the next cycle.

Minor protocol violations included continued dosing of blinded study drug in patients with grade 3-4 adverse events lasting 21-42 days, incorrect study drug administration, dosing errors, delays in Institutional Review Board processing of a protocol amendment, and study gaps of greater than 42 days between Treatment Periods 1 and 2.

- Incorrect study drug administration refers to patients who were given the incorrect blinded study drug kit. When the blind was later broken, it was determined that these patients had received the incorrect study drug.
- Dosing errors refers to an error in the calculation of the first dose of 5-fluorouracil or irinotecan or, more commonly, a failure to dose reduce as indicated for diarrhea or neutropenia.
- Delays in Institutional Review Board approval of a protocol amendment captures any delay of greater than six months. This is expressed in terms of the number of patients affected at the site. Adverse events that may have occurred as a result of delays in this approval (such as new dose modification criteria) were not assessed.
- Finally, delays in the delivery of study drug of greater than 42 days that occurred between Treatment Periods (following first progression and prior to initiation of second line therapy) were considered to be a minor protocol violation.

Demographic and Tumor Characteristics

The incidence of baseline entry characteristics was examined between arms. The characteristics of patients in the IFL + Placebo and IFL + Bevacizumab arms are examined followed by an examination of patients concurrently enrolled to Arms 1-3.

	IFL + Placebo N = 411	IFL + Bevacizumab N = 402
Age		
Median (years)	60	60
Sex		
Male	248 (60.3%)	237 (59.0%)
Female	163 (39.7%)	165 (41.0%)
Race		
White	328 (79.9%)	317 (78.9%)
Black	46 (11.2%)	49 (12.2%)
Hispanic	23 (5.6%)	18 (4.5%)
Asian	14 (3.4%)	12 (3.0%)
Other	0	6 (1.5%)
Performance Status[1]		
0	227 (55.2%)	234 (58.4%)
≥ 1	184 (44.8%)	167 (41.5%)
Duration of Disease[1]		
Median (range)	3 mo (1-142)	3 mo (1-170)
Duration of Metastatic Disease		
Median (range)	2 mo (1-125)	2 mo. (1-91)
Primary Site		
Colon	334 (81.3%)	310 (77.1%)
Rectum	77 (18.7%)	92 (22.9%)

Prior Therapy		
Surgery	360 (87.6%)	350 (87.1%)
Radiation Therapy	59 (14.4%)	60 (14.9%)
Adjuvant Chemotherapy	113 (27.5%)	96 (23.9%)
Neoadjuvant Chemotherapy	10 (2.4%)	11 (2.7%)
Sites of Disease[2]		
Bone	8 (2.0%)	5 (1.2%)
Liver	316 (77.3%)	315 (78.4%)
Lung	196 (47.9%)	199 (49.5%)
Dominant Metastatic Location		
Hepatic	158 (38.6%)	153 (38.1%)
Intra-abdominal	26 (6.4%)	21 (5.2%)
Extra-abdominal	225 (55.0%)	228 (56.7%)
Tumor Burden		
Median SLD cm (range)	11 (1-72)	10 (2-41)

[1]Data is not available for one patient in the IFL + Bevacizumab arm.

[2]May be > 100%

Patients concurrently enrolled in Arms 1-3.

	IFL + Placebo N = 100	IFL + Bevacizumab N = 103	5FU/LV/Bevacizumab N = 110
Age			
Median	59.5	61	61.5
Sex			
Male	63 (63.0%)	57 (55.3%)	69 (62.7%)
Female	37 (37.0%)	46 (44.7%)	41 (37.3%)
Race			
White	87 (87.0%)	87 (84.5%)	90 (81.8%)
Black	8 (8.0%)	8 (7.8%)	14 (12.7%)
Hispanic	4 (4.0%)	3 (2.9%)	2 (1.8%)
Asian	1 (1.0%)	3 (2.9%)	4 (3.6%)
Other	0	1 (1.0%)	0
Performance Status			
0	45 (45.0%)	60 (58.3%)	61 (55.5%)
$\geq$ 1	55 (55.0%)	43 (41.7%)	49 (44.5%)
Duration of Disease (mos)			
Median (range)	3 (1-125)	3 (1-101)	3 (1-107)
Duration of Metastatic Disease (mos)			
Median (range)	2 (1-125)	2 (1-91)	2 (1-70)
Primary Site			
Colon	75 (75.0%)	81 (78.6%)	77 (70.0%)
Rectum	25 (25.0%)	22 (21.4%)	33 (30.0%)
Prior Therapy			
Surgery	87 (87.0%)	93 (90.3%)	89 (80.9%)

Radiation Therapy	18 (18.0%)	18 (17.5%)	24 (21.8%)
Adjuvant Chemotherapy	25 (25.0%)	35 (34.0%)	36 (32.8 %)
Sites of Disease[1]			
Bone	1 (1.0%)	1 (1.0%)	2 (1.8%)
Liver	79 (79.0%)	81 (78.6%)	90 (81.8%)
Lung	47 (47.0%)	46 (44.7%)	43 (39.1%)
Dominant Metastatic Location			
Hepatic	44 (44.0%)	45 (43.7%)	52 (47.3%)
Intra-abdominal	4 (4.0%)	4 (3.9%)	6 (5.5%)
Extra-abdominal	52 (52.0%)	54 (52.4%)	52 (47.3%)
Tumor Burden			
Median SLD cm (range)	10 (2-33)	10 (2-37)	9 (2-49)

[1]May be > 100%

The two principal arms were well balanced. Of interest was the extreme range in the duration of metastatic disease. The numbers of patients with extreme values was small in each arm. It was also noted that although the medians were very similar, the range in the sum of the longest diameter varied in the IFL + Placebo versus the IFL + Bevacizumab arms. The number of patients with extreme values in each arm was small. However, the tumor burden appeared to be slightly increased in the IFL + Placebo arm.

When patients enrolled concurrently in Arms 1-3 were examined, imbalances were noted in several categories. These include performance status, primary site, prior use of radiation therapy, and prior use of adjuvant chemotherapy. The imbalances did not consistently favor any arm.

Drug Delivery

Drug delivery was examined in terms of the number of patients that receiving study treatment, the dose density of administration, gaps in drug delivery, and study drug infusion time. Of the 923 patients randomized, 897 patients received at least one dose of study drug. The reasons that 26 patients did not receive study drug are included in the table below.

	IFL + Placebo	IFL + Bevacizumab	5FU/LV/Bevacizumab
Progressive Disease	2	2	0
Adverse Event	1	2	0
Physician Decision	3	3	0
Patient Decision	9	3	1
Total	15	10	1

Dose Intensity

Drug delivery in patients in the two principle arms was examined in terms of dose intensity by cycle. A cycle was defined by the cycle and day recorded on the infusion form rather than the calendar.

Treatment Cycles	Median Dose Intensity (Range)	
	IFL + Placebo	IFL + Bevacizumab
Cycle 1		
Bevacizumab/Placebo	100% (18-112)	100% (32-145)
5-Fluorouracil	89% (3-123)	88% (22-110)
Leucovorin	97% (24-1610)	96% (24-126)
Irinotecan	90% (24-207)	88% (24-111)
Cycle 2		
Bevacizumab/Placebo	100% (30-123)	100% (30-117)
5-Fluorouracil	78% (20-123)	77% (16-130)
Leucovorin	97% (22-688)	97% (23-750)
Irinotecan	78% (19-155)	77% (15-142)
Cycle 3		
Bevacizumab/Placebo	100% (32-123)	100% (30-112)
5-Fluorouracil	77% (13-105)	74% (19-108)
Leucovorin	98% (24-137)	97% (24-133)
Irinotecan	76% (10-105)	74% (19-111)
Cycle 4		
Bevacizumab/Placebo	100% (30-113)	100% (26-131)
5-Fluorouracil	76% (10-107)	67% (19-130)
Leucovorin	97% (25-121)	98% (24-127)
Irinotecan	76% (8-107)	68% (16-127)
Cycle 5		
Bevacizumab/Placebo	100% (33-133)	100% (30-118)
5-Fluorouracil	72% (12-105)	64% (11-109)
Leucovorin	98% (24-1262)	97% (25-563)
Irinotecan	71% (10-106)	60% (8-111)
Cycle 6		
Bevacizumab/Placebo	100% (30-133)	100% (29-130)
5-Fluorouracil	68% (13-106)	64% (10-110)
Leucovorin	98% (25-875)	97% (23-579)
Irinotecan	66% (10-105)	61% (8-111)

The applicant also examined the total dose intensity. Here, dose intensity was calculated as the total dose received as a percentage of the expected total dose. The expected total dose was calculated as the dose that that should have been administered between the date of the first and last dose during Treatment Period 1.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Study Drug		
Mean	96.3%	94.3%
Median	99%	97%
25-75	94-101	90-100
5-Fluorouracil		
Mean	79.3%	74.3%
Median	80%	73%
25-75	66-96	61-89
Irinotecan		
Mean	78.4%	72.7%
Median	81%	73%
25-75	65-96	58-89

The applicant also calculated the total dose intensity for the 309 patients concurrently enrolled on Arms 1-3.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Study Drug			
Mean	96.2%	94.1%	94.8%
Median	99%	97%	97%
25-75	95-101	90-101	90-100
5-Fluorouracil			
Mean	80.1%	74.2%	87.5%
Median	80%	72%	91%
25-75	69-95	64-88	80-98
Irinotecan			
Mean	79.3%	72.7%	0
Median	81%	72%	
25-75	69-96	61-88%	

Given the changes in dose modification criteria throughout the study, compliance with appropriate dose modification criteria was not examined.

Both of these analyses are notable for the high levels of study drug administered. In part, this is related to the dose modification criteria for bevacizumab. Bevacizumab was held for high grade toxicities, but was not given at a reduced dose for lesser toxicities. These analyses are also remarkable for the nearly equal dose intensities of 5-fluorouracil and irinotecan. It is interesting to note that despite the controversies surrounding irinotecan, the median percent dose reductions of irinotecan and 5-fluorouracil are nearly identical. Finally, it should be noted that by cycle 6, the median dose density of both 5FU and irinotecan was slightly greater than 50%.

On review, the number of cycles in which no doses of 5FU, irinotecan, leucovorin, or bevacizumab/placebo were missed was examined.

	IFL + Placebo	IFL + Bevacizumab
Study Drug		
No cycles with a missed dose	52.0%	42.3%
1 cycle with a missed dose	33.8%	35.5%
2 cycles with a missed dose	9.7%	13.4%
5-Fluorouracil		
No cycles with a missed dose	34.4%	26.1%
1 cycle with a missed dose	38.8%	30.6%
2 cycles with a missed dose	15.6%	21.6%
Irinotecan		
No cycles with a missed dose	35.6%	28.3%
1 cycle with a missed dose	38.8%	30.3%
2 cycles with a missed dose	14.3%	20.0%

Although the percentage of patients with one to two cycles in which they missed one or more doses appears high, given the large number of doses administered this becomes a small percentage of the total.

Extent of Exposure

	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Duration (months)		
Mean	9.1	8.5
Median (25-75)	8 (4-14)	7 (3-12)
≤ 12 Months	69.6%	76.1%
> 12 Months	30.4%	23.9%

Additional Issues

Two additional issues concerning drug delivery are systematic pharmacy errors that occurred in the delivery of blinded placebo/bevacizumab and the number of gaps in the dosing of study drug. Seven patients on the IFL + Placebo, three patients on the IFL + Bevacizumab, and four patients on the 5FU/LV/Bevacizumab arm received the incorrect study drug on one occasion due to the administration of the incorrect blinded study drug kit. Since these events occurred on one occasion, it is unlikely that they affected outcome.

Twenty-one patients in the IFL + Placebo, 67 patients in the IFL + Bevacizumab, and 25 patients in the 5FU/LV/Bevacizumab group had a gap in the delivery of bevacizumab/placebo greater than 42 days. The category, Other, includes events ranging from patient vacation to the delivery of radiation therapy. The applicant was able to supply additional information concerning 21 patients in which the cause of the

study drug gap was initially reported as unknown. This information is included in the table below. However, the applicant considers this information to be preliminary. Reasons for these gaps were as follows:

	IFL + Placebo	IFL + Bevacizumab	5FU/LV/Bevacizumab
Total # Gaps	21	52	19
Serious Adverse Events	12	20	6
Thromboembolic Events	2	11	3
Adverse Events	1	10	5
Procedures/Surgery	4	5	2
Other	2	5	3
Unknown	0	1	0

In addition, 15 patients in the IFL + Bevacizumab and six in the 5FU/LV/Bevacizumab arm had a gap in study drug administration of greater than 42 days following progression during Treatment Period 1 and prior to further administration of bevacizumab during Treatment Period 2.

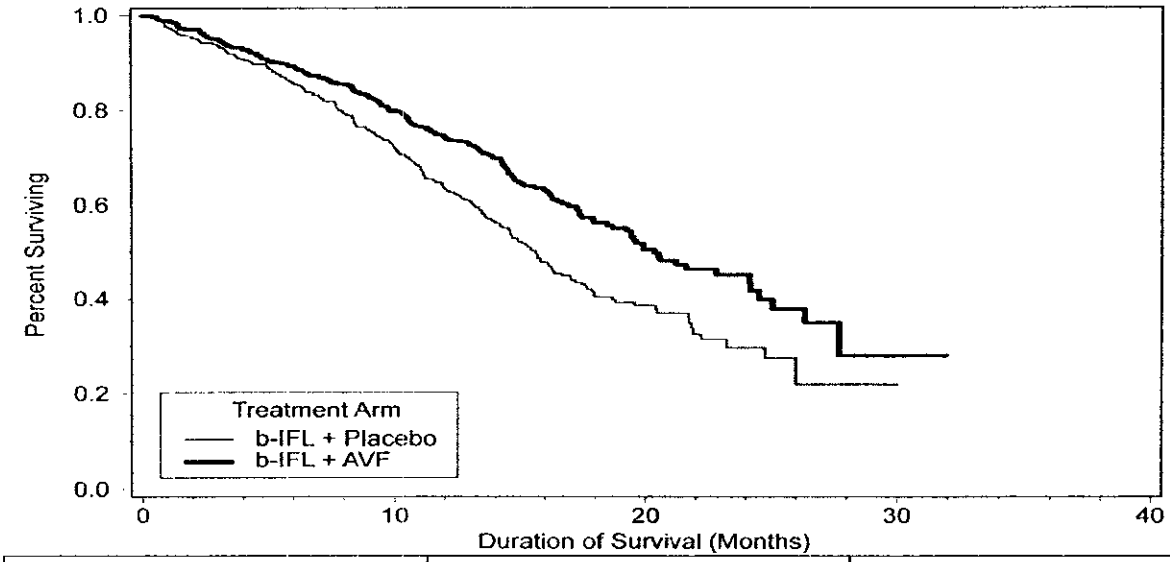
A final area is the length of infusion of study drug. The protocol states that the first dose should be given over 90 minutes, the second over 60 minutes and the third over 30 minutes. Subsequent doses were then given over 30 minutes. If a reaction was thought to have occurred, the infusion time could be increased. Increases in infusion time are discussed under adverse events. The majority of infusions were given over these time intervals.

Cycle	Infusion Duration	IFL + Placebo	IFL + Bevacizumab
Cycle 1 Day 0	76-115 minutes	85.1%	84.8%
Cycle 1 Day 14	46-75 minutes	79.4%	79.5%
Cycle 1 Day 28	16-45 minutes	79.1%	77.9%

Efficacy

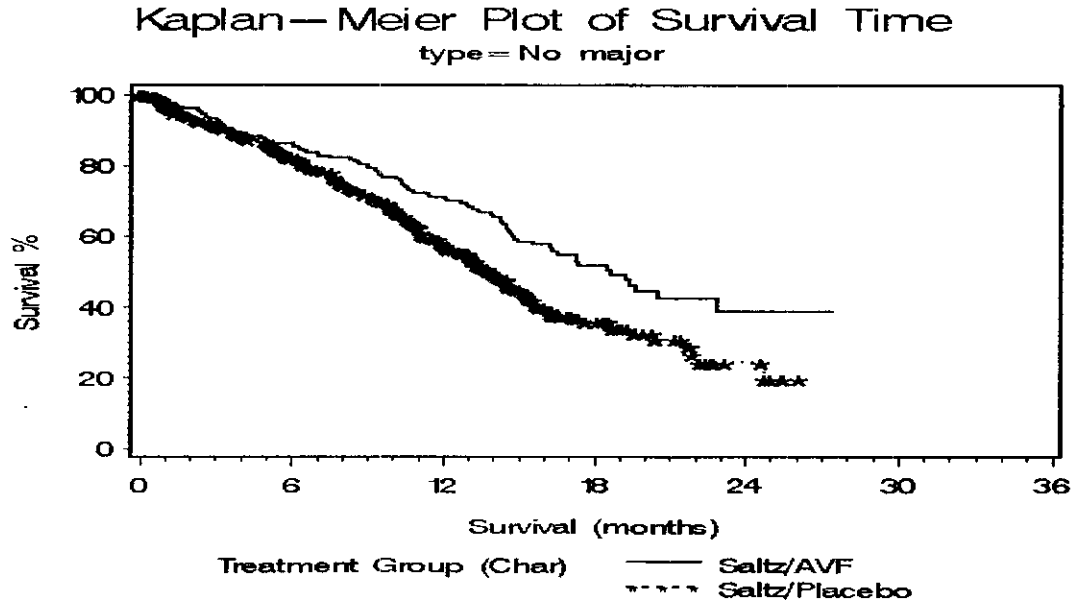
Overall Survival

The addition of bevacizumab to IFL provided a significant survival advantage when compared to IFL alone. A comparison of the two principal arms using the intent to treat population is as follows.



	IFL + Placebo N = 411	IFL + Bevacizumab N = 402
Median Survival (months)	15.6	20.3
Hazard Ratio		0.66
p value (stratified logrank)		< 0.0001

Given the large number of protocol violations and patients with deviations from specified therapy, a sensitivity analysis was performed which excluded patients with major protocol treatment violations and/or major eligibility violations. In the IFL + Placebo arm, 164 of 411 patients (39.9%) had a major eligibility and/or protocol violation while 199 of 402 patients (49.5%) in the IFL + Bevacizumab arm had a major eligibility and/or protocol violation. The figure below illustrates the overall survival of patients without major eligibility or protocol violations (n = 450). The result remains significant (p = 0.0012, stratified logrank test).



Overall survival was also examined in patients with major protocol or eligibility violations in the two principal arms (N = 363). This comparison was not statistically significant (p = 0.0879, stratified logrank test).

An additional sensitivity analysis was performed which excluded patients with major and minor eligibility and/or major and minor protocol treatment violations. Removal of these patients resulted in a decrease from 813 patients to 301 patients in the two principal arms. Despite this, the survival advantage remained significant (p = 0.0364, stratified logrank test). Among the 512 patients with major and minor protocol and or eligibility violations, the difference in overall survival was statistically significant (p = 0.0009, logrank test).

Therapy Beyond First Progression

The applicant also examined the use of subsequent therapies for their possible effect on overall survival. The table below includes all therapies beyond first line and patients may be counted more than once. The applicant was able to obtain follow up information concerning second or later line therapies in 95% of patients.

	IFL + Placebo	IFL + Bevacizumab
All Chemotherapies Beyond 1st Line[1]		
Oxaliplatin	109 (26.5%)	97 (24.1%)
Irinotecan	42 (10.2%)	43 (10.7%)
Capecitabine	94 (22.9%)	93 (23.1%)
Other	168 (40.9%)	146 (36.3%)
Metastasectomy		
1st Line	2 (0.5%)	2 (0.5%)
Beyond 1st Line	4 (1.0%)	5 (1.2%)
Radioablation		
Beyond 1st Line	3 (0.7%)	4 (1.0%)

[1]All chemotherapies regardless of use alone or with bevacizumab.

Therapy on Study Beyond First Progression

The study allowed patients to be unblinded following first progression. Patients could then choose to receive additional chemotherapy regimens on or off study. Information on subsequent therapies, on or off study, was collected in all patients. Patients randomized to the bevacizumab arms who chose to remain on study could continue bevacizumab alone, bevacizumab plus investigator determined chemotherapy, or chemotherapy alone. Of the patients who received study drug and progressed, 47 in the IFL + Placebo, 110 in the IFL + Bevacizumab, and 55 in the 5FU/LV/Bevacizumab arm continued to receive second line therapy on study. Of these, 100 of the 110 patients initially treated with IFL + Bevacizumab and 51 of the 55 patients initially treated with 5FU/LV/Bevacizumab choose to receive bevacizumab alone or with chemotherapy. Survival was then examined from the time of first progression in terms

of initial second line therapy. This table includes only the first second line regimen and provides information only on patients who progressed on first line therapy.

	Number of Patients	Overall Survival (mo)
Initial Treatment w/ IFL + Placebo		
None/Other	96	4.1
Chemotherapy	170	10.1
Initial Treatment w/ IFL + Bevacizumab		
None/Other	63	2.7
Chemotherapy	52	9.4
Chemotherapy + Bevacizumab	94	10.0
Bevacizumab	6	7.6
Initial Treatment w/ 5FU/LV/Bevacizumab		
None/Other	12	4.5
Chemotherapy	11	Not reached
Chemotherapy + Bevacizumab	50	11
Bevacizumab	1	

Survival from initiation of salvage chemotherapy was similar regardless of whether the patient received chemotherapy or chemotherapy plus bevacizumab. That is, the improvement in overall survival seen with bevacizumab was primarily due to its addition to first line therapy. This lack of benefit may have been affected by the chemotherapy received alone or with bevacizumab and by selection bias in the patients who continued to receive bevacizumab versus those who did not. The applicant has pooled patients initially enrolled in the IFL + Placebo and IFL + Bevacizumab arms who chose to receive chemotherapy alone. Thus, it is difficult to draw conclusions concerning the effect of additional chemotherapy on survival following first progression. The applicant did provide an analysis of prognostic factors in patients who received bevacizumab following first progression versus those who did not. In general, the patients who received bevacizumab had more favorable prognostic factors.

Subset Analyses

The applicant examined the effect of bevacizumab on overall survival in terms of baseline entry characteristics in the two principal arms. All hazard ratios are a comparison of IFL + Placebo to IFL + Bevacizumab for each subset.

	Number of Patients	Hazard Ratio (95% Confidence Intervals)
Intent-to-Treat	813	0.67 (0.55-0.82)
Performance Status		
PS 0	461	0.66 (0.49-0.88)
PS $\geq$ 1	352[1]	0.69 (0.53-0.90)
Number of Metastatic Sites[2]		
1	306	0.75 (0.53-1.04)

> 1	507	0.62 (0.49-0.80)
Location of Primary		
Colon	644	0.74 (0.59-0.92)
Rectum	169	0.47 (0.30-0.73)
Age		
< 40	35	0.50 (0.19-1.30)
40-64	507	0.71 (0.55-0.92)
≥ 65	271	0.61 (0.43-0.87)
Sex		
Female	328	0.73 (0.54-0.99)
Male	485	0.64 (0.49-0.83)
Race		
White	645	0.68 (0.55-0.85)
Non-White	168	0.61 (0.38-0.98)
Prior Adjuvant Chemotherapy		
Yes	209	0.64 (0.42-0.97)
No	604	0.67 (0.53-0.84)
Prior Radiotherapy		
Yes	119	0.64 (0.38-1.09)
No	694	0.67 (0.46-0.78)
Duration of Disease		
< 12 Months	527	0.72 (0.56-0.91)
≥ 12 Months	285	0.57 (0.40-0.82)
Duration of Metastatic Disease		
< 12 Months	760	0.71 (0.58-0.87)
≥ 12 Months	53	0.29 (0.13-0.66)
Albumin		
< Median	305	0.67 (0.51-0.89)
> Median	476	0.66 (0.49-0.89)
Alkaline Phosphatase		
< Median	385	0.63 (0.46-0.86)
> Median	397	0.69 (0.53-0.90)
Lactate Dehydrogenase		
< Median	386	0.67 (0.48-0.92)
> Median	391	0.67 (0.52-0.88)
Sum of the Longest Diameter		
< Median	400	0.77 (0.57-1.04)
≥ Median	410	0.60 (0.46-0.78)

[1] In one patient performance status was never recorded. In this analysis, the applicant assumed that the performance status of this patient was ≥ 1.
[2] Refers to the number of organs involved with tumor rather than the number of metastatic lesions

Subset analyses show that the effect of bevacizumab on overall survival is consistent in all subgroups examined. The number of metastatic sites and tumor burden appeared to have an interaction with bevacizumab. Patients with a larger number of metastatic sites

appear to derive additional benefit when compared to patients with a smaller number of metastatic sites. The sum of the longest diameter more directly evaluates tumor burden. The applicant examined this in terms of patients with tumor burden below the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile of patients. As is usual, patients with the smallest tumor burden (below the 10^{th} percentile) had the lowest hazard ratio. However, this was not a continuous pattern with an increase in hazard ratio with increasing tumor burden. Instead, patients above the 75^{th} percentile and the 90^{th} percentile had a lower hazard ratio than those with tumor burdens below the 75^{th} percentile.

This is consistent with information concerning the clearance of bevacizumab. Males had a more rapid clearance of bevacizumab (as would be hypothesized in patients with a larger tumor burden). Despite this more rapid clearance, the hazard ratio was noted to be lower in males than that in females.

Overall Survival in Patients Concurrently Enrolled in Arms 1 through 3

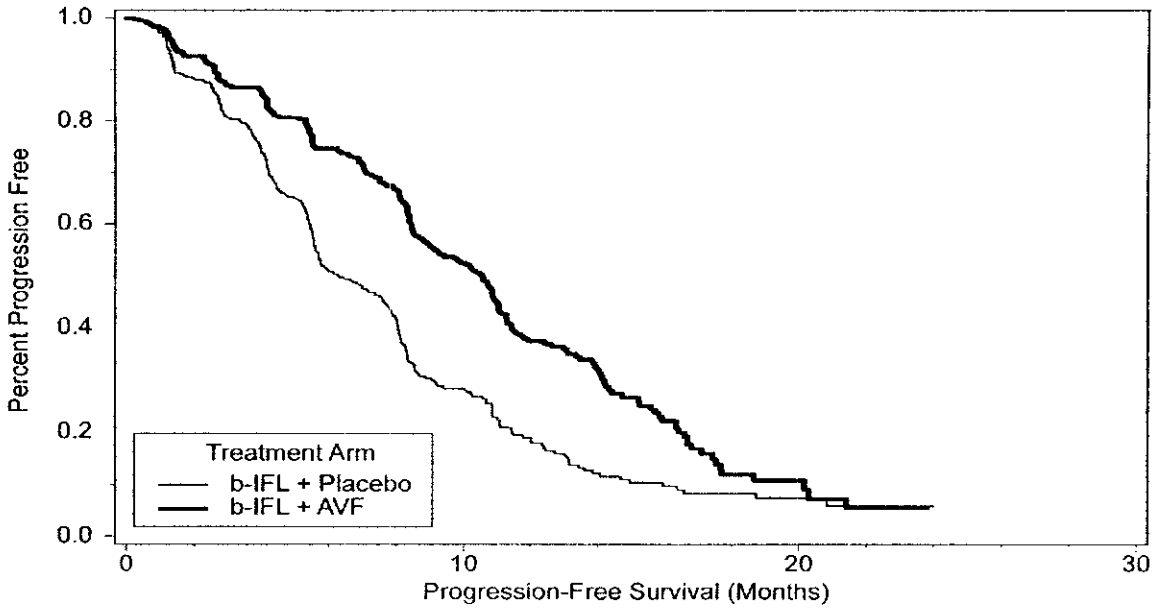
The applicant also examined the overall survival in patients randomized to the original three arms.

	IFL + Placebo N = 100	IFL + Bevacizumab N = 103	5FU/LV/Bevacizumab N = 110
Median Survival (months)	15.08	20.50	18.27
Hazard Ratio		0.72	0.821
p value		0.0668	0.2521

Note that while overall survival was improved, none of these comparisons is statistically significant.

Secondary endpoints included progression free survival, response rate, duration of response, and changes in the FACT-C score. Progression free survival was examined in the two primary arms.

Progression Free Survival



	IFL + Placebo N = 403	IFL + Bevacizumab N = 397
Progression Free Survival (months)	6.2	10.6
Hazard Ratio		0.54
p value (stratified logrank test)		< 0.0001

The addition of bevacizumab to IFL resulted in a significant improvement in progression free survival. The effect of bevacizumab on progression may have been magnified by the schedule of tumor assessment. Tumor assessments were performed every six weeks for the first 24 weeks (6 months) and then every 12 weeks. However, the magnitude of the difference in the median time to progression between arms is similar to that seen with the median overall survival (4.4 versus 4.7 months).

On review, 41 patients in the IFL + Placebo and 26 in the IFL + Bevacizumab arm, were noted to be ineligible on the basis of their tumor measurements. This was due to the lack of two measurable lesions or the small size of the lesions measured. When these patients were removed from the analysis, median progression free survival was 6.3 months in the IFL + Placebo and 10.6 months in the IFL + Bevacizumab arm ($p < 0.0001$, stratified logrank test).

Given the proposed mechanism of action of bevacizumab, some believe that bevacizumab is more likely to inhibit the growth of existing tumors and would have little effect on the occurrence of new lesions. With this in mind, the criterion for declaring progression was examined. In the intent to treat population, 263 patients receiving IFL + Placebo had progressive disease. Among these, 67.3% had a new lesion at the time of progression. Among those receiving IFL + Bevacizumab, 215 patients had

progressive disease. At the time of progression, 71.6% had a new lesion. The percentage of patients with progressive disease and a new lesion is similar in those who received bevacizumab and those who did not.

Progression Free Survival in Patients Concurrently Enrolled in Arms 1-3

Progression free survival in patients concurrently enrolled in Arms 1-3 is illustrated in the table below. As with survival, these differences are not statistically significant.

	IFL + Placebo N = 100	IFL + Bevacizumab N = 103	5FU/LV/Bevacizumab N = 110
Progression Free Survival (mos)	6.83	10.87	8.77
Hazard Ratio		0.657	0.862
p value		0.0382	0.4192

Response Rate

Response rates, per applicant and FDA, during first line therapy are provided in the table below. Separate tables are provided for the two principal arms and for patients concurrently enrolled on Arms 1, 2, and 3.

	IFL + Placebo N = 411		IFL + Bevacizumab N = 402	
	Applicant	FDA	Applicant	FDA
Response Rate	143 (34.8%)	142 (34.6%)	180 (44.8%)	179 (44.5%)
p value (χ^2 test)			0.0036	0.0036
Complete Response	9 (2.2%)	8 (2.0%)	15 (3.7%)	12 (3.0%)
Partial Response	134 (32.6%)	134 (32.6%)	165 (41.0%)	167 (41.5%)

FDA examined tumor measurements, as recorded on the case report forms, rather than scans. The values in the table above represent an intent-to-treat analysis and include patients who were ineligible based on their baseline tumor measurements. Forty-one patients in the IFL + Placebo and 26 in the IFL + Bevacizumab arm, were noted to be ineligible on the basis of their tumor measurements. This was due to the lack of two measurable lesions or the small size of the lesions measured. When these ineligible patients are excluded, the response rate per FDA is 32.3% in those receiving IFL + Placebo and 43.3% in those receiving IFL + Bevacizumab.

In reviewing patient response, 48 patients in the IFL + Placebo and 42 in the IFL + Bevacizumab arm showed an unusual metastatic pattern. These included patients with target lesions in the pancreas, kidney, axilla, and adrenal gland. There were also patients with lung lesions in which hilar and mediastinal lymph nodes were considered target lesions. These metastatic patterns were discussed with the applicant. The applicant cited an autopsy series of patients with metastatic colorectal cancer that examined metastatic patterns. The article noted that the following percentage of

patients had metastatic disease to the organs listed: 7.0% adrenal, 2.9% kidney, 0.3% mediastinum, and 1.9% pancreas.

In reviewing the response data, it was also noted that lymph nodes greater than 1 cm, but less than or equal to 1.5 cm were occasionally identified as target lesions. These would not normally be considered a pathologic finding in the absence of a biopsy confirming disease. This was noted in 36 patients receiving IFL + Placebo and 35 patients receiving IFL + Bevacizumab.

Response Rate Patients Concurrently Enrolled in Arms 1-3

	IFL + Placebo N = 100		IFL + Bevacizumab N = 103		5FU/LV/Bevacizumab N = 110	
	Applicant	Review	Applicant	Review	Applicant	Review
Response Rate	37 (37.0%)	37 (37.0%)	47 (45.6%)	47 (45.6%)	44 (40.0%)	43 (39.0%)
p value			0.2119		0.6556	
Complete Response	2 (2.0%)	2 (2.0%)	6 (5.8%)	6 (5.8%)	4 (3.6%)	2 (1.8%)
Partial Response	35 (35.0%)	35 (35.0%)	41 (39.8%)	41 (39.8%)	40 (36.4%)	41 (37.3%)

The applicant reported durations of response of 7.06 months in patients receiving IFL + Placebo and 10.35 months in patients receiving IFL + Bevacizumab. In patients concurrently enrolled on Arms 1-3, the respective durations of response were 7.16, 11.66, and 8.54 months. Duration of response was confirmed in the IFL + Placebo and IFL + Bevacizumab arms.

Quality of Life

The applicant examined the time to deterioration in various components of the FACT-C score. Change was expressed as the time to a deterioration of three points in the Colorectal Cancer Specific Score of the FACT-C questionnaire. The median time to a three point deterioration was 2.73 months in patients receiving IFL + Placebo and 2.89 months in those receiving IFL + Bevacizumab. Thirty-five of 127 patients in the IFL + Placebo and 25 of 122 patients in the IFL + Bevacizumab arm experienced disease progression or death without a decrease in their score.

Safety

Safety is examined in terms of deaths, serious adverse events, adverse events leading to discontinuation, Grade 3-4 adverse events, Grade 1-4 adverse events, pre-specified adverse events, and additional adverse events of interest noted during BLA review. Pre-specified adverse events included proteinuria, hypertension, bleeding, thromboembolic events, and diarrhea. Note that grade 1-4 adverse events were collected in patients concurrently entered on Arms 1-3. Grade 3 and 4 adverse events were collected in all patients enrolled in the IFL + Placebo and IFL + Bevacizumab arms. In addition, grade 1-4 proteinuria, thromboembolism, and hypertensive adverse events were collected in all patients throughout the study.

Study Populations

The study populations in which adverse event will be presented and the types of adverse events collected for each population are illustrated in the tables below.

Two Principal Arms

	IFL + Placebo	IFL + Bevacizumab
Intent to Treat[1]	411	402
Not Treated with Study Drug	15	10
Safety Population[2]	396	392

[1]Excludes patients enrolled at a site under criminal investigation.
[2]Collection of all Grade 3-4 adverse events and Grade 1-4 thrombosis, proteinuria, and hypertension.

Concurrently Enrolled Arms 1-3

	IFL + Placebo	IFL + Bevacizumab	5FU/LV/Bevacizumab
Intent to Treat[1]	100	103	110
Not Treated with Study Drug	2	1	1
Progressive Disease	1	1	0
Patient/Physician Decision	1	0	1
Safety Population[2]	98	102	109

[1]Excludes patients enrolled at a site under criminal investigation
[2]Grade 1-4 adverse events collected.

Deaths

The summary of deaths is based on the intent to treat population.

	IFL + Placebo N = 411	IFL + Bevacizumab N = 402	5FU/LV/Bevacizumab N = 110
All Deaths	246	207	78
Colorectal Cancer	225	192	68
Other	21	15	10
Cardio-respiratory	6	2	3
Sepsis	8	5	3
Thromboembolism	3	2	1
Hemorrhage	0	1	0
Other/Unknown	4	5	3

The majority of deaths in all arms were reported to be due to colorectal cancer. There is a slight increase in the percentage of non-cancer deaths in the 5FU/LV/Bevacizumab arm. This is due to both an increase in cardio-respiratory events (myocardial infarction and congestive heart failure) and sepsis.

Serious Adverse Events

Arms 1 and 2

The following table illustrates the number and type of serious adverse events that differ by at least 2% among patients in the safety population (all patients who received blinded study drug) on the two principal arms of AVF2107g during first line therapy.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall	171 (43.2%)	200 (51.0%)
Cardiovascular		
Deep Vein Thrombosis	19 (4.8%)	34 (8.7%)

Only deep vein thrombosis differs by at least 2% between arms.

Patients Concurrently Enrolled in Arms 1, 2, and 3

The table below provides information on serious adverse events during first line therapy in the safety population of patients concurrently enrolled in Arms 1-3. Serious adverse events that differ by at least 2% are included.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
All	44 (44.9%)	59 (57.8%)	51 (46.8%)
Body as a Whole			
Abdominal Pain	2 (2.0%)	5 (4.9%)	5 (4.6%)
Cardiovascular			
Pulmonary Embolism	6 (6.1%)	2 (2.0%)	3 (2.8%)
Deep Thrombophlebitis	4 (4.1%)	9 (8.8%)	6 (5.5%)
Line Related Thrombosis	3 (3.1%)	2 (2.0%)	0
Intra-abdominal Thrombosis	2 (2.0%)	3 (2.9%)	1 (0.9%)
Myocardial Ischemia/Infarction	1 (1.0%)	2 (2.0%)	5 (4.6%)
Hypertension	0	3 (2.9%)	0
Subarachnoid Hemorrhage	0	2 (2.0%)	0
Digestive			
Diarrhea[1]	12 (12.2%)	9 (8.8%)	14 (12.8%)
Vomiting	3 (3.1%)	7 (6.9%)	3 (2.8%)
Ileus[2]	3 (3.1%)	6 (5.9%)	9 (8.3%)
Gastrointestinal Hemorrhage[3]	1 (1.0%)	2 (2.0%)	4 (3.7%)
Constipation	0	5 (4.9%)	0
Hemic/Lymphatic			
Leukopenia	4 (4.1%)	8 (7.8%)	2 (1.8%)
Metabolic			
Hyperglycemia	2 (2.0%)	0	0

Urogenital			
Kidney Failure	0	2 (2.0%)	2 (1.8%)

[1]Diarrhea includes diarrhea, enteritis, and gastroenteritis
[2]Ileus includes ileus and intestinal obstruction
[3]GI hemorrhage includes gastrointestinal hemorrhage, hematemesis, hemorrhage (where it is gastrointestinal), melena, and rectal hemorrhage

In this table comparing serious adverse events in patients concurrently enrolled in Arms 1-3, a number of serious adverse events are increased between arms. Most are discussed further under Targeted Adverse Events and Other Adverse Events of Interest.

Adverse Events Leading to Discontinuation

In the IFL + Placebo arm, 7.1% of patients discontinued due to an adverse event during Treatment Period 1. The most common events leading to discontinuation were asthenia, pulmonary embolism, and diarrhea. In the IFL + Bevacizumab arm, 8.7% of patients discontinued during Treatment Period 1. The most common events were asthenia and diarrhea. In the 5FU/LV/Bevacizumab arm, 9.2% of patients discontinued due to an adverse event during Treatment Period 1. The most common events were deep vein thrombosis and myocardial infarction.

Grade 3-4 Adverse Events

The following table lists Grade 3 and 4 adverse events that occurred on the two principal arms during Treatment Period 1. Events that differed by at least 2% are included. Note that several events that differ by slightly less than 2% are included. When these values are rounded to whole numbers, they then differ by 2% and are included in the package insert.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Gr 3 or 4 Adverse Events	295 (74.5%)	340 (86.7%)
Gr 3	279 (70.4%)	331 (84.4%)
Gr 4	86 (21.7%)	121 (30.9%)
Body as a Whole		
Asthenia[1]	28 (7.0%)	38 (9.7%)
Abdominal Pain	20 (5.0%)	32 (8.2%)
Pain[2]	21 (5.3%)	30 (7.6%)
Cardiovascular		
Deep Vein Thrombosis	19 (4.8%)	34 (8.7%)
Hypertension	10 (2.5%)	46 (11.7%)
Intra-Abdominal Thrombosis	5 (1.3%)	13 (3.3%)
Syncope	4 (1.0%)	11 (2.8%)
Digestive		
Diarrhea[3]	99 (25.0%)	133 (33.9%)

Vomiting	42 (10.6%)	30 (7.6%)
Nausea	37 (9.3%)	26 (6.6%)
Constipation	9 (2.3%)	14 (3.6%)
Hemic/Lymphatic		
Leukopenia	122 (30.8%)	145 (37.0%)
Metabolic/Nutrition		
Hyperglycemia	17 (4.3%)	9 (2.3%)

[1]Asthenia includes asthenia and somnolence where the verbatim term for somnolence is lethargy or fatigue
[2]Pain includes back, bone, chest, flank, kidney, neck, and pelvic pain as well as pain
[3]Diarrhea includes diarrhea, enteritis, and gastroenteritis

The overall incidence of grade 3 and 4 events is increased in the bevacizumab arm. This is primarily due to increases in hypertension, diarrhea, and leukopenia. A striking finding in this table is the high overall incidence of NCI CTC life threatening grade 4 events in this study.

Grade 1-4 Adverse Events

This table illustrates grade 1-4 adverse events that occurred during first line therapy in the 309 patients concurrently enrolled and treated on Arms 1-3. Individual adverse events are included in which the difference in incidence is at least 2%.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Total			
Gr 1	96 (98.0%)	99 (97.1%)	108 (99.1%)
Gr 2	95 (96.9%)	97 (95.1%)	96 (88.1%)
Gr 3	74 (75.5%)	93 (91.2%)	80 (73.4%)
Gr 4	23 (23.5%)	33 (32.4%)	23 (21.1%)
Body as a Whole			
Asthenia[1]	68 (69.4%)	75 (73.5%)	80 (73.4%)
Pain[2]	54 (55.1%)	62 (60.8%)	67 (61.5%)
Abdominal Pain	54 (55.1%)	62 (60.8%)	55 (50.5%)
Edema[3]	25 (25.5%)	21 (20.6%)	25 (22.9%)
Fever	23 (24.5%)	29 (28.4%)	30 (27.5%)
Headache/Migraine	19 (19.4%)	27 (26.5%)	30 (25.7%)
Chills	15 (15.3%)	15 (14.7%)	13 (11.9%)
Accidental Injury	9 (9.2%)	13 (12.7%)	6 (5.5%)
Abdominal Distension	5 (5.1%)	0	6 (5.5%)
Allergic Reaction[4]	3 (3.1%)	5 (4.9%)	3 (2.8%)
Hernia	1 (1.0%)	3 (2.9%)	5 (4.6%)
Cardiovascular			
Hypertension	14 (14.3%)	23 (22.6%)	37 (33.9%)
Hypotension/Postural Hypotension	7 (7.1%)	15 (14.7%)	8 (7.3%)
Tachycardia	7 (7.1%)	6 (5.9%)	9 (8.3%)

Flushing	6 (6.1%)	2 (2.0%)	8 (7.3%)
Pulmonary Embolism	6 (6.1%)	2 (2.0%)	3 (2.8%)
Line Related Thrombosis	5 (5.1%)	2 (2.0%)	1 (0.9%)
Deep Vein Thrombosis	4 (4.1%)	9 (8.8%)	6 (5.5%)
Syncope	2 (2.0%)	6 (5.9%)	2 (1.8%)
Intra-abdominal Thrombosis	2 (2.0%)	4 (3.9%)	1 (0.9%)
Hemorrhage	1 (1.0%)	3 (2.9%)	2 (1.8%)
Myocardial Ischemia[5]	1 (1.0%)	2 (2.0%)	5 (4.6%)
Congestive Heart Failure[6]	0	3 (2.9%)	2 (1.8%)
Subarachnoid Hemorrhage	0	2 (2.0%)	0
Digestive			
Diarrhea[7]	85 (86.7%)	91 (89.2%)	92 (84.4%)
Nausea	68 (69.4%)	73 (71.6%)	72 (66.1%)
Vomiting	46 (46.9%)	53 (52.0%)	51 (46.8%)
Anorexia/Cachexia	29 (29.6%)	44 (43.1%)	38 (34.9%)
Constipation	28 (28.6%)	41 (40.2%)	32 (29.4%)
Stomatitis/Mucositis	18 (18.4%)	33 (32.4%)	33 (30.3%)
Dyspepsia	15 (15.3%)	25 (24.5%)	19 (17.4%)
Weight Loss	10 (10.2%)	15 (14.7%)	18 (16.5%)
Flatulence	10 (10.2%)	11 (10.8%)	21 (19.3%)
Ileus/Intestinal Obstruction	7 (7.1%)	6 (5.9%)	10 (9.2%)
GI Hemorrhage[8]	6 (6.1%)	25 (24.5%)	21 (19.3%)
Gastroesophageal Reflux	5 (5.1%)	8 (7.8%)	1 (0.9%)
Oral Moniliasis	3 (3.1%)	5 (4.9%)	1 (0.9%)
Dry Mouth	2 (2.0%)	7 (6.9%)	4 (3.7%)
Ascites	2 (2.0%)	0	1 (0.9%)
Colitis/Enterocolitis	1 (1.0%)	6 (5.9%)	1 (0.9%)
Dysphagia	1 (1.0%)	4 (3.9%)	4 (3.7%)
Periodontal Abscess	1 (1.0%)	4 (3.9%)	0
Proctitis	1 (1.0%)	3 (2.9%)	0
Jaundice	0	3 (2.9%)	4 (3.7%)
Gingivitis	0	3 (2.9%)	3 (2.8%)
Gum hemorrhage	0	2 (2.0%)	3 (2.8%)
Gastritis	0	2 (2.0%)	1 (0.9%)
Eruction	0	2 (2.0%)	0
Hemic/Lymphatic			
Leukopenia	53 (54.1%)	58 (56.9%)	12 (11.0%)
Anemia/Hypochromic Anemia	30 (30.6%)	36 (35.3%)	27 (24.8%)
Ecchymosis	6 (6.1%)	7 (6.9%)	10 (9.2%)
INR Increased	4 (4.1%)	2 (2.0%)	1 (0.9%)
Thrombocytopenia	0	5 (4.9%)	5 (4.6%)
Petechia	0	2 (2.0%)	1 (0.9%)
Metabolic/Nutrition			
Dehydration/Hypovolemia	21 (21.4%)	23 (22.5%)	17 (15.6%)
Hypokalemia	11 (11.2%)	12 (11.8%)	18 (16.5%)

Hyperglycemia	9 (9.2%)	7 (6.9%)	5 (4.6%)
Hypocalcemia	3 (3.1%)	2 (2.0%)	1 (0.9%)
Hyponatremia	2 (2.0%)	2 (2.0%)	5 (4.6%)
Hypomagnesemia	2 (2.0%)	1 (1.0%)	6 (5.5%)
Weight Gain	2 (2.0%)	0	3 (2.8%)
Hypoproteinemia	2 (2.0%)	0	2 (1.8%)
Creatinine Increased	0	4 (3.9%)	0
Bilirubinemia	0	1 (1.0%)	7 (6.4%)
Musculoskeletal			
Myalgia[9]	7 (7.1%)	8 (7.8%)	16 (14.7%)
Arthralgia/Arthritis	6 (6.1%)	7 (6.9%)	11 (10.1%)
Nervous			
Insomnia	24 (24.5%)	25 (23.5%)	22 (20.2%)
Dizziness	20 (20.4%)	27 (26.5%)	21 (19.3%)
Depression	18 (18.4%)	13 (12.8%)	15 (13.8%)
Anxiety and agitation	16 (16.3%)	11 (10.8%)	8 (7.3%)
Neuropathy[10]	9 (9.2%)	11 (10.8%)	13 (11.9%)
Ataxia	5 (5.1%)	3 (2.9%)	1 (0.9%)
Extrapyramidal Syndrome	2 (2.0%)	0	0
Tic	2 (2.0%)	1 (1.0%)	0
Confusion	1 (1.0%)	1 (1.0%)	6 (5.5%)
Abnormal Gait	0	1 (1.0%)	5 (4.6%)
Respiratory			
Upper Respiratory Infection[11]	38 (38.8%)	48 (47.1%)	44 (40.4%)
Dyspnea	15 (15.3%)	26 (25.5%)	27 (24.8%)
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Singultus	8 (8.2%)	5 (4.9%)	1 (0.9%)
Chest Congestion	4 (4.1%)	2 (2.0%)	1 (0.9%)
Hyperventilation	4 (4.1%)	1 (1.0%)	1 (0.9%)
Asthma	3 (3.1%)	0	3 (2.8%)
Voice Alteration/Laryngitis	2 (2.0%)	9 (8.8%)	6 (5.5%)
Pneumonia	2 (2.0%)	3 (2.9%)	2 (1.8%)
Allergic Rhinitis/Sinusitis	2 (2.0%)	0	2 (1.8%)
Hypoxia	0	1 (1.0%)	3 (2.8%)
Skin/Appendages			
Alopecia	25 (25.5%)	33 (32.3%)	6 (5.5%)
Rash/Maculopapular Rash	22 (22.4%)	19 (18.6%)	21 (19.3%)
Sweating	15 (15.3%)	14 (13.7%)	10 (9.2%)
Dry Skin	7 (7.1%)	7 (6.9%)	22 (20.2%)
Pruritus	5 (5.1%)	7 (6.9%)	5 (4.6%)
Exfoliative Dermatitis	3 (3.1%)	3 (2.9%)	21 (19.3%)
Herpetic Infection	3 (3.1%)	4 (3.9%)	7 (6.4%)
Nail disorder	3 (3.1%)	2 (2.0%)	9 (8.3%)
Skin discoloration	3 (3.1%)	2 (2.0%)	17 (15.6%)
Skin Ulcer	1 (1.0%)	6 (5.9%)	7 (6.4%)

Acne	1 (1.0%)	0	4 (3.7%)
Benign Skin Neoplasm	1 (1.0%)	2 (2.0%)	0
Special Senses			
Taste Loss/Perversion	9 (9.2%)	14 (13.7%)	23 (21.1%)
Abnormal Vision	2 (2.0%)	4 (3.9%)	2 (1.8%)
Excess Lacrimation	2 (2.0%)	6 (5.9%)	20 (18.3%)
Conjunctivitis	2 (2.0%)	2 (2.0%)	5 (4.6%)
Parosmia	0	2 (2.0%)	3 (2.8%)
Urogenital			
Proteinuria	24 (24.5%)	37 (36.3%)	39 (35.8%)
Urinary Tract Infection[12]	14 (14.3%)	16 (15.7%)	12 (11.0%)
Dysuria	6 (6.1%)	8 (7.8%)	6 (5.5%)
Hematuria	5 (5.1%)	3 (2.9%)	8 (7.3%)
Oliguria	3 (3.1%)	0	2 (1.8%)
Vaginal Hemorrhage	2 (2.0%)	4 (3.9%)	1 (0.9%)
Urinary Frequency/Urgency	1 (1.0%)	3 (2.9%)	6 (5.5%)
Kidney Calculus	1 (1.0%)	0	4 (3.7%)
Urinary Retention/Impairment	0	6 (5.9%)	2 (1.8%)
Nocturia	1 (1.0%)	0	3 (2.8%)
Vaginal Moniliasis	0	3 (2.9%)	0

[1]Asthenia includes the preferred terms asthenia, malaise, and somnolence where the verbatim term is malaise or lethargy.
[2]Pain includes back, bone, chest, flank, neck, or pelvic pain as well as pain.
[3]Edema includes edema, generalized edema, genital edema, peripheral edema and scrotal edema.
[4]The majority of the allergic reactions listed are unrelated to study drug. This is discussed further below.
[5]Myocardial ischemia includes myocardial infarction, myocardial ischemia, and angina.
[6]Congestive heart failure includes congestive heart failure, lung edema, cardiomyopathy, heart failure, and left heart failure.
[7]Diarrhea includes diarrhea, enteritis, and gastroenteritis.
[8]Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, hematemesis, hemorrhage where bleeding is gastrointestinal, melena, and rectal hemorrhage.
[9]Myalgia also include hypertonia where the verbatim term is muscle spasm.
[10]Neuropathy includes neuralgia, neuropathy, paresthesias, and peripheral neuritis.
[11]Upper respiratory infection includes bronchitis, flu syndrome, otitis media, pharyngitis, rhinitis, sinusitis, and viral infection. It also includes ear pain, infection, and respiratory disorder where those appear to be related to an upper respiratory infection.
[12]Urinary tract infection includes pyelonephritis

Pre-Specified Adverse Events and Adverse Events of Interest

Perforation and Wound Healing

The applicant noted a disproportionate number of patients in the IFL + Bevacizumab arm who experienced intestinal perforation and created the following table of patients with intestinal perforation and abnormal wound healing.

- Patient 10764 developed bowel obstruction and underwent emergency surgery. Six days later the patient developed an anastomotic leak and peritonitis. The patient died during this hospitalization.
- Patient 10202 had abdominal wall cellulitis at the ostomy site. This was complicated by the development of a subhepatic abscess that communicated with a fluid collection under the patient's original surgical incision. The patient underwent incision and drainage of this abscess that was complicated, one month later, by wound dehiscence associated with an abdominal wall abscess.

Abscess
Patients 10202, 11454, and 12762 developed an intra-abdominal or abdominal wall abscess.

- Patient 10202 is described above.
- Patient 11454 underwent surgery for a possible incarcerated hernia. Instead, the patient was found to have an abdominal wall abscess.
- Patient 12762 presented with an abdominal mass and underwent drainage on an abdominal wall abscess.

Ischemic Bowel/Mesenteric Vein Thrombosis
Patient 10781 developed a thrombosis of the mesenteric vein. This was found on routine CT scan and treated with anti-coagulation.

Arm 2: IFL + Bevacizumab

Overall, 19 patients in the IFL + Bevacizumab arm had a complication related to perforation or abnormal wound healing.

Perforation
Seven patients experienced colonic perforation: 10966, 11066, 11242, 12225, 12325, 12763, and 13202.

- Patient 10966 underwent an exploratory laparotomy for small bowel obstruction and then developed perforation at two sites of previous lysis of adhesions. Since this is unlikely to be spontaneous, this event is not included in the table above. The patient's last dose of bevacizumab was 36 days prior to this event. A second surgery following the development of perforation was complicated by an anastomotic leak and a third surgery was performed. This was complicated by an enterocutaneous fistula.
- Patient 11066 presented with an intra-abdominal abscess and underwent an exploratory laparotomy that revealed a colonic perforation.
- Patient 11242 also presented with an intra-abdominal abscess and at exploration was found to have a possible perforation in the transverse colon. This patient died as a result of this event.
- Patient 12225 underwent surgery for small bowel obstruction and was found to have ischemic necrosis and perforation.

- Patient 12325 had a perforated pyloric ulcer and underwent surgery that was complicated by a post-operative fistula.
- Patient 12763 presented with abdominal pain and was found to have free air on KUB. This was treated without surgical intervention.
- Patient 13202 also presented with pain and free air and underwent surgery that revealed carcinomatosis and perforation.

The mechanism by which bevacizumab increases the risk of intestinal perforation is unclear. Pathologic findings at the site of perforation varied. One patient, 12225, had ischemic necrosis at the site of perforation. Patient 13202 was noted to have a rapid tumor response, but it is unknown if perforation occurred at a site of tumor. Only one patient, 12763, had not undergone prior resection of their primary lesion, a risk factor for intestinal perforation. Two patients had a history of diverticulosis, but it is unknown if perforation occurred at the diverticulum. Overall, 8.7% of patients in the IFL + Bevacizumab arm had a history of diverticulosis. The timing of the events relative to the initiation of study drug was examined. Two of the seven patients had received study drug for long periods prior to the event and their last doses of study drug prior to the event were given at C16D14 and C10D0. Five of the patients had been on study drug a relatively short time and received the following doses prior to the event: C1D1, C1D28 (two patients), C2D28, and C3D0.

Dehiscence

Patients 10304, 10966, 11354, and 11831 developed wound dehiscence.

- Patient 10304 presented with a pelvic abscess and at surgery was found to have an anastomotic dehiscence. The patient's initial surgery was four months prior to the event. The patient's last dose of bevacizumab was 13 days prior to the event. This patient died while in hospital. The death was considered to be secondary to a pulmonary embolism.
- Patient 10966 is discussed in the section on perforation above.
- Patient 11354 developed dehiscence of a thoracotomy incision. Surgery occurred 56 days after the last dose of bevacizumab. This patient died of a cardiac arrest during this hospitalization. Patient 11831 underwent elective surgery for impending obstruction 37 days after the last dose of bevacizumab. This was complicated by anastomotic dehiscence.

Fistula

Patients 10966, 12325, and 12494 developed a fistula.

- Patients 10966 and 12325 are discussed in the section on perforation above.
- Patient 12494 developed a rectovaginal fistula requiring repair. This was complicated by a perineal abscess.

Abscess

Patients 10304, 11066, 11242, and 12684 developed an abscess.

- Patient 10304 is discussed in the section on dehiscence above. Note that although patient 10304 is considered to have a dehiscence that an intra-abdominal abscess was also present.

- Patients 11006, and 11242 are discussed in the section on perforation above. Patient 12684 had a peri-rectal abscess that communicated with the rectum and required surgical drainage.
- Six patients: 10691, 11453, 11862, 12090, 13383 had grade 3 peri-anal abscesses and one patient, 12494 had a perineal abscess. No additional information is available in these patients.

Abnormal Wound Healing
Two patients developed wound healing complications: 11602 and 12603.

- Patient 11602 developed a post-operative hemothorax that required re-exploration. Study drug was held for one month prior to the initial surgery.
- Patient 12603 had a non-healing ulcer over the pre-sacral region. This may have been a pilonidal cyst.

Ischemic Bowel/Mesenteric Vein Thrombosis
Four patients experienced ischemic bowel or mesenteric vein thrombosis: 10122, 10882, 11883, and 12225.

- Patient 10122 had a grade 3 mesenteric vein thrombosis identified on CT scan.
- Patient 10882 received one dose of study drug and chemotherapy. The patient died at home and at autopsy was found to have ischemic necrosis at the anastomotic site.
- Patient 11883 had multiple (mesenteric, splenic, and ovarian) thrombosis of the intra-abdominal vasculature.
- Patient 12225 is described in the section on perforation above.

Arm 3: 5FU/LV/Bevacizumab

Overall, nine patients in the 5FU/LV/Bevacizumab arm had a complication related to perforation or abnormal wound healing.

Perforation
Patients 10063, 10762, 11353, and 11347 developed perforation.

- Patient 10063 developed a gastrointestinal bleed that was investigated with sigmoidoscopy. The patient presented 10 days later with rectal perforation and died of post-operative complications.
- Patient 10762 developed tumor necrosis in the lateral rectal wall with a fistula leading to the deep gluteal region. This required surgical debridement. This patient had not undergone primary resection prior to study entry.
- Patient 11353 had a pelvic abscess requiring debridement.
- Patient 11347 had percutaneous drainage of a left lower quadrant abscess that was causing obstruction of her ostomy.

Again the etiology of intestinal perforation is unclear. It should be noted that patient 11347 had undergone multiple dilations of an anastomotic stricture.

Dehiscence
Patient 10621 developed grade 2 wound dehiscence. Surgery occurred 1 day prior to this event. The applicant did not provide additional information in the patient narrative.

Abscess
Patients 11353, 11502, and 13222 developed an abscess.

- Patient 11353 had a pelvic abscess that is also referred to as a perineal abscess and was drained and packed. This was considered a grade 3 event by the investigator.
- Patient 11502 developed an abdominal wall abscess at a prior surgical site. This was considered a grade 3 event.
- Patient 13222 presented with hypotension, positive blood cultures (multiple organisms) and underwent surgery. During surgery, pus was noted in the retroperitoneum at the level of the sacral promontory.
- Patients 10901, and 11001 had a grade 3 anal abscess.

Abnormal Wound Healing
Patients 10683 and 11021 had a grade 2 delay in wound healing.

Summary

The incidence of perforation, dehiscence, impaired/delayed wound healing, fistula formation, and intra-abdominal abscess was increased in patients receiving bevacizumab as compared to controls. See table on page 33. These events tended to occur early in the course of treatment.

The etiology remains unclear. The administration of bevacizumab is known to result in delayed wound healing in animal models. An increased incidence of post-operative complications was seen in patients receiving bevacizumab (see below). One possible mechanism for both intestinal perforation and hemoptysis (see Summary of Clinical Safety) is that patients who receive bevacizumab and have tumor shrinkage are unable to heal in these areas. This results in hemoptysis or perforation in the form of peritonitis or abscess formation. A second possible mechanism is that endothelial damage leads to localized clot formation and necrosis of a portion of the bowel or bronchi. The applicant believes that perforation is associated with areas of prior inflammation and note, in particular, the patient with perforation of a pyloric ulcer.

Post-Operative Complications

The applicant provided an overall summary of patients who had undergone major surgery on study.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
# Undergoing Major Surgery	25	39	15
# Procedures	28	45	18
# Procedures within 105 Days of	N/A	43	18

Last Dose of Bevacizumab[1]			
# Procedures within 21 Days of Last Dose of Bevacizumab[1]	N/A	16	9
# Post-Operative Complications	1	6[2]	1

[1]5 half-lives and one half-life
[2]Pt 10708 is not considered in this total.

Note that six of 392 patients in the IFL + Bevacizumab arm and one of 396 patients in the IFL + Placebo group developed a post-operative complication.

The table below provides information on the timing of study drug and on the complications seen.

Arm	Patient	Days from Last Dose Study Drug to Surgery	Complication
IFL + Placebo	10764	10	Intestinal anastomotic leak
IFL + Bevacizumab	10304	13	Intestinal anastomotic leak, 4 mo p initial surgery
IFL + Bevacizumab	10708	32	Gr 1 rectal bleed
IFL + Bevacizumab	10966	36	Intestinal anastomotic leak, fistula
IFL + Bevacizumab	11354	56	Thoractotomy dehiscence
IFL + Bevacizumab	11602	32	Hemothorax requiring re-exploration
IFL + Bevacizumab	11831	37	Intestinal anastomotic dehiscence
IFL + Bevacizumab	12325	10	Fistula
5FU/LV/Bevacizumab	10044	36	Gr 2 ecchymosis at incision
5FU/LV/Bevacizumab	10621	1	Gr 2 wound dehiscence

Post-operative complications were not limited to patients who received study drug shortly before surgery, but included patients who received their last dose of study drug as late as 56 days pre-operatively. However, 14 patients in the IFL + Bevacizumab arm underwent procedures within 20 days of the last dose of bevacizumab (one half-life) that were not associated with post-operative complications.

Hemorrhage

Grade 3-4 Hemorrhagic Events in Arms 1 and 2

The overall incidence of grade 3-4 bleeding was relatively low 10/396 (2.5%) in the IFL + Placebo arm and 13/392 (3.3%) in the IFL + Bevacizumab arm. The incidence of grade 3 and 4 events in the two principal arms during first line therapy is shown below.

	IFL + Placebo N = 392	IFL + Bevacizumab N = 392
Gastrointestinal Bleeding[1]	8 (2.0%)	7 (1.8%)
Gr 3	8	6
Gr 4	0	1
Epistaxis	0	1 (0.3%)
Gr 3	0	1
Hematuria	1 (0.3%)	0
Gr 3	1	0
Hemorrhage	1 (0.3%)	1 (0.3%)
Gr 3	1	1
Retroperitoneal Hemorrhage	0	2 (0.5%)
Gr 3	0	1
Gr 4	0	1
Subarachnoid Hemorrhage	0	2 (0.5%)
Gr 3	0	1
Gr 4	0	1

[1] Includes the terms gastrointestinal hemorrhage, hemorrhage (where it is gastrointestinal), rectal hemorrhage, and melena.

Subarachnoid hemorrhage was associated with severe hypertension in one patient and with stroke in two patients.

- Patient 12121 had moderate hypertension throughout the study and presented with bilateral embolic strokes with associated hemorrhage.
- Patient 10685 had an earlier upper extremity deep venous thrombosis that was line related and was on warfarin (INR unknown). The patient also had moderate untreated hypertension and then presented with severe hypertension and was found to have a subarachnoid hemorrhage.
- Patient 11455 presented with a blood pressure of 125/53, headache, and diplopia. The patient was found to have a subarachnoid hemorrhage and associated temporal lobe infarction. On the patient's most recent study visit, blood pressure was 150/104. Of note, his last dose of study drug was six weeks prior to the event.

Retroperitoneal hemorrhage was associated with an increase in INR (6.9 and 12.4) due to warfarin use in two patients.

One patient in the 5FU/LV/Bevacizumab arm, 10502, was noted to have grade 3 bleeding from his rectal anastomosis.

Hemorrhagic Events of Any Severity in Patients Concurrently Enrolled in Arms 1-3

While there was a minimal increase in grade 3-4 bleeding, the increase in grade 1-2 bleeding in patients receiving bevacizumab was striking. This includes a high incidence

of epistaxis and of low grade gastrointestinal bleeding. Low grade gastrointestinal bleeding consisted of hemorrhoidal bleeding and bleeding from the stoma.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Gr 1	10	35	35
Gr 2	0	0	0
Gr 3	0	1	0
Gastrointestinal Hemorrhage	6 (6.1%)	25 (24.5%)	22 (20.2%)
Gr 1	5	19	16
Gr 2		3	1
Gr 3	1	2	5
Gr 4		1	
Gum Hemorrhage	0	2 (2.0%)	3 (2.8%)
Gr 1	0	2	3
Vaginal Hemorrhage	2 (2.0%)	4 (3.9%)	1 (0.9%)
Gr 1	2	3	0
Gr 2		1	1
Hematuria	5 (5.1%)	3 (2.9%)	7 (6.4%)
Gr 1	4	3	3
Gr 2	1	0	2
Gr 3	0	0	2
Hemorrhage	1 (1.0%)	3 (2.9%)	2 (1.8%)
Gr 1	1	3	2
Hemoptysis	1 (1.0%)	2 (2.0%)	2 (1.8%)
Gr 1	1	2	2

One event of particular interest occurred in a patients who had received two doses of 5FU/LV/Bevacizumab prior to his presentation with melena and gross blood through his ostomy. He was transfused and one day later became hypotensive and dyspneic. He was intubated. While in the ICU, he developed pancytopenia, renal failure, and a CXR patter consistent with acute respiratory distress syndrome or congestive failure. Initial cultures were negative. However, subsequent stool cultures were positive for C. difficile. He ultimately died of this illness. It is unknown if he experienced intestinal perforation.

Patients considered to be at risk for bleeding complications were examined. These included patients on low dose warfarin, patients who had not undergone removal of their primary tumor, patients who had undergone an operative procedure on study, and patients who had undergone surgery less than 28 days prior to entry.

Among patients with grade 3-4 bleeding, four patients in the IFL + Placebo arm and five in the IFL + Bevacizumab arm were on warfarin prior to the event.

Patients with their primary tumor in place did not have grade 3-4 bleeding events.

Seven patients on the bevacizumab arms experienced post-operative complications. These are detailed in the section on Perforation and Wound Healing. Three involved hemorrhagic complications, persistent bloody chest tube drainage requiring re-exploration, ecchymosis at the incision, and a grade 1 rectal hemorrhage.

Sixty-two patients, 27 in the IFL + Placebo, 32 in the IFL + Bevacizumab, and three in the 5FU/LV/Bevacizumab arm underwent major surgery less than 28 days prior to randomization. This ranged from nine to 27 days with a median of 22 days. In the IFL + Placebo arm, one patient who underwent surgery 14 days prior to entry had grade 1 hematochezia reported on day 10. In the IFL + Bevacizumab arm, one patient who underwent surgery 18 days prior to entry had grade 1 hematochezia on day 56 while a second patient who underwent surgery 27 days prior to entry had a grade 1 rectal hemorrhage on day 56.

During second line therapy, five patients originally in the IFL + Bevacizumab and two in the 5FU/LV/Bevacizumab arm developed grade 3-4 hemorrhage. This included subarachnoid hemorrhage in one patient, hematuria in three patients, and gastrointestinal hemorrhage in three patients.

Thromboembolic Events

Thromboembolic events regardless of severity were collected in all patients throughout the study. The applicant states that the overall incidence of thromboembolic events during first line therapy is 16.4% with IFL + Placebo and 19.6% in the IFL + Bevacizumab arm. The applicant further divides these into arterial and venous events. Events classified as arterial or venous along with their overall incidence are included in the table below.

Patients Experiencing Thromboembolic Events During First Line Therapy

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall		
Thromboembolic Events	65 (16.4%)	77 (19.6%)
Gr 1	1 (0.3%)	1 (0.3%)
Gr 2	6 (1.5%)	6 (1.5%)
Gr 3	35 (8.8%)	47 (12.0%)
Gr 4	23 (5.8%)	23 (5.0%)
Overall Arterial Events	5 (1.3%)	13 (3.3%)
Gr 1	1 (0.3%)	0
Gr 2	0	1 (0.3%)
Gr 3	1 (0.3%)	3 (0.3%)
Gr 4	3 (0.8%)	9 (2.3%)
Cardiac Ischemia/Infarction		
Gr 3	1 (0.3%)	0
Gr 4	3 (0.8%)	6 (1.5%)

Arterial Thrombosis		
Gr 1	1 (0.3%)	0
Gr 2	0	1 (0.3%)
Gr 3	0	2 (0.5%)
Cerebrovascular Ischemia		
Gr 3	0	1 (0.3%)
Gr 4	0	2 (0.5%)
Intestinal Necrosis		
Gr 4	0	1 (0.3%)
Vascular Anomaly		
Gr1	1 (0.3%)	0
Overall Venous Events	60 (15.2%)	66 (16.8%)
Gr 1	0	1 (0.3%)
Gr 2	6 (1.5%)	6 (1.3%)
Gr 3	34 (8.6%)	45 (11.5%)
Gr 4	20 (5.1%)	15 (3.8%)
Deep Venous Thrombosis	25 (6.3%)	35 (8.9%)
Pulmonary Embolism	20 (5.1%)	15 (3.8%)
Thrombophlebitis		
Gr 1	0	1 (0.3%)
Gr 2	3 (0.8%)	2 (0.5%)
Gr 3	10 (2.5%)	13 (3.3%)
Thrombosis		
Gr 2	2 (0.5%)	3 (0.8%)
Gr 3	2 (0.5%)	4 (1.0%)
Mesenteric Vein Occlusion		
Gr 3	1 (0.3%)	2 (0.5%)
Upper Extremity Embolus		
Gr 2	0	1 (0.3%)
Phlebitis		
Gr 2	1 (0.3%)	0

The applicant notes the relative increase (13 vs. 5) in arterial events in the bevacizumab containing arm and provides further information on these patients. The applicant notes that the majority of patients with an arterial event had underlying atherosclerotic disease. Of these 13 patients, three died as a result of the event and four discontinued from the study.

Reports of thromboembolic events were examined and the FDA reviewer re-categorized events as pulmonary embolism, deep venous thrombosis, intra-abdominal thrombosis, line related thrombosis, and thrombophlebitis. This re-categorization was initiated for two purposes. First, line related thromboses were distinguished from deep vein thrombosis that occurred spontaneously since the risk factors for these events may be different. Second, it was noted that events categorized as thrombosis or

thrombophlebitis frequently occurred intra-abdominally and this was thought to be more descriptive of the events.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall	65 (16.4%)	79 (20.2%)
Gr 3-4	58 (14.6%)	72 (18.4%)
Cerebrovascular Event	0	4[1]
Myocardial Ischemia	4[2]	6
Pulmonary Embolism	20	16
Deep Venous Thrombosis	19	34
Catheter Related	11	7
Thrombophlebitis	3	3
Intra-abdominal Thromboembolism	7	14

[1]One event is a TIA.
[2]One event is angina.

The FDA reviewer's case definition for deep venous thrombosis includes all thromboses of the lower extremities, as well as, thromboses of the upper extremity or jugular vein that were not line related.

The term intra-abdominal thrombosis included the following events: two patients with thrombosis of the portal vein, two with thrombosis of the inferior vena cava, one with thrombosis of the superior mesenteric vein, one with iliac vein thrombosis, and one with an aortic thrombus. Five of these are grade 3 events. In the IFL + Bevacizumab arm, intra-abdominal thrombosis includes the following events: one patient with mesenteric vein thrombosis; three with an inferior vena cava thrombosis; one with a renal vein thrombosis; one with thrombosis of the with renal, portal, and splenic veins; two with a portal vein thrombosis; three with an aortic thrombosis; one with thrombosis of the mesenteric, splenic, and ovarian veins; two with an iliac vein thrombosis; one patient with grade 4 ischemic bowel. Thirteen are grade 3-4 events.

While the overall incidence of venous and arterial thromboembolic events combined is not significantly different between arms, there is an increase in cerebrovascular and myocardial events in the IFL + Bevacizumab arm. Cerebrovascular events occurred only in the IFL + Bevacizumab arm while myocardial infarction occurred at twice the rate in the bevacizumab arm when compared to placebo. There was also an increase in intra-abdominal thrombosis in the bevacizumab arm (see details of events considered intra-abdominal above). While many of these were discovered on routine CT scan, most were coded as grade 3-4 (5 in the IFL + Placebo and 13 in the IFL + Bevacizumab arm) events based on the NCI CTC criteria. Also note that this was a blinded study suggesting that there was not an ascertainment bias in the bevacizumab arm.

There was a suggestion of an increased risk of upper extremity thrombosis in patients in the IFL + Bevacizumab arm and in the simultaneous occurrence of thromboses in both

the upper and lower extremities. Two patients in the IFL + Bevacizumab arm had deep venous thromboses of both the upper and lower extremities. Neither of the upper extremity events was line related. Two additional patients in this arm had upper extremity thromboses that were not line related. One patient in the IFL + Placebo arm had a thrombosis of the jugular vein that was not line related.

Following submission of the Safety Update, an expedited adverse event report was submitted in which a patient developed a dissection of the carotid artery resulting in a massive cerebrovascular accident and death. The patient had received 30 doses of bevacizumab over an 18 month period. The patient had a history of hypertension although blood pressure at the time of the event was 149/90 and a history of thrombosis of the inferior vena cava.

Thrombotic events during second line therapy occurred in 3/47 patients originally randomized to the IFL + Placebo and 4/110 patients originally randomized to the IFL + Bevacizumab arm.

Risk Factors for Thrombosis

The applicant conducted a series of post hoc analyses to assess the association between thrombotic events and various risk factors. Given the exploratory nature of these analyses, they were not reviewed by the FDA.

Past Medical History and the Incidence of Thromboembolism

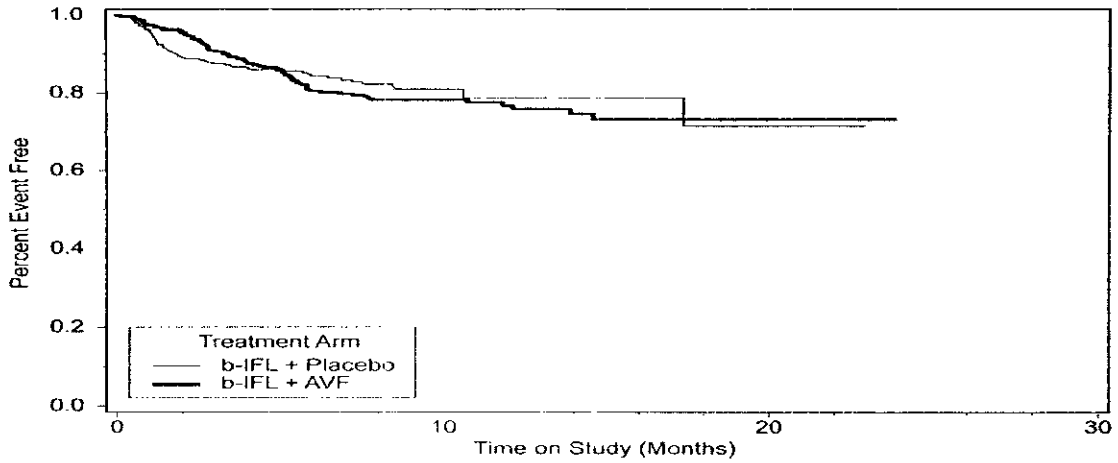
In the IFL + Placebo arm, 31 patients had active coronary disease on study entry. Four patients in this arm had an adverse event of either myocardial infarction (3) or angina/coronary artery disease (1) during study treatment. None of these four patients was among the 31 with a pre-existing condition.

In the IFL + Bevacizumab arm, 26 patients had active coronary disease on study entry. Six patients in this arm had an adverse event of myocardial infarction during study treatment. Two of these six patients had prior angioplasty, 11242 and 11501.

In the 5FU/LV/Bevacizumab arm, nine patients had active coronary disease on study entry. Seven patients in this arm had an adverse event of either myocardial infarction (5) or angina (2). On of these seven patients had prior angioplasty, 12003, and one prior stent placement, 10063 stents.

Time to Thrombosis

The time to first thromboembolic event of any severity during first line therapy in the IFL + Placebo and IFL + Bevacizumab arms is illustrated below.



Thromboembolic events appear to occur at a more rapid pace early in the study. Conclusions about the rate of late events are limited by the decrease in the number of patients on study.

Thromboembolic Events and the Use of Full Dose Anti-Coagulation

Patients requiring full dose anti-coagulation were required to discontinued blinded study drug. Despite this, 83 patients remained on study in the two principal arms while receiving full dose warfarin. The applicant did not provide information concerning the adherence to this aspect of the protocol for patients in the 5FU/LV/Bevacizumab arm. The table below illustrates patient disposition by arm. Note that a disproportionate number of patients in the bevacizumab arm remained on study.

IFL + Placebo		IFL + Bevacizumab	
55		64	
Remained on Treatment	Discontinued Study	Remained on Treatment	Discontinued Study
30	25	53	11

Patients in the bevacizumab arm were examined for tumor burden, response status, and history of a prior bleeding event in an effort to determine whether there was bias in the choice to continue or discontinue therapy. The median sum of the longest diameter in patients who discontinued was lower as compared to those who remained on treatment. A larger number (19/53) but a similar percentage (35.8%) of patients who remained on treatment had achieved a partial remission while 4/11 patients who discontinued (36.4%) had a partial remission prior to the event. None of the patients in either study arm had an earlier grade 3-4 bleeding event that may have influenced the decision to discontinue study drug.

More important than concerns about bias in the choice of patients who remained on study drug is the safety of continued bevacizumab use with the administration of full dose anti-coagulation in patients receiving bevacizumab.

	IFL + Placebo	IFL + Bevacizumab
	On Treatment	On Treatment
# Patients	30	53
# Thromboembolic Events		
Gr 4	0	5
Gr 3	1	6
# Bleeding Events		
Gr 4	0	1
Gr 3	2	1

Very few bleeding events occurred in patients receiving bevacizumab and full dose anti-coagulation and the incidence of grade 3-4 bleeding similar between arms. However, 11 patients on IFL + Bevacizumab and only one patient on IFL + Placebo had a second grade 3-4 thromboembolic event following full dose anti-coagulation. In the IFL + Placebo arm, one patient had a deep vein thrombosis of the left leg identified three months after the diagnosis of pulmonary embolism. In the IFL + Bevacizumab arm, there were several instances in which deep vein thrombosis was diagnosed several months prior to pulmonary embolism and in which a thrombus was seen to progress despite anti-coagulation.

Proteinuria

Both adverse events coded as proteinuria and all laboratory abnormalities identified as 1+ or greater proteinuria were examined.

Proteinuria Based on Reported Adverse Events

The table below illustrates the incidence of events coded with the adverse event term proteinuria in the two principal arms during first line therapy.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Gr 1	62 (15.6%)	92 (23.5%)
Gr 2	22 (5.6%)	18 (4.6%)
Gr 3	3 (0.8%)	3 (0.8%)
Gr 4	0	0

In patients concurrently enrolled on Arms 1-3, the evidence of proteinuria based on reports coded with that term during first line therapy was as follows:

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Gr 1	19 (19.4%)	33 (32.4%)	23 (21.1%)
Gr 2	5 (5.1%)	4 (3.9%)	14 (12.8%)
Gr 3	0	0	1 (0.9%)
Gr 4			1 (0.9%)

During second line therapy, 29 of 165 patients (from both bevacizumab arms) were reported to have proteinuria. Nineteen developed grade 1 proteinuria, nine grade 2, and one grade 3. An important finding is that patients initially treated on the 5FU/LV/Bevacizumab arm were more likely to have proteinuria (14/55) than those initially treated with IFL + Bevacizumab (15/110).

Risk Factors

The applicant conducted a series of post hoc analysis examining the association of various baseline characteristics and the development of proteinuria. These analyses were based on the coding of adverse events and baseline information obtained in the case report forms. These analyses utilize data from Treatment Periods 1 and 2 that was included in the initial submission and do not contain information from the safety update. One of the analyses examines the association of proteinuria and hypertension. This is shown in the tables below. Percentages are of the entire safety population

IFL + Placebo

	Proteinuria		
Hypertension	Yes	No	Total
Yes	9 (2.3%)	25 (6.3%)	34
No	77 (19.4%)	285 (72.0%)	362
Total	86	310	396

IFL + Bevacizumab

	Proteinuria		
Hypertension	Yes	No	Total
Yes	41 (10.5%)	57 (13.0%)	98
No	71 (18.1%)	223 (56.9%)	294
Total	112	280	392

The percentage of patients with both hypertension and proteinuria is higher in the IFL + Bevacizumab arm when compared to those in the IFL + Placebo group. This does not, however, imply that these events are associated. This represents the findings of a post hoc analysis of a large number of baseline characteristics and adverse events. Given the exploratory nature of these analyses, statistical testing was not performed.

Proteinuria Based on Laboratory Reports

Compliance with Performance of Urine Dipsticks

To examine compliance with the performance of urine dipsticks prior to each dose of bevacizumab, the number of patients with testing on Day 0 of the first four cycles was examined. Roughly 10% of dipsticks associated with these visits were listed as not performed.

	IFL + Placebo	IFL + Bevacizumab
Cycle 1 Day 0		
Not Done (% urinalyses)	42/341 (9.8%)	61/435 (14.0%)
Negative-Trace	341	334
1+	34	30
2+	11	7
3+	1	3
4+	1	
Cycle 2 Day 0		
Not Done (% pts dosed)	42/365 (11.5%)	34/380 (8.9%)
Negative-Trace	288	315
1+	30	24
2+	5	7
Cycle 3 Day 0		
Not Done (% pts dosed)	32/329 (9.7%)	30/346 (8.7%)
Negative-Trace	276	297
1+	19	15
2+	2	4
Cycle 4 Day 0		
Not Done	21/271 (7.7%)	26/313 (8.3%)
Negative-Trace	234	269
1+	14	10
2+	1	7
3+	1	1

Results of Urine Dipsticks During First Line Therapy

During first line therapy, 40.2% of patients in the IFL + Placebo arm, 49.7% in the IFL + Bevacizumab arm, and 53.2% of those receiving 5FU/LV/Bevacizumab had a dipstick reading 1+ or greater. This table below includes the number of patients with positive urine dipsticks during first line therapy. Each patient is counted only once at their highest grade and screening and cycle 1 day 0 values are excluded. Note that despite the exclusion of screening laboratories, the number of patients in the IFL + Bevacizumab arm does not equal that in the safety population.

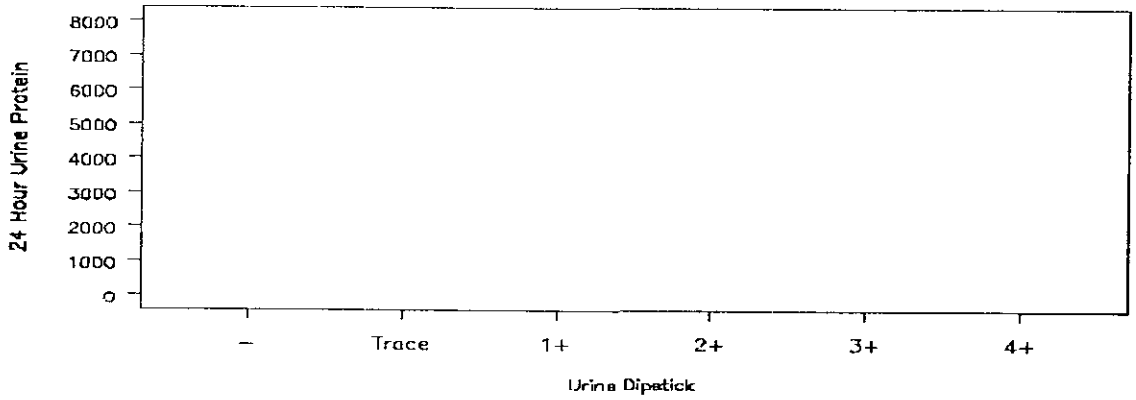
	IFL + Placebo N = 396	IFL + Bevacizumab N = 394	5FU/LV/Bevacizumab N = 109
Urine Dipsticks			
1+	104 (26.3%)	130 (33.0%)	27 (24.8%)
2+	41 (10.4%)	42 (10.7%)	15 (13.8%)
3+	9 (2.3%)	18 (4.6%)	12 (11.0%)
4+	5 (1.3%)	6 (1.5%)	4 (3.7%)

Compliance with Performance of 24 H Urine Collections and Correlation with Dipstick Results

Compliance with the collection of 24 hour urines was also examined. Patients with ≥ 1+ proteinuria were to have 24 hour urines collected. In practice, only patients with a worsening of their dipstick value had 24 hour urines collected. That is, patients who were 1+ at baseline and had a 24 hour collection would not be retested for a subsequent reading of 1+, but were to have a collection if the reading was 2+ or greater. During the first four cycles, seven patients in IFL arms with at least 3+ proteinuria by dipstick were identified. These patients were then evaluated for compliance with 24 hour collections. Two of the seven collections were not performed. The adequacy of these collections could not be assessed with the information provided. All collections were completed within four days of the dipstick result. Importantly, none showed a correlation between dipstick value and 24 hour collection.

Patient Number	Dipstick Result	24 H Collection
10802	4+	659 mg
13402	3+	126.2 mg
11227	3+	484 mg
13423	3+	112 mg
13721	3+	690 mg

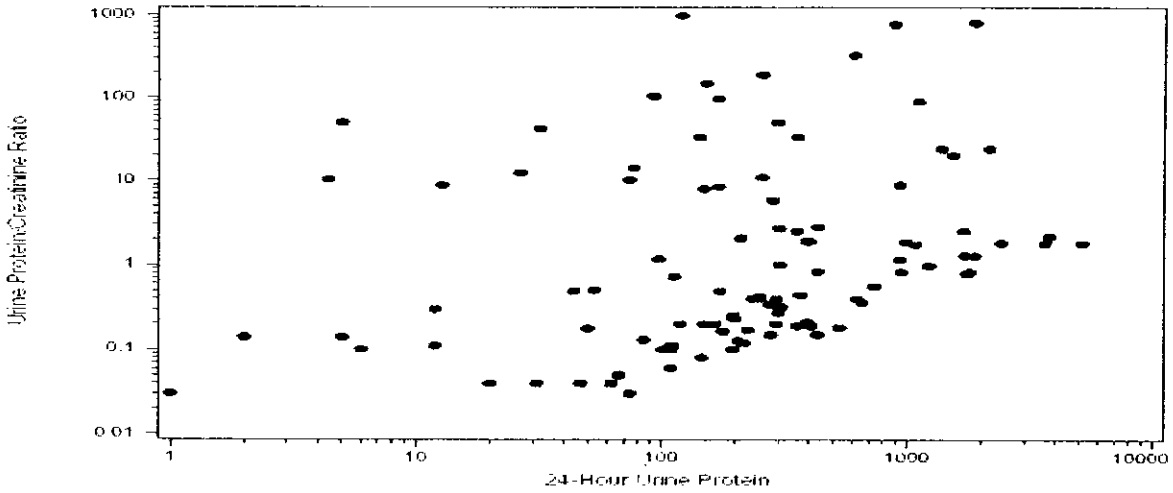
The applicant also noted the lack of correlation between dipstick values and 24 hour urine results and provided a graphic display.



While there is a trend toward an increase in 24 hour urinary protein with increasing dipstick, there are a number of low dipstick values, which are associated with significant proteinuria. The applicant provided further analysis of the correlation between dipstick and 24 hour results at sites of high enrollment. Correlation varied by site, but all of the sites examined showed some correlation between dipstick and 24 hour urine results.

The applicant also provided information on the value of the urine protein to creatinine ratio in predicting 24 hour urine results. The applicant obtained a limited amount of

information concerning urine protein creatinine ratios during this study. Collection of this data was not systematic.



This scatter plot suggests an improved correlation. With a cutoff ratio of 2, no patients with more than 2 grams of urinary protein would fail to undergo testing. However, several patients with more than 2 grams of urinary protein have a ratio very close to 2 and several patients with a ratio of less than 2 had a 24 hour collection with more than 1 gram.

24 Hour Collections

Three hundred and twenty six patients had a 24 hour collection during first line therapy. These results are examined in terms of the highest value recorded per patient during first line therapy.

24 Hour Collections by Absolute Value

	IFL + Placebo N = 118	IFL + Bevacizumab N = 158	5FU/LV/Bevacizumab N = 50
≤ 150 mg	53	68	17
151-1000 mg	59	82	21
1000-1999 mg	5	6	5
2000-2999 mg	1		4
3000-3999 mg			1
4000-4999 mg			1
≥ 5000 mg		3	1

No patients in the placebo group, three in the IFL + Bevacizumab arm, and three in the 5FU/LV/Bevacizumab arm had a 24 hour collection with greater than 3.5 grams of proteinuria (NCI CTC Grade 3). This table suggests an overall trend towards an increased, but low incidence of proteinuria with the use of bevacizumab. Proteinuria appears to be further increased in the 5FU/LV/Bevacizumab arm when compared to the IFL+ Bevacizumab group. It is unclear whether this is due to the open label use of

bevacizumab in this arm, measurement error, or to due to the change in the schedule of 5FU/LV in this arm compared to the IFL + Bevacizumab group.

The applicant provided subject narratives on 30 patients identified as having NCI CTC grade 2-4 proteinuria as an adverse event term in both bevacizumab arms. Three of these patients had renal stones or stent placement which may have resulted in proteinuria. Of the remaining 27 patients, 20 had documentation of proteinuria with a 24 hour collection. Two of these 20 patients did not have more than 150 mg in a 24 hour collection. The timing of proteinuria and its relationship to hypertension and diabetes was examined among the remaining 18 patients. There was no clear trend concerning the number of prior doses of bevacizumab and the development of proteinuria. Blood pressures were reviewed nearest to the date of the event. Six of these 18 patients had moderate or severe hypertension surrounding the report of proteinuria. Eleven had a history of hypertension. Five of the 18 patients had a history of diabetes.

In the IFL + Placebo arm, 25 patients were identified as having NCI CTC grade 2-4 proteinuria as an adverse event. Eighteen patients had documentation with a 24 hour collection. One of these 18 patients did not have more than 150 mg in a 24 hour collection. Five of these 17 patients had more than 1 gram of protein in their 24 hour collection. Three of these patients had renal stones or ureteral obstruction and which may have contributed to proteinuria. In one of these patients, the investigator stated that proteinuria was secondary to a urinary tract infection.

Continued Dosing and Retreatment

Limited information is available on the effect of retreatment following the development of proteinuria. This information is presented below.

Patient #	Dipstick (Date)	24 h Collection (Date)	Bevacizumab Dosing (Date)
10101	2+ (—)		
		1890 (—	
			—
	3+ (—		
		1872.5 (—	
			—
	2+ (—	4801 (—)	No additional dosing
10108	3+ (—)	1870 (—	
			—
	3+ (—	2413 (—)	
	2+ (—		—
		2765 (—	
11187		5112 (—	
	4+ (—		
		2268.8 (—	
	Neg (—)		

It is difficult to draw conclusions from this table given the limited information available.

Resolution of Proteinuria

The timing of resolution of proteinuria can also be examined only in a limited number of patients. During Treatment Periods 1 and 2, three patients had a decrease in their 24 hour collections to less than 2 grams. This occurred from one to five months after the initial event.

Upon termination of dosing the following results are available. In the IFL + Placebo arm, 374 patients had a visit listed as termination. Of these, 144 (38.5%) had a urine dipstick performed. Fourteen of these 144 dipsticks (9.7%) were at least 1+. Additional follow up is available in two patients. One patient who was 2+ at termination had 640 mg in a 24 hour collection performed three months later. A second patient who was 4+ at termination was 1+ one month later.

In the IFL + Bevacizumab arm, 318 patients had a visit listed as termination. Of these, 111 (34.9%) had a urine dipstick performed. Eighteen of these 111 dipsticks (16.2%) were at least 1+. Additional follow up information is available in two patients. One patient who was 1+ at termination had a 24 hour urine two months later that contained 240 mg and was trace positive on dipstick two months after that. A second patient was 2+ at termination and was 2+ one month later.

In the 5FU/LV/Bevacizumab arm, 101 patients had a visit listed as termination. Of these, 40 (39.6%) had a urine study performed. Seventeen of 40 (42.5%) were at least 1+. Additional follow up information is available in seven patients. This information is presented below.

Patient	Termination Value	Follow Up Value
10101	2+	4054 mg
		1495 mg
		746 mg
10683	3+	1+
10804	1+	190 mg
10841	3+	2137 mg
		1881 mg
11181	2+	177 mg
11187	4+	5811 mg
		4547 mg
		1673 mg
12222	2+	2+

There is too little information to draw definitive conclusions. However, some patients do have a decrease in urine protein over a one to four month period. No patient had a normal 24 hour collection.

Nephrotoxicity

The database was examined for potential consequences of proteinuria, specifically, increased creatinine and renal failure. Seven patients with an increase in creatinine were identified. These increases can all be explained by associated events such as post operative complications, sepsis, and ureteral obstruction. Six patients developed renal failure. Most of these events were due to sepsis and dehydration. However, two patients are of concern.

- Patient 11824 developed hypertensive encephalopathy. Four to five months later the patient was noted to have grade 3 renal failure.
- Patient 11161 presented with dehydration and a creatinine of 2.5 mg/dL. The investigator considered this a grade 4 event and discontinued from study drug. Several months later, he presented with renal failure. The patient had been evaluated for proteinuria one to two months prior to this and was found to have 433 mg of protein.

Proteinuria and Edema

Using the levels obtained throughout treatment, the median serum albumin was similar between arms.

Tabular listings of serum albumin and edema were also examined. Four patients, 11187, 11347, 11367, 12006 had grade 2 or greater proteinuria and edema.

- Patient, 11187, had greater than 4 grams of protein in a 24 hour collection and 3+ edema. This patient was not considered to have nephrotic syndrome by the investigator. This was changed to a grade 4 event in the table above.
- Patient 11347 had 3001 mg of protein in her urine. This was temporally related to the adverse event grade 2 edema.
- Patient 11367 did not have a 24 hour urine documenting proteinuria.
- Patients 12006 did have a 24 hour urine documenting proteinuria. This collection contained 1438 mg of protein.

Hypertension

Adverse Event Hypertension

Hypertension of any severity was to be captured on all patients throughout the study. The incidence of hypertension based on adverse events coded with the term hypertension during first line therapy is shown in the table below.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall Hypertension	34 (8.6%)	92 (23.5%)
Gr 1	19 (4.8%)	32 (8.2%)
Gr 2	5 (1.3%)	14 (3.6%)
Gr 3	10 (2.5%)	44 (11.2%)
Gr 4	0	2 (0.5%)

Subject narratives and case report forms related to hypertension were examined and two patients were reclassified by the FDA as grade 4 hypertension. This included:

- Patients 11521 who presented with nausea, vomiting, edema, and a blood pressure of 200/110.
- Patient 11824 who developed hypertension and confusion following elective surgery and required a nitroprusside drip.

Serious adverse events associated with grade 3 hypertension occurred in patients 10685 and 10693.

- Patient 10685 had a subarachnoid hemorrhage associated with a blood pressure of 208/102.
- Patient 10693 had a motor vehicle accident associated with syncope. Blood pressure recorded near the time of the event was 160/120.

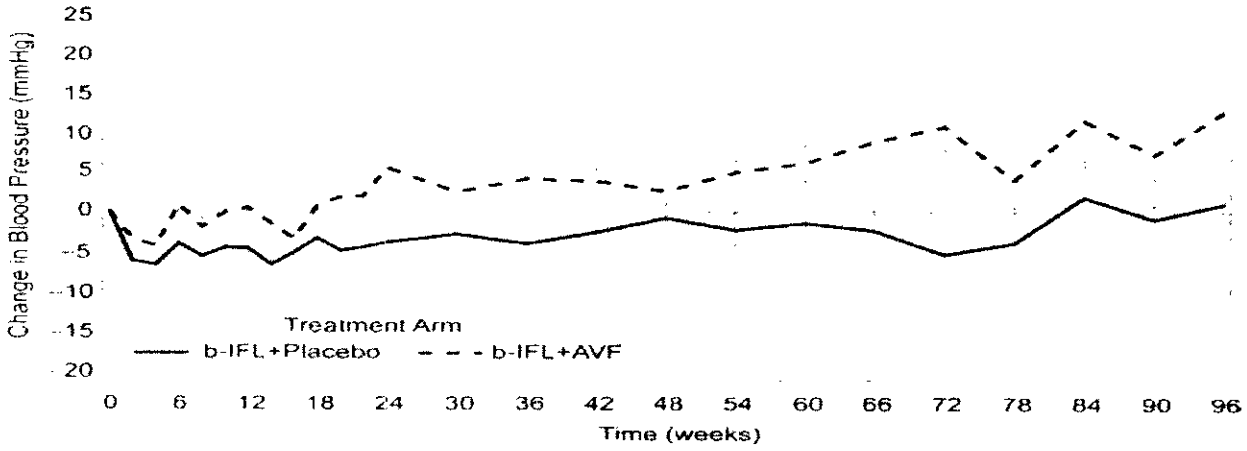
Change in Blood Pressure

The applicant also examined the change in blood pressure during fist line therapy from baseline by week on study in terms of the mean and median change. This yielded the following table. Information on the mean change was provided in the Safety Update submitted November 21, 2003. Median changes in blood pressure were included in the original BLA submission.

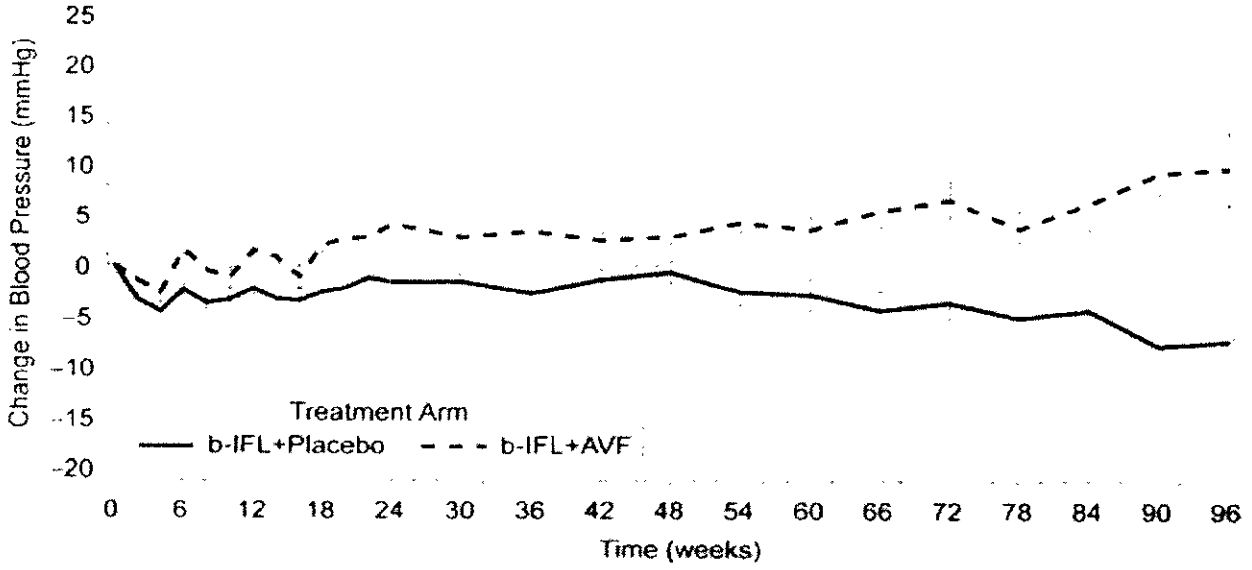
	IFL + Placebo	IFL + Bevacizumab
Week 6		
Mean SBP/DBP	126.4 / 73.9	132 / 77.8
Mean Change SBP/DBP	-4 / -2.4	1 / 1.6
Median SBP/DBP (25-75)	126 / 74 (114-140 / 66-80)	130 / 78 (120-142 / 70-86)
Week 12		
Mean SBP/DBP	127.2 / 74.9	132.1 / 78.1
Mean Change SBP/DBP	-4.7 / -2.2	0.6 / 1.6
Median SBP/DBP (25-75)	126/ 74 (114-140 / 68-80)	130 / 78.6 (120-142 / 70-84)
Week 24		
Mean SBP/DBP	129.1 / 76.2	135.6 / 79.4
Mean Change SBP/DBP	-3.9 / -1.6	5.5 / 3.2
Median SBP/DBP (25-75)	128 / 78 (116-140 / 68-82)	134 / 80 (122-146 / 72-88)
Week 48		
Mean SBP/DBP	131.5/77.5	134.4/79.1

Mean Change SBP/DBP	-2.0/-1.1	3/2.9
Median SBP/DBP (25-75)	131.5 / 78.5 (124-141 / 70-87)	133 / 80 (120-145 / 70-86)

The applicant also presents graphs to illustrate the change in blood pressure compared to baseline over time for the group as a whole. Their conclusion from these graphs is that blood pressure increases gradually over time in the bevacizumab groups. The graph below represents the change in systolic blood pressure compared to baseline over time.



The graph below represents the change in diastolic blood pressure compared to baseline over time.



The increase in the incidence of severe hypertension in the bevacizumab arm is of concern. The following table illustrates the number of patients in each arm during first line therapy with either a systolic and/or diastolic reading above the cutoff values.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
> 140/90	261 (65.9%)	310 (79.1%)	89 (81.6%)
> 150/100	169 (42.7%)	234 (59.7%)	73 (67.0%)
> 200/110	10 (2.5%)	26 (6.6%)	11 (10.1%)

The percentage of patients with either a systolic reading more than 140 and/or a diastolic reading greater than 90 is higher in the bevacizumab arms as compared to placebo. However, the difference between the bevacizumab and placebo arms becomes more striking as higher cutoff values are used.

Since a single reading with either a systolic greater than 200 or diastolic greater than 110 would have less weight than multiple elevated readings, these values where further examined. One of 10 patients in the IFL + Placebo, 11 of 26 in the IFL + Bevacizumab, and five of 11 in the 5FU/LV/Bevacizumab arm had these extreme values recorded on more than one occasion.

Thirty-seven of the 505 patients in the bevacizumab arms (7.3%) had either a systolic or diastolic reading greater than 200/110. Whether these values were primarily systolic or diastolic was examined. The majority of these extreme values were due to a diastolic reading greater than 110.

	Both Bevacizumab Arms
# of Patients	37
# Patients SBP > 200 Only	12 (32.4%)
# Patients DBP > 110 Only	19 (51.4%)
# Patients both SBP/DBP >200/110	6

Anti-Hypertensive Medications

Differences in the number of events can give some indication of the difficulty with which hypertension was controlled. The table below lists the number of events by grade. Patients are represented more than once.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Hypertensive Events		
Gr 1	36	110
Gr 2	8	59
Gr 3	18	131
Gr 4	0	1

While there is a clear difference in the number of patients coded with the adverse event grade 3-4 hypertension (2.5 vs. 11.7%), this difference becomes more striking when the number of events is evaluated. There may be several reasons behind the occurrence of

multiple events in the same patient including patient compliance, the need for closer medical management, or difficulty in controlling the patient's blood pressure.

Ten patients in the IFL + Placebo and 46 in the IFL + Bevacizumab arm had a grade 3-4 hypertension (requiring medication or more intensive therapy). In the IFL + Placebo arm, six of 10 patients were given a new class of drug. In the IFL + Bevacizumab arm, 36 of 46 patients were given a new class of drug. It is possible that doses of existing medications were altered in remaining patients. No information was collected on drug dose.

	IFL + Placebo		IFL + Bevacizumab	
Total Gr 3-4 Events	10		46	
	Before Event	After Event	Before Event	After Event
Using New Class of Anti-HTN	5	6	15	36
ACE Inhibitor	1	2	8	11
Angiotensin Receptor Blocker	0	0	1	3
Beta Blocker	3	1	5	9
Calcium Channel Blocker	1	2	2	13
Diuretic	0	2	3	11
Other	1	1	5	10

In addition to class of medication, the number of new medications and the length of time the medication was used was more closely examined in patients in the IFL + Bevacizumab arm. Twenty-six of these patients received a single new medication, of these four received less than one week of therapy and 20 received combination therapy. The ability of these medications to adequately control hypertension was examined by determining the number of additional reports of grade 3 hypertension (requiring therapy or more intensive therapy) following the first report. In 29 of the 46 patients in the IFL + Bevacizumab arm, grade 3 hypertension was reported on more than one occasion. In nine of these patients, it was reported twice. However, in 20 patients grade 3 hypertension was reported on three to eight occasions.

Ongoing Hypertension

Thirty-six patients entered the follow up phase with ongoing hypertension. In eight of 10 patients in the IFL + Placebo arm, hypertension remained ongoing four months after discontinuation of study drug. In 18 of 26 patients in the IFL + Bevacizumab arm, hypertension remained ongoing four months after discontinuation of study drug.

Risk Factors

The applicant conducted a series of post hoc analyses to assess the association between adverse events coded as hypertension and various risk factors. Given the exploratory nature of these analyses, they were not closely reviewed. Information on the relationship between proteinuria and hypertension is included under proteinuria above.

Time to Onset

The occurrence of hypertension over time was also examined to determine whether there is any relationship to time on study. Here, percentages are of the number of patients who had a blood pressure result recorded at a given time rather than the entire safety population. Also note that here > 140/90 and > 200/100 refers to either as systolic or diastolic pressure greater than that value. The onset of hypertension does not appear to be clearly associated with time on study.

	Arm 1		Arm 2	
Screening				
> 140/90	120/410	(29.3%)	111/400	(27.8%)
> 200/100	7/410	(1.7%)	9/400	(2.2%)
Cycle 2 Day 0				
> 140/90	108/343	(31.5%)	144/352	(40.9%)
> 200/100	3/343	(0.9%)	9/352	(2.6%)
Cycle 4 Day 0				
> 140/90	91/254	(35.8%)	123/291	(42.3%)
> 200/100	2/254	(0.8%)	15/291	(5.2%)
Cycle 6 Day 0				
> 140/90	55/170	(32.4%)	119/240	(49.6%)
> 200/100	2/170	(1.2%)	8/240	(3.3%)
Cycle 8 Day 0				
> 140/90	34/89	(38.2%)	82/167	(49.1%)
> 200/100	0		5/167	(3.0%)

Hypertension Related Events

The association of hypertension with events such as subarachnoid hemorrhage, cerebrovascular accident, myocardial infarction, and headache was examined. Two of the three patients with subarachnoid hemorrhage had moderate to severe hypertension. Of the 10 patients experiencing myocardial infarction, cerebrovascular accident or transient ischemic attack, two had moderate hypertension.

The association of hypertension with headache was also examined. In the IFL + Placebo arm, four of 29 patients with the adverse event headache also had the adverse event hypertension (13.8%). The incidence of hypertension in this arm was 8.6%. In the IFL + Bevacizumab arm, 12 of 38 patients with headache also had hypertension (31.6%). The incidence of hypertension in this arm was 23.5%. In the 5FU/LV/Bevacizumab arm, 15 of 30 patients with headache also had hypertension (50.0%). This incidence of hypertension in this arm is 33.9%.

Congestive Heart Failure

The terms congestive heart failure, cardiomyopathy, left heart failure, and lung edema during Treatment Periods 1 and 2 were examined. Only one of these events occurred

during second line therapy. Note that patients in the three arms were not concurrently enrolled.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Congestive Heart Failure			
Gr 1	0	0	0
Gr 2	0	0	0
Gr 3	2	3	3
Gr 4	2	0	0

Two patients in the IFL + Bevacizumab arm, 10693 and 12043, developed congestive heart failure five and 11 months after their last dose of bevacizumab. They are not included in the table above. In addition, one patient (11354) with grade 2 lung edema experienced this adverse event following a thoracotomy that was complicated by wound dehiscence and pneumothorax.

Two patients in 5FU/LV/Bevacizumab arm included in the above table are of concern.

- Patient 12362 died during hospitalization from grade 3 congestive heart failure and culture negative sepsis. The grading of congestive heart failure in this patient appears to be incorrect.
- Patient 12003 developed a myocardial infarction and remained on bevacizumab. One year later, the patient presented with symptoms of congestive heart failure and an ejection fraction of 20%. It is unclear whether the patient would have developed congestive failure as an expected consequence of myocardial infarction.

Of the three patients in the IFL + Bevacizumab arm with, two continued bevacizumab following the event. No further cardiac events are recorded in these patients, but specific cardiac follow up information is not available.

Reports coded with the adverse event terms edema and dyspnea were reviewed. Both adverse events occurred in four patients in the IFL + Placebo, eight in the IFL + Bevacizumab, and 12 patients in the 5FU/LV/Bevacizumab arm. Further analysis was restricted to grade 2 or greater events. Grade 2 or greater events were then examined for their temporal relationship (within 1 month of each other). Two patients in the IFL + Bevacizumab arm had grade 2 or greater events. The events were temporally related in one patient.

- Patient 10061 in the IFL + Bevacizumab arm had a past medical history of myocardial infarction and coronary bypass. Dyspnea is referred to as dyspnea on exertion. However, dyspnea was also temporally related to an upper respiratory infection.

Six patients in the 5FU/LV/Bevacizumab arm had grade 2 or greater events. The events were temporally related in five. Of these five, patient 12003 was also coded as having congestive heart failure and patient 11401 had a pulmonary embolism and deep vein thrombosis. In the remaining three patients:

- Patient 10502 had dyspnea that was thought to be related to lung metastases and edema of the lower extremities and later right lower extremity edema.
- Patient 11364 had chest pain and dyspnea on —— Chest pain was said to related to obstructive jaundice. Edema was noted on —— and the patient was removed from study due to progressive disease.
- Patient 11922 underwent surgery for an abdominal mass. Seven days later the patient was noted to have edema. This was followed by dyspnea three weeks after the initial report of edema. The patient discontinued due to physician decision shortly afterward. Termination scans were not done to assess the contribution of progressive disease to edema and dyspnea.

Past Medical History and the Development of Congestive Failure

The FDA reviewed the association of a past history of congestive heart failure with the occurrence of cardiac events on study. In the IFL + Placebo arm, eight patients had active congestive heart failure on study entry. In seven additional patients, the condition edema was active on study entry. Of the four patients in this arm who developed congestive heart failure during study therapy, one (11470) had trace pedal edema on study entry.

In the IFL + Bevacizumab arm, three patients had active congestive heart failure on study entry. In six additional patients, the condition edema was active on study entry. Of the three patients with congestive failure during study therapy and the two additional patients who developed congestive failure following the completion of dosing, one patient had the condition congestive heart failure on study entry.

- Patient 13423 had congestive failure listed as an active condition on entry. After seven months of bevacizumab, the patient developed orthopnea which responded to medication. The patient remained on treatment following this event.

In the 5FU/LV/Bevacizumab arm, three patients had active congestive heart failure on study entry and three additional patients had peripheral edema. Of the three patients with congestive heart failure in this arm during study therapy, one had the condition on study entry.

- Patient 10048 had congestive heart failure listed as an active condition on entry. After six months of bevacizumab, a decrease in ejection fraction was noted and after nine months, the patient developed dyspnea and occasional chest pain which was treated with medication. The patient discontinued study treatment.

Additionally, patient 11522 in the 5FU/LV/Bevacizumab arm was noted to have hypertrophic cardiomyopathy on study entry. After nine months on study, the patient experienced sudden death.

Diarrhea

The incidence of grade 3 and 4 diarrhea in the two principal arms during first line therapy is shown in the table below.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Diarrhea[1]		
Gr 3	95 (24.0%)	119 (30.4%)
Gr 4	4 (1.0%)	14 (3.6%)
Colitis/Enterocolitis		
Gr 3	4 (1.0%)	4 (1.0%)
Gr 4	1 (0.3%)	1 (0.3%)

[1]Includes diarrhea, enteritis, and gastroenteritis.

In patients concurrently enrolled in Arms 1-3 the incidence of grade 1-4 diarrhea is as follows. Here diarrhea again includes diarrhea, enteritis, and gastroenteritis.

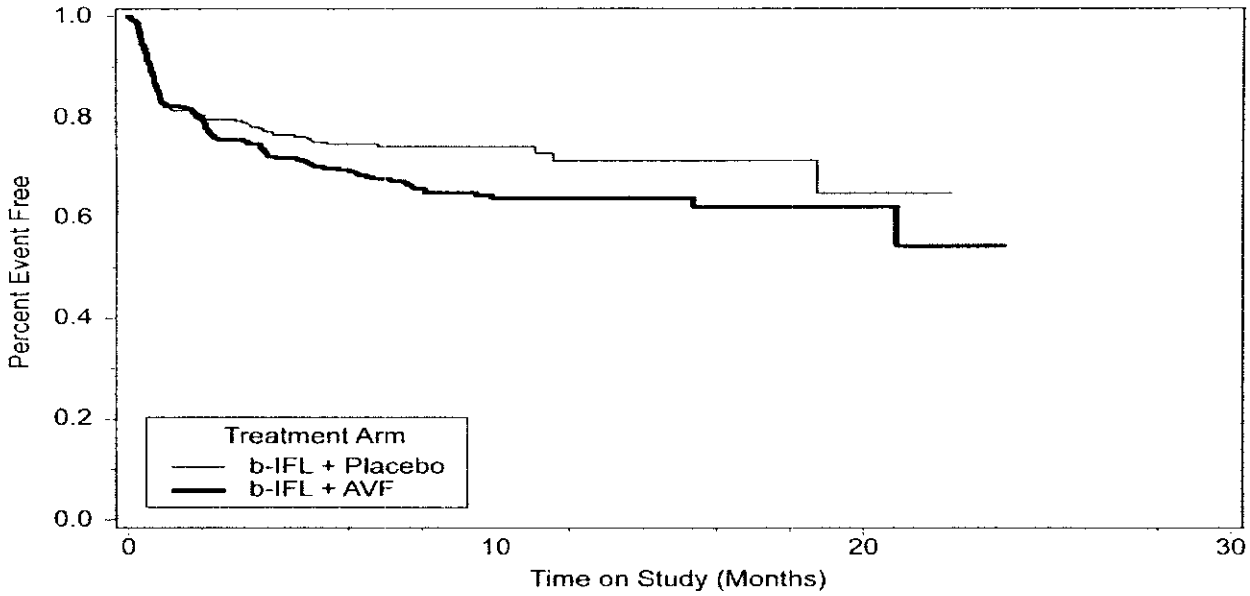
	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Overall	85 (86.7%)	91 (89.2%)	92 (84.4%)
Gr 1	25 (25.5%)	27 (26.5%)	25 (22.9%)
Gr 2	34 (34.7%)	18 (17.6%)	26 (23.8%)
Gr 3	23 (23.5%)	42 (41.2%)	39 (35.8%)
Gr 4	3 (3.1%)	4 (3.9%)	2 (1.8%)

The incidence of grade 3 diarrhea is increase in patients receiving bevacizumab in both analyses. However, the incidence of grade 1-4 diarrhea in the subset of 309 patients in the table directly above is similar across the study arms.

Risk Factors

The applicant conducted a post hoc analysis to examine factors associated with diarrhea in the two principal arms. Diarrhea was associated with increasing age in the placebo group. In the bevacizumab group, diarrhea was increased in those at least 65 when compare to patients 40-64, but was also increased in patients less than 40. Decreased performance status and prior radiation therapy were associated with an increase in diarrhea in both arms.

Time to First Event



One possible interpretation of this graph is that there is an increased slope between five and 10 months in the bevacizumab arm with a more equal slope between arms at earlier and later time points. However, later time points should be viewed with caution due to the small number of patients remaining on study.

Grade 3-4 diarrhea occurred more commonly in the bevacizumab than in the placebo group. Possible explanations are a longer time on study in the bevacizumab arm, an imbalance in patient characteristics that are related to an ability to tolerate chemotherapy, or a lack of appropriate dose reduction in the bevacizumab arm. The time to event analysis suggests that this difference is not related to an increased time on study. In reviewing the initial demographics, patients appeared to be well balanced between arms making this an unlikely cause of this difference in diarrhea (although this balance may not have persisted through each cycle).

Differences in dose reduction were then examined by computing the total dose of bevacizumab in each arm in patients with and without grade 3-4 diarrhea. This computation uses data in the initial BLA submission.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
5-Fluorouracil		
Grade 3-4 Diarrhea	12140	17375
No Grade 3-4 Diarrhea	15759	18048
Irinotecan		
Grade 3-4 Diarrhea	2957	4170
No Grade 3-4 Diarrhea	3879	4384

The increase in total dose in the bevacizumab arm is likely to be due to a longer time on study. However, the gap in dose between patients with and without diarrhea is smaller in the bevacizumab arm when compared to placebo. One possibility is that these patients have undergone fewer dose reductions than those in the placebo group. However, the median number of dose reductions for 5-fluorouracil and irinotecan in both arms was identical and the mean was slightly higher in the bevacizumab arm, suggesting that dose reductions were greater in this arm.

The increase in the incidence of diarrhea may be related to the increase in SN-38 levels with bevacizumab. In the pharmacokinetics subset, it was noted that patients in the bevacizumab arm had on average a 33% higher level of SN-38. However, SN-38 levels are variably associated with diarrhea (this is linked more closely to SN-38 glucuronide which was not measured). Further, there is typically a great deal of variability in SN-38 levels due to allelic differences in the enzymes which metabolize irinotecan. Therefore, it is difficult to draw conclusions concerning the relevance of this increase in SN-38 or its relationship to an increased incidence of severe diarrhea.

In addition to diarrhea, a gastrointestinal event of interest identified during the BLA review is ileus/intestinal obstruction. A large number of grade 4 events appear to have occurred. However, these events are balanced between arms.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Intestinal Obstruction/Ileus	22 (6%)	23 (6%)
Gr 3	14	16
Gr 4	8	7

Adverse Events of Interest Identified During BLA Review

Leukopenia

Adverse Event

The applicant reported a slightly higher incidence of the adverse event grade 3-4 leukopenia during first line therapy in patients receiving IFL + bevacizumab.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Leukopenia		
Gr 3	92 (23.2%)	98 (25.0%)
Gr 4	30 (7.6%)	47 (12.0%)

The incidence of leukopenia is not consistent with the literature that reports that the incidence of grade 3-4 neutropenia is 40-53.8% of patients receiving IFL. Further, the increase in leukopenia in the bevacizumab arm is not consistent with the lower dose density in the IFL + Bevacizumab arm. While the dose density of 5-fluorouracil and

irinotecan are lower in the IFL + Bevacizumab arm when compared to IFL + Placebo, the total dose is higher due to a longer time on study. This difference in leukopenia could be due to an increased time on study in the IFL + Bevacizumab arm or be related to the change in SN-38 levels discussed under diarrhea above. It seems unlikely that leukopenia is related to a direct effect of bevacizumab. For further details please see the Summary of Clinical Safety which discusses the adverse event profile of single agent therapy.

Despite the increase in the incidence of leukopenia, an increase in sepsis was not seen. The incidence of grade 3-4 sepsis was 2.5% in the IFL + Placebo and 3.1% in the IFL + Bevacizumab arm.

Laboratory Abnormalities

The applicant also provided the results of the central laboratory measurement of absolute neutrophil count, hemoglobin, and platelet count during first line therapy. Central laboratories were collected on days 1 and 21 of each cycle. The applicant's analysis of laboratory events is based on central laboratory data. A laboratory event occurred if there was at least a one grade change in value. Note that patients were allowed to enter with grade 1 neutropenia, grade 2 anemia, and grade 1 thrombocytopenia. Patients are counted once at their highest level. This analysis is not based on the safety population, but is based on patients with central laboratory values who had a laboratory event.

Laboratory Events

	IFL + Placebo N = 299	IFL + Bevacizumab N = 279
Absolute Neutrophil Count		
Gr 1	42 (14.0%)	49 (17.6%)
Gr 2	52 (17.4%)	58 (20.8%)
Gr 3	35 (11.7%)	49 (17.6%)
Gr 4	6 (2.0%)	8 (2.9%)
Hemoglobin		
Gr 1	93 (31.1%)	88 (31.5%)
Gr 2	39 (13.0%)	23 (8.2%)
Gr 3	6 (2.0%)	1 (0.4%)

	IFL + Placebo N = 291	IFL + Bevacizumab N = 277
Platelet Count		
Gr 1	22 (7.6%)	22 (7.9%)
Gr 2	0	1 (0.4%)
Gr 3	1 (0.3%)	1 (0.4%)

Central laboratory events for patients concurrently enrolled in Arms 1-3 are as follows.

	IFL + Placebo N = 93	IFL + Bevacizumab N = 96	5FU/LV/Bevacizumab N = 106
Absolute Neutrophil Count			
Gr 1	18 (19.4%)	17 (17.7%)	5 (4.7%)
Gr 2	21 (22.6%)	24 (25.0%)	4 (3.8%)
Gr 3	14 (15.1%)	26 (27.1%)	1 (0.9%)
Gr 4	4 (4.3%)	5 (5.2%)	0
Hemoglobin			
Gr 1	35 (37.6%)	37 (38.5%)	18 (17.0%)
Gr 2	14 (15.1%)	13 (13.5%)	6 (5.7%)
Gr 3	2 (2.2%)	1 (1.0%)	0

	IFL + Placebo N = 92	IFL + Bevacizumab N = 96	5FU/LV/Bevacizumab N = 106
Platelet Count			
Gr 1	11 (12.0%)	7 (7.3%)	10 (9.4%)

Patients in the IFL + Placebo and IFL + Bevacizumab arms that were concurrently enrolled with patients in the 5FU/LV/Bevacizumab arm seem to have a greater level of neutropenia and anemia than those enrolled to these arms later in the study. One possibility is a change in the dose modification criteria. A second is an increased familiarity with the regimen used. This seems unlikely given the widespread use of these regimens.

FDA reviewed central laboratories collected on days one and 21 of each cycle during first line therapy. Percentages were then calculated in terms of the number of patients with a central laboratory value beyond screening or cycle 1 day 0. All patients are included. That is, the analysis is not restricted to those with a laboratory event (a one grade change in value) as in the applicant's analysis.

Neutropenia

	IFL + Placebo N = 303	IFL + Bevacizumab N = 276
Absolute Neutrophil Count		
Gr 1	43 (14.2%)	48 (17.4%)
Gr 2	55 (18.2%)	58 (21.0%)
Gr 3	35 (11.5%)	49 (17.8%)
Gr 4	6 (2.0%)	9 (3.3%)

Grade 3-4 non-scheduled local laboratories were collected separately. In the IFL + Placebo group, 17 absolute neutrophil counts were recorded during first line therapy. One was a grade 3 event. In the IFL + Bevacizumab arm, there are 32 values. One is a grade 4 event and there are no grade 3 events. White blood cell counts were also

recorded from local laboratories. Fifteen patients in the IFL + Placebo and 25 in the IFL + Bevacizumab arm had grade 3-4 leukopenia.

Anemia

	IFL + Placebo N = 304	IFL + Bevacizumab N = 276
Hemoglobin		
Gr 1	157 (51.6%)	154 (55.8%)
Gr 2	51 (16.8%)	35 (12.7%)
Gr 3	6 (2.0%)	1 (0.4%)
Gr 4	0	0

Non-scheduled local laboratories were recorded separately. In the IFL + Placebo arm, one patient had a grade 4 hemoglobin and four patients a grade 3 hemoglobin. In the IFL + Bevacizumab arm, one patient had a grade 4 and five patients a grade 3 hemoglobin.

The seven patients in the IFL + Bevacizumab arm with a central or unscheduled grade 3-4 hemoglobin were evaluated for associated bleeding events. Two of the seven patients had grade 3 gastrointestinal bleeding. A third had an anastomotic dehiscence and a fourth developed myelodysplasia on study.

Thrombocytopenia

	IFL + Placebo N = 297	IFL + Bevacizumab N = 275
Platelet Count		
Gr 1	24	22
Gr 2	0	1
Gr 3	1	1
Gr 4	0	0

Non-scheduled local laboratories were recorded separately. In the IFL + Placebo arm, two patients, 11190 and 12485, had grade 3 thrombocytopenia. In the IFL + Bevacizumab arm, two patients, 11371 and 13421 had grade 3 thrombocytopenia.

Adverse Events Associated with the First Dose

Adverse events occurring with the first dose of study drug were examined in the first 309 patients concurrently enrolled to Arms 1-3. Adverse events experienced by at least 5% of patients are listed below.

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Overall	47 (48.0%)	53 (52.0%)	44 (40.4%)
Abdominal Pain	10 (10.2%)	7 (6.9%)	6 (5.5%)
Asthenia	7 (7.1%)	11 (10.8%)	5 (4.6%)
Nausea	11 (11.2%)	22 (21.6%)	12 (11.0%)
Diarrhea	9 (9.2%)	15 (14.7%)	4 (3.7%)
Vomiting	5 (5.1%)	4 (3.9%)	4 (3.7%)
Insomnia	5 (5.1%)	6 (5.9%)	2 (1.8%)
Sweating	6 (6.1%)	1 (1.0%)	1 (0.9%)

First dose adverse events were also collected in patients enrolled in the two principal arms. The incidence of grade 3-4 first dose adverse events was 2% in the IFL + Placebo arm and 3% in the IFL + Bevacizumab arm.

Other terms typically associated with first dose, infusional syndromes are provided below:

	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Fever			
Gr 1	1 (1.0%)	0	3 (2.8%)
Chills			
Gr 1	1 (1.0%)	0	1 (0.9%)
Allergic Reaction			
Gr 1	0	1 (1.0%)	0
Injection Site Hypersensitivity			
Gr 1	0	1 (1.0%)	0
Injection Site Pain			
Gr 1	0	0	1 (0.9%)
Flushing			
Gr 1	4 (4.1%)	0	0
Arthralgia			
Gr 2	0	0	2 (1.8%)
Myalgia			
Gr 2	0	0	2 (1.8%)
Rhinitis			
Gr 1	3 (3.1%)	2 (2.0%)	0
Dyspnea			
Gr 2	1 (1.0%)	1 (1.0%)	1 (0.9%)
Rash			
Gr 1	0	1 (1.0%)	0

Few first dose events were seen and none were markedly increased in the bevacizumab arms. Events such as allergic reaction and rash are discussed further below.

Allergic Reactions

The incidence and severity of hypersensitivity reactions were examined using the adverse event preferred terms "allergic reaction", "asthma", "facial edema", and "urticaria".

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Allergic Reaction			
Gr 1	3 (0.8%)	5 (1.3%)	2 (1.8%)
Gr 2	0	0	1 (0.9%)
Gr 3	1 (0.3%)	0	0
Asthma			
Gr 1	5 (1.3%)		3 (2.8%)
Gr 2	2 (0.5%)		
Urticaria			
Gr 1	1 (0.3%)	2 (0.5%)	1 (0.9%)
Gr 2	1 (0.3%)	0	1 (0.9%)
Stridor			
Gr 2	1 (0.3%)	0	0
Laryngismus			
Gr 1	1 (0.3%)		

All reports of the term "allergic reaction" were examined for patients in the bevacizumab arms. In the IFL + Bevacizumab arm, five patients were reported to have an allergic reaction. Three of these patients had a defined etiology other than bevacizumab (contrast dye, food allergy, hay fever). In two patients with grade 1 reactions, the cause was unclear. In one the investigator stated that there was no clear cause and in the other that the allergic reaction was due to chemotherapy. Both patients continued to receive bevacizumab. In the 5FU/LV/Bevacizumab arm, three patients were reported to have an allergic reaction. Two were clearly unrelated to study drug (contrast dye, environmental allergy). In the third patient, the allergy is attributed to a concurrent medication.

Grade 1 urticaria occurred in the two patients on the IFL + Bevacizumab arm. One event is attributed to chemotherapy and the other to a concurrent medication. Both patients continued to receive bevacizumab without recurrence. In two patients with urticaria in the 5FU/LV/Bevacizumab arm, the cause of urticaria is unknown in one and said to be due to a non-drug intervention in the second.

Infusional Reactions

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392	5FU/LV/Bevacizumab N = 109
Rash			
Gr 1	24 (6.0%)	19 (4.8%)	17 (15.6%)
Gr 2	6 (1.5%)	6 (1.5%)	4 (3.7%)
Gr 3	0	0	0
Flushing			
Gr 1	10 (2.5%)	2 (0.5%)	7 (6.4%)
Gr 2	2 (0.5%)	1 (0.3%)	1 (0.9%)

Rash and flushing was slightly more common in the IFL + Placebo arm when compared to the IFL + Bevacizumab arm. The incidence is highest in the 5FU/LV/Bevacizumab arm.

Another way to examine the occurrence of infusion reactions is to evaluate patients who had an increase in their infusion time. Per protocol, patients with an infusion reaction were to have an increase in the infusion time with their next treatment. For example, patients who develop a reaction associated with a 30 minute infusion should receive their next infusion over 60 minutes. An analysis was conducted of patients who, following their third dose had an infusion time of 30 minutes and then a subsequent increase in infusion time.

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Increase from		
30 to 60 minutes	74 (18.7%)	66 (16.8%)
30 to 90 minutes	9 (2.3%)	17 (4.3%)
60 to 90 minutes	7 (1.8%)	5 (1.3%)

Overall, there is a slight increase in the number of patients in the bevacizumab arm with an increase in their infusion time. A significant number of patients in the placebo arm also had an increase in infusion time.

Injection Site Reactions

Injection site reactions were also examined. A variety of terms were used including injection site reaction, injection site pain, injection site edema, and injection site hypersensitivity. In the IFL + Bevacizumab arm, injection site reactions were seen in seven patients. These involved pain and redness at the line site, extravasation, and in one instance pain and edema at the site. In the 5FU/LV/Bevacizumab arm, injection site reactions were seen in eight patients. These involved pain and redness at the line site and extravasation. One patient experienced hyperpigmentation at the injection site. Finally one patient with three episodes of injection site reaction, all grade 1, has no case

report form documentation of this reaction. In this patient, grade 1-2 reactions that occurred during second line therapy were deleted from the case report forms.

Changes in Adverse Event Patterns Over Time

The applicant examined the change in the pattern of grade 3-4 adverse events during Treatment Period 1 using intervals of 0-4, 4-8, 8-12, and more than 12 months. Note that patients could remain on this study 96 weeks. The analysis did not clearly identify a type of adverse events that increased over time.

Additional Adverse Events of Interest

None of these events was submitted as an expedited report.

Myelodysplasia
The vascular endothelial growth factor receptor 2 is expressed on precursor cells of the vascular lineage. Hematologic consequences are, therefore, of increased interest. One patient on this study developed myelodysplasia. This patient had not received prior chemotherapy or radiation therapy. However, at screening, his platelet count was 114,000/mm^3. The patient was randomized to the IFL + Bevacizumab arm and received two doses of chemotherapy. Approximately one month after the last dose of chemotherapy, the patient was noted to be pancytopenic, but despite this continued to receive bevacizumab. Pancytopenia continued. He then developed pneumonia and hyponatremia (119 mEq/L) and was discontinued from the study.

Myasthenia
Several patients on AVF2107g developed low grade myasthenia. One patient developed proximal muscle weakness associated with dark urine and a creatinine kinase of 35,201 U/L 21 days after his last dose of study drug. The patient was also taking gemfibrozil and simvastatin. Muscle biopsy showed non-specific Type II fiber atrophy. He required dialysis. Approximately six weeks after the last dose of study drug, the patient developed pancytopenia. Bone marrow was normocellular without dysplasia. Additional complications included rectal ulcer with gastrointestinal bleeding, line sepsis, and jaundice. The patient died of possible intra-abdominal sepsis and rhabdomyolysis.

Guillian-Barre Syndrome
Approximately one month after receiving IFL + Bevacizumab, the patient presented with diarrhea and leukopenia. He continued to receive this regimen. Approximately 1 week after his last dose of IFL + Bevacizumab, he presented with inability to walk. The patient had proximal weakness associated with distal muscle atrophy. Nerve conduction studies showed a demyelinating component. He was given a diagnosis of Guillian-Barre Syndrome.

Neuropathy
This patient began to experience difficulty lifting his arms over his head after 10 months of 5FU/LV/Bevacizumab. He discontinued study drug. One month later, he continued to have difficulty lifting his arms.

Respiratory Distress
After two months of IFL + Bevacizumab, the patient presented with shortness of breath and a room air oxygen saturation of 77%. Hemoglobin was 8.4 g/dL. The patient was treated with antibiotics and steroids. Her respiratory status continued to deteriorate and she was placed on a ventilator. Bronchoscopy was negative for infection, but transbronchial biopsy did show interstitial fibrosis and acute inflammation. The patient ultimately recovered, but discontinued study drug.

APPEARS THIS WAY
ON ORIGINAL

6.1.2 AVF0780g

Study Design

AVF780g is a randomized Phase 2 study that was conducted to establish the activity of bevacizumab in colorectal cancer and to determine the appropriate dose for use in Phase 3 studies. AVF780g randomized patients with newly diagnosed metastatic colorectal cancer to 5-fluorouracil/leucovorin, 5-fluorouracil/leucovorin + 5 mg/kg bevacizumab, or 5-fluorouracil/leucovorin + 10 mg/kg bevacizumab. This serves as a supportive study in this application.

Study Objectives

Primary Efficacy Outcome Measures

- Time to disease progression
- Best (confirmed) tumor response rates

Secondary Efficacy Outcome Measures

- Overall survival
- Duration of response
- Change in the FACT-C questionnaire

Safety Outcome Measures

- Incidence and severity of adverse events
- Changes in vital signs during rhuMAb VEGF infusions
- Clinical laboratory evaluations

Pharmacokinetic Outcome Measures

- Pharmacokinetic parameters derived from the concentration time profile of rhuMAb VEGF administered intravenously
- Plasma concentration of 5-fluorouracil

Exploratory Outcome Measures

- Plasma concentration of VEGF

Subject Selection

Subjects with histologically confirmed metastatic colorectal cancer were eligible for participation in this study. Resected or biopsied primary tumors served as the basis for histologic confirmation.

Inclusion Criteria

- Ability to provide written informed consent
- Histologically confirmed colorectal carcinoma with evidence of metastases, by radiographic imaging or biopsy
- Bi-dimensionally measurable disease, metastases >1 cm^2 in size

- ECOG performance status of 0 or 1
- Life expectancy of >3 months
- Willingness and capability to be accessible for follow-up
- Age ≥ 18 years

Exclusion Criteria

- Prior administration of chemotherapy other than adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole
- Administration of adjuvant fluoropyrimidines in combination with leucovorin and/or levamisole completed ≤ 12 months prior to Day 0
- Prior radiotherapy to a bi-dimensionally measurable, metastatic lesion that will be used to measure response
- Radiation therapy within 28 days prior to Day 0
- Prior administration of biotherapy for colorectal cancer
- Evidence of clinically detectable ascites prior to Day 0
- Other invasive malignancies within 5 years of screening (other than basal cell carcinoma of the skin)
- Serious, non-healing wound, ulcer, or bone fracture
- Clinically significant cardiovascular disease (e.g., uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or Grade II or greater peripheral vascular disease within 1 year prior to Day 0
- Any history or evidence upon physical examination of CNS disease (e.g., primary brain tumor, seizures not controlled with standard medical therapy, or any brain metastases)
- Active infection requiring parenteral antibiotics at the time of the first rhuMAb VEGF infusion
- Major surgical procedure within 28 days prior to Day 0, or open biopsy, significant traumatic injury, or anticipation of need for major surgical procedure during the course of the study; fine needle aspiration within 7 days prior to Day 0
- Current or recent (within the 10 days prior to Day 0) use of oral or parenteral anticoagulants (except as required to maintain patency of preexisting, permanent indwelling IV catheters) or aspirin; therapeutic anticoagulation
- Current or recent (within the 28 days prior to Day 0) participation in another experimental drug study
- Pregnancy (positive pregnancy test) or lactation
- Screening clinical laboratory values as outlined below
    - WBC count of ≥ 3000/μL
    - Platelet count of ≤ 75,000/μL
    - Total bilirubin of >2.0 mg/dL
    - AST or ALT of ≥ 5 times the upper limit of normal for subjects with

documented liver metastases or >2.5 times the upper limit of normal for subjects without evidence of liver metastases

- Serum creatinine of >2.0 mg/dL
- Hemoglobin of <9 g/dL (may be transfused to maintain or exceed this level)
- Inability to comply with the study visit and follow-up schedule or procedures
- History of another disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications

Stratification

Patients were stratified by prior adjuvant 5-fluorouracil use, prior pelvic radiation, and center.

Treatment

Control Arm

1. Leucovorin 500 mg/M^2 over 2 h weekly for 6 weeks followed by a 2 week rest
2. 5-Fluorouracil 500 mg/M^2 IVB 1 h after initiation of leucovorin weekly for 6 weeks followed by a 2 week rest

5 mg/kg

1. Leucovorin 500 mg/M^2 over 2 h weekly for 6 weeks followed by a 2 week rest
2. 5-Fluorouracil 500 mg/M^2 IVB 1 h after initiation of leucovorin weekly for 6 weeks followed by a 2 week rest
3. Bevacizumab 5 mg/kg every 2 weeks

10 mg/kg

1. Leucovorin 500 mg/M^2 over 2 h weekly for 6 weeks followed by a 2 week rest
2. 5-Fluorouracil 500 mg/M^2 IVB 1 h after initiation of leucovorin weekly for 6 weeks followed by a 2 week rest
3. Bevacizumab 10 mg/kg every 2 weeks

Patients in all arms could receive a maximum on six cycles. Upon progression, patients in the chemotherapy alone arm were able to cross over to bevacizumab 10 mg/kg every 2 weeks. Patients in the chemotherapy alone arm who crossed over to bevacizumab could receive treatment for up to 322 days on AVF780g.

Patients in the 5 mg/kg or 10 mg/kg arms who completed six cycles without progression could then enter a six month observation period. Patients who developed progressive disease during the observation period could receive one year of additional chemotherapy plus bevacizumab on an extension study, AVF778g.

Patients in the chemotherapy alone arm who crossed over to bevacizumab and who had not completed 322 days of therapy without further progression could immediately enter the extension study, AVF778g. An observation period was not required.

Endpoints and Assessments

The co-primary endpoints, progression free survival and response, were verified by an independent radiology facility (IRF). However, the IRF charted was agreed to following study initiation. If scans were unavailable for review by the IFL, investigator assessment was used. The availability of scans and any bias their lack of availability may have created in endpoint interpretation is discussed below.

Amendment History

The original protocol was finalized on April 6, 1998 and the first patient entered on June 20, 1998. On June 23, 1998, the first amendment was issued. The first amendment increased the dose of leucovorin from 20 to 500 mg/M^2 and maintained the same schedule. The first amendment also made two alterations in the entry criteria. Patients were now required to have previously untreated metastatic disease. Patients were also required to have completed adjuvant chemotherapy more than 12 months (previously 6 months) prior to entry. Amendment 2 clarified the previous information concerning survival follow up.

Patient Demographics

One hundred and four patients were randomized to this study. The following table examines the balance between arms in terms of patient demographics and prior cancer therapy.

	5FU/LV N = 36	5 mg/kg N = 35	10 mg/kg N = 33
Age			
Median (25-75)	63 (54-72)	64 (54-69)	64 (53-72)
Sex			
Male	27 (75%)	17 (48.6%)	15 (45.4%)
Female	9 (25%)	18 (51.4%)	18 (54.5%)
Performance Status			
0	22 (61.1%)	21 (60%)	18 (54.5%)

≥ 1	14 (38.9%)	14 (40%)	15 (45.4%)
Time from Diagnosis (days)			
Median (25^{th} –75^{th} quartiles)	109 (73-628)	109 (73-287)	112 (72-493)
Mean	612	505	440
Prior Cancer Therapy			
Chemotherapy	8 (22.2%)	5 (14.3%)	7 (21.2%)
Radiation	5 (13.9%)	4 (11.4%)	4 (12.1%)
Surgery	35 (97.2%)	28 (80.0%)	28 (84.8%)
Number of Metastatic Sites			
1	23 (63.9%)	20 (57.1%)	17 (51.5%)
2	10 (27.8%)	9 (25.7%)	10 (30.3%)
3+	3 (8.3%)	6 (17.1%)	6 (18.2%)
Metastatic Sites			
Liver	25 (69.4%)	29 (82.9%)	27 (81.8%)
Lung	8 (22.2%)	14 (40.0%)	12 (36.4%)
Liver and Lung	4 (11.1%)	9 (25.7%)	8 (24.2%)
Tumor Burden-cross product			
Median (25^{th}-75^{th} quartiles)	30.3 (15-59)	38 (17-77)	31.1 (18-71)
Mean	43.4	58.5	49.8
Albumin < 3 g/dL	2 (6.0%)	6 (17.0%)	5 (15.0%)

In this small study, several imbalances in baseline entry variables across the study arms were noted. These include an imbalance in the male to female ratio, performance status, baseline albumin, the presence of liver and lung metastases, prior surgery, and the use of prior adjuvant chemotherapy. These imbalances would, in general, favor the control arm. Note that fewer patients in the 10 mg/kg arm had a performance status of 0. In addition, patients in the 5 mg/kg arm were less likely to have had prior adjuvant chemotherapy, potentially favoring this arm.

Study Populations

	5FU/LV	5 mg/kg	10 mg/kg
Intent to Treat	36	35	33
Safety Population	35	35	32

One patient in the control arm and one in the 10 mg/kg arm discontinued due to progressive disease prior to receipt of study specified therapy.

Study Conduct

Eligibility

The applicant states that three patients had major eligibility violations, one in each arm. These include surgery within 28 days of entry, warfarin use within 10 days of entry, and adjuvant chemotherapy within 12 months of entry. Minor

eligibility exceptions occurred in four patients. These included aspirin use and an abnormal screening laboratory.

Violations in Study Treatment

The applicant states that one patient in the 10 mg/kg arm had a major protocol violation. This patient received the incorrect chemotherapy dose on day 0. Two patients in the control arm crossed over to bevacizumab treatment prior to the development of progressive disease. The applicant classified this as a minor protocol deviation. This has been reclassified as a major deviation. Four patients in the 5 mg/kg arm remained on treatment despite the need for full dose anti-coagulation for deep venous thrombosis. The applicant classified this as a minor protocol deviation. Again, this has been reclassified as a major deviation. Approximately one-third of patients in the study had minor protocol deviations. These involved the inappropriate dose reduction of 5-fluorouracil following diarrhea.

Drug Delivery

One hundred and four patients were randomized to this study and 102 received at least one dose of study therapy. Two patients progressed prior to treatment, one in the control arm and one in the 10 mg/kg arm. The table below illustrates drug delivery in terms of the median number of doses administered.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Bevacizumab			
Median # Doses	NA	17	14
5-Fluorouracil			
Median # Doses	15	28	20
Leucovorin			
Median # Doses	15	28	20

The sponsor notes that 70% of patients in the bevacizumab arms did not miss a dose of bevacizumab. The applicant did not analyze the reason that doses were missed. Information concerning the reason that doses were missed was not Forty-two percent did not miss a chemotherapy dose. No information is provided in the application on dose intensity.

Efficacy

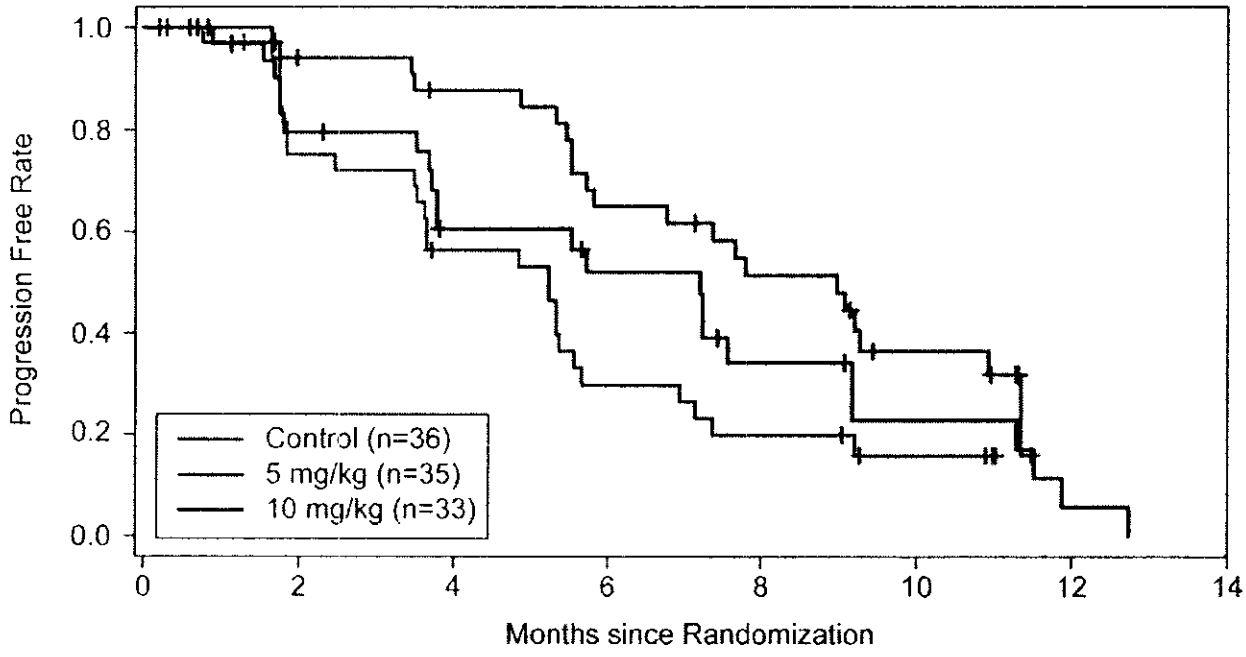
The primary endpoints of this study were progression free survival (PFS) and response rate. Overall survival, duration of response, and changes in the FACT-C questionnaire served as secondary endpoints. Both progression and response were verified through the use of an independent radiology facility. Where scans

could not be independently reviewed, investigator assigned response or progression was used.

Progression Free Survival

	Control N = 36	5 mg/kg N = 35	10 mg/kg N = 33
Number of Progressions	26	22	23
Median PFS (mos)	5.2	9	7.2
Hazard Ratio		0.44[1]	0.69[2]
p value (logrank test)		0.005[1]	0.236[2]

[1]control versus 5 mg/kg
[2]control versus 10 mg/kg



In the primary analysis of progression free survival, no adjustment was made for multiple analyses. If a Bonferroni adjustment is used, the comparison of the 5 mg/kg arm to control remains significant. The 10 mg/kg arm showed some improvement in progression free survival when compared to control. However, the benefit appears to be less than that seen with 5 mg/kg and was not statistically significant. Imbalances in prognostic factors are unlikely to explain this finding.

The assessment of progression may have been affected by early dropouts and by crossover from the control arm prior to progression. Nine patients, three in the control, one in the 5 mg/kg, and five in the 10 mg/kg arm, discontinued prior to their first radiologic assessment. Three of these nine patients discontinued due to investigator assessment of progressive disease in the absence of radiologic evaluation. Five discontinued due to an adverse event and one due to

patient decision shortly after an episode of severe diarrhea. Seven of the nine were censored from the analysis of progression free survival. One patient who who is said to have discontinued due to an adverse event (control arm) and one who discontinued due to progressive disease (10 mg/kg) died on study and were included in the analysis. One additional patient chose to discontinue following the development of significant diarrhea.

The assessment of progression may also have been affected by the crossover of five patients in the control arm to open-label, single agent bevacizumab without IRF confirmation of progression.

Patients Who Crossed Over	22
INV determined PD prior to crossover	20
IRF determined PD prior to crossover	17

In two patients, films were unavailable for IRF review. These patients were censored in the analysis of progression free survival. In two patients, progressive disease was assessed by the investigator, but the IRF reading was of stable disease. In one patient, 6015, the date of used in the analysis of progression free survival was near the date of crossover. In the second patient, 6607, the date of progression during crossover rather than the date of progression on chemotherapy was used. In one patient who crossed over, both the investigator and IRF assessed stable disease. This patient was censored from the analysis. The pattern of censoring in these five patients was somewhat unusual. However, it would tend to favor a longer PFS in the control arm.

Correlation between IRF and Investigator Assessed Progression

The number of scans and patients available for evaluation by the IRF and investigator were examined.

	5FU/LV N = 36	5FU/LV + 5 mg/kg N = 35	5FU/LV + 10 mg/kg N = 33
# Investigator PD Only	3	3	1

Nine patients did not have scans available for review by either the investigator or IRF due to discontinuation prior to their first radiological assessment. Seven of these nine patients were censored and two were included in the analysis of progression (see above under Progression Free Survival).

Seven other patients did not have scans available for review by the IRF. The date of progression in these patients was determined by the investigator based on radiological assessment.

Next the correlation between investigator and IRF progression was reviewed.

	5FU/LV	5FU/LV + 5 mg/kg	5FU/LV + 10 mg/kg
# IRF Reviewed Scans / # Scans	87 (88.8%)	105 (77.8%)	75 (74.3%)
Investigator-IRF Reading Agree/# Scans	59 (67.0%)	74 (70.5%)	50 (66.7%)
PD Earlier by IRF	9	7	10
PD Earlier by Investigator	4	2	2
Difference in Time to PD (IRF-INV)			
Median (range) months	0 (-1.8 to 0)	0 (-1.2 to 2)	0 (-1.8 to 0)
Continued with Investigator PD	5	9	8

The investigator and IRF were in agreement approximately 70% of the time. In general, progressive disease was determined earlier by the IRF. However, in eight instances it was determined earlier by the investigator. Of concern are the number of patients who continued the present regimen despite investigator determined progressive disease.

Exploratory Analysis

The sponsor was asked to conduct a sensitivity analysis in which patients with major protocol or eligibility violations were excluded. In this analysis, the improvement in PFS in the 5 mg/kg group versus control remained significant. However, both the primary analysis and in this sensitivity analysis, patients who crossed over from control to open label bevacizumab prior to progression were censored at crossover. This issue is discussed further below.

	Control N = 36	5 mg/kg N = 35	10 mg/kg N = 33
Median PFS (mos)	5.23	8.98	7.2
p value (logrank)		0.0041[1]	0.206[2]

[1]control versus 5 mg/kg
[2]control versus 10 mg/kg

Response Rate

The response rate was higher in the 5 mg/kg arm (versus control) and was also increased, but to a lesser degree, in the 10 mg/kg arm.

IRF/Investigator Response

	5FU/LV N = 36	5FU/LV + 5 mg/kg N = 35	5FU/LV + 10 mg/kg N = 33
Response Rate	6 (16.7%)	14 (40.0%)	8 (24.2%)
p value (χ^2)		0.03	0.43
Complete Response	0	2	0
Partial Response	6	12	8

Note that since co-primary endpoints were used (progression free survival and response rate) that after adjustment for multiplicity the comparison between the 5 mg/kg arm and control is not considered statistically significant.

Correlation between Investigator and IRF Assessed Response

The number of scans and patients available for evaluation by the IRF and investigator were examined.

	5FU/LV N = 36	5FU/LV + 5 mg/kg N = 35	5FU/LV + 10 mg/kg N = 33
# Investigator Response Only	0	1	1

Due to discontinuation prior to the first assessment, nine patients did not have a scan available for review. These patients were considered non-responders. Three patients did not have an IRF assessment of response. In one of these patients, the investigator assessment was not confirmed and it was not used in the determination of response rate. Two investigator determined responses, one in the 5 mg/kg and one in the 10 mg/kg arm, were used in establishing the response rate. The investigator assessment in the 5 mg/kg arm was stable disease and in the 10 mg/kg arm partial response.

Response as determined by investigator and the independent review facility were then compared.

	Control N = 36	5 mg/kg N = 35	10 mg/kg N = 33
INV/IRF Response	6	14	8
Response by both IRF and Investigator	5	10	5
Response by IRF Only	1	3	2
Response by Investigator Only	0	1	1

[1]INV/IRF response includes all patients with responses determined by the IRF. If there is not IRF assessment of response, the investigator response is used.

The investigator and IRF, in general, agreed concerning the assessment of response. The independent radiology facility (Response by IRF Only) did assess several patients, which by investigator assessment did not demonstrate tumor response, as having had a response.

Response on Crossover

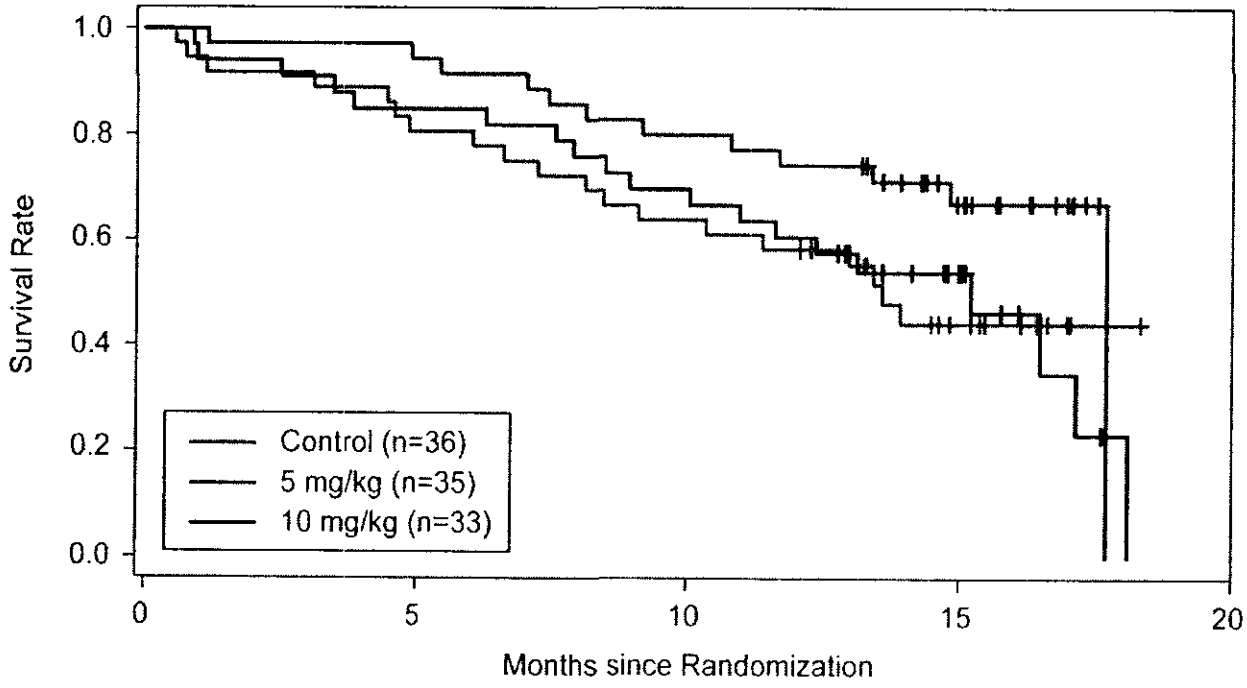
Among the 22 patients who crossed over, 14 had progressive disease at their first assessment following crossover. In the remaining eight patients, one patient was not assessed. There was one partial response in the remaining seven patients.

Secondary Endpoints

Overall Survival

Overall survival was not significantly different between arms. There is, however, a trend toward improvement in the 5 mg/kg arm.

	5FU/LV N = 36	5FU/LV + 5 mg/kg N = 35	5FU/LV + 10 mg/kg N = 33
Number of Deaths	19	12	19
Overall Survival (mo)	13.6	17.7	15.2
Hazard Ratio			
p value (logrank)		p = 0.52	p = .978



Subsequent regimens, crossover from the control arm, and lack of follow up information may have affected overall survival. No data were collected on subsequent regimens and the influence of this factor cannot be assessed. Further, at the time of the final study report, survival data was available on only 44% of patients in the 5 mg/kg arm. However, the survival in the 5 mg/kg arm, 17.7 months is similar to overall survival in the 5FU/LV/Bevacizumab arm (18.2 months) in study AVF2107g conducted by the applicant.

The crossover of patients from the control arm to single agent bevacizumab may have affected overall survival. There are two ways in which this may have theoretically altered survival. The first is crossover that would have improved survival in the control arm by use of an active agent, thus deleting the survival difference. The second is crossover, prior to the assessment of progression,

from effective chemotherapy to an ineffective single agent, thereby resulting in inferior survival and artificially inflating the survival difference. It is difficult to definitively determine which of these effects occurred in this study. However, the following should be noted. Five patients in the control arm crossed to single agent therapy prior to IRF determined progression. Of the 22 patients who crossed over to single agent bevacizumab, one patient had a partial response. Despite this, the overall survival in the control group, 13.6 months was similar to that in the literature, 11.1 months and 13.5 months (see Background, 2.1 Clinical Context of Application).

Duration of Response

	5FU/LV N = 36	5 mg/kg N = 35	10 mg/kg N = 33
IRF/INV[1]			
Number of Responding Patients	6	14	8
Number of Censored Events	4	7	1
Median (months)	NR	9.3	5.0

[1]INV/IRF response includes all patients with responses determined by the IRF. If there is not IRF assessment of response, the investigator response is used.

In this table, the median duration of response has not yet been reached in the control group. This is due to the availability of data on only two of six responding patients. In both patients, the duration of response was verified by the IRF. In both the 5 mg/kg and the 10 mg/kg arm, data on the duration of response was verified by the IRF in six of the seven patients.

Quality of Life

The sponsor examined changes in the FACT-C score from baseline to cycle 3 in all arms. The mean change in the colorectal cancer specific score was 1 in the control arm, 0.7 in the 5 mg/kg, and –1.9 in the 10 mg/kg arm. An increase in score is considered of benefit.

Additional Exploratory Analyses

Ten patients had vascular endothelial growth factor (VEGF) concentrations above the limit of detection of the assay at baseline. Given the small number of patients, the relationship between baseline VEGF and response was not explored. Vascular endothelial growth factor increased over time in a dose dependent manner. This may be due to the formation of complexes, but specific testing to determine whether complex formation had occurred was not performed. The relationship between bevacizumab concentration and response was also explored. There was no clear relationship between AUC and response.

Safety

Adverse events are examined in terms of death, serious adverse events, and all adverse events. Adverse events are further broken down into those that occurred in all three arms during the regular study period and those that occurred in control patients who crossed over to bevacizumab.

Deaths

	5FU/LV	5 mg/kg	10 mg/kg
Number of Deaths	19	12	19
Cause of Death			
Progressive Disease	18	10	18
Adverse Events	1	2	1

In the control arm, the category Other includes one patient who died of diarrhea and neutropenia. In the 5 mg/kg arm, this category includes one patient with respiratory distress and one with hypertension and renal failure. The patient with respiratory distress died nine months after study discontinuation. This was not an event during active therapy. In the 10 mg/kg arm, one patient died of pulmonary embolism.

Serious Adverse Events

Serious adverse events that were increased by at least 2% in the bevacizumab arms compared to control are included in the table below.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Overall	11 (31.4%)	16 (45.7%)	15 (46.9%)
Body as a Whole			
Fever	0	1 (2.9%)	3 (9.4%)
Abdominal Pain	0	0	2 (6.3%)
Ascites	0	0	1 (3.1%)
Catheter Infection	0	0	1 (3.1%)
Sepsis	0	1 (2.9%)	0
Cardiovascular			
Hypertension	0	1 (2.9%)	1 (3.1%)
Deep Vein Thrombosis	0	2 (5.7%)	0
Cerebrovascular Accident	0	0	1 (3.1%)
Congestive Heart Failure	0	0	1 (3.1%)
Pulmonary Embolism	0	0	1 (3.1%)
Thromboembolism	0	1 (2.9%)	1 (3.1%)
Intra-Abdominal Thrombosis	0	1 (2.9%)	0
Shock	0	1 (2.9%)	0
Digestive			

Gastrointestinal Hemorrhage	1 (2.9%)	0	3 (9.4%)
Vomiting	0	1 (2.9%)	2 (6.3%)
Colitis	0	0	2 (6.3%)
Constipation	0	0	1 (3.1%)
Liver Damage	0	0	1 (3.1%)
Nausea	0	0	1 (3.1%)
Esophageal Ulcer	0	1 (2.9%)	0
Ileus[1]	0	2 (5.7%)	2 (6.3%)
Jaundice	0	1 (2.9%)	0
Hemic/Lymphatic			
Leukopenia	1 (2.9%)	3 (8.6%)	0
Metabolic/Nutrition			
Hypovolemia	0	0	1 (3.1%)
Healing Abnormal	0	1 (2.9%)	0
Hypocalcemia	0	1 (2.9%)	0
Nervous			
Convulsion	0	1 (2.9%)	0
Respiratory			
Hiccup	0	1 (2.9%)	0
Urogenital			
Kidney Failure	0	1 (2.9%)	0
Urinary Tract Infection	0	1 (2.9%)	0

[1]Ileus includes intestinal obstruction where intestinal obstruction involved the intestinal tract.

Serious adverse events that deserve special consideration include hypertension, thromboembolism, cerebrovascular accident, heart failure, gastrointestinal hemorrhage, leukopenia, abnormal healing, convulsion, and kidney failure. Seizure is stated to be due to disease progression. No additional information is available.

Serious adverse events that occurred in patients who crossed over from the control arm to single agent bevacizumab include pleural effusion and cardiac arrest, ascites, seizure, dehydration and hypotension, right ovarian mass, gastroenteritis, diarrhea, biliary obstruction, pain, and gastrointestinal hemorrhage. Here, seizure was thought to be secondary to the use of pain medication. The right ovarian mass was a metastasis of the patient's underlying colorectal cancer.

Adverse Events

Grade 3-4 Adverse Events

Grade 3-4 adverse events that are increased by at least 2% in the bevacizumab arms are included in the following table.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Overall			
Gr 3	10 (28.6%)	17 (48.6%)	18 (56.3%)
Gr 4	9 (25.7%)	9 (25.7%)	7 (21.9%)
Body as a Whole			
Pain[1]	2 (5.7%)	3 (8.6%)	1 (3.1%)
Asthenia[2]	0	4 (11.5%)	3 (9.4%)
Abdominal Pain	1 (2.9%)	3 (8.6%)	4 (12.5%)
Sepsis	0	1 (2.9%)	1 (3.1%)
Fever	0	0	1 (3.1%)
Headache/Migraine	0	0	1 (3.1%)
Ascites	0	0	1 (3.1%)
Cardiovascular			
Deep Vein Thrombosis	0	4 (11.4%)	0
Hypertension	0	3 (8.6%)	8 (25.0%)
Intra-abdominal Thrombosis	0	1 (2.9%)	0
Thromboembolism	0	1 (2.9%)	1 (3.1%)
Shock	0	1 (2.9%)	0
Cerebrovascular Accident	0	0	1 (3.1%)
Transient Ischemic Attack	0	0	1 (3.1%)
Congestive Heart Failure	0	0	1 (3.1%)
Pulmonary Embolism	0	0	1 (3.1%)
Syncope	0	0	1 (3.1%)
Digestive			
Constipation	0	1 (2.9%)	1 (3.1%)
Ileus[3]	0	1 (2.9%)	1 (3.1%)
Jaundice	0	1 (2.9%)	0
Colitis	0	0	2 (6.3%)
Dyspepsia	0	0	1 (3.1%)
Fecal Incontinence	0	0	1 (3.1%)
Liver Damage	0	0	1 (3.1%)
Hemic/Lymphatic			
Leukopenia	1 (2.9%)	2 (5.8%)	1 (3.1%)
Thrombocytopenia	0	1 (2.9%)	0
Anemia/Hypochromic Anemia	0	0	1 (3.1%)
Metabolic/Nutrition			
Hypokalemia	1 (2.9%)	1 (2.9%)	3 (9.4%)

Healing Abnormal[4]	0	1 (2.9%)	1 (3.1%)
Weight Loss	0	1 (2.9%)	0
Hyperglycemia	0	1 (2.9%)	0
Hypocalcemia	0	1 (2.9%)	0
Hypovolemia	0	0	1 (3.1%)
Hypomagnesemia	0	0	1 (3.1%)
Hyponatremia	0	0	1 (3.1%)
Musculoskeletal			
Arthralgia/Arthritis	0	1 (2.9%)	1 (3.1%)
Nervous			
Convulsion	1 (2.9%)	1 (2.9%)	0
Ataxia	0	1 (2.9%)	1 (3.1%)
Anxiety	0	1 (2.9%)	0
Vertigo	0	1 (2.9%)	0
Altered Mental Status	0	0	1 (3.1%)
Respiratory			
Upper Respiratory Infection[5]	0	0	1 (3.1%)
Skin			
Rash/Maculopapular Rash	0	1 (2.9%)	0
Special Senses			
Excess Tearing	0	0	1 (3.1%)
Conjunctivitis	0	0	1 (3.1%)
Urogenital			
Urinary Tract Infection	0	1 (2.9%)	0
Hydronephrosis	0	0	1 (3.1%)

[1]Pain includes back, bone, chest, flank, kidney, neck, and pelvic pain as well as pain.
[2]Asthenia includes asthenia, malaise, and somnolence where the verbatim term is lethargy or fatigue.
[3]Ileus includes ileus and intestinal obstruction, but excludes biliary obstruction.
[4]Healing abnormal includes wound dehiscence and eye disorder where eye disorder involves abnormal scarring of the lacrimal ducts.
[5]Upper respiratory infection includes bronchitis, ear pain, flu syndrome, infection, lung disorder, pharyngitis, rhinitis, sinusitis, and viral syndrome where these involve infection of the upper respiratory tract.

The overall incidence of grade 3 adverse events is increased in the bevacizumab arms. This is primarily due to an increase in pain, asthenia, hypertension, and deep vein thrombosis. It is interesting to note that in the 5 mg/kg arm, the arm with the highest response rate, has an increased rate of asthenia. Hypertension and thrombosis will be discussed further below.

Grade 1-4 Adverse Events

Adverse events that are increased by ≥ 5% in either of the bevacizumab arms compared to control are presented below.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Body as a Whole			
Pain[1]	16 (45.7%)	19 (54.3%)	17 (53.1%)
Fever	4 (11.4%)	13 (37.1%)	11 (34.4%)
Headache/Migraine	5 (14.3%)	11 (31.4%)	13 (40.6%)
Chills	1 (2.9%)	5 (14.3%)	5 (15.6%)
Injection Site Reaction	0	0	2 (6.3%)
Allergic Reaction	0	2 (5.7%)	0
Cardiovascular			
Hypertension	1 (2.9%)	4 (11.4%)	9 (28.1%)
Tachycardia	1 (2.9%)	3 (8.6%)	3 (9.4%)
Deep Vein Thrombosis	0	4 (11.4%)	0
Vasodilatation	0	3 (8.6%)	0
Palpitation	0	2 (5.7%)	0
Arrhythmia	0	0	2 (6.3%)
Poor Venous Access	0	0	2 (6.3%)
Digestive			
Diarrhea[2]	29 (82.9%)	32 (91.4%)	24 (75.0%)
Nausea	24 (68.6%)	27 (77.1%)	23 (71.9%)
Stomatitis/Mucositis	13 (37.1%)	16 (45.7%)	13 (40.6%)
Vomiting	12 (34.3%)	16 (45.7%)	14 (43.8%)
Constipation	6 (17.1%)	9 (25.7%)	10 (31.3%)
GI Hemorrhage[3]	1 (2.9%)	11 (31.4%)	12 (37.5%)
Gum Hemorrhage	0	3 (8.6%)	2 (6.3%)
Dysphagia	0	2 (5.7%)	1 (3.1%)
Fecal Incontinence	0	2 (5.7%)	1 (3.1%)
Liver Tenderness	0	2 (5.7%)	1 (3.1%)
Ileus[4]	0	3 (8.6%)	1 (3.1%)
Jaundice	0	2 (5.7%)	0
Periodontal Abscess	0	1 (2.9%)	2 (6.3%)
Thirst	0	0	3 (9.4%)
Colitis	0	0	2 (6.3%)
Hemic/Lymphatic			
Leukopenia	1 (2.9%)	4 (11.4%)	1 (3.1%)
Lymphadenopathy	0	2 (5.7%)	0
Metabolic/Nutrition			
Hyperglycemia	2 (5.7%)	6 (17.1%)	0
Hypokalemia	2 (5.7%)	4 (11.4%)	5 (15.6%)
Healing Abnormal[5]	0	4 (11.4%)	2 (6.3%)

Hyperuricemia	0	2 (5.7%)	0
Weight Gain	0	2 (5.7%)	0
Musculoskeletal			
Arthritis/Arthralgia	3 (8.6%)	4 (11.4%)	6 (18.7%)
Myalgia[6]	2 (5.7%)	0	5 (14.3%)
Myasthenia	0	2 (5.7%)	2 (6.3%)
Nervous			
Dizziness	6 (17.1%)	8 (22.9%)	7 (21.9%)
Amnesia	2 (5.7%)	0	4 (12.5%)
Ataxia	0	2 (5.7%)	1 (3.1%)
Nervousness	0	2 (5.7%)	1 (3.1%)
Respiratory			
Upper Respiratory Infection[7]	14 (40.0%)	23 (65.7%)	19 (59.4%)
Cough Increased	5 (14.3%)	9 (25.7%)	8 (25.0%)
Epistaxis	3	16 (45.7%)	17 (53.1%)
Dyspnea	3 (8.6%)	7 (20.0%)	5 (15.6%)
Hiccup	0	3 (8.6%)	1 (3.1%)
Voice Alteration	0	1 (2.9%)	2 (6.3%)
Skin			
Rash/Maculopapular Rash	7 (20.0%)	16 (45.7%)	12 (37.5%)
Pruritis	1 (2.9%)	6 (17.1%)	6 (18.8%)
Skin Ulcer	1 (2.9%)	4 (11.4%)	1 (3.1%)
Sweating	1 (2.9%)	3 (8.6%)	2 (6.3%)
Vesiculobullous Rash	0	2 (5.7%)	2 (6.3%)
Special Senses			
Excess Tearing	3 (8.6%)	4 (14.3%)	6 (18.8%)
Dry Eyes	0	3 (8.6%)	2 (6.3%)
Taste Loss	0	3 (8.6%)	0
Eye Disorder	0	0	3 (9.4%)
Urogenital			
Urinary Tract Infection	2 (5.7%)	5 (14.3%)	2 (6.3%)
Hydronephrosis	0	2 (5.7%)	1 (3.1%)

[1]Pain includes back, bone, chest, flank, neck, and pelvic pain as well as pain.
[2]Diarrhea includes diarrhea, enteritis, and gastroenteritis.
[3]Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, hematemesis, hemorrhage (where it is gastrointestinal), melena, and rectal hemorrhage.
[4]Ileus includes ileus and intestinal obstruction. It excludes biliary obstruction.
[5]Healing abnormal includes healing abnormal and eye disorder where the verbatim term is scar tissue over lacrimal ducts.
[6]Myalgia includes myalgia and hypertonia where the verbatim term is muscle spasm.
[7]Upper respiratory infection includes bronchitis, ear pain, flu syndrome, infection, lung disorder, pharyngitis, rhinitis, sinusitis, and viral syndrome where these involve infection of the upper respiratory tract.

In this table, several additional adverse events become prominent. These include fever, headache, chills, allergic reaction, gastrointestinal hemorrhage, ileus, leukopenia, upper respiratory infection, cough increased, epistaxis, dyspnea, and hydronephrosis.

An increase in serious adverse events and grade 3-4 events related to leukopenia is noted in the 5 mg/kg arm. The increase in leukopenia does not appear to be dose related, making the association more tenuous. The cause of this increase is unclear, but it is noted that most events occurred within one to three months of initiation of therapy (as opposed to leukopenia with the first or second dose). The small number of patients involved makes determination of causality difficult.

Ileus is also increased in the bevacizumab arms when compared to control and again is primarily increased in the 5 mg/kg arm. Note that diarrhea is also increased in this arm when compared to control and to 10 mg/kg suggesting that there is an association between diarrhea and ileus.

The cause of the increase in upper respiratory infections seen in the bevacizumab arms is unclear. These are primarily events captured as rhinitis, pharyngitis, and infection where the verbatim term is upper respiratory infection or cold. To evaluate whether events such as rhinitis were related to a syndrome of infusion associated adverse events, rhinitis and rash were examined for their temporal association. These events were temporally associated in only one patient.

Crossover

Adverse events reported in more than 10% of the crossover population (more than two patients) are identified in the table below.

	Crossover N = 22
Body as a Whole	
Pain[1]	15 (68.2%)
Abdominal Pain	11 (50.0%)
Asthenia[2]	10 (45.5%)
Fever	3 (13.6%)
Headache/Migraine	3 (13.6%)
Cardiovascular	
Hypertension	5 (22.7%)
Digestive	
Nausea	10 (45.5%)
Anorexia	8 (36.4%)
Diarrhea[3]	8 (36.4%)
Vomiting	6 (27.3%)

Constipation	5 (22.7%)
Dyspepsia	5 (22.7%)
Dry Mouth	3 (13.6%)
Hepatomegaly	3 (13.6%)
Stomatitis/Mucositis[4]	4 (18.2%)
Hemic/Lymphatic	
Anemia/Hypochromic Anemia	3 (13.6%)
Metabolic/Nutrition	
Weight Loss	5 (22.7%)
Edema[5]	5 (22.7%)
Nervous	
Insomnia	5 (22.7%)
Anxiety	3 (13.6%)
Depression	3 (13.6%)
Neuropathy[6]	3 (13.6%)
Musculoskeletal	
Arthritis/Arthralgia	3 (13.6%)
Respiratory	
Upper Respiratory Infection[7]	3 (13.6%)
Dyspnea	3 (13.6%)
Epistaxis	3 (13.6%)
Skin	
Rash/Maculopapular Rash	3 (13.6%)

[1]Pain includes back, bone, chest, flank, neck, and pelvic pain as well as pain.
[2]Asthenia includes asthenia, malaise, and somnolence where the verbatim term is lethargy or fatigue.
[3]Diarrhea includes diarrhea, enteritis, and gastroenteritis.
[4]Stomatitis includes stomatitis, ulcerative stomatitis, mucous membrane disorder, and mouth ulceration where the cause is non-infectious.
[5]Edema includes edema, generalized edema, peripheral edema, genital edema, and scrotal edema.
[6]Neuropathy includes neuropathy, paresthesias and peripheral neuritis where the verbatim term is peripheral neuropathy.
[7]Upper respiratory infection includes bronchitis, ear pain, flu syndrome, infection, lung disorder, pharyngitis, rhinitis, sinusitis, and viral syndrome where these involve infection of the upper respiratory tract.

When compared to the previous pattern of adverse events in these patients, headache and hypertension have increased. Note that diarrhea and stomatitis are reported in this population despite the discontinuation of chemotherapy. Most of these events are recorded in cycle one of crossover and may be a residual effect of chemotherapy. However, events are recorded as late as cycles 3 and 4.

Laboratory Abnormalities

The sponsor provided information on abnormal laboratory values in the three arms. Decreases in serum calcium and sodium were seen primarily in the 5 mg/kg arm. New cases of hypoalbuminemia were seen in 6% of patients in the 5 mg/kg arm. It was not seen in the control or 10 mg/kg group. Grade 3-4 neutropenia occurred in 3% of patients in the control arm, 14% in the 5 mg/kg arm, and 5% in the 10 mg/kg arm.

Additional Adverse Events of Interest

Abnormal Healing

Three patients had difficulty with wound healing. In one patient, it was noted that their abdominal scar opened and drained with heavy lifting. A second patient, 6618, was also noted to have wound drainage. One grade 3 event is included in this group. Patient 6613 developed fascial dehiscence 41 days after her initial surgery. She had received her first dose of bevacizumab 30 days after the initial surgery. However, three days prior to her first dose of bevacizumab, she was noted to have remaining open areas in her incision. This progressed to fascial dehiscence on therapy. Bevacizumab was held in this patient until the wound was completely healed and she was able to resume study drug without further complications.

Thromboembolism

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Overall	3 (8.6%)	9 (25.7%)	4 (12.5%)
Cerebrovascular Accident	0	0	1
Transient Ischemic Attack	1	0	1
Pulmonary Embolism	0	0	1
Thromboembolism	1	1	1
Deep Vein Thrombosis	0	4	
Intra-Abdominal Thrombosis	0	1	
Line Related Thrombosis	0	1	
Thrombophlebitis	1	1	1

There is an overall increase in the incidence of thromboembolism in the bevacizumab arms. However, this increase is largely confined to the 5 mg/kg arm and is primarily due to an increase in the incidence of deep venous thrombosis.

While there is not a clear increase in the absolute incidence, the patterns and presentations of thrombosis should also be examined.

- In the control arm, two patients developed significant thromboembolic events. One patient had a transient ischemic attack and a second a retinal vein thrombosis. No information is available concerning the transient ischemic attack. The patient with retinal vein thrombosis, 6109, had a past history of congestive heart failure and hypertension. The event occurred while the patient was on the control arm and did not worsen with crossover to bevacizumab 10 mg/kg every two weeks.
- In the 5 mg/kg arm, a superior mesenteric vein thrombosis was found on routine CT scan in one patient. A second patient developed a femoral artery embolus (origin unknown) followed a prolonged hospitalization. The patient was also noted to be lethargic at the time the femoral artery embolism became apparent. It is unknown whether additional embolization to the brain may have occurred.
- In the 10 mg/kg arm, one patient had a transient ischemic attack and one a cerebrovascular accident. The transient ischemic attack involved hypertension and dizziness requiring hospitalization. It should be noted that the patient in the 10 mg/kg arm with a fatal pulmonary embolism also had a left ventricular thrombosis. During the extension phase of the study, one patient in this arm had a myocardial infarction.
- One patient in the control arm had angina following crossover to single agent bevacizumab.

Hemorrhage

Hemorrhage was also seen in this study and should be examined further.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Overall	10	22	25
Epistaxis	4	16	17
Gum Hemorrhage	0	3	2
Vaginal Hemorrhage	1	1	0
Gastrointestinal Hemorrhage	1	11 (1)	12 (3)
Hematuria	4	1	0
Hemoptysis	0	0	1
Other[1]	2	0	0

[1]Includes hematoma and drainage from umbilicus

The majority of bleeding events involved low grade bleeding from the nose and to a much lesser extent from the gums and vagina. Rectal hemorrhage, typically hemorrhoidal bleeding, was also seen.

The majority of gastrointestinal hemorrhagic events involve low grade rectal bleeding. However, four patients had a grade 3-4 hemorrhage.

- One patient in the 5 mg/kg arm developed multiple esophageal ulcers.

- Three patients in the 10 mg/kg arm had significant gastrointestinal bleeding. One patient had a Mallory-Weiss tear not associated with retching. A second had hematemesis associated with retching. A third patient presented with diarrhea and melena.
- One patient developed anemia associated with a gastric ulcer during crossover to single agent bevacizumab.

Hypertension

An increased incidence of hypertension was noted in the bevacizumab arms.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Hypertension	1 (2.9%)	4 (11.4%)	9 (21.9%)
Gr 1	1	1	1
Gr 2	0	0	0
Gr 3	0	2	8
Gr 4	0	1	0

The increase in hypertension is seen in both bevacizumab arms and appears to be dose related. Note, however, that the only grade 4 event occurred in the 5 mg/kg group. Patient 6610 presented with nausea, vomiting, and diarrhea. Blood pressure was elevated at 250/150 and blood sugar was also increased (value unknown). The patient did not have a history of diabetes. The patient rapidly developed increasing somnolence and renal failure, both thought to be related to the increase in blood pressure. She died of electrolyte imbalance and at autopsy the cause of death was determined to be hypertensive encephalopathy and renal failure.

Association of Headache and Hypertension

There is also an increase in the incidence of headache with the use of bevacizumab. This was reviewed for its association with hypertension. Among the 11 patients in the 5 mg/kg group with headache, two (18.2%) also had the adverse event hypertension. This is compared to an 11.4% incidence of hypertension in this group as a whole. In the 10 mg/kg group, seven of the 13 patients (53.8%) with headache also had hypertension. This compares with a 28.1% incidence of hypertension in the 10 mg/kg group as a whole. If the number of patients with hypertension is reviewed, the results are as follows. Among the four patients with hypertension in the 5 mg/kg group, two had headache. The incidence of headache in the 5 mg/kg group is 31.4%. Among the nine patients with hypertension in the 10 mg/kg arm, seven had headache. The incidence of headache in the 10 mg/kg group is 40.6%. This suggests that there is an association between the development of headache and hypertension although hypertension is not associated with each event and the number of patients involved is small.

Association of Epistaxis and Hypertension

A similar comparison was performed in patients with epistaxis. Thirty-seven patients had epistaxis, four in the control, 16 in the 5 mg/kg, and 17 in the 10 mg/kg arm. Among the 16 patients with epistaxis in the 5 mg/kg group, three had hypertension (18.8%). The incidence of hypertension is 11.4% in the group as a whole. Among the 17 patients with epistaxis in the 10 mg/kg group, seven had hypertension (21.9%). This is identical to the incidence of hypertension in the group as a whole.

Proteinuria

On this study, urine dipsticks were obtained every eight weeks and 24 hour urines were not required. All patients had negative or trace urine dipsticks at baseline. The number of patients with a positive value is listed by arm in the following table.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32
Urine Dipstick[1]			
1+	4	1	3
2+		4	3
3+		2	3
4+			

[1]This table converts patients with a urine dipstick value expressed as mg/dL into 1+, 2+, etc.

Six patients on this study had a 24 hour urine collection. These values ranged from 403 mg to 1365 mg. Two patients had 24 hour collections done before and after bevacizumab infusion. Results did not change with infusion.

Hydronephrosis was also seen in this study. This involved three patients, two in the 5 mg/kg and one in the 10 mg/kg arm. One patient had a pelvic mass and two had stents in place at the time of the event.

Congestive Heart Failure

One patient in the 10 mg/kg arm experienced heart failure during the study period and a second patient in the control arm with a history of heart failure developed hypertension and dyspnea during the crossover portion of the study. During the study period, patient 6602 presented with dyspnea and bilateral effusions. The case report tabulations give the patient's diagnosis as congestive heart failure, but notes that a thoracentesis is planned. The patient narrative included in the final study report does not include information on heart failure or the thoracentesis. One patient who experienced hypertension and dyspnea after crossover had a past history of congestive failure.

Allergic Reaction

The following adverse events were examined to assess for and characterize allergic reactions: fever, chills, rash, urticaria, dyspnea, and asthma. Two patients were considered to have an allergic reaction. One was reported to be a reaction to contrast dye. The second was reported as "allergies" and was not considered to be related to study drug. One patient developed urticaria on the foot during the crossover portion of the study. This event was considered unrelated to bevacizumab by the investigator. Three patients had the adverse event asthma. One of these events is considered to be possibly related to bevacizumab by the investigator. The verbatim term in this patient is "lungs occasional wheezes". The event began seven days after bevacizumab dosing. The table below illustrates the distribution of fever, chills, rash, and dyspnea.

	5FU/LV N = 35	5 mg/kg N = 35	10 mg/kg N = 32	Crossover N = 22
Fever				
Gr 1	2	9	6	1
Gr 2	2	4	5	2
Gr 3	0	0	1	0
Gr 4	0	0	0	0
Chills				
Gr 1	1	5	3	0
Gr 2	0	0	2	0
Gr 3	0	0	0	0
Gr 4	0	0	0	0
Rash				
Gr 1	6	12	10	3
Gr 2	1	3	2	0
Gr 3	0	0	0	0
Gr 4	0	1	0	0
Dyspnea				
Gr 1	0	4	4	2
Gr 2	2	2	1	0
Gr 3	1	0	0	0
Gr 4	0	0	0	0

All of these events are increased when compared to control. However, the majority of events are considered to be unrelated to study drug with 50 of 154 events considered to be possibly related and two considered to be probably related to bevacizumab. The two events thought to be probably related were reviewed further. Patient 6552 had grade 2 fever. This was not associated with other symptoms of an allergic reaction. One of six events in this patient occurred on the day of dosing. Patient 6651 had acral erythema that in the case report tabulations is considered to be probably related. However, on review of the case report form, this event is considered not related.

6.2 Summary of Clinical Safety

The Summary of Clinical Safety includes a review of safety information obtained under BB-IND 7921 as well as information from the Genentech database.

Integrated Summary of Safety

The Integrated Summary of Safety is based on baseline entry data and post-treatment safety information obtained from 1032 patients treated with bevacizumab in Genentech-sponsored studies. This database is supplemented with baseline entry data and post-treatment safety information in individual study report datasets for patients in the control arms of Genentech-sponsored studies (listed below). FDA also reviewed selected safety information submitted to the NCI-sponsored IND for bevacizumab, BB-IND 7921.

Patient Population

Genentech provided baseline entry and post-treatment safety information in the form of tabular line listings, analyses, and narrative summaries for serious adverse events from the following studies in a dataset and report of the Integrated Summary of Safety (ISS) for bevacizumab.

ISS Database- Genentech-Sponsored Studies

1. AVF737g: Patients with advanced malignancies received Bevacizumab 0.1, 0.3, 1, 3, or 10 mg/kg bevacizumab on days 1, 28, 35, and 42.

2. AVF761g: Patients whose solid tumors will be treated with doxorubicin, carboplatin/paclitaxel, or 5-fluorouracil/leucovorin received, in addition, bevacizumab 3 mg/kg weekly.

3. — Patients with newly diagnosed Stage IIIB or IV non-small cell lung cancer were randomized to carboplatin and paclitaxel, carboplatin/paclitaxel plus bevacizumab 7.5 mg/kg every three weeks, or carboplatin/paclitaxel plus bevacizumab 15 mg/kg every three weeks.

4. — Patients with — were treated with bevacizumab 10 mg/kg every two weeks.

5. — Patients with — who progressed following treatment with an anthracycline and/or taxane received bevacizumab 3, 10, or 20 mg/kg every two weeks.

6. AVF778g: Phase 2 extension study

7. AVF780g: Patients with newly diagnosed Stage IV colorectal cancer were randomized to 5-fluorouracil and leucovorin (5FU/LV), 5FU/LV plus bevacizumab 5 mg/kg every two weeks, or 5FU/LV plus bevacizumab 10 mg/kg every two weeks.

8. AVF2119g: Patients with metastatic breast cancer who progressed following treatment with an anthracycline and a taxane were randomized to capecitabine or capecitabine plus bevacizumab 15 mg/kg every three weeks.

9. AVF2107g: Patients receiving initial treatment for metastatic colorectal cancer were randomized to irinotecan, 5FU, and leucovorin (IFL) vs. IFL plus 5 mg/kg bevacizumab every two weeks vs. 5FU/LV plus bevacizumab 5 mg/kg every two weeks.

Following disease progression on conventional chemotherapy, patients in the control (non-bevacizumab containing) arms of Phase 2 studies were permitted to receive single agent bevacizumab during the regular study period. Following treatment in the parent study, patients in the bevacizumab arms and those originally in the control arm who had crossed over to single agent bevacizumab could enter the extension protocol. Data from both the regular study period and the extension study is included under the parent study in the case report tabulations. However, data obtained during the extension period is not included in the final study report of the parent study, but is included in the final study report of the extension study.

Individual Study Datasets from Genentech-Sponsored Studies

Genentech provided baseline entry and post-treatment safety information in the form of tabular line listings for both the control group and the bevacizumab-treated groups in the following studies:

- —
- AVF780g
- AVF2107g
- AVF2119g

Genentech also provided baseline entry and post-treatment safety information in the form of tabular line listing for the following single arm studies:

- —
- AVF761g
- —
- —

Limited Data from Other Genentech-Sponsored Studies

Additional information was submitted in a safety update amendment to the BLA received on November 20, 2003.

A preliminary report was provided for the Phase 2 extension study AVF778g. Data was not provided for the Phase 3 extension study, AVF2540g. Serious adverse event information was provided for AVF2192g, a Phase 2 study which randomized patients with metastatic colorectal cancer to 5FU/LV with or without bevacizumab 5 mg/kg every two weeks.

Data from NCI-Sponsored Studies

The National Cancer Institute (NCI) extramural program also holds an IND for bevacizumab (BB-IND 7921). As of May 30, 2003, 32 studies, involving 1870 patients were initiated or completed under BB-IND 7921. The NCI granted FDA permission to access safety information submitted to BB-IND 7921 in support of STN 125085. The safety information was submitted to BB-IND 7921 on September 30, 2003 and consisted of the following:

- All serious and unexpected adverse events submitted by investigators to the NCI Adverse Events Expedited Reporting System (AdEERS) database through May 30, 2003.
- Individual study report information limited to tabular listings of baseline entry information, adverse event reports, and limited laboratory data for the following studies:

    - E3200: A Phase 3 study in patients with metastatic colorectal cancer who have failed irinotecan based therapy in which patients are randomized to FOLFOX4 with and without bevacizumab or to bevacizumab alone.

    - T98-0035: A Phase 2, dose-ranging, placebo-controlled single institution study of single agent bevacizumab (3 or 10 mg/kg every two weeks) in the treatment of patients with metastatic renal cell carcinoma.

    - Study 2940: A single arm study of bevacizumab 10 mg/kg in combination with high-dose cytarabine and mitoxantrone for the treatment of relapsed/ refractory acute non-lymphocytic leukemia

    - Study 2772: A single arm study of bevacizumab 15 mg/kg followed by bevacizumab, docetaxel, and doxorubicin every three weeks prior to loco-regional therapy in patients with inflammatory breast cancer

- Study 2722: A single arm study of bevacizumab 10 mg/kg every two weeks in combination with docetaxel in patients with locally advanced breast cancer

Applicant's Dataset and Analyses

Genentech organized the dataset in terms of the underlying disease (colorectal versus other cancers) and across non-colorectal cancers by the regimen (bevacizumab alone or in combination with chemotherapeutic agents). Of note, 23 (14.6%) of the 157 patients in the "single agent" group have colorectal cancer.

The table below illustrates the studies, disease types, and number of patients included in each Treatment/Disease grouping.

Number of Patients in the ISS Database by Disease/Treatment Group Category and Individual Study		
Disease/Treatment Group and Study	Disease	Number of Bevacizumab Treated Patients
Colorectal Studies		568
AVF2107g	Colorectal	501
AVF780g	Colorectal	67
In Combination with Chemotherapy		307
AVF2119g	Breast	229
—	Non-Small Cell Lung	66
AVF761g	Solid Tumors	12
As a Single Agent		157
AVF737g	Solid Tumors	25
—	—	15
—	Breast	75
AVF780g	Crossover Colorectal	22
—	Crossover Non-Small Cell Lung	19
AVF780g	Extension Colorectal	1
Total		1032

For patients randomized to the bevacizumab containing arm, data from the extension study is included within the parent study and presented under Combination Therapy in the table above. For patients randomized to the control arm of Phase 2 studies who crossed over to single agent bevacizumab, data from both the parent and the extension study is presented under Single Agent therapy.

Approximately one-quarter of the patients in the Single Agent group were originally randomized to the control arms of —— and AVF780g. The one patient in AVF780g listed as Extension Colorectal was also originally randomized

to on the control arm, but crossed over at the end of the regular study period to single agent bevacizumab.

When inspecting analyses of toxicity by diagnosis/treatment group, it is important to note that the assessment for toxicity, protocol specified monitoring and monitoring schedule, differed by study. In addition, the groups differ in terms of duration of bevacizumab dosing, dose and schedule of bevacizumab, and concomitant anti-neoplastic treatment, as well as, underlying cancer subtype. Thus all analyses by diagnosis/treatment groupings should be considered exploratory and comparisons between groups should be interpreted cautiously.

Duration of Bevacizumab Administration

Duration of Bevacizumab Dosing as a Function of Diagnosis/Treatment Group				
	Colorectal	Combination	Single Agent	Total
Duration				
Mean (months)	10.5	6.4	3.6	8.2
Median (months) (25 ;75 quartiles)	9 (4;16)	5 (2;9)	2 (1;4)	6 (2;13)
≤ 12 Months	60.7%	85%	94.3%	73.1%
> 12 Months	39.3%	15%	5.7%	26.9%

The duration of bevacizumab dosing varies greatly between diagnosis/treatment groups. Visual inspection of differences in the incidences of toxicities between such groupings should be interpreted cautiously and consider the potential contribution of variations in duration of dosing in any between group differences.

Exposure by Dose

Several doses and schedules of bevacizumab were studied in the development period. The average weekly dose by study is displayed in the following table. Note that the following patients were not included in this analysis:

- 25 patients enrolled in the Phase 1 study, AVF737g
- 12 patients enrolled in a second Phase 1 study, AVF761g
- 42 patients who crossed over from the control arm of randomized Phase 2 studies to single agent bevacizumab
- Patients who developed adverse events during Treatment Period 2

While analyses by average weekly dose permit the exploration of dose-response relationships, visual inspection of differences in the incidences of toxicities as a function of average weekly dose should be interpreted cautiously, given that the assessment of average weekly dose assumes that exposure is more predictive of toxicity than C_{max} or other pharmacokinetic parameters.

Average Weekly Dose of Bevacizumab in Genentech-sponsored Studies (ISS database)				
Study	1.5 mg/kg/wk	2.5 mg/kg/wk	5 mg/kg/wk	10 mg/kg/wk
—	0	32	34	0
—	0	0	15	0
—	18	0	41	16
AVF780g	0	35	32	0
AVF2119g	0	0	229	0
AVF2107g	0	501	0	0
Total	18	568	351	16

Given the small numbers of patients in the 1.5 and 10 mg/kg/week groups (comprised entirely of 34 patients in — who were treated with 3 and 20 mg/kg/week every two weeks) were also excluded from further analyses.

The 2.5 and 5 mg/kg/week groups include 919/1032 (89.1%) of the ISS database. Genentech utilized this subgroup to investigate relationships between dose and targeted adverse events, grade 1-4 hypertension, proteinuria, thromboembolism and grade 3-4 hemorrhage.

Demographics

	Colorectal	Combination	Single Agent	Total
Age				
Median yrs (25-75)	61 (23-88)	53 (27-80)	54 (21-83)	57 (21-88)
Gender				
Male	330 (58.1%)	41 (13.4%)	54(34.4%)	425 (41.2%)
Female	238 (41.9%)	266 (86.6%)	103 (65.6%)	607 (58.8%)
Race				
White	448 (78.9%)	251 (81.8%)	137 (87.3%)	836 (81.0%)
Black	68 (12.0%)	38(12.4%)	12 (7.6%)	118 (11.4%)
Hispanic	27 (4.8%)	9(2.9%)	3(1.9%)	39 (3.8%)
Asian	19 (3.3%)	8(2.6%)	2(1.3%)	19 (2.8%)
Other	6 (1.1%)	1(0.3%)	3(1.9%)	10 (1.0%)
Weight (kg)				
Median	77	69	70	74
Performance Status				
0	328 (57.8%)	157 (51.1%)	88 (56.1%)	573 (55.6%)
1	236 (41.6%)	144 (46.9%)	68 (43.3%)	448 (43.5%)
2	3 (0.5%)	6(2.0%)	1 (0.6%)	10 (1.0%)
Medical History				
Thrombosis	21 (3.7%)	13(4.2%)	4 (2.5%)	38 (3.7%)
Prior Cancer Treatment	248 (43.7%)	74(24.4%)	42 (26.8%)	365 (35.4%)

Hypertension				
Yes	494(87.1%)	261 (85.0%)	143 (91.1%)	898 (87.1%)
No	73(12.9%)	46 (15.0%)	14 (8.9%)	133 (12.9%)
Tumor Type				
Colon	568(100%)	3 (1.0%)	23 (14.6%)	594 (57.6%)
Breast	0	230(74.9%)	80 (51.0%)	310 (30.0%)
Lung	0	68 (22.1%)	21 (13.4%)	89 (8.6%)
Other	0	6 (2.0%)	33 (21.0%)	39 (3.8%)

Patients in the Colorectal group were older and had a higher proportion of males. The Combination and Single Agent group is largely composed of females, approximately 75% of patients in the Combination and 50% of those in the Single Agent group, who had metastatic breast cancer. Also note that a higher proportion of patients in the Colorectal group had a history of hypertension. The proportion of patients with a history of thrombosis was low and similar in all three groups.

Safety

The incidence of adverse events in the overall population and in the three subgroups was determined by organ system and severity (NCI common toxicity criteria grading scale). The incidence of all adverse events and adverse events associated with death, serious outcomes, discontinuation of bevacizumab, and those of grade 3 or 4 severity were calculated using the ISS database. The ISS database, data from individual studies (both Genentech-sponsored and NCI-sponsored), and the NCI AdEERS database was used to characterize the incidence of "targeted adverse events". This data was also used to characterize additional adverse events identified during the conduct of the major efficacy trial and other clinical trials. Targeted adverse events, hypertension, proteinuria, and thromboembolic events were pre-specified prior to initiation of the major efficacy study (AVF2107g). Because of heightened interest, specific monitoring for these events was included in some but not all trials in the development program. For each of the targeted adverse events, medically significant events from the Genentech and NCI databases are summarized.

The applicant conducted a series of exploratory, post-hoc analyses to further characterize targeted adverse events. These include assessment of incidence by average weekly dose, time to onset of event, and assessment for factors associated with the targeted event. These analyses are presented for information only. Due to the exploratory nature, conclusions regarding risk factors (including dose) cannot be drawn. A number of post-marketing studies will be conducted to obtain additional data for characterization of these events.

FDA and the applicant conducted analyses of the incidence of overall and severe adverse events as a function of age, gender, and race. Only those events that

differed in absolute incidence between subgroups in these exploratory analyses are presented.

Deaths

Investigator-Assessed Cause of Death Overall and by Diagnosis/Treatment Subgroup				
	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Total	309 (54.4%)	195 (63.5%)	72 (45.9%)	576 (55.8%)
Cause of Death (% of all deaths)				
Progressive Disease	282 (91.3%)	177 (90.8%)	72 (100%)	531 (92.2%)
Bleeding	1 (0.3%)	3 (1.5%)	0	4 (0.7%)
Cardiac	5 (1.6%)	0	0	5 (0.9%)
Infection	7 (2.3%)	2 (1.0%)	0	9 (1.6%)
Pulmonary Embolism	3 (1.0%)	0	0	3 (0.5%)
Ischemic Bowel	1 (0.3%)	0	0	1 (0.2%)
Other	5 (1.6%)	8 (4.1%)	0	13 (2.3%)
Unknown	5 (1.6%)	5 (2.6%)	0	10 (1.7%)

Serious Adverse Events

Serious adverse events are defined as events resulting in death, permanent disability, hospitalization, or requiring medical intervention to avoid death, disability or hospitalization. The following table lists all serious adverse events reported in $\geq$ 2% of patients in the ISS database overall or in one of the Diagnosis/Treatment subgroups.

Number and Percentage of Serious Adverse Events Occurring in $\geq$ 2% of Bevacizumab-Treated Patients in All Genentech-sponsored Studies and by Diagnosis/Treatment Subgroups				
	Colorectal N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	311 (54.8%)	102 (33.2%)	37 (23.6%)	450 (43.6%)
Body as a Whole				
Abdominal Pain	27 (4.8%)	4 (1.3%)	2 (1.3%)	33 (3.2%)
Sepsis	19 (3.3%)	5 (1.6%)	1 (0.6%)	25 (2.4%)
Fever	14 (2.5%)	5 (1.6%)	0	19 (1.8%)
Cardiovascular				
Deep Vein Thrombosis	46 (8.1%)	8 (2.6%)	3 (1.9%)	57 (5.5%)
Pulmonary Embolus	19 (3.3%)	4 (1.3%)	0	23 (2.2%)
Thrombophlebitis	13 (2.3%)	2 (0.7%)	0	15 (1.4%)
Myocardial Infarction	12 (2.1%)	0	1 (0.6%)	13 (1.3%)
Hypertension	6 (1.1%)	1 (0.3%)	5 (3.2%)	12 (1.2%)
Digestive				
Diarrhea	69 (12.0%)	9 (2.9%)	1 (0.6%)	79 (7.7%)
Ileus	34 (6.0%)	2 (0.7%)	0	36 (3.5%)

Vomiting	20 (3.5%)	3 (1.0%)	1 (0.6%)	24 (2.3%)
Hemic/Lymphatic				
Leukopenia	32 (5.6%)	8 (2.6%)	0	40 (3.9%)
Metabolic/Nutrition				
Dehydration	22 (3.9%)	0	0	22 (2.1%)
Respiratory				
Dyspnea	6 (1.1%)	7 (2.3%)	1 (0.6%)	14 (1.4%)
Pneumonia	6 (1.1%)	2 (0.7%)	5 (3.2%)	13 (1.3%)

The reported incidence of all serious adverse events is higher in the Colorectal subgroup as compared to other subgroups, with the exception of dyspnea (highest incidence in the Combination therapy subgroup) and pneumonia and hypertension (highest incidences are in the Single Agent subgroup).

Many of the serious adverse events occurring at a higher incidence in the Colorectal group may be also be associated with the underlying disease or chemotherapeutic regimen. An exception to this may be deep venous thrombosis which is not expected to occur at a higher patients with colorectal cancer as compared to other primary cancers.

With regard to the higher incidence of hypertension as a serious adverse event in the Single Agent subgroup, it is possible that since single agent studies were performed earlier in the drug development program; patients may have been more likely to be hospitalized for the very high blood pressure readings seen with bevacizumab. It is notable that the incidence of NCI CTC grade 3 or 4 hypertension is similar across the subgroups and lowest in incidence in the Single Agent subgroup (16.5% vs. 18.2% vs. 13.4%).

Note that one patient in the Single Agent group developed leukopenia. This patient received bevacizumab in combination with chemotherapy on the extension study.

Serious Adverse Events on AVF780g by treatment arm (See AVF780g study report in Section 6.1)

Serious Adverse Events on AVF2107g by treatment arm (See AVF2107g study report in Section 6.1)

Serious Adverse Events on AVF2192g by Treatment Arm

AVF2192g randomizes patients with newly diagnosed metastatic colorectal cancer who cannot tolerate IFL to 5FU/LV with or without bevacizumab 5 mg/kg every two weeks. The incidence of serious adverse events that occurred in more than 2% of patients is included below, by treatment arm.

Number and Percentage of Patients with Serious Adverse Events Occurring in >2% of Patients in AVF2192g by Treatment Arm		
	5FU/LV/Placebo N = 104	5FU/LV/Bevacizumab N = 100
Overall	53 (51.0%)	73 (73.0%)
Body as a Whole		
Sepsis	4 (3.8%)	7 (7.0%)
Pain	3 (2.9%)	5 (5.0%)
Abdominal Pain	2 (1.9%)	2 (2.0%)
Accident	1 (1.0%)	4 (4.0%)
Cardiovascular		
Deep Thrombophlebitis	10 (9.6%)	8 (8.0%)
Pulmonary Embolism	3 (2.9%)	5 (5.0%)
Myocardial Ischemia	3 (2.9%)	4 (4.0%)
Cerebrovascular Ischemia	2 (1.9%)	5 (5.0%)
Atrial Fibrillation	2 (1.9%)	4 (4.0%)
Hypotension	2 (1.9%)	2 (2.0%)
Syncope	0	4 (4.0%)
Congestive Heart Failure	0	3 (3.0%)
Supraventricular Tachycardia	0	2 (2.0%)
Gastrointestinal		
Diarrhea	14 (13.5%)	25 (25.0%)
Vomiting	6 (5.8%)	2 (2.0%)
Intestinal obstruction	4 (3.8%)	14 (14.0%)
Gastrointestinal Hemorrhage	3 (2.9%)	3 (3.0%)
Colitis	2 (1.9%)	3 (3.0%)
Nausea	2 (1.9%)	0
Intra-abdominal Abscess	1 (1.0%)	2 (2.0%)
Intestinal Perforation	0	2 (2.0%)
Fistula	0	2 (2.0%)
Hemic/Lymphatic		
Leukopenia	4 (3.8%)	2 (2.0%)
Anemia	0	3 (3.0%)
Metabolic/Nutrition		
Dehydration	9 (8.7%)	12 (12.0%)
Respiratory		
Pneumonia	2 (1.9%)	1 (1.0%)
Hypoxia	0	3 (3.0%)
Dyspnea	0	2 (2.0%)

Additional serious adverse events in the bevacizumab arm that occurred at a incidence of <2% (one patient each) are hemoptysis, arterial occlusion, abdominal wall abscess, and intra-abdominal hemorrhage.

In this study of patients who are unable to tolerate IFL, the overall incidence of serious adverse events in the bevacizumab arm was higher than in the other trials in colorectal cancer. The following serious adverse events occurred at a substantially increased incidence in bevacizumab-treated patients as compared to the control group: diarrhea and intestinal obstruction. Additional serious adverse events that occurred at an increased incidence in the bevacizumab arm were: cerebrovascular accidents and transient ischemic attacks grouped as cerebral ischemia above, congestive heart failure, intestinal perforation, hypoxia, and dyspnea. Given the small overall study size and the limited number of patients with certain types of events (e.g., dyspnea and hypoxia) it is difficult to determine whether the observed differences are real.

Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation in more than 1% of patients are listed in the following below.

Number and Percentage of Adverse Events Leading to Discontinuation of Study Drug in ≥ 1% of Bevacizumab-Treated Patients in All Genentech-sponsored Studies and by Diagnosis/Treatment Subgroup

	Colorectal N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	68 (12.0%)	55 (17.9%)	19 (12.1%)	142 (13.8%)
Body as a Whole				
Asthenia	8 (1.4%)	3 (1.0%)	3 (1.9%)	14 (1.4%)
Cardiovascular				
Deep Vein Thrombosis	4 (0.7%)	8 (2.6%)	0	12 (1.2%)
Hypertension	0	6 (2.0%)	3 (1.9%)	9 (0.9%)
Pulmonary Embolism	3 (0.5%)	4 (1.3%)	0	7 (0.7%)
Digestive				
Diarrhea	12 (2.1%)	0	0	12 (1.2%)
Metabolic				
Hypercalcemia	0	0	2 (1.3%)	2 (0.2%)
Urogenital				
Proteinuria	1 (0.2%)	3 (1.0%)	2 (1.3%)	6 (0.6%)

Adverse Events

Grade 3-4 Adverse Events

The following table lists all NCI CTC grade 3 and 4 adverse events, by organ system, reported in ≥ 5% of patients in the ISS database or in one of the Diagnosis/Treatment subgroups.

Number and Percentage of Grade 3 and 4 Adverse Events in ≥ 5% of Bevacizumab-Treated Patients in All Genentech-sponsored Studies and by Diagnosis/Treatment Subgroup

	Colorectal Studies N = 568	Other Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	500 (88.0%)	240 (78.2%)	73 (46.5%)	813 (78.8%)
Body as a Whole				
Asthenia[1]	72 (12.7%)	31 (10.1%)	14 (8.9%)	117 (11.3%)
Abdominal Pain	61 (10.7%)	8 (2.6%)	6 (3.8%)	75 (7.3%)
Pain[2]	56 (9.9%)	34 (11.1%)	20 (12.7%)	110 (10.7%)
Cardiovascular				
Hypertension	94 (16.5%)	56 (18.2%)	21 (13.4%)	171 (16.6%)
Deep Vein Thrombosis	50 (8.8%)	13 (4.2%)	3 (1.9%)	66 (6.4%)
Digestive				
Diarrhea[3]	216 (38.0%)	36 (11.7%)	3 (1.9%)	255 (24.7%)
Vomiting	48 (8.5%)	10 (3.3%)	1 (0.6%)	59 (5.7%)
Nausea	41 (7.2%)	15 (4.9%)	1 (0.6%)	57 (5.7%)
Ileus[4]	38 (6.7%)	4 (1.3%)	0	42 (4.1%)
Hemic/Lymphatic				
Leukopenia	172 (30.3%)	51 (16.6%)	0	223 (21.8%)
Metabolic/Nutrition				
Dehydration	48 (8.5%)	6 (2.0%)	0	54 (5.2%)
Hypokalemia	33 (5.8%)	6 (2.0%)	1 (0.6%)	40 (3.9%)
Respiratory				
Dyspnea	23 (4.0%)	34 (11.1%)	11 (7.0%)	68 (6.6%)
Skin				
Exfoliative Dermatitis	9 (1.6%)	66 (21.5%)	0	75 (7.3%)

[1]Asthenia includes asthenia, malaise, and somnolence where the verbatim term is lethargy or fatigue.
[2]Pain includes back, bone, chest, flank, kidney, neck, and pelvic pain as well as pain.
[3]Diarrhea includes diarrhea, enteritis and gastroenteritis.
[4]Ileus contains the preferred terms ileus and intestinal obstruction.

The overall incidence of Grade 3 and 4 events was lowest (46.5%) in patients receiving single agent bevacizumab. The most common serious or life-threatening adverse events in the Single Agent subgroup were hypertension and pain. In contrast to the differences in incidence of serious adverse events by subgroup, the incidences of grade 3-4 hypertension, asthenia, and pain are

similar in patients receiving single agent bevacizumab and those receiving chemotherapy plus bevacizumab. Consistent with the reported incidences of serious adverse events, the percentage of patients with deep vein thrombosis was higher in the Colorectal subgroup than in the other two subgroups.

Two patients in the single agent subgroup were reported to have grade 3-4 leukopenia. One of these patients (described in the section on serious adverse events) received concurrent chemotherapy. In the second, this was a coding error. This patient crossed over from the control arm to single agent therapy, however the adverse event resolution date is prior to the crossover date.

Grade 1-4 Adverse Events

In approximately one-quarter of the patients in the ISS database, grade 1 and 2 adverse events (except proteinuria, thromboembolism and hypertension) were not recorded on case report forms. Study AVF2107g collected grade 1 and 2 adverse events in only a subset of patients. In 290 patients enrolled in the IFL + Bevacizumab arm, only grade 3 and 4 adverse events (except proteinuria, thromboembolism, and hypertension) were collected and recorded. Genentech was asked to provide an analysis of overall adverse events that included only those subjects in the ISS dataset in which all adverse events were collected. The 290 patients from AVF2107g are omitted from the table below.

Number and Percentage of All Adverse Events in ≥10% of Bevacizumab-Treated 742 Patients in All Genentech-sponsored Studies and by Diagnosis/Treatment Subgroup

	Colorectal Studies N = 278	Other Combination N = 307	Single Agent N = 157	Total N = 742
Body as a Whole				
Asthenia[1]	217 (78.1%)	198 (64.5%)	109 (69.4%)	524 (70.6%)
Pain[2]	168 (60.4%)	176 (57.3%)	108 (68.8%)	452 (60.9%)
Abdominal Pain	149 (53.6%)	64 (20.8%)	35 (22.3%)	307 (41.4%)
Headache/Migraine	82 (29.5%)	110 (35.8%)	64 (40.8%)	256 (34.5%)
Fever	86 (30.9%)	55 (17.9%)	29 (18.5%)	183 (24.7%)
Chills	40 (14.4%)	20 (6.5%)	8 (5.1%)	68 (9.2%)
Accidental Injury	28 (10.1%)	24 (7.8%)	13 (8.3%)	65 (8.8%)
Cardiovascular				
Hypertension	88 (31.7%)	82 (26.7%)	30 (19.1%)	200 (27.0%)
Flushing	13 (4.7%)	24 (7.8%)	17 (10.8%)	54 (7.3%)
Digestive				
Diarrhea[3]	245 (88.1%)	161 (52.4%)	50 (31.8%)	456 (61.5%)
Nausea	195 (70.1%)	155 (50.5%)	69 (43.9%)	419 (56.5%)
Vomiting	135 (48.6%)	91 (29.6%)	48 (30.6%)	274 (36.9%)
Anorexia/Cachexia	110 (39.6%)	92 (30.0%)	50 (31.8%)	252 (34.0%)
Stomatitis/Mucositis	101 (36.3%)	125 (40.7%)	25 (15.9%)	251 (33.8%)
Constipation	95 (34.2%)	72 (23.5%)	45 (28.7%)	212 (28.6%)

GI Hemorrhage[4]	72	(26.0%)	22	(7.2%)	4	(2.5%)	98	(13.2%)
Dyspepsia	59	(21.2%)	40	(13.0%)	25	(15.9%)	124	(16.7%)
Flatulence	42	(15.1%)	19	(6.2%)	8	(5.1%)	69	(9.3%)
Hemic/Lymphatic								
Leukopenia	85	(30.6%)	79	(25.7%)	4	(2.5%)	168	(22.6%)
Anemia[5]	70	(25.2%)	52	(16.9%)	25	(15.9%)	147	(19.8%)
Metabolic/Nutrition								
Edema[6]	65	(23.4%)	55	(17.9%)	28	(17.8%)	148	(19.9%)
Dehydration	51	(18.3%)	21	(6.8%)	4	(2.5%)	76	(10.2%)
Weight Loss	46	(16.5%)	34	(11.1%)	23	(14.6%)	103	(13.9%)
Hypokalemia	40	(14.4 %)	14	(4.6%)	6	(3.8%)	60	(8.1%)
Musculoskeletal								
Arthralgia/Arthritis	32	(11.5%)	58	(18.9%)	49	(31.2%)	139	(18.7%)
Myalgia[7]	31	(11.2%)	58	(18.9%)	31	(19.7%)	120	(16.2%)
Nervous								
Dizziness	67	(24.1%)	41	(13.4%)	26	(16.6%)	134	(18.1%)
Insomnia	61	(21.9%)	42	(13.7%)	20	(12.7%)	123	(16.6%)
Depression	35	(12.6%)	36	(11.7%)	18	(11.5%)	89	(12.0%)
Neuropathy[8]	43	(7.6%)	87	(28.3%)	53	(33.8%)	183	(17.7%)
Hyperesthesia	3	(1.1%)	11	(3.6%)	17	(10.8%)	31	(4.2%)
Respiratory								
Upper Respiratory Infection[9]	138	(49.6%)	144	(46.9%)	84	(53.5%)	366	(49.3%)
Epistaxis	104	(37.4%)	67	(21.8%)	20	(12.7%)	191	(25.7%)
Dyspnea	72	(25.9%)	102	(33.2%)	49	(31.2%)	223	(30.1%)
Cough Increased	63	(22.7%)	70	(22.8%)	46	(29.3%)	179	(24.1%)
Skin								
Rash/Maculopapular Rash	69	(24.8%)	55	(17.9%)	24	(15.3%)	148	(20.0%)
Alopecia	46	(16.5%)	57	(18.6%)	15	(9.6%)	118	(15.9%)
Dry Skin	39	(14.0%)	14	(4.6%)	9	(5.7%)	62	(8.4%)
Exfoliative Dermatitis	34	(12.2%)	193	(62.9%)	1	(0.6%)	228	(30.7%)
Sweating	31	(11.2%)	20	(6.5%)	6	(3.8%)	57	(7.7%)
Pruritis	25	(9.0%)	18	(5.9%)	22	(14.0%)	65	(8.8%)
Special Senses								
Taste Disorder	46	(16.5%)	17	(5.5%)	5	(3.2%)	68	(9.2%)
Excess Tearing	40	(14.4%)	17	(5.5%)		0	57	(7.7%)
Urogenital								
Proteinuria	92	(33.1%)	84	(27.4%)	8	(5.1%)	184	(24.8%)
Urinary Tract Infection	38	(13.7%)	19	(6.2%)	11	(7.0%)	68	(9.2%)

[1]Asthenia includes asthenia, malaise, and somnolence where the verbatim term is lethargy or fatigue.

[2]Pain includes back, bone, chest, flank, kidney, neck, and pelvic pain as well as pain.

[3]Diarrhea includes diarrhea, enteritis, and gastroenteritis.

[4]Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, hematemesis, hemorrhage where it is gastrointestinal, melena, and rectal hemorrhage.

[5]Anemia includes anemia and hypochromic anemia.
[6]Edema includes edema, generalized edema, peripheral edema, genital edema, and scrotal edema.
[7]Myalgia includes myalgia and hypertonia where the verbatim term is muscle spasm.
[8]Neuropathy includes neuropathy, paresthesia and peripheral neuritis where the verbatim term is peripheral neuropathy.
[9]Upper respiratory infection includes bronchitis, flu syndrome, otitis media, pharyngitis, rhinitis, sinusitis, and viral infection. It also includes ear pain, infection, lung disorder, and respiratory disorder where the verbatim terms appear to be related to an upper respiratory infection.

Several adverse event categories included in the table above were comprised of predominantly mild or moderate (grade 1 or 2) events and thus were not present in the tables listing the most common serious and severe (grade 3 or 4) adverse events. These common, moderate or mild adverse events are headache, stomatitis, gastrointestinal hemorrhage, edema, epistaxis, rash, and proteinuria.

In comparing the relative incidence of specific adverse events across subgroups, the incidences of epistaxis and of proteinuria are lower in the Single Agent subgroup than in other subgroups. Conversely, the incidence of headache was higher in the Single Agent subgroup as compared to those in which bevacizumab was given in combination with chemotherapy. One possible explanation for this higher incidence is that, in general, the dose administered to patients in the Single Agent subgroup was higher than with combination therapy. The doses of bevacizumab used in the single agent group included 3, 10, and 20 mg/kg every two weeks with the majority of patients receiving 10 mg/kg. In the Combination group, patients received either 5-10 mg/kg every two weeks or 7.5-15 mg/kg every three weeks, with the majority of patients receiving 15 mg/kg. In Phase 1 clinical studies, headache was a dose-related toxicity with an increase in the incidence and severity with higher doses (20 mg/kg/dose). Gastrointestinal hemorrhage is primarily increased in the Colorectal Studies.

Targeted Adverse Events

At the time of initiation of the major efficacy study (AVF2017g), data from the Phase 1 and 2 development program indicated that hypertension, proteinuria, and thromboembolic events were bevacizumab-related toxicities. Therefore, while the design of AVF2107g required collection of all adverse events regardless of severity in a subset (first 100 patients enrolled in each study arm), the protocol required that specific monitoring and collection for targeted adverse events (grade 1-4 hypertension, proteinuria, and thromboembolic events) be obtained in all study patients regardless of severity in order to further characterize the incidence and severity of these bevacizumab-associated adverse events.

The overall incidence and incidence of severe events, narrative descriptions of serious and severe adverse events, incidence of events in controlled studies, and results of exploratory, post-hoc analyses by FDA and/or Genentech to assess for

potential factors associated with an increased incidence of these targeted adverse events are provided in the sections below.

Hypertension

The incidence of hypertension, based upon adverse event reports, in the Treatment/Disease subgroups and in the ISS population are shown in the table below.

Number and Percentage of Patients with Hypertension, by Severity, in All Genentech-sponsored Studies and in Diagnosis/Treatment Subgroups				
	Colorectal N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Hypertension				
Gr 1	45 (7.9%)	17 (5.5%)	3 (1.9%)	65 (6.3%)
Gr 2	27 (4.8%)	9 (2.9%)	4 (2.5%)	40 (3.9%)
Gr 3	94 (16.5%)	56 (18.2%)	20 (12.7%)	170 (16.5%)
Gr 4	0	0	1 (0.6%)	1 (0.1%)
Total				

The overall incidence and the incidence of severe (grades 3 and 4) hypertension is similar was similar across the subgroups, despite differences in the populations and in concomitant treatment. For example, 43.5% of patients in the Colorectal subgroup, had a history of past hypertension as compared to 24.4% in the Combination subgroup, and 26.8% in the Single Agent subgroup. There was also a difference in median age (61 years vs. 53 and 54 years in the other subgroups) between the groups that did not translate into a difference in the incidence of hypertension.

Risk Factors

Genentech provided the results of a series of univariate, exploratory, post-hoc analyses for associations between the following baseline entry variables (gender, race, performance status, age, history of hypertension, history of atherosclerosis) and proteinuria. The association between hypertension and the adverse event proteinuria and on study was also examined. While these analyses provide interesting data for further speculation, the exploratory nature of these analyses does not allow conclusions to be drawn from these analyses. In selecting analyses for further discussion, the significance of the Chi-squared test was used. Given the exploratory nature of these analyses, levels of significance should not utilized in applying the results of these analyses, but in selecting factors for further prospective evaluation.

In examining the entire ISS database, an association was noted between the development of the adverse event proteinuria on study and the report of the adverse event hypertension. Among the 239 patients with the adverse event

proteinuria, the adverse event hypertension was also reported in 103 (43.1%). Among the 793 patients without the adverse event proteinuria, the adverse event hypertension was reported in 161 (20.3%). This association was also noted in the Colorectal Studies and Combination group.

Among patients enrolled in the colorectal studies, race was noted to associated with the adverse event hypertension. Here, race was categorized as White/Hispanic versus Other. The 93 patients in the Other group had a 40.9% incidence of hypertension was seen while among the 475 patients in the White/Hispanic group, the incidence was 25.7%. This association was not noted in the Combination or Single Agent group.

Dose Effect

Hypertension	2.5 mg/kg/week	5 mg/kg/week
Gr 1	44 (7.7%)	13 (3.7%)
Gr 2	25 (4.4%)	7 (2.0%)
Gr 3	69 (12.1%)	62 (17.7%)
Gr 4	0	0

There appears to be a slight increase in the incidence of hypertension in the 5 mg/kg/week group. The applicant examined hypertension in individual Phase 2 studies in which two doses of bevacizumab were used in the same randomized population. In [redacted], no patients in the 2.5 mg/kg/week group had grade 3 hypertension (N = 32), but in the 5 mg/kg/week arm (N = 34), 5.9% had grade 3 hypertension. This difference is also seen in AVF780g. Here, 8.6% of patients in the 2.5 mg/kg/week arm (N = 35) had hypertension while 25% of patients in the 5 mg/kg/week arm (N = 32) had grade 3 hypertension.

In an investigator-conducted study in renal cell carcinoma, patients were randomized to placebo, bevacizumab 3 mg/kg every two weeks, or bevacizumab 10 mg/kg every two weeks. Patients in the placebo arm could crossover on progression to bevacizumab 3 mg/kg every two weeks and later to 3 mg/kg of bevacizumab in combination with thalidomide. In this study, seven patients (17.9%) in the 10 mg/kg group developed grade 3 hypertension. No patients in the 3 mg/kg group, placebo group, or in the placebo group who crossed over to bevacizumab 3 mg/kg experienced grade 3 hypertension.

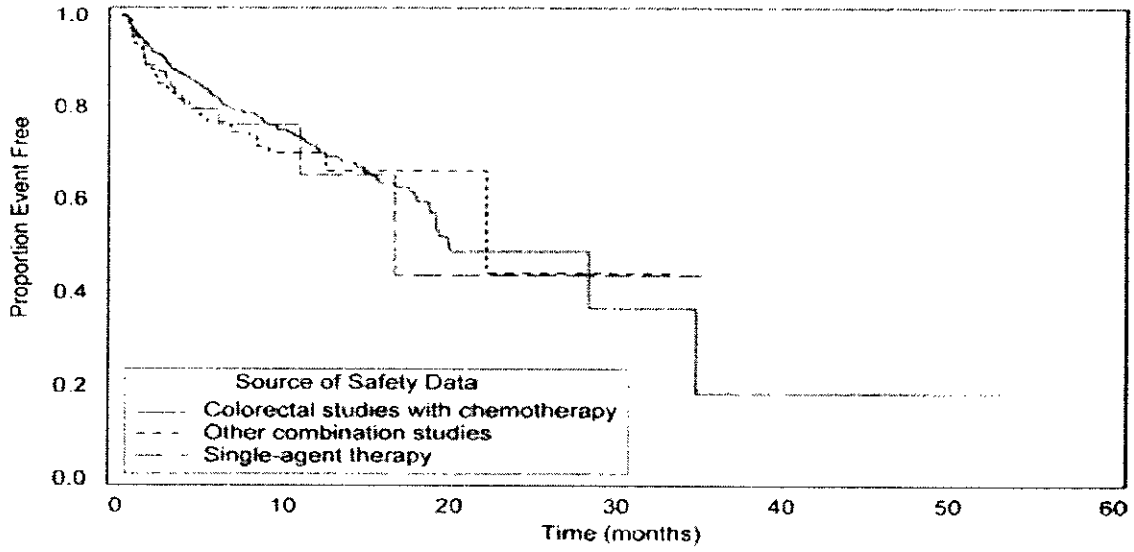
Use of Anti-Hypertensives

The sponsor examined the use of anti-hypertensive medications before and after the patient's first grade 3-4 hypertensive event. Only anti-hypertensive medications with a known start date are included in the table. The proportion of data this represents is unclear.

	Colorectal Studies N = 94	Other Combination N = 56	Single Agent N = 21	Total N = 171
Prior to Grade 3 Event				
Overall	37 (39.4%)	11 (19.6%)	9 (42.9%)	57 (33.3%)
After the 1st Grade 3 Event				
Overall	77 (77.8%)	42 (84.0%)	18 (85.7%)	138 (80.7%)
Angiotensin II Receptor Antagonist	8 (8.5%)	6 (10.7%)	0	14 (8.2%)
Angiotensin Converting Enzyme Inhibitor	25 (26.6%)	23 (41.1%)	4 (19.0%)	52 (30.4%)
Beta Blocker	19 (20.2 %)	18 (32.1%)	4 (19.0%)	41 (24.0%)
Calcium Channel Blocker	29 (30.9%)	14 (25.0%)	14 (66.7%)	57 (33.3%)
Diuretic	22 (23.4%)	12 (21.4%)	4 (19.0%)	38 (22.2%)
Other	20 (21.3%)	10 (17.9%)	3 (14.3%)	33 (19.3%)

The percentage of patients who received an anti-hypertensive medication following the first grade 3 event is not 100%. This may be due to changes in the dose of existing medications or the lack of data. No data was presented on blood pressure control following the first grade 3 event and the institution of the medications above.

Time to Onset



Hypertension developed at a constant rate and was not an early or late effect.

Hypertensive Complications

Four patients on Genentech sponsored studies developed hypertensive encephalopathy.

- On AVF2107g, patient 11824 developed hypertension, confusion, and somnolence following elective splenectomy. He required a nitroprusside infusion for blood pressure control. He was able to be discharged and resumed study treatment.
- Also on AVF2107g, patient 11521 presented with nausea, vomiting, edema, and a blood pressure of 200/110.
- On — patient 7103 (3 mg/kg arm) presented with a blood pressure of 220/130, headache, and blurred vision. This was associated with thrombocytopenia and an increase in d-dimer. Treatment included a nitroprusside infusion. This event was associated with the development of nephrotic syndrome. She was discharged following this event, but was readmitted five days later and died during that hospitalization.
- On AVF780g, patient 6610 (5 mg/kg arm) presented with nausea, vomiting, and diarrhea. Blood pressure was 250/150. The patient rapidly developed increasing somnolence and renal failure. She died of electrolyte imbalance and at autopsy the cause of death was determined to be hypertensive encephalopathy and renal failure.

Two patients in the National Cancer Institute database developed hypertensive encephalopathy.

- One patient on T98-0035 presented with headache and a blood pressure of 233/80. She was discharged on oral medications following this event.
- Patient 32457 on E3200 developed grade 4 hypertension. No additional information is available.

Hypertension requiring hospitalization (Serious adverse event)

Two patients on Genentech sponsored studies were admitted due to hypertension, but did not clearly have hypertensive encephalopathy.

- On — patient 21765 presented with headache, vomiting, photophobia, and a blood pressure of 181/107. She was able to resume bevacizumab.
- On — patient 7106 (3 mg/kg arm) had a past medical history of severe hypertension and marked hypertension was noted on study (203/119). The patient presented to the emergency room with marked hypertension (blood pressure unknown), malaise, weakness, and EKG changes consistent with hypertension (no additional information).

Several additional patients had significant hypertensive complications.

- On AVF2107g, patient 10685, developed a subarachnoid hemorrhage in association with headache and a blood pressure of 208/102. MRI showed a hemorrhage involving the third and fourth ventricles. The patient was on full

dose warfarin. However, with this event PT was 12.7. On AVF2107g, patient 10693 had syncope and a resultant motor vehicle accident that was associated with a blood pressure of 160/120.

- On AVF780g, patient 6615 (10 mg/kg arm) developed a transient ischemic attack and was noted to be hypertensive.
- On AVF780g, patient 6109 developed dyspnea, angina, and moderate hypertension (blood pressure unknown) requiring study withdrawal. The patient had a past history of congestive heart failure.

National Cancer Institute AdEERs Database

Several patients on NCI sponsored studies were hospitalized with hypertension. It is often difficult to determine whether the primary cause of hospitalization was hypertension or was related to another adverse event.

- In the NCI database, patient 33033 on E3200 presented with a hemorrhagic stroke and blood pressure of 197/124.
- One patient on study 2710 presented with nausea and vomiting and was hospitalized for hypertension.

Proteinuria

There are several limitations in the interpretation of data concerning proteinuria in the Genentech ISS database. The monitoring assessments for proteinuria (urine dipsticks) was not standardized across the various studies, which requiring urinalyses as frequently as weekly and as infrequently as every eight weeks. An additional limitation of the database is that 24 hour urine collections were not required in patients with proteinuria by dipstick in the Phase 2 studies. The database can be used to describe proteinuria in two ways: by adverse event report submitted by the investigator and by inspection of urinalysis results and the findings on 24 hour urine collection.

The toxicity grading system for proteinuria is based primarily on laboratory data (urine protein by dipstick and/or 24 hour urinary protein) with the exception of grade 4 toxicity, which is based upon the clinical findings of nephrotic syndrome. While some data are missing due to lack of compliance with protocol-specified collection of urinalyses, there are sufficient samples to confirm the findings of the investigator-reported adverse events as well as to identify additional patients who may not have been correctly reported as experiencing proteinuria.

Twenty-four hour urine collections were done sporadically, therefore laboratory-identified proteinuria for the overall dataset will be based on urinalysis findings; results of individual studies may also include information on proteinuria by 24 hour urine collections. A lack of correlation between dipstick values and 24 hour urine collections was seen in AVF2107g. In some instances the lack of correlation may be due to inadequate collection of the 24 hour urine specimen, in this situation, the dipstick result would be considered a "false positive" result.

Because no data were obtained on the adequacy of the 24 hour urine collections, one cannot determine how often this occurred. However, the data do suggest that urine dipstick is not a highly sensitive and specific test for identification of proteinuria. This finding led to a post-marketing commitment to identify better screening strategies for this bevacizumab toxicity.

Also note that information concerning risk factors for proteinuria is based on the adverse event proteinuria as reported by the investigator. The time to onset of proteinuria was analyzed for both the adverse event proteinuria and the laboratory abnormality.

Proteinuria (Adverse Event Reports)

Incidence and Severity of Investigator-Reported Events of Proteinuria in ISS Database and Treatment/Diagnosis Subgroups				
Proteinuria[1]	Colorectal N = 568	Combination N = 307	Single Agent N = 157	Total
Gr 1	134 (23.6%)	56 (18.2%)	5 (3.2%)	195 (18.9%)
Gr 2	43 (7.6%)	26 (8.5%)	1 (0.6%)	70 (6.8%)
Gr 3	6 (1.1%)	0	1 (0.6%)	7 (0.7%)
Gr 4	0	3 (1.0 %)	2 (1.3%)	5 (0.5%)
	183 (32.2%)	85 (27.7%)	9 (5.7%)	277(26.8%)

[1]Includes reports coded with the adverse event terms "proteinuria" or "nephrosis"

The majority of adverse events were mild (grade 1). The incidence of proteinuria was lowest in patients receiving single agent bevacizumab and appears to be similar in patients receiving bevacizumab in combination with chemotherapy, regardless of underlying cancer/concurrent chemotherapy (Colorectal and Combination subgroups).

The reported incidence of proteinuria varied across studies. The incidence can be best assessed in the Phase 3 studies with large homogeneous populations receiving a standardized chemotherapy regimen, and standard monitoring for proteinuria. The incidence of proteinuria by severity is presented below for two of the Phase 3 trials.

AVF2119g was a randomized trial conducted in patients with metastatic breast cancer, which had progressed following anthracyclines and taxanes. Patients were randomized to capecitabine alone or capecitabine plus open label bevacizumab 15 mg/kg every three weeks. Urinalyses were collected at the beginning of each cycle (every three weeks). The incidence and severity of proteinuria based on adverse event reports is presented below.

Incidence and Severity of Investigator-Reported Events of Proteinuria in AVF 2119g by Treatment Arm		
Proteinuria	Capecitabine N = 215	Capecitabine + Bevacizumab N = 229
Overall	16 (7.4%)	51 (22.3%)
Gr 1	14 (6.5%)	42 (18.3%)
Gr 2	2 (0.9%)	7 (3.1%)
Gr 3	0	2 (0.9%)
Gr 4	0	0

AVF 2107g, the major efficacy study, randomized patients undergoing first-line treatment of metastatic colorectal cancer to IFL plus placebo, IFL plus bevacizumab 5 mg/kg every two weeks, or to 5FU/LV plus bevacizumab 5 mg/kg every two weeks. Urinalyses were collected at the beginning of each cycle (every two weeks). The incidence and severity of proteinuria based on adverse event reports in patients randomized to blinded study drug in the two principal arms is presented in the table below

	IFL + Placebo N = 396	IFL + Bevacizumab N = 392
Overall	87 (22.0%)	113 (28.9%)
Gr 1	62 (15.6%)	92 (23.5%)
Gr 2	22 (5.6%)	18 (4.6%)
Gr 3	3 (0.8%)	3 (0.8%)
Gr 4	0	0

The incidence of grade 1-2 proteinuria is lower in AVF2119g than in AVF2107g. This is true both for patients who received bevacizumab and those who did not. In AVF2107g, the incidence of grade 1 proteinuria was lower (15.6% vs. 23.5%) in the placebo arm when compared to the bevacizumab arm. Although the incidence of grade 1 proteinuria is lower in AVF2119g, both the absolute increase (11.8% vs. 7.6%) and the relative increase (2.8-fold vs. 1.5 fold) are greater in AVF2119g as compared to AVF2107g. This is in contrast to the overall incidence of proteinuria. In AVF2119g, the overall incidence was 7.4% in the control and 22.3% in the bevacizumab arm. However, in AVF2107g, the overall incidence was 22.0% in the control and 28.9% in the bevacizumab arm. The most important conclusion from these two studies is that the incidence of proteinuria is increased in the bevacizumab arm.

Proteinuria (Based on Inspection of Urinalysis Results)

The incidence and severity of proteinuria based on urinalysis (dipstick) results are summarized in the table below. Note that 24 h urine values are not substituted for dipstick values as in the pivotal trial. Also note that the sponsor

considered a laboratory event to have occurred only when a value worsened in grade from baseline.

Incidence and Severity of Proteinuria (based on urinalysis results) in ISS Database and Treatment/Diagnosis Subgroups				
Protein dipstick value (NCI CTC grade)	Colorectal N = 530	Combination N = 284	Single Agent N = 103	Total 917
Proteinuria				
1+ (Gr 1)	145 (27.4%)	67 (23.6%)	12 (11.7%)	224
2-3+ (Gr 2)	112 (21.1%)	49 (17.3%)	7 (6.8%)	168
4+ (Gr 3)	10 (1.9%)	5 (1.8%)	6 (5.8%)	21
Total	267 (50.4%)	121 (42.6%)	25 (24.3%)	413(45.0%)

By both adverse event reports and review of urinalysis results, the incidence of proteinuria is lowest in the subgroup of the ISS that received bevacizumab alone. Since both investigator-reported events and urinalysis-based events are based on the urinalysis results, differences in monitoring schedules could lead to ascertainment bias and an erroneously low incidence rate. Forty-one of 157 patients in the Single Agent subgroup (26.1%), were in the control arms of studies , —— and AVF780g. Here, urinalyses were required on a less frequent (than every 2 weeks) schedule. However, a similar percentage of patients in the Combination subgroup, 66 of 307 patients (21.5%), had similar monitoring schedule for urinalyses as those in the crossover study. Despite this, the incidence of proteinuria in the Combination subgroup is similar to the Colorectal subgroup that also received bevacizumab in combination with chemotherapy. Thus the lower incidence of proteinuria in the Single Agent group may reflect the true rate and the incidence of proteinuria may be increased when bevacizumab is used in combination with chemotherapy. This conclusion, however, should be viewed with caution.

Dose Effect

Incidence and Severity of Proteinuria (based on urinalysis results) by Average Weekly Dose		
	2.5 mg/kg/week	5 mg/kg/week
Urine dipstick value (NCI CTC grade)		
1+ (Gr 1)	140 (26.6%)	64 (20.1%)
2-3+ (Gr 2)	89 (16.9%)	39 (12.2%)
4+ (Gr 3)	10 (1.9%)	8 (2.5%)
Nephrotic Syndrome (Gr 4)	0	0
Total		

The overall incidence of proteinuria is similar between the subgroup receiving an average weekly dose of 2.5 and 5 mg/kg/week.

However, data from randomized, dose ranging studies indicate that there may be an association between dose and proteinuria. In an NCI-sponsored study of patients with metastatic renal cell carcinoma (described in the section on hypertension), the incidence of proteinuria appeared to be dose-related. Data from this study should be interpreted with caution since urine dipsticks and 24 hour urines were not required per-protocol. Data on the incidence of proteinuria (overall and by severity), based upon investigator-generated adverse event reports, urine dipstick results, and 24 hour urine collections, are presented below.

Adverse Event

Adverse event information in the following table is from the Clinical Data Update System (CDUS) of the National Cancer Institute. Patients in this study were initially randomized to blinded study drug (placebo, 3 mg/kg bevacizumab or 10 mg/kg bevacizumab). Data concerning the treatment received is still in some instances listed as blinded. Unique patient numbers are available and patients in the blinded category are not also included in the placebo, 3 mg/kg or 10 mg/kg arm.

	10 mg/kg N = 39	3 mg/kg N = 37	Placebo N = 40	Crossover		
				10 mg/kg N = 4	3 mg/kg N = 10	3 mg/kg +Thalidomide N = 12
Gr 1	13 (33.3%)	11 (29.7%)	7 (20.6%)	2 (50.0%)	2 (20.0%)	9 (75.0%)
Gr 2	9 (23.1%)	2 (5.4%)	7 (20.6%)	1 (25.0%)	2 (20.0%)	0
Gr 3	3 (7.7%)	2 (5.4%)	0	0	0	0
Gr 4	1 (2.6%)	0	0	0	0	0

Urine Dipsticks

Incidence and Severity of Proteinuria (based on urinalysis results) NCI Phase 2 study in Renal Cell Cancer by Treatment Arm				
Urine dipstick value (NCI CTC grade)	10 mg/kg N = 39	3 mg/kg N = 37	Crossover	
			3 mg/kg N = 10	3 mg/kg + Thalidomide N = 12
Neg/Trace (Gr 0)	6	10	1	
1+ (Gr 1)	18	20	7	11
2+ (Gr 2)	8	4	2	1
3+ (Gr 2)	6	3		
4+ (Gr 3)	1			
Total (Gr 1-4)	85% (33/39)	73% (27/37)	90% (9/10)	100% (12/12)

The study information submitted to BB-IND 7921 did not include dipstick results for the placebo arm or for patients who crossed over to 10 mg/kg of bevacizumab. On examination, there appears to be a trend towards a dose-

related increase in severe (≥ 3 g/24 hours) proteinuria, when the 10 mg/kg and 3 mg/kg arms are compared. However, the overall incidence of proteinuria is similar, 84.6% in the 10 mg/kg and 73.0% in the 3 mg/kg arm.

24 Hour Collections

The incidence and severity of proteinuria can also be assessed in the one-third of patients who had 24 hour urine collections during treatment. Note that the information submitted to BB-IND 7921 does not contain 24 hour urines in the patients who crossed over from placebo to high dose therapy.

Since these patients have underlying renal cell carcinoma, the degree of baseline proteinuria must also be considered. Baseline 24 hour collection were obtained in 11 patients in the 10 mg/kg arm. Seven patients remained within 500 mg of their baseline, most much closer. Four patients had an increase in proteinuria: one from 165 to 2471 mg, a second from 158 to 2178 mg, a third from 108 to 1151 mg, and a fourth from 335 to 5193 mg. Baseline 24 hour collections were obtained in 11 patients in the 3 mg/kg arm. Ten patients remained within 500 mg of their baseline, most much closer. One patient had an increase in proteinuria from 1137 to 4084 mg. Baseline 24 hour collections were obtained in 13 patients in the placebo arm. Eleven remained within 500 mg of their baseline, most much closer. Two patients had an increase in proteinuria; one from 138 to 2622 mg and the second from 274 to 2345 mg. Among the nine patients who crossed over, all remained within 500 mg of their baseline, most much closer.

Severity of Proteinuria (based on 24 hour urine collection) in NCI Phase 2 study in Renal Cell Cancer by Treatment Arm					
				Crossover	
Urinary Protein (g/24 hours)	10 mg/kg N = 19	3 mg/kg N=14	Placebo N = 15	3 mg/kg N = 7	3 mg/kg + Thalidomide N = 5
< 1 gm	10	12	12	7	5
1 to < 2 g	2		1		
2 to < 3 g	3		1		
3 to < 4 g			1		
4 to < 5 g	1	2			
≥ 5 g	3				
≥ 3.5g/24 hrs (Gr 3)	21% (4/19)	14%(2/14)	0%(0/15)		

The incidence of severe proteinuria (≥ 3.5 g/24 hours [NCI CTC grade 3]) is dose-related in this study.

Risk Factors

Genentech provided the results of a series of univariate, exploratory, post-hoc analyses for associations between the following baseline entry variables (age, gender, race, performance status, history of hypertension, renal insufficiency,

use of an angiotensin converting enzyme inhibitor, and diabetes) and proteinuria. The association between proteinuria and on study factors; the report of the adverse event hypertension and the use of a concomitant medication associated in the literature with proteinuria, and the report of the adverse event proteinuria was also examined. While these analyses provide interesting data for further speculation, the exploratory nature of these analyses does not allow conclusions to be drawn from these analyses. In selecting analyses for further discussion, the significance of the Chi-squared test was used. Given the exploratory nature of these analyses, levels of significance should not utilized in applying the results of these analyses, but in selecting factors for further prospective evaluation.

In the entire ISS database, the report of the adverse event proteinuria was associated with the adverse event hypertension. Among the 264 patients with the adverse event hypertension, 103 (39.0%) had proteinuria. This can be compared to the 768 patients without hypertension in which 136 (17.7%) had proteinuria. This association between the adverse events proteinuria and hypertension was also seen in the Colorectal Studies and the Combination group.

In the entire ISS database, the report of the adverse event proteinuria was associated with a history of hypertension. Among the 364 patients with a history of hypertension, 112 (30.8%) had proteinuria. This can be compared to the 668 patients without a history of hypertension. Proteinuria occurred in 127 (19.0%) of these patients. This association was also seen in the Combination group.

In AVF2119g, Genentech provided a series of univariate, exploratory, post-hoc analyses of the association between proteinuria reported as an adverse event and the following baseline entry variables (history of hypertension, use of an angiotensin converting enzyme inhibitor, use of pamidronate, and creatinine clearance). Genentech also provided an analysis of the association between the adverse event proteinuria and the occurrence of the adverse event hypertension on study. A chi-squared test was also used in these analyses and similar caveats apply.

An association was noted between the adverse event proteinuria and a history of hypertension and the development of the adverse event hypertension on study. Among the 51 patients with a history of hypertension, the adverse event proteinuria was reported in 19 (37.3%). This can be compared to the 178 patients without a history of hypertension. The adverse event proteinuria was reported in 32 (18.0%) of these patients. Among 51 patients with the adverse event hypertension, the adverse event proteinuria was reported in 24 (47.1%). This can be compared to 178 patients without the adverse event hypertension. The adverse event proteinuria was reported in 30 (16.9%) of these patients.

A weaker association between the adverse event proteinuria and the use of pamidronate at study entry was also noted. This association is shown in the tables below.

Capecitabine + Bevacizumab

Proteinuria	Use of Baseline Pamidronate	No Use of Baseline Pamidronate	Total
Yes	19	32	51
No	37	141	178
Total	56	173	229

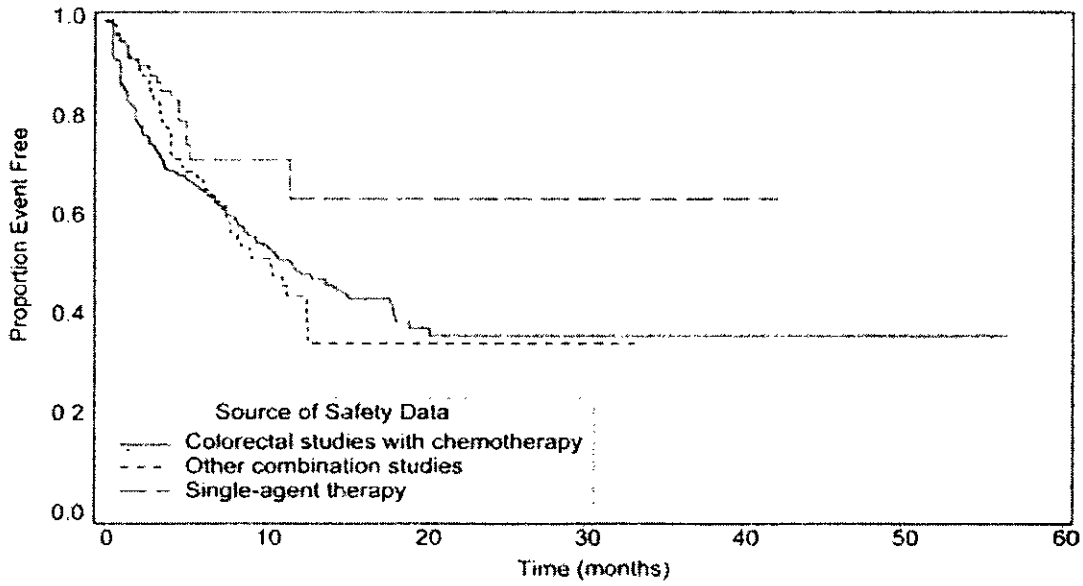
Capecitabine

Proteinuria	Use of Baseline Pamidronate	No Use of Baseline Pamidronate	Total
Yes	4	12	16
No	64	135	199
Total	68	147	215

Note that in the capecitabine plus bevacizumab arm, proteinuria developed in 19/56 (33.9%) patients receiving pamidronate at baseline and in 32/173 (18.5%) of patients not receiving pamidronate. This relationship was not seen in the capecitabine alone arm. Here, 4/68 (5.9%) of patients receiving pamidronate at baseline developed proteinuria.

Time to Onset of the Laboratory Event Proteinuria

Genentech presented an analysis of time to development of proteinuria, based on adverse event reports, in the three diagnosis/treatment subgroups.



The time to development of proteinuria is similar across all three subgroups, however the "plateau" differs for the Single Agent subgroup as compared to subgroups in which bevacizumab is administered with chemotherapy. In both the Combination and Single Agent subgroups, there were few patients for whom data were collected at late time points and for approximately 25% of patients in these subgroups, the sampling intervals were less frequent.

Nephrotic Syndrome and Significant Proteinuria

Nephrotic Syndrome

Five patients in the Genentech database developed nephrotic syndrome and eight had clinically significant proteinuria.

- Patient 7103 in study —— had no past medical history of hypertension or renal disease. Following two doses of bevacizumab, she developed of significant hypertension (219/121), blurred vision, and headache. She was treated with nitroprusside. A 24 hour urine contained 5 g of protein and she was noted to have edema and an albumin of 2.3 g/dL. She was able to be discharged, but was admitted five days later and died during that admission.
- Patient 7032 in study —— developed a 3+ urine dipstick and her 24 hour urine showed 5.7 g of protein. Albumin was 3.3 g/dL. She was also noted to have ureteral obstruction secondary to tumor and a stent was placed. Proteinuria gradually improved.
- Patient 21886 enrolled in AVF2119g had a history of hypertension and a baseline creatinine of 1.8 mg/dL. However, her urine dipstick was negative at screening. On study, she had 6328 mg of protein in a 24 hour collection. Albumin at that time was 3.8 g/dL and edema was not noted. Bevacizumab was discontinued, but she continued to experience proteinuria. A 24 h collection done approximately four months after discontinuation of bevacizumab showed 8.4 g and six months after discontinuation 13 g. She developed an increase in creatinine and an albumin of 2.7 g/dL. She ultimately required dialysis. Renal biopsy showed focal segmental glomerulosclerosis.
- Patient 20468, enrolled in AVF2119g, developed hypertension (190/110). This was followed, three months later, by the development of proteinuria with 4249 mg of protein in a 24 hour collection. Bevacizumab was discontinued. One month later, her urine contained 3798 mg. Three months after discontinuation it contained 2313 mg and four months after discontinuation 4505 mg. Seven months after discontinuation, a 24 hour collection contained 1890 mg. Serum albumin is not available in this patient and edema is not commented upon. However, the patient was considered by the investigator to have nephrotic syndrome.
- Patient 11187, enrolled in AVF2107g, had a history of diabetes and a baseline creatinine of 1.6 mg/dL. On study she developed proteinuria with 4832.8 mg in a 24 hour collection. This was associated with edema. Albumin is not reported. She continued bevacizumab with no further urine collections.

A follow up collection two months after discontinuation of study drug contained 1673.8 mg of protein.

BB-IND 7921

- One patient enrolled in the NCI study of patients with metastatic renal cell carcinoma developed nephritic syndrome on treatment – the treatment arm is not given in the report.

Proteinuria associated with renal failure and death

- On AVF780g, patient 6610 developed hypertension (250/150) associated with somnolence and renal failure. A 24 hour urine was not collected. The patient died of an electrolyte imbalance. Autopsy determined the cause of death to be hypertensive encephalopathy and renal failure.

Proteinuria associated with medical intervention/morbidity (serious adverse event)

- Patient 7018 did not develop nephrotic syndrome. However, this case should be discussed since a renal biopsy was performed in association with significant proteinuria. This patient developed hypertension (160/120) followed by the development of 2.7 grams of protein in a 24 hour collection. Albumin was 3.5 g/dL. Renal biopsy showed membranoproliferative glomerulonephritis.

Proteinuria (Grade 3)

- On AVF2107g, patient 10101 developed significant hypertension (230/103). This was followed, seven months later, by a 24 hour collection contained 2588 mg of protein. He remained on study drug and over one year later, had 4801 mg was recorded. Two months after discontinuation, his urine protein was 4358 mg and three months later it was 1495 mg. Five months after discontinuation a 24 hour urine contained 746 mg.
- Patient 10108 developed 3632 mg of protein in his 24 hour collection while receiving IFL + Bevacizumab. Two weeks later this, increased to 5144 mg. He did not have edema and blood pressure was 170/80. Bevacizumab was discontinued. Approximately one month later, a 24 hour urine contained 2765 mg and three months after discontinuation a urine collection contained 2033 mg.
- Patient 11784 on AVF2107g had a 24 hour collection containing 5056 mg of protein. A 24 hour collection one month after discontinuation of bevacizumab contained 4007 mg of protein.
- Two additional patients, 11121 and 13583, on the bevacizumab arms of AVF2107g developed greater than 3.5 g of proteinuria.
  - One was associated with stent placement and hematuria.
  - The second was associated with a kidney stone.

Clinically Significant Proteinuria

- On AVF2107g, patient 10541 developed hypertension and a 3+ urine dipstick that was associated with a creatinine of 3 mg/dL and a serum protein of 2.9 g/dL.
- Patient 11347 on AVF2107g developed 3001 mg of protein in a 24 hour collection.
- Patient 12422 on AVF2107g had a history of diabetes, but a normal serum creatinine and no evidence of proteinuria at baseline. He developed 2559 mg of proteinuria one month after his last dose of bevacizumab.

In the NCI database, significant proteinuria is largely confined to a study involving patients with metastatic renal cell carcinoma that was described above.

Thromboembolic Events

The incidence of any and specific subtypes of thromboembolic events in the ISS database in the treatment/diagnosis subgroups are presented in the table below. Since several patients had multiple events (e.g., a patient may be included in both the deep vein thrombosis and in the pulmonary embolism categories), the number of patients with thromboembolic events is less than the sum of the patients in the individual categories.

Incidence of Overall and Individual Categories of Thromboembolic Events in the ISS Database and in Treatment/Diagnosis Subgroups

	Colorectal Studies N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	111 (19.5%)	28 (9.1%)	6 (3.8%)	145 (14.0%)
Pulmonary Embolism	20 (3.5%)	5 (1.6%)	0	25 (2.4%)
Deep Vein Thrombosis	50 (8.8%)	14 (4.6%)	4 (2.5%)	68 (6.6%)
Line Related Thrombosis	11 (1.9%)	2 (0.6%)	1 (0.6%)	14 (1.4%)
Intra-Abdominal Thrombosis[1]	17 (3.0%)	5 (1.6%)	0	22 (2.1%)
Thrombophlebitis	9 (1.6%)	0	1 (0.6%)	10 (1.0%)
Thromboembolism[2]	1 (0.2%)	4 (1.3%)	1 (0.6%)	6 (0.6%)
Myocardial Infarction	13 (2.3%)	0	1 (0.6%)	14 (1.4%)
Angina Pectoris	1 (0.2%)	0	1 (0.6%)	2 (0.2%)
Cerebrovascular Accident	4 (7.0%)	3 (1.0%)	1 (0.6%)	6 (0.6%)
Transient Ischemic Attack	2 (2.3%)	1 (0.3%)	0	5 (0.5%)

[1] includes inferior vena cava thrombosis, iliac vein thrombosis (4), mesenteric vein thrombosis, renal vein thrombosis, portal vein thrombosis (4), splenic vein thrombosis, aortic thrombosis, ovarian vein thrombosis, ischemic bowel, and pelvic vein thrombosis

[2] includes left ventricular thrombosis, lower extremity embolism (but not thrombosis), retinal vein thrombosis, and superior vena cava thrombosis

In the analysis presented above, thromboses of the upper extremity, subclavian vein, or jugular vein are either considered line related (if that information is

available) or as a deep venous thrombosis if it is not line related or if information is not available. All subcategories of thromboembolic events were considered serious or life-threatening (NCI CTC grades 3 or 4) with the exception of thrombophlebitis, which included events of grade 1 and 2 in severity.

The overall incidence of thromboembolic events is highest in the Colorectal Studies subgroup and is lowest in Single Agent subgroup. This observed difference in incidence rates could be due to a true effect (higher incidence in colorectal cancer patients receiving concurrent 5FU-based chemotherapy), a spurious finding, or a function of the longer duration of treatment time on study. Time on study is an unlikely explanation (see below). Given that a higher incidence was observed for all subcategories (with the exception of thromboembolism which was highest in the Combination subgroup) of events, the observed differences are more likely to be real.

In study AVF2107g, there was some suggestion of an unusual pattern of events with an increased incidence of non-line-related deep venous thromboses of the upper extremities in the bevacizumab-treated patients (1% [4/392]) as compared to control patients (0.2% [1/396]). Two of the four patients in the bevacizumab arm had deep venous thromboses of both the upper and lower extremities. There was also an increase in intra-abdominal thrombosis in bevacizumab-treated patients (3.6% [14/392]) as compared to control patients (1.8% [7/396]).

Dose Effect

Incidence and Severity of Thromboembolic Events by Average Weekly Dose		
Thromboembolic Events	2.5 mg/kg/week N = 568	5 mg/kg/week N = 351
Overall	103 (18.1%)	27 (7.7%)
Gr 1	3 (0.5%)	1 (0.3%)
Gr 2	11 (1.9%)	5 (1.4%)
Gr 3	58 (10.2%)	14 (4.0%)
Gr 4	31 (5.5%)	7 (2.0%)

The overall incidence and the incidence of Grades 3 and 4 thromboembolic events are higher in the subgroup receiving the lower average weekly dose (2.5 mg/kg/week) as compared to the 5 mg/kg/week group. However, it should be noted that the 2.5 mg/kg/week group is comprised primarily of patients with colorectal cancer.

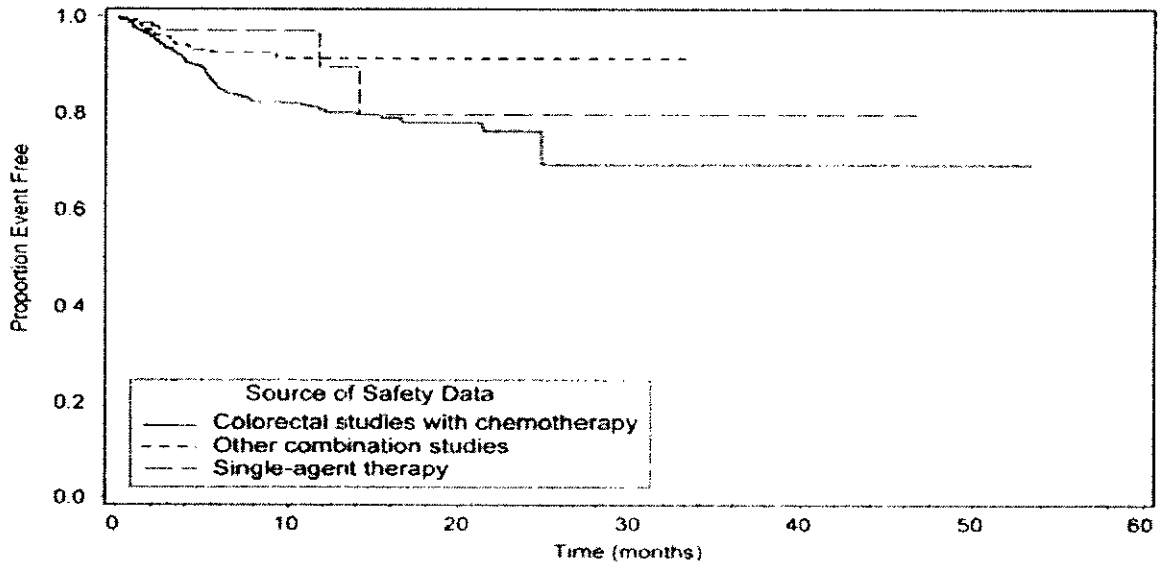
Risk Factors

The sponsor presented a series of exploratory post-hoc analyses of the relative incidence of thromboembolic event by baseline factors in study AVF2107g but not in the ISS database. In AVF2107g risk factors examined were age, prior history of venous thrombosis, performance status, use of megestrol acetate,

elevated d-dimer, Factor VIII, von Willebrand Factor levels, and concurrent use of low dose warfarin. In both the control and bevacizumab arms, an elevated Factor VII level and elevated von Willebrand's factor level were associated with a higher incidence of thromboembolic events, however the magnitude of the increase was more marked in the bevacizumab arm. The use of low dose warfarin did not correlate with a reduction in incidence of thromboembolic events.

Time to Onset of Grade 3-4 Thromboembolic Events

Genentech presented an analysis of time to development of thromboembolic events in the three diagnosis/treatment subgroups.



This suggests that the relatively small number of thromboses seen in the Single Agent and Combination subgroups tended to occur early, assuming similar intensity in post-treatment follow up. In the colorectal patients, the slope of events appears greater during the first six months of exposure than at later time points. Given the differences in median duration of bevacizumab treatment in the three subgroups (2, 5, and 9 months), the pattern above is consistent with a constant risk of thrombosis throughout treatment. Conclusions about the risk of thrombosis following active therapy in the treatment/disease groups are hampered by differences in the follow up information obtained.

Thromboembolic Events as Serious Adverse Events

- Patient 21141 on study AVF2119g developed small bowel necrosis secondary to a mesenteric vein thrombosis. Post-operatively, the patient developed worsening thrombocytopenia. She died three days after surgery.
- Patient 10122 on study AVF2107g presented with ileus and on CT was noted to have several thickened loops of bowel. At surgery a mesenteric vein thrombus was found. Note that the patient did not present with an acute abdomen.

- Patient 10882 on AVF2107g presented with nausea, vomiting and crampy abdominal pain. This was treated symptomatically. Two days later, the patient died at home. Autopsy revealed ischemic necrosis of the bowel at the anastomotic site.
- Patient 11883 was found, on routine CT scan, to have thrombi involving the superior mesenteric vein, ovarian vein, and portal vein. She was treated with anti-coagulation.
- Patient 6408, enrolled on the 5 mg/kg arm of AVF780g, was found to have a thrombosis of the superior mesenteric vein on routine CT scan. The patient was anti-coagulated.

Hemorrhage

Across several controlled clinical studies, the incidence of overall and serious (grade 3 and 4) hemorrhage was increased in bevacizumab-treated patients as compared to randomized controls. This includes both an increased incidence of grade 1-2 events as well as a much smaller incidence of serious grade 3-4 bleeding. Grade 3-4 events hemorrhagic events reported in clinical studies included hemoptysis in patients with non-small cell lung cancer, subarachnoid hemorrhage, central nervous system hemorrhage associated with stroke, and gastrointestinal hemorrhage. The table below includes events that occurred during Treatment Periods 1 and 2.

Overall Incidence of Grade 3-4 Hemorrhage and Incidence of Subtypes of Hemorrhage in the ISS database and in Treatment/Diagnosis Subgroups				
	Colorectal Studies N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Overall	30 (5.3%)	14 (4.6%)	4 (2.5%)	48 (4.7%)
Gr 3	25 (4.4%)	8 (2.6%)	3 (1.9%)	36 (3.5%)
Gr 4	5 (0.9%)	6 (2.0%)	1 (0.6%)	12 (1.2%)
GI Hemorrhage	18 (3.2%)	2 (0.6%)	2 (1.3%)	22 (2.1%)
Hemoptysis	0	6 (2.0%)	0	6 (0.6%)
Hematuria	5 (0.9%)	1 (0.3%)	0	6 (0.6%)
Hemorrhage	6 (1.1%)	2 (0.6%)	2 (1.3%)	10 (1.0%)
Epistaxis	1 (0.2%)	3 (1.0%)	0	4 (0.4%)

The incidence of Grades 3 and 4 hemorrhage events was similar in all subgroups however the type of event differed, across subgroups. The increased incidence of hemorrhage is best illustrated by analyses of randomized, control studies.

[redacted] was a Phase 2 study in patients with newly diagnosed non-small cell lung cancer. Patients were randomized to carboplatin/paclitaxel (N = 32), carboplatin/paclitaxel plus 7.5 mg/kg bevacizumab every three weeks (N = 32), or carboplatin/paclitaxel plus 15 mg/kg bevacizumab every three weeks (N = 35). Six cases of severe or fatal hemoptysis were seen. This represents an overall incidence of 9.1% (6/67) in the bevacizumab-treated patients. The expected

incidence is less than 1% (no events were observed in the control arm). An analysis done at the time of these events suggested that these events were associated with squamous histology. Note that three of these events were also associated with cavitation. The characteristics of patients enrolled in —— who experienced hemoptysis are illustrated in the table below.

Clinical Characteristics of Patients with Severe/Fatal Hemoptysis in ——						
Patient ID	5010	5016	5454	5107	5261	5117
Age/Gender	66 yo F	76 yo M	61 yo M	73 yo M	62 yo M	57 yo M
Histology	squamous	squamous	adenocarcinoma	squamous	squamous	adenocarcinoma
Tumor Size (cm^2)	30	12.59	36.5	125	evaluable	41.34
Treatment (mg/kg)	7.5	7.5	7.5	7.5	7.5	15
Event	Bleeding from mouth	Recurrent hemoptysis req ICU	Massive hemoptysis	Hemoptysis, epistaxis	Bleeding from mouth	Massive hemoptysis
Days since 1st/ last infusion	13/13	12/12	93/8	247/15	202/26	282/0
Outcome	Fatal	ICU	Fatal	Hospitalized	Fatal	Fatal
Tumor Response		Cavitation	Cavitation	Cavitation	SD	SD

The Eastern Cooperative Oncology Group initiated E4599, which is ongoing at this time. This study randomizes patients with newly diagnosed non-small cell lung cancer to carboplatin/paclitaxel or carboplatin/paclitaxel plus 15 mg/kg bevacizumab every three weeks. Patients with squamous cell histology are excluded from this study. After the first two events, patients with a history of gross hemoptysis were also excluded. Despite this, five cases of fatal hemoptysis have been seen on the bevacizumab arm among the approximately 200 patients enrolled (4% mortality). This information is based on Alert Reports issued by the IND holder. Again note that these events are associated with cavitation. All had a central tumor location.

Clinical Characteristics of Patients with Fatal Hemoptysis in E4599					
Patient ID #	1314613	1925404	1151871	1972478	1512689
Age/Gender	61F	58F	35M	79F	49F
PMH	Hemoptysis	Hemoptysis			
Tumor Characteristics	Cavitation	Cavitation	Cavitation	Extensive necrosis at autopsy	Cavitation
Days from 1st/Last Course	46/4	55/35	7/7	19/19	115/41

Mild/Moderate Hemorrhagic Events

While the discussion above deals with grade 3-4 hemorrhage, the incidence of grade 1-2 hemorrhage is also increased with bevacizumab-treatment. Genentech did not provide an analysis of the incidence of grade 1-2 hemorrhagic events in the ISS database or treatment/diagnosis subgroups. The data regarding the increased incidence of grades 1-2 hemorrhagic events is apparent in analysis of the two multicenter, active-control, Phase 3 trials included in this submission, AVF2107g and AVF2119g. AVF2107g enrolled patients receiving initial treatment for metastatic colorectal cancer who were randomized to IFL vs. IFL plus 5 mg/kg bevacizumab every two weeks vs. 5FU/LV plus bevacizumab 5 mg/kg every two weeks. In AVF2107g, collection of grade 1-4 events was confined to the first 309 patients enrolled. The table below illustrates the incidence and severity of hemorrhagic events in these 309 patients first-line therapy.

Incidence and Severity of Hemorrhage in AVF2107g by Treatment Arm in a Subset of Patients in which Hemorrhage of Any Severity Was Collected			
Hemorrhagic Event NCI CTC Grade	IFL + Placebo N = 98	IFL + Bevacizumab N = 102	5FU/LV/Bevacizumab N = 109
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Gr 1	10	35	35
Gr 2	0	0	0
Gr 3	0	1	0
Gastrointestinal Hemorrhage	6 (6.1%)	25 (24.5%)	22 (20.2%)
Gr 1	5	19	16
Gr 2	0	3	1
Gr 3	1	2	5
Gr 4	0	1	0

The incidence of epistaxis and of low grade gastrointestinal hemorrhage is markedly increased with bevacizumab treatment as compared to the control population.

AVF2119g enrolled patients with metastatic breast cancer who progressed following treatment with an anthracycline and a taxane who were randomized to capecitabine or capecitabine plus bevacizumab 15 mg/kg every three weeks. The incidence of grade 1-4 hemorrhage was also examined in AVF2119g and presented in the following table.

Incidence and Severity of Hemorrhage in AVF2119g by Treatment Arm		
Hemorrhagic Event NCI CTC Grade	Capecitabine N = 215	Capecitabine + Bevacizumab N = 229
Epistaxis		
Gr 1	3 (1.4%)	37 (16.2%)
Gum Hemorrhage		

Gr 1	2 (0.9%)	6 (2.6%)
Gastrointestinal Hemorrhage		
Gr 1	1 (0.5%)	11 (4.8%)
Gr 2	1 (0.5%)	1 (0.4%)
Hematuria		
Gr 1	1 (0.5%)	7 (3.1%)
Gr 2	1 (0.5%)	1 (0.4%)
Gr 3	1 (0.5%)	0
Hemorrhage		
Gr 1	2 (0.9%)	6 (2.6%)
Gr 2	0	0
Gr 3	0	1 (0.4%)
Vaginal Hemorrhage		
Gr 1	2 (0.9%)	2 (0.8%)
Gr 2	2 (0.9%)	1 (0.4%)

Here, the incidence of epistaxis, gastrointestinal hemorrhage are markedly increased in the bevacizumab-containing arm as compared to controls, however for all categories except vaginal hemorrhage, the bevacizumab arm had a higher incidence of events.

Dose Effect

Genentech presented an analysis of grade 3-4 bleeding by average weekly dose. This table includes only events during Treatment Period 1.

Incidence and Severity of Serious Hemorrhage by Average Weekly Dose		
Hemorrhage	2.5 mg/kg/week	5 mg/kg/week
Overall	26 (4.6%)	5 (1.4%)
Gr 4	7 (1.2%)	2 (0.6%)
Gr 3	19 (3.3%)	3 (0.9%)

The incidence of both Grade 3 and Grade 4 hemorrhage is higher in the 2.5 mg/kg/week group. Given that this subgroup is comprised of colorectal cancer patients, it is possible that that incidence of severe/life-threatening hemorrhage is higher in patients with colorectal cancer patients or in patients with longer treatment duration.

Risk Factors

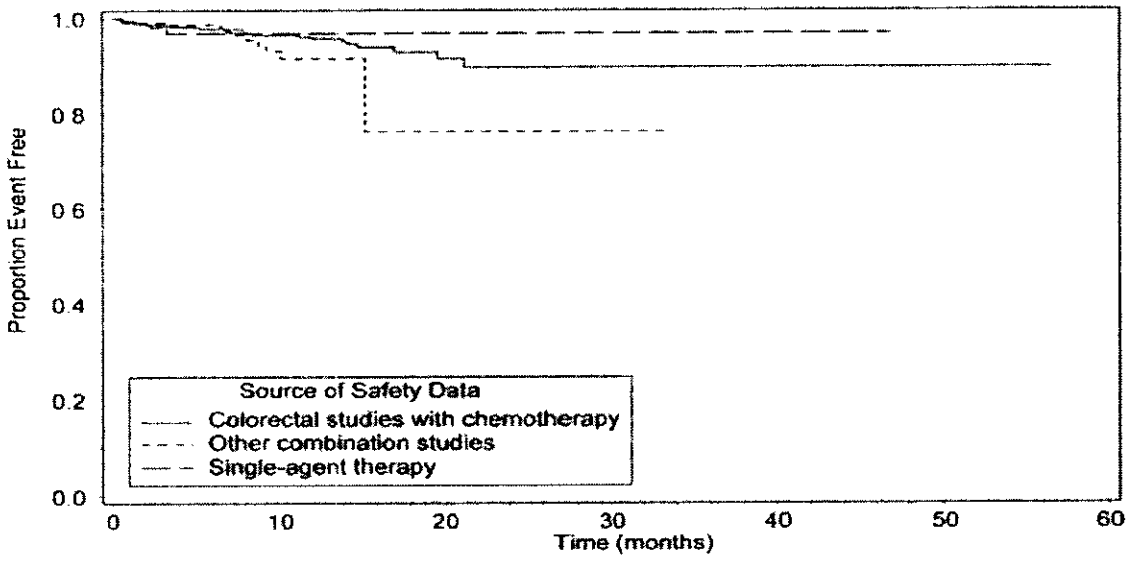
Genentech provided the results of a series of univariate, exploratory, post-hoc analyses for associations between the following baseline entry variables (age, gender, tumor type, baseline use of warfarin/aspirin, and prior thrombus resulting in the use of warfarin) and grade 3-4 hemorrhage. The association between grade 3-4 hemorrhage and on study factors; the use of warfarin/aspirin on study or a surgical procedure, was also examined. While these analyses provide

interesting data for further speculation, the exploratory nature of these analyses does not allow conclusions to be drawn from these analyses. In selecting analyses for further discussion, the significance of the Chi-squared test was used. Given the exploratory nature of these analyses, levels of significance should not utilized in applying the results of these analyses, but in selecting factors for further prospective evaluation.

Examining the entire ISS database, no factors appeared to be related to the presence of hemorrhage. In the Combination therapy group, gender appeared to be related to the development of hemorrhage. Grade 3-4 hemorrhage occurred in 6/41 males(14.6%) compared to 6/266 (2.3%) of females.

Time to Onset of Grade 3-4 Hemorrhage

Genentech presented the results of an exploratory analysis of time to the development of a grade 3-4 hemorrhagic event in the ISS database. Among the 48 Grade 3-4 hemorrhagic events in the database, 3 of the events occurred in control patients who crossed over to bevacizumab and 11 occurred during second-line therapy.



In the studies of colorectal cancer, hemorrhage appears to occur at a fixed rate. In the Combination studies, few patients are followed at late time points making interpretation of the late drops difficult.

Hemorrhage-Serious Adverse Events

Many of the significant hemorrhagic events that have been seen in patients treated with bevacizumab, such as hemoptysis, are described above. Additional hemorrhagic events include three patients on AV2107g who developed

subarachnoid hemorrhage. Two cases were associated with cerebrovascular accidents and one with severe hypertension.

- A patient [redacted] had an occult cerebral metastasis and experienced a central nervous system bleed 14 days after her first infusion of study drug.
- A second patient [redacted] developed spontaneous hemorrhage into a necrotic tumor mass in her thigh. Embolization of the mass was required to control bleeding.

In the NCI database, the following hemorrhagic events have been seen:

- Cerebrovascular accidents in four patients, 3 grade 4, 1 grade 4
- Two patients with bleeding into central nervous system metastases and seizure
- Subdural hematoma
- One patient with bleeding into a liver metastasis and hematobilia
- Five patients have had grade 3-4 epistaxis.

Congestive Heart Failure

In NCI-sponsored trials, expedited adverse event reports from a trial in relapsed acute non-lymphocytic leukemia suggested a higher than expected incidence of congestive heart failure (CHF). This trial will be discussed further below. Based on this finding, Genentech was asked to conduct analyses of the incidence and severity of CHF across the ISS database. The results are presented in the table below.

Incidence and Severity of Congestive Heart Failure in ISS Database and Treatment/Diagnosis Subgroups				
Congestive Heart Failure[1]	Colorectal N = 568	Combination N = 307	Single Agent N = 157	Total N = 1032
Gr 1	0	0		0
Gr 2	0	1 (0.3%)	1 (0.6%)	2 (0.2%)
Gr 3	7 (1.2%)	9 (2.9%)	2 (1.3%)	18 (1.7%)
Gr 4	0	1 (0.3%)	1 (0.6%)	2 (0.2%)
Total	7 (1.2%)	11 (3.6%)	4 (2.5%)	22 (2.1%)

[1]Note that one patient, 20889, is not included in this table due to lack of information concerning the grading of CHF. Pulmonary edema in this patient was noted to be mild.

The incidence of CHF is highest in the Combination subgroup, 75% of whom had metastatic breast cancer. The next highest incidence was in the Single Agent subgroup, approximately half of whom had metastatic breast cancer.

Studies involving patients receiving or previously exposed to cardiotoxic agents (predominantly metastatic breast cancer) are analyzed separately and presented below.

AVF2119g

AVF2119g, a Phase 3 study in metastatic breast cancer, randomized patients who had progressed on anthracycline and taxane therapy to capecitabine or capecitabine plus bevacizumab. In this study, 11 of 229 (4.8%) patients on the bevacizumab arm developed congestive heart failure compared to two of 215 (0.9%) patients in the control group. Tables summarizing the clinical characteristics and course of patients with CHF on AVF2119g are presented by treatment arm.

Capecitabine

Patient ID	Cardiotoxins	XRT to Left Chest	PMH	Baseline EF	EF w/ Event	Resolution
20811	doxorubicin	Y	No cardiac	71%	45%	Ongoing
21316	doxorubicin	Y	CHF due to doxorubicicn	38% on medication	14%	EF 28%

Capecitabine + Bevacizumab 15 mg/kg q 3 wks

Patient	Cardiotoxin	XRT to Left Chest	PMH	Baseline EF	EF w/ Event	Resolution
20147	doxorubicin	N	No cardiac			Pulmonary edema resolved
20182	trastuzumab	N	Cardio-myopathy	39%	19% global	42 % on medication
20241	doxorubicin	N	No Cardiac		40-45%	
20344	doxorubicin trastuzumab	Y	SLE	30%	20%	55% on medication
20382	doxorubicin	Y	No Cardiac	55%	20-25%	Symptoms improved
20464	doxorubicin	N	Sickle trait			
20641	doxorubicin	Y	No Cardiac	46%	20-25%	
21327	doxorubicin	Y	No Cardiac	66%	40-45%, global	
22141	doxorubicin trastuzumab	N	Arrhythmia		20-25%, global	Symptoms improved w/ medication
22761	doxorubicin	N	No Cardiac	48%	20-25%	30% on medication
22802	doxorubicin	N	No Cardiac	56%	10% global	1 mo: 30-40%, 2 mo: 50% on medication

Two patients, 20241 and 21327, continued bevacizumab following the event. Specific cardiac follow up information is not available. However, additional adverse events were not reported. One additional patient in the bevacizumab arm, 21781, developed pulmonary edema in the setting of superior vena cava syndrome. One additional patient developed congestive heart failure during her presentation with AML and sepsis.

A second study in patients with metastatic breast cancer, treated patients who had failed anthracycline and/or taxane therapy with 3, 10, or 20 mg/kg of bevacizumab every two weeks. In this study, two patients, one of 41 in the 10 mg/kg arm and one of 16 in the 20 mg/kg arm, developed congestive heart failure. None of the 18 patients in the 3 mg/kg arm developed CHF. One of these patients continued bevacizumab following the event. One month after the event, her ejection fraction was unchanged. One additional patient on this study, 7119, developed shortness of breath in association with atrial fibrillation.

Other Studies

Nine additional events were seen in patients without metastatic breast cancer.

- In AVF2107g, six patients developed congestive heart failure. Two additional patients developed congestive heart failure five and 11 months after discontinuation of bevacizumab. Of the six patients in the bevacizumab arms, two continued study drug. No cardiac follow up is available for these two patients, but no additional adverse events were recorded.
- Two patients developed congestive heart failure following cross over to single agent bevacizumab.
- One patient on AVF780g developed congestive heart failure two months after discontinuation of study drug. A second patient on AVF780g developed worsening hypertension associated with dyspnea during crossover. The patient had a history of congestive failure.

The National Cancer Institute database was also reviewed for instances of congestive heart failure.

Study 2490

This study treated patients with relapsed/refractory acute myelogenous leukemia with high dose cytarabine, mitoxantrone 40 mg/M^2, and bevacizumab 10 mg/kg. Mitoxantrone and bevacizumab are given once each cycle. The second cycle was to be given by day 60. Early in the study, six cases of congestive heart failure were seen. No additional cases were seen and 44 patients were ultimately enrolled. The overall incidence is 13.6%. Details of these events are included below.

Clinical Characteristics and Course of Patients with CHF in Study 2490						
Pt #	Cardiotoxins	Cycle	Baseline EF	EF w/ Event	Follow Up	Comments
314717	None	1	62%	30-35%		
1323701	Doxorubicin	1	60%	34% global	4 mo later 52%	H/o CHF w/prior doxorubicin
1348418	Mitoxantrone, Idarubicin	2	47%	30-35%		Associated w/chest pain
1358059	Mitoxantrone, Idarubicin	2	67%	< 30%	3 mo later 55-60%	
1361385	Mitoxantrone	1	49%	< 30% global		
1409358	Doxorubicin, Mitoxantrone	1	54%	30-35%	Assoc with AF	

Six additional patients in the NCI database have developed congestive heart failure.

Overall, there is an increased risk of CHF in patients receiving bevacizumab. This is largely confined to patients who are receiving an anthracycline or have previously received cardiotoxic agents.

Abnormal Healing

Following the reports of several patients with abnormal wound healing on AVF2107g, the sponsor retrospectively examined the experience with abnormal wound healing with bevacizumab across all Genentech-sponsored studies. In the randomized, controlled study in metastatic colorectal cancer, the number of patients with impaired wound healing was higher in the bevacizumab arm as compared to the control (1% vs. 0.5%). Discussion of impaired wound healing in patients enrolled in AVF2107g is described in detail in the study report (Section 6.1). Although the incidence is low, the clinical consequences of impaired wound healing have been serious, requiring surgical intervention and in some cases resulting in death.

The sponsor the following additional patients with serious adverse events as a result of impaired wound healing.

- One patient on AVF2119g who underwent surgery 26 days after her last dose of bevacizumab. Surgery was associated with excessive intra-operative blood loss requiring a transfusion.
- One additional patient on AVF780g was also identified. This patient received bevacizumab 30 days after her initial surgery. Forty-one days after the initial surgery, she developed wound dehiscence.

NCI-Sponsored Studies

A recent expedited report identified a patient who had received chemotherapy plus bevacizumab for multiple pulmonary metastatses of her sarcoma. The lesions were noted to cavitate and several were noted to be near the pleural surface. This was considered a possible cause of recurrent pneumothorax. The patient ultimately died of respiratory failure as a result of pneumothorax.

Allergic Reactions

Allergic reactions have been uncommon with the use of bevacizumab. Urticaria has been reported with initial infusion, but has not recurred on re-challenge. Events that appear consistent with hypersensitivity to bevacizumab are summarized below.

- One patient on study 2119g developed a maculopapular rash over her upper chest and arms following her second cycle of bevacizumab plus capecitabine. The rash progressed to her cheeks and back. Additional chemotherapy was administered. The narrative notes that following cycle four, she developed pain and stiffness in her hand with discolored nodular areas on the fingers. This was accompanied by skin peeling at the finger and toes. The patient had developed hand-foot syndrome earlier in the study. Capecitabine was discontinued, but she continued bevacizumab alone. Her rash worsened and punctate areas that were thought to be suggestive of central bleeding were noted within the rash. A skin biopsy showed interface dermatitis. The dermatologist did not believe this was a drug eruption. She received a topical steroid. She was noted to have a marked improvement in the rash on June 25, 2001, the date of her last dose of bevacizumab. On July 30, 2001, her rash had resolved.

- One patient — experienced an anaphylactoid reaction. This occurred approximately three years after the initiation of bevacizumab and nine days after dosing. The patient developed upper airway obstruction requiring intubation. Prior to study entry the patient had no history of allergy. However, the narrative notes that two months after study entry, she began cromolyn sodium. There are no additional details. Concomitant medications at the time of event included trandolapril, aspirin, trastuzumab, paroxetin, and levothyroxine. The event was thought by the investigator to be secondary to trandolapril. The patient had developed hypertension on study and initiated trandolapril approximately three years prior to the event. The patient was rechallenged with bevacizumab and trastuzumab without recurrence.

In the NCI database, nine allergic events are recorded. One is clearly related to the use of bevacizumab and a second is possibly related.

- One patient developed stridor and wheezing during bevacizumab infusion. The patient responded to epinephrine, diphenhydramine, and steroids and did not require hospitalization. This event occurred with her first dose of bevacizumab.
- The second patient received carboplatin/paclitaxel followed by bevacizumab. During the bevacizumab infusion, she developed chills and flushing. The infusion was discontinued and the patient was hospitalized. The patient died due to massive hemoptysis shortly after this event and was not rechallenged.

Infusional toxicity

Intravenous infusion of immunoglobulins, including monoclonal antibodies, has been commonly associated with a symptom complex of fever, chills, headache, flushing, and infrequently hypotension and bronchospasm. The incidence and severity of such reactions generally diminishes with subsequent infusions, thus distinguishing these events from true allergic reactions that recur with re-exposure. An examination of adverse events occurring with 48 hours of the first dose in the pivotal study AVF2107g is included in Section 6.1. Infusional reactions associated with the first dose were also examined in AVF2119g. The table below includes adverse events that occurred within two days of the first dose of bevacizumab plus capecitabine or capecitabine alone.

Incidence of Adverse Events within 48 hours of Initiation of Therapy by Treatment arm in AVF2119g		
Adverse Event Term	Capecitabine N = 215	Capecitabine + Bevacizumab N = 229
Tachycardia	5 (2.3%)	4 (1.7%)
Myalgia	3 (1.4%)	5 (2.2%)
Dyspnea	2 (0.9%)	4 (1.7%)
Cough Increased	2 (0.9%)	4 (1.7%)
Rhinitis	1 (0.5%)	0
Sinusitis	1 (0.5%)	0
Pruritus	1 (0.5%)	1 (0.4%)
Arthralgia	1 (0.5%)	1 (0.4%)
Vasodilation	0	4 (1.7%)
Fever	0	4 (1.7%)
Urticaria	0	1 (0.4%)

Delayed Adverse Events

Genentech presented an analysis of the incidence of adverse events occurring during Treatment Periods 1 and 2. Data is divided into events occurring from 0-4

months, 4-8 months, 8-12 months, and more than 12 months from initiation of bevacizumab. These were evaluated in terms of Treatment/Disease category. Events, which were increased by at least 5% in the population as a whole or within a Treatment/Disease group at the 4-8, 8-12 or > 12 month time point as compared to 0-4 months is included in the applicant's summary. Only data for the total population is presented below.

	0-4 Months N = 1032	4-8 Months N = 722	8-12 Months N = 492	> 12 Months N = 329
Body as a Whole				
Anaphylactoid Reaction	0	0	0	1 (0.3%)
Infection	6 (0.6%)	2 (0.3%)	2 (0.4%)	5 (1.5%)
Cardiovascular				
Cardiomyopathy	3 (0.3%)	2 (0.3%)	0	2 (0.6%)
Cerebral Ischemia	2 (0.2%)	0	1 (0.2%)	1 (0.3%)
Deep Thrombophlebitis	36 (3.5%)	20 (2.8%)	4 (0.8%)	7 (2.1%)
Hypertension	85 (8.2%)	31 (4.3%)	23 (4.7%)	27 (8.2%)
Vascular Disorder	1 (0.1%)	0	0	1 (0.3%)
Digestive				
Vomiting	36 (3.5%)	7 (1.0%)	9 (1.8%)	5 (1.5%)
Hemic/Lymphatic	188 (18.2%)	37 (5.1%)	21 (4.3%)	19 (5.8%)
Leukopenia	164 (15.9%)	32 (4.4%)	14 (2.8%)	14 (4.3%)
Musculoskeletal	13 (1.3%)	9 (1.2%)	4 (0.8%)	7 (2.1%)
Arthralgia	5 (0.5%)	3 (0.4%)	1 (0.2%)	3 (0.9%)
Nervous			1	
Anxiety	3 (0.3%)	0	1 (0.2%)	2 (0.6%)
Depression	6 (0.6%)	1 (0.1%)	1 (0.2%)	3 (0.9%)
Respiratory	65 (6.3%)	17 (2.4%)	20 (4.1%)	14 (4.3%)
Pneumonia	6 (0.6%)	5 (0.7%)	1 (0.2%)	4 (1.2%)
Urogenital	25 (2.4%)	8 (1.1%)	12 (2.4%)	13 (4.0%)
Prostatic Disorder	0	0	0	1 (0.3%)
Uterine Neoplasm	0	0	0	1 (0.3%)

Additional Adverse Events

Additional adverse events of interest are those that occurred in a small number of patients, but were unusual and severe. These are included below.

Hematologic
The vascular endothelial growth factor receptor 2 is expressed on precursor cells of the hematopoietic lineage. Hematologic consequences are, therefore, of increased interest.

- On AVF2107g, one patient developed **myelodysplasia.** The patient had not received prior chemotherapy or radiation therapy. However, at screening, his platelet count was 114,000/mm^3.
- Patient 21062 on AVF2119g developed persistent neutropenia while receiving capecitabine plus bevacizumab 15 mg/kg. A bone marrow biopsy revealed **acute myelogenous leukemia**. Prior therapy included cyclophosphamide, methotrexate, 5-fluororuracil, radiation therapy, doxorubicin, and docetaxel. She attained a complete remission of her acute leukemia, but subsequently died from metastatic breast cancer.
- Patient 20889 on AVF2119g was noted to have persistent neutropenia while receiving capecitabine plus bevacizumab 15 mg/kg. This was followed by her presentation with fever and circulating blasts. Prior therapy included cyclophosphamide, methotrexate, 5-fluorouracil, radiation therapy, paclitaxel, and doxorubicin. During this presentation, she was also noted to have congestive heart failure and microangiopathic ischemic changes in the brain. The patient subsequently died from **acute leukemia**.

Musculoskeletal/Neurologic

- One patient on AVF2107g developed proximal muscle weakness associated with dark urine and a creatinine kinase of 35,201 U/L 21 days after his last dose of study drug. The patient was also taking gemfibrozil and simvastatin. Muscle biopsy showed non-specific Type II fiber atrophy. He required dialysis. Approximately six weeks after the last dose of study drug, the patient developed pancytopenia. Bone marrow was normocellular without dysplasia. The patient died of possible intra-abdominal sepsis and **rhabdomyolysis**.
- Patient 11728 on AVF2107g presented, approximately one week after his last dose of IFL + Bevacizumab, with an inability to walk. Proximal weakness and distal muscle atrophy were noted. Nerve conduction studies showed a demyelinating component. He was given a diagnosis of **Guillian-Barre Syndrome**.
- After 10 months of 5FU/LV/Bevacizumab, one patient on AVF2107g began to experience **difficulty lifting his arms**. He discontinued study drug. One month later, he continued to have difficulty lifting his arms.
- Patient 11824, in the IFL + Bevacizumab arm of AVF2107g, is noted in the case report tabulations to have an adverse event of **myasthenia gravis** on [redacted] This patient's last dose of study drug was [redacted] A narrative is provided for this patient, but this adverse event is not included. The patient does not have a history of myasthenia gravis.

The applicant also included an expedited report from an investigator-sponsored study in the BLA submission.

- This patient with a past medical history of myasthenia gravis developed increasing difficulty swallowing during therapy with bevacizumab and erlotinib for metastatic renal cell carcinoma. The patient had a history of a resected

brain metastasis prior to entry. This event was thought to represent a relapse of **myasthenia gravis**. Also of note, this patient had a recent history of a tick bite and of a peri-oral rash.

Respiratory

- One patient [redacted] presented with flu like symptoms approximately two weeks after her last dose of bevacizumab. She had an interstitial infiltrate and bilateral effusions. Thoracentesis was negative for malignancy. Open lung biopsy revealed non-diffuse **fibrointimal hyperplasia** and patchy bronchiolitis. The patient presented one month later with worsening liver function and a left upper extremity thrombosis related to an indwelling catheter. The patient became hypotensive and apneic and required intubation. An echocardiogram revealed severely reduced left ventricular function with generalized hypokinesis and a right ventricular mass. The patient was able to be discharged following this event. Her functional cardiac status gradually improved. Medication use is unknown. On [redacted] she resumed bevacizumab.
- After two months of IFL + Bevacizumab, one patient on AVF2107g presented with shortness of breath and a room air oxygen saturation of 77%. Her respiratory status continued to deteriorate and she was placed on a ventilator. Bronchoscopy was negative for infection, but transbronchial biopsy did show **interstitial fibrosis and acute inflammation**. The patient ultimately recovered, but discontinued study drug.

Adverse Event Profile in Special Populations

Age

Of the 742 patients who have received bevacizumab on Genentech sponsored trials in which grade 1-4 adverse events were collected, 530 were less than 65 and 212 at least 65 years of age. Forty-three were at least age 75. Adverse events in patients greater than 75 years of age were not assessed. The table below contains a selected listing of adverse events, i.e., adverse events that differed in absolute incidence by at least 5% between those less than 65 and those at least 65 years of age.

Incidence of Selected Adverse Events by Age in ISS Database		
	< 65 years N = 530	≥ 65 years N = 212
Overall	529 (99.9%)	211 (99.5%)
Body as a Whole		
Asthenia	357 (67.4%)	155 (73.1%)
Headache	197 (37.2%)	47 (22.2%)
Digestive		
Diarrhea	316 (59.6%)	149 (70.3%)
Anorexia/Cachexia	162 (30.6%)	90 (42.4%)

Dyspepsia	80 (15.1%)	44 (20.8%)
GI Hemorrhage	15 (2.8%)	17 (8.0%)
Hemic/Lymphatic		
Leukopenia	107 (20.2%)	61 (28.8%)
Anemia	83 (15.7%)	48 (22.6%)
Metabolic/Nutrition		
Edema	88 (16.6%)	69 (32.5%)
Respiratory		
Epistaxis	128 (24.2%)	63 (29.7%)
Cough Increased	118 (22.3%)	61 (28.8%)
Voice Alteration	26 (4.9%)	24 (11.3%)
Skin		
Exfoliative dermatitis	201 (37.9%)	27 (12.7%)

Note that headache and exfoliative dermatitis are reported at a lower incidence in the elderly, but that the remainder of the adverse events are reported at a higher incidence those at least 65 when compared to patients less than 65. Also note that adverse events that have been associated with bevacizumab such as hypertension and thrombosis are not increased.

Gender

Of the 1032 patients treated with bevacizumab in the Genentech database, 607 were female and 425 male. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., events that differed in absolute incidence by at least 2% between males and females, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Gender in ISS Database		
	Female N = 607	Male N = 425
Grade 3-4 Events		
Body as a Whole		
Asthenia	76 (12.5%)	37 (8.7%)
Pain	37 (6.1%)	16 (3.8%)
Headache	22 (3.6%)	3 (0.7%)
Digestive		
Diarrhea	126 (20.8%)	123 (28.9%)
Skin		
Exfoliative Dermatitis	71 (11.7%)	4 (0.9%)

In general, the incidence of grade 3-4 adverse events was similar in females and males, an exception is exfoliative dermatitis. Modest differences in the incidence of adverse events may be attributed to the underlying cancer type and chemotherapeutic regimen employed. Slightly less than half of the female patients were enrolled in the two studies of patients with metastatic breast

cancer, — and AVF2119g. — administered single agent bevacizumab while AVF2119g administered capecitabine plus bevacizumab. Exfoliative dermatitis has been reported in association with the use of capecitabine. In AVF2119g, the incidence of exfoliative dermatitis was 75.3% in the capecitabine arm and 84.3% in the capecitabine plus bevacizumab arm.

Race/Ethnicity

Of the 1032 patients treated with bevacizumab in the Genentech database, 836 were White, 118 Black, and 78 Hispanic or Other. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., those reported at higher absolute incidence (at least 2% higher) in patients whose race was categorized as Black or Hispanic/Other as compared to White, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Race in ISS Database			
	White N = 836	Black N = 118	Hispanic/Other N = 78
Adverse Event Term	Grade 3-4	Grade 3-4	Grade 3-4
Hypertension	138 (16.5%)	25 (21.2%)	8 (10.3%)
Hypokalemia	30 (3.6%)	7 (5.9%)	3 (3.8%)

Hypertension was reported at a higher incidence in Black patients when compared to Whites or patients characterized as Hispanic/Other.

Renal Dysfunction

Patients with significant renal dysfunction were excluded from Genentech sponsored studies. Eligibility criteria for the Phase 3 program required patients to have a creatinine less than 2 mg/dL. The eligibility criteria for the Phase 1 and 2 program required patients to have a creatinine of less than 1.5 mg/dL. The one exception to this was — which required a creatinine less than 1.8 mg/dL.

Of the 1032 patients treated with bevacizumab in the Genentech database, 33 patients had a calculated creatinine clearance of less than 50 mL/min at study entry. Events, which are increased by at least 2% in these patients, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Renal Function in ISS Database		
	With Renal Dysfunction N = 33	Without Renal Dysfunction N = 999
Body as a Whole		
Abdominal Pain	5 (15.2%)	70 (7.0%)
Cardiovascular		
Pulmonary Embolism	3 (9.1%)	21 (2.1%)
Congestive Heart Failure	2 (6.1%)	11 (1.1%)

Digestive		
Diarrhea	9 (27.3%)	240 (24.0%)
Anorexia	2 (6.1%)	23 (2.3%)
GI Hemorrhage	1 (3.0%)	15 (1.5%)
Hemic/Lymphatic		
Anemia	2 (6.1%)	28 (2.8%)
Metabolic/Nutrition		
Hypokalemia	3 (9.1%)	37 (3.7%)
Hypercalcemia	2 (6.1%)	8 (0.8%)
Respiratory		
Dyspnea	3 (9.1%)	65 (6.5%)
Urogenital		
Proteinuria	2 (6.1%)	7 (0.7%)
Urinary Tract Infection	2 (6.1%)	9 (0.9%)

Since the number of patients with an abnormal creatinine clearance is small it is difficult to draw conclusions concerning differences in the adverse event profile of patients with renal dysfunction. However, patients with an abnormal calculated creatinine clearance had a higher incidence of electrolyte abnormalities, diarrhea, pulmonary embolism, CHF and proteinuria. The incidence of hypertension was similar in patients with normal and abnormal renal function and is not included in this table.

Hepatic Dysfunction

Patients with significant hepatic dysfunction (NCI CTC grade 3 or greater) were excluded from Genentech sponsored studies of bevacizumab. Of the 1032 patients treated with bevacizumab in the Genentech database, 333 had abnormal liver function tests at baseline. Adverse events of Grade 3 or 4 severity were collected in all patients. Selected adverse events, i.e., higher absolute incidence of at least 2% in patients abnormal hepatic function, are included in the table below.

Incidence of Selected Grade 3-4 Adverse Events by Hepatic Function in ISS Database		
	With Hepatic Dysfunction N = 334	Without Hepatic Dysfunction N = 698
	Grade 3-4	Grade 3-4
Abdominal Pain	28 (8.4%)	47 (6.7%)
Fever	4 (1.2%)	8 (1.1%)
Stomatitis	4 (1.2%)	4 (0.6%)
Epistaxis	2 (0.6%)	2 (0.3%)
Exfoliative Dermatitis	28 (8.4%)	47 (6.7%)

Approximately half the patients in the ISS database had underlying colorectal cancer. In the pivotal study, AVF2107g, only seven patients in the IFL + Placebo and 10 patients in the IFL + Bevacizumab arm had grade 3-4 hepatic dysfunction

during therapy. This number was too small to permit analysis of adverse event profile in patients with severe hepatic dysfunction.

6.3 Literature Review and Other Relevant Materials

6.3.1 Drug Safety Review of Intestinal Perforation

DATE: February 9, 2004

FROM: Charlene M. Flowers, R.Ph.
Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Patricia Keegan, M.D., Director
Division of Therapeutic Biologic Oncology Products (DTBOP), HFM-573

SUBJECT: Office of Drug Safety (ODS) Postmarketing Safety Review (PID #D030708)
Adverse Event: Gastrointestinal Perforation
Drug: Irinotecan, fluorouracil, and leucovorin
NDA#'s 20-571 (6/14/1996*), 12-209 (4/25/1962*), and 08-107 (6/20/1952*)
*FDA approval date

Executive Summary

In response to your request, we searched the AERS database for cases of gastrointestinal perforation in association with irinotecan, fluorouracil, and leucovorin. This search identified four unduplicated cases of gastrointestinal perforation in males of a mean age of 58 years involving sites in the colon (2) and stomach (2). Two patients developed peritonitis and died due to respiratory arrest or septic shock. Two other patients required a surgical ileostomy and a colostomy. Although temporally related to drug administration, it is difficult to conclude that gastrointestinal perforation was causally related to the use of irinotecan-fluorouracil-leucovorin as underlying metastatic conditions (i.e. metastatic disease, surgical complications), may have contributed to the event.

Background

Bevacizumab is a humanized monoclonal antibody to the vascular endothelial growth factor used in combination with fluorouracil as first line treatment of metastatic colorectal cancer. During a review of a BLA application, Dr. Ellen Maher noted a case of Bevacizumab-fluorouracil related bowel perforation. For

comparison, a request was made to ODS to search the AERS database and to identify cases of gastrointestinal perforation associated with a regimen irinotecan-fluorouracil-leucovorin, an approved (June 14, 1996) regimen similarly indicated for first-line treatment of metastatic colorectal cancer.

Product label

The product label for irinotecan, fluorouracil, and leucovorin contains the following information relevant to gastrointestinal adverse events.

Irinotecan (Camptosar): Warnings: Camptosar can induce both early and late forms of diarrhea. . Post Marketing Experience: . . . Cases of colitis complicated by ulceration, bleeding, ileus, or infection have been observed. . .

Fluorouracil (5 FU): Precautions: . . . *Diarrhea, frequent bowel movements or watery stools, gastrointestinal ulceration and bleeding* . . . Adverse Reactions: *Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy . . . gastrointestinal ulceration and bleeding . . .*

No gastrointestinal adverse events are mentioned in the product label for leucovorin (Wellcovorin).

Medical Literature

Medline was searched for case reports of gastrointestinal perforation occurring with the use of irinotecan, fluorouracil, and leucovorin. No cases were identified.

Selection of Cases

On January 6, 2004, the AERS database was searched utilizing the drug interaction field to identify reports of any nature in association with a chemotherapy regimen of irinotecan, fluorouracil, and leucovorin. This search identified 664 reports. The serious outcomes were death (131), hospitalization (423), life-threatening adverse events (38), disability (10), and congenital anomaly (1). The outcome was serious in 81% of reports. The 10 most frequently reported adverse event terms in descending order of count were DIARRHEA (165), NEUTROPENIA (137), PYREXIA (93), VOMITING (85), DEHYDRATION (78), ABDOMINAL PAIN (63), NAUSEA (63), DRUG TOXICITY (46), ASTHENIA (44), and DEEP VEIN THROMBOSIS (36). These are expected adverse events listed in the current product label of irinotecan, fluorouracil, and/or leucovorin.

A second AERS search using the higher level group term (HLGT) of GASTROINTESTIONAL ULCERATION and PERFORATION identified seven unduplicated cases of gastrointestinal disorders. Three cases were excluded

from further summary. In two cases, the diagnosed event was unrelated to the topic of interest, and a third case had a diagnosis of a small bowel ileus without perforation. The remaining four cases of gastrointestinal perforation are summarized below.

Summary of Cases

Four cases of gastrointestinal perforation originated from the United States (1) and foreign (3) sources. All four cases in men with an average age of 58 years (range 49 to 64 years) were treated with a regimen of irinotecan, fluorouracil, and leucovorin for colorectal cancer. The duration of therapy before symptoms appeared ranged from one to five cycles. One patient had received the dual combination of fluorouracil and leucovorin in the first four of six cycles then irinotecan was added to cycles five and six. In three patients where presenting symptoms were described, abdominal pain was the most common symptom. Two of the three patients experienced other events such as pneumonia, cardiac compromise, pyrexia, pancytopenia, and/or septic shock. The site of gastrointestinal perforation was the colon (2) or stomach (2). Two cases reported death as an outcome. One patient who experienced colon perforation died of respiratory arrest and the other who experienced peritonitis from gastric perforation, subsequently died of septic shock. The remaining two patients required a surgical ostomy to repair stomach and small bowel perforation. Both were hospitalized for 26 and nine days respectively and recovered. Chemotherapy in both patients was delayed and then restarted; however, irinotecan was eventually discontinued in one patient. The four cases are summarized below.

(AERS/MFR# 3054424-8/83442; March13, 1998; USA; study report)
A 57 year old male who weighed 160 pounds with a medical history of thromboembolic disease received chemotherapy of fluorouracil 800 mg, and leucovorin 37.6 mg for four cycles to treat colorectal cancer, starting in June 1997. He experienced anemia and deep vein thrombosis. Treatment included blood transfusion and heparin then he recovered. The events were likely related to underlying medical conditions. On February 5, 1998, irinotecan (235mg/week intravenous infusion) was added into the chemotherapy regimen at cycles five and six. On —— the patient developed abdominal pain, abdominal distention, and difficulty breathing. One day later, he experienced liquid brown bloody stools. At some unknown date, he developed cardiac compromise, and it was medically treated with defibrillation, epinephrine, dopamine, norepinephrine, and a normal saline infusion. Objective medical findings included a peritoneal lavage that was positive for stool indicating a perforated colon, and a chest x-ray revealed patchy right lower lobe infiltrates consistent with infection or aspirations. Chemotherapy was stopped on February 12, 1998. The patient died due to respiratory arrest on ——

(FDA/MFR#4162355-5/2003161029IT; August 1, 2003; Italy)

A 64 year old male with a history of liver metastasis and neoplastic infiltration of the abdominal posterior wall received irinotecan 288 mg, fluorouracil 960 mg, and leucovorin 160 mg for three cycles (last cycle was 4/22/03) to treat colorectal cancer. On —, the patient experienced gastric pain, febrile neutropenia, and leucopenia. On — gastric wall perforation with septic shock was suspected, he developed thrombocytopenia, and an abdominal CT scan revealed possible ascites and bubbles. On —, the patient died. An autopsy revealed peritonitis. The reporter stated the patient's adverse events may have been related to chemotherapy, to neoplastic cell infiltration in the abdominal wall, or to an existing gastric ulcer that perforated.

(FDA/MFR# 3852055-0/2001084771IT; January 14, 2002; —
A 49 year old male with a history of sigmoid cancer requiring an anastamosis received irinotecan 300 mg, fluorouracil 700 mg, and leucovorin 350 mg for one cycle on June 1, 2001. On —, he required hospital admission for peritonitis from bowel perforation at a perianastomotic site. On —, he received an iliac colostomy. A biopsy for abdominal histology was negative for neoplastic cells. On August 7, cycle two of chemotherapy was restarted, and he developed a post-surgical anatomotic fistula requiring medication. He recovered in five days then the third cycle was given on December 5, without irinotecan.

(FDA/MFR#3670150-6/2001043595GB; February 23, 2001; — study report)
A 64 year old male with a history of metastatic disease in the liver, lymph nodes, and stomach (primary site) received study drug of irinotecan 180 mg, fluorouracil 2,800 mg, and leucovorin 175 mg for five cycles (treatment ended December 2, 2000) to treat advanced colorectal cancer. He presented to the hospital with gastric pain, and an examination revealed gastric perforation with subsequent peritonitis. Treatment included medical support and antibiotics; however, surgery was ultimately required for an ileostomy. Following a —, hospital stay, he was discharged on — Chemotherapy continued, but cycle six was delayed due to the adverse event.

Conclusion

We identified four cases of gastrointestinal perforation associated with irinotecan-fluorouracil- leucovorin. Two patients died. In these cases involving sites in the colon (2) or stomach (2), underlying medical conditions or a complicated clinical course may have contributed to the adverse event. Three patients reported a medical history of abdominal neoplastic infiltrates (2) or a prior surgical anastamosis in the colon (1). One remaining patient developed a complex medical course and died of respiratory failure. Although temporally related to drug administration, it is difficult to determine a causal relationship. Please let me know if you need further assistance.

Signatures

Reviewer Signature /S/

Supervisor Signature /S/ Concurrence Yes ✓ No

Date 2/26/2004