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Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 125085.0
Drug Name: AVASTIN (Bevacizumab)
Indication(s): AVASTIN in combination with 5-fluorouracil-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon and rectum,
Applicant: Genentech, Inc.
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

A large randomized, double-blind, well-controlled Phase III study demonstrated that the addition of bevacizumab 5 mg/kg every 2 weeks to bolus irinotecan/5-fluorouracil/leucovorin (bolus-IFL) chemotherapy improve survival, time to disease progression, and response rate, compared with those receiving bolus-IFL + placebo. The results from a Phase II randomized trial with 5-FU/leucovorin chemotherapy also support the efficacy findings. It appears that bevacizumab treatment was associated with slightly higher incidence of adverse events. However, the benefits (e.g.: 34% decrease in the hazard of death) outweigh the increase of adverse events due to the addition of bevacizumab.

The efficacy results from the Phase III trial support the claim of using bevacizumab for first-line treatment of patients with metastatic carcinoma of the colon and rectum in combination with bolus-IFL chemotherapy.

1.2 Brief Overview of Clinical Studies

AVASTIN (Bevacizumab) is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Neutralizing the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth. The sponsor is seeking the indication of Bevacizumab in combination with 5-fluorouracil based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon and rectum. The recommended dose is 5 mg/kg every 2 weeks administered intravenously, in combination with bolus-IFL chemotherapy.

Results from two randomized clinical trials are provided, as the key studies, to support the addition of bevacizumab to standard chemotherapy in the first-line treatment of carcinoma of the colon and rectum. Study AVF2107g is a large, randomized, active-controlled, double-blind, Phase III trial. Supportive data are provided from Study AVF0780g, a randomized, controlled, dose-ranging, Phase II study. Data from seven other trials are also used to support the safety findings.

Study AVF2107g

Study AVF2107g was a large, randomized, double-blind, active-controlled, three-arm, Phase III Study designed to evaluate the efficacy and safety of bevacizumab in combination with bolus-IFL chemotherapy (bolus irinotecan/5-FU/leucovorin) or 5-FU/leucovorin chemotherapy as first-line therapy for previously untreated metastatic colorectal cancer. Eligible subjects were initially randomized to one of three treatment arms: Arm 1 (bolus-IFL + placebo), Arm 2 (bolus-IFL + bevacizumab, 5 mg/kg every 2

weeks), or Arm 3 (5-FU/leucovorin + bevacizumab, 5 mg/kg every 2 weeks). The planned study enrollment was 900 subjects.

The third arm (5-FU/leucovorin + bevacizumab) was included in this trial because the safety of combining bevacizumab with the bolus-IFL regimen was unknown. If undue toxicity had been seen with Arm 2 (bolus-IFL + bevacizumab), enrollment in this arm would have been discontinued and Arm 3 would have been the comparator arm versus the Arm 1 control. After approximately 100 subjects had been enrolled in each arm, the independent Data Monitoring Committee (DMC) reviewed unblinded safety data and determined that the safety profile of bolus-IFL + bevacizumab was acceptable. Thus, enrollment in Arm 3 was discontinued, and an additional 300 subjects per arm were enrolled in Arms 1 and 2.

The primary efficacy endpoint was duration of survival. The secondary efficacy endpoints were progression-free survival (PFS), objective response, duration of objective response, and time to deterioration in quality of life (TDQ). The stratified log-rank test was used to compare survival between the two arms.

A total of 923 eligible subjects were randomized into the three treatment arms in this study: 411 subjects in Arm 1 (bolus-IFL + placebo), 402 subjects in Arm 2 (bolus-IFL + bevacizumab), and 110 subjects in Arm 3 (5-FU/leucovorin + bevacizumab). Demographic and baseline characteristics were well balanced across Arms 1 and 2 and were typical of patients with metastatic colorectal cancer in the United States.

The addition of bevacizumab to bolus-IFL chemotherapy as first-line therapy for metastatic colorectal cancer resulted in a clinically meaningful and statistically significant prolongation of survival (see Table 1 and Figure 1), with a corresponding increase in median duration of survival from 15.6 months in Arm 1 to 20.3 months in Arm 2. The survival benefit from bevacizumab was seen in all pre-specified subject subgroups defined by age, sex, race, ECOG performance status, location of primary tumor, prior adjuvant therapy, duration of metastatic disease, number of metastatic sites, years since colorectal cancer diagnosis, prior radiotherapy, baseline tumor burden, baseline albumin, baseline alkaline phosphatase, and baseline LDH.

The addition of bevacizumab to bolus-IFL chemotherapy also resulted in a significant improvement in PFS (median PFS changed from 6.2 months in the placebo arm to 10.6 in the bevacizumab arm). Among all randomized subjects, the objective response rate was statistically significantly higher in Arm 2 (45%) than in Arm 1 (35%) ($p=0.0036$). There was no statistically significant difference in TDQ as measured by the colorectal cancer-specific (CCS) score between treatment arms. Median TDQ in CCS scores was 2.73 months in Arm 1 and 2.89 months in Arm 2.

It appears that bevacizumab treatment was associated with slightly higher incidence of adverse events such as diarrhea and leukopenia, as well as an increase in the number of chemotherapy dose reductions and a small decrease in chemotherapy dose intensity.

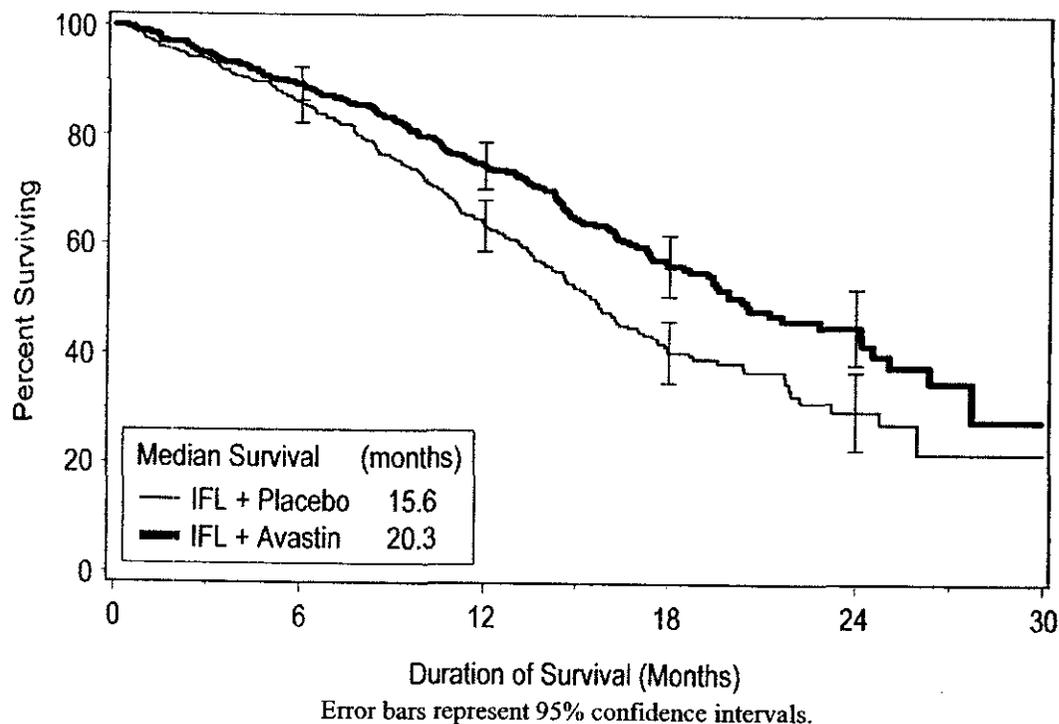
Table 1
Duration of Survival in Study AVF2107g

	Arm 1 b-IFL + Placebo (n=411)	Arm 2 b-IFL + Bevacizumab (n=402)
Subjects who died	225	174
Censored observations	186 (45.3%)	228 (56.7%)
Duration of survival (months)		
Median	15.61	20.34
95% CI	(14.29, 16.99)	(18.46, 24.18)
Stratified analysis ^a		
Hazard ratio	—	0.660
95% CI	—	(0.54, 0.81)
p-value (log-rank)	—	0.00004
Proportion of subjects alive		
at 6 months	85.5%	89.3%
at 12 months	63.4%	74.3%
at 24 months	29.7%	45.1%

b-IFL = bolus irinotecan/5-fluorouracil/leucovorin.

^a Factors: ECOG PS, site of primary disease, number of metastatic sites.

Figure 1
Duration of Survival in Study AVF2107g



Study AVF0780g

Study AVF0780g was a randomized, open-label, multi-dose, Phase II study designed to evaluate the efficacy, safety, and pharmacokinetics of bevacizumab combined with 5-FU/leucovorin chemotherapy in subjects with previously untreated metastatic colorectal cancer. Eligible subjects were randomized to one of three treatment arms: control (5-FU/leucovorin alone), 5-FU/leucovorin + bevacizumab 5 mg/kg every 2 weeks, or 5-FU/leucovorin + bevacizumab 10 mg/kg every 2 weeks. The planned enrollment was 90 subjects.

The primary efficacy endpoints were time to disease progression and objective response, with the primary analysis based on the investigator tumor assessments. Secondary efficacy endpoints were overall survival, duration of response, and change in quality-of-life scores.

A total of 104 subjects were randomized to the three treatment arms: 36 subjects to the 5-FU/leucovorin alone arm, 35 subjects to the 5-FU/leucovorin + 5 mg/kg/2wk bevacizumab arm, and 33 subjects to 5-FU/leucovorin + 10 mg/kg/2wk bevacizumab. The efficacy results are presented in Table 2. The results of this study demonstrate that bevacizumab 5 mg/kg every 2 weeks, in combination with 5-FU/leucovorin chemotherapy, increased response rate, prolonged time to disease progression, and prolonged survival compared with 5-FU/leucovorin chemotherapy alone.

Table 2
Efficacy Results for Study AVF0780g in Colorectal Cancer

Endpoint	Control (n=36)	Bevacizumab	
		5 mg/kg/2wk (n=35)	10 mg/kg/2wk (n=33)
Time to disease progression			
Number of progressions	26 (72%)	22 (63%)	23 (70%)
Median (months)	5.2	9.0	7.2
Hazard ratio	—	0.440	0.692
p-value (log-rank)	—	0.005	0.217
Objective response rate (IRF + investigator)			
Objective response	6 (17%)	14 (40%)	8 (24%)
p-value (χ^2)	—	0.029	0.434
Duration of survival			
Number of deaths	19 (53%)	12 (34%)	19 (58%)
Median (months)	13.6	17.7	15.2
Hazard ratio	—	0.521	1.009
p-value (log-rank)	—	0.073	0.978

Notes: Of the 36 control subjects, 22 crossed over to bevacizumab after disease progression. Independent review facility (IRF)/investigator endpoints were based on the IRF assessment in all but 3 subjects; in these subjects, the investigator assessment was used.

1.3 Statistical Issues and Findings

1.3.1 Conservation of the overall type I error rate

In the large, randomized, double-blind, Phase III trial (AVF2107g), one arm was dropped in the middle of the trial. There was an interim analysis intended to stop the trial earlier if the efficacy evidence is striking.

As the combination of bolus-IFL + rhuMab VEGF (Arm 2) had not been tested in clinical trials, the initial part of the trial included a real-time assessment of safety. The results of the interim safety analysis were used to decide whether the bolus-IFL + rhuMab VEGF combination (Arm 2) was safe. If the DMC determined that Arm 2 was safe, enrollment in Arm 3 would be discontinued after 100 subjects had been randomized to that arm, and enrollment in Arms 1 and 2 would be continued until a total of 400 subjects per treatment arm had been enrolled. If the DMC determined that Arm 2 was unsafe, enrollment in Arm 2 would be immediately discontinued, and enrollment in Arms 1 and 3 would be continued until a total of 400 subjects per treatment arm were enrolled. Following the interim safety analysis, the DMC notified Genentech that the safety profile of Arm 2 was acceptable. Accordingly, the 5-FU/leucovorin + rhuMab VEGF arm (Arm 3) was closed to further enrollment of new subjects, as specified in the original protocol. Because Arm 3 was dropped based on safety evaluation, it should not have any impact on the overall Type I error rate.

An interim analysis of efficacy was scheduled when approximately half this number of deaths had occurred. To control for the Type I error rate for the primary endpoint of duration of survival, the Lan-DeMets implementation of the O'Brien-Fleming α spending function was used. The α -level for the final analysis is approximately equal to — a level not substantially different from 0.05. The actual p-value associated with the chi-square test statistic for the primary analysis is —. Thus, the difference between the two arms in overall survival is statistically significant at 0.05 in the final analysis after adjusting for the α spending at the interim analysis.

1.3.2 Potential Biases for Efficacy Evidence

The large, randomized, double-blind, Phase III trial (AVF2107g) demonstrated that the addition of rhuMab VEGF to bolus-IFL chemotherapy improves survival, as reflected in the 34% decrease in the daily risk of death for subjects receiving bolus-IFL + rhuMab VEGF compared with those receiving bolus-IFL alone. Corresponding significant increases in progression-free survival, objective response rate, and duration of response support this finding. This reviewer has checked the sponsor's analyses and found that the results agree with what the sponsor has presented.

However, a couple of concerns were raised during the review process 1) there was a substantial number of patients with eligibility and/or protocol violation which may have significant impact on the efficacy results; 2) we were not sure if the difference between

the two arms in survival was due to the addition of bevacizumab or due to the less amount of chemotherapy received by patients in the placebo group.

This reviewer re-analyzed the survival endpoint with eligibility and/or protocol violation data and results are presented in Section 4.2.1. As shown from Figures 8-11, there was an overall consistent trend for increased median duration of survival for subjects in Arm 2 (bevacizumab) compared with those in Arm 1 (placebo) regardless of patients with eligibility and/or protocol violations or not. It is unlikely that eligibility and/or protocol violation could have any significant impact on the efficacy results.

From Table 18 in Section 3.2 (Safety Evaluation), one can see that the number of doses of study drug received was higher for subjects in Arm 2 than for those in Arm 1. However, this may be due to the difference between the two arms in length on study and follow-up since patients in the placebo arm were likely to progress and die earlier. As shown in Table 19, the number of subjects with at least one chemotherapy dose level reduction was higher in Arm 2 than in Arm 1. Dose intensity percentages for study drug and chemotherapy were also slightly lower for subjects in Arm 2 compared with those in Arm 1 (see Table 20). These results indicate that patients in the placebo arm did not receive less dosage of chemotherapy agents **per unit of time**, compared to those who were enrolled in the bevacizumab arm. Thus, the difference between the two arms in survival was very unlikely due to the less amount of chemotherapy received by patients in the placebo group.

Therefore, the efficacy evidence remains strong regardless of the concerns.

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2. INTRODUCTION

2.1 Overview

AVASTIN (Bevacizumab) is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralizing the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth.

The sponsor is seeking the indication of Bevacizumab in combination with 5-fluorouracil based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon and rectum. The recommended dose is 5 mg/kg every 2 weeks administered intravenously, in combination with bolus irinotecan/5-fluorouracil/leucovorin (bolus-IFL) chemotherapy.

Bevacizumab is being developed to treat patients with solid tumors, including metastatic colorectal cancer. A tabular listing of all studies and related information is provided in Table 3.

Table 3
Listing of Clinical Studies

Phase	Study	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Route of Administration	Number of Subjects	Indication	Duration of Treatment	Study Status; Type of Report
I	AVF0737g	5.3.3.2	Safety, tolerability, pharmacokinetics	Open-label, multiple dose	Bevacizumab, IV	25	Solid tumor	Up to 42 days	Final CSR 1 Oct 1997
I	AVF0761g	5.3.3.2	Safety, tolerability, pharmacokinetics	Open-label, multiple dose	Bevacizumab, IV	12	Solid tumor	Up to 49 days	Final CSR 14 Jan 1999
			Efficacy, safety, pharmacokinetics, pharmacodynamics	Multiple dose	Bevacizumab, IV	99	NSCLC	Up to 357 days	Final CSR 8 Feb 2002
			Biologic activity, safety, pharmacokinetics, quality of life	Open-label, multidose	Bevacizumab, IV	15	—	Up to 168 days	Final CSR 4 Feb 2000
			Efficacy, safety, pharmacokinetics	Open-label, multiple dose	Bevacizumab, IV	75	Breast cancer	Up to 168 days	Final CSR 7 Mar 2002
II	AVF0780g	5.3.5.1	Efficacy, safety, pharmacokinetics, pharmacodynamics, quality of life	Multidose, randomized	Bevacizumab, IV	104	Colorectal cancer	322 days	Final CSR 8 Mar 2002
II	AVF2192g ^a	5.3.5.1	Efficacy, safety, pharmacokinetics	Randomized	Bevacizumab, IV	214	Colorectal cancer	Up to 96 weeks	NA Study ongoing

IV = intravenous; NA = not applicable; NSCLC = non-small cell lung cancer.

^a Ongoing study; protocol synopsis provided.

Table 3
Listing of Clinical Studies (cont'd)

Phase	Study	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product, Route of Administration	Number of Subjects	Indication	Duration of Treatment	Study Status; Type of Report
III	AVF2107g	5.3.5.1	Efficacy, safety, pharmacokinetics, quality of life	Randomized	Bevacizumab, IV	925	Colorectal cancer	Up to 96 weeks	Final CSR 25 Aug 2003
	—		Efficacy, safety, pharmacokinetics, pharmacodynamics, quality of life	Open-label, randomized	Bevacizumab, IV	462	Breast cancer	Up to 35 doses	Final CSR 31 Jul 2003
NA	AVF0778g	5.3.5.2	Collect safety data for long-term administration	Open-label	Bevacizumab, IV	56	Extension	Up to 2 years	NA Study ongoing
NA	AVF2540g ^a	5.3.5.2	Collect safety data for long-term administration	Open-label	Bevacizumab, IV	39	Extension	Up to 2 years	NA Study ongoing

IV = intravenous; NA = not applicable; NSCLC = non-small cell lung cancer.

^a Ongoing study; protocol synopsis provided.

Results from the two randomized clinical trials are provided to support the addition of bevacizumab to standard chemotherapy in the first-line treatment of carcinoma of the colon and rectum. Study AVF2107g is a large, randomized, active-controlled, double-blind, Phase III trial. Supportive data are provided from Study AVF0780g, a randomized, open-label, dose-ranging, Phase II study. The data used to define the safety profile of bevacizumab come primarily from the above nine Genentech-sponsored studies: AVF0737g, —, AVF0761g, AVF0778g, AVF0780g, AVF2107g, and AVF2119g. It should be mentioned that in this BLA submission data are not available from the two ongoing studies: AVF2192g and AVF2540g.

This review mainly focuses on the two randomized trials (Studies AVF2107g and AVF0780g).

2.2 Data Sources

This is a paperless BLA submission. All data were provided electronically and were installed in the Electronic Document Room (EDR) with a STN: 125085\0 and the Roadmap: \\CBS5042329\M\EDR Submissions\2003 BLA\DCC130280\roadmap.pdf.

Data sources include all material reviewed, e.g. applicant study reports, data sets analyzed, and literature referenced.

This reviewer has no problem to access the study reports, locate and download the data sets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

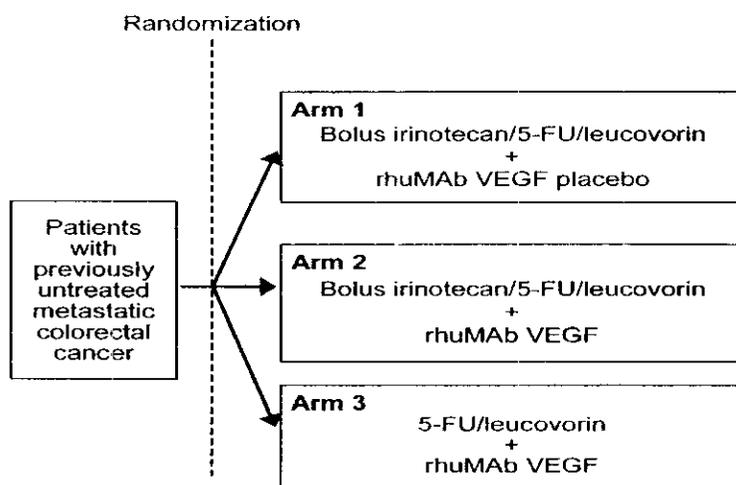
3.1.1 Study AVF2107g

3.1.1a Study Design and Endpoints

Study AVF2107g was a multicenter, Phase III, randomized, active-controlled trial to evaluate the efficacy and safety of rhuMab VEGF added to the standard first-line chemotherapy used to treat metastatic colorectal cancer. Study drug assignment was double-blind for the two principal treatment arms, Arms 1 and 2 (see below). Enrollment of approximately 900 subjects with histologically confirmed, previously untreated, bi-dimensionally measurable metastatic colorectal cancer was planned.

At the beginning of the trial, eligible subjects were randomized to one of three treatment arms, as shown in Figure 2 (Throughout the remainder of this report, CPT-11 will be referred to as irinotecan. The regimen of CPT-11/5-fluorouracil/leucovorin will be referred to as bolus-IFL).

Figure 2
Study Schema: First-Line Therapy prior to the Interim Safety Analysis



In Arms 1 and 2, subjects received study drug (placebo in Arm 1 and 5 mg/kg rhuMab VEGF in Arm 2) by IV infusion every other week in a double-blind fashion. In addition, all subjects in Arms 1 and 2 received the bolus-IFL regimen (125 mg/m² irinotecan, 500 mg/m² 5-FU, and 20 mg/m² leucovorin, administered in repeating 6-week cycles consisting of weekly treatments for 4 weeks followed by 2 weeks of rest). Subjects in Arm 3 received 5 mg/kg rhuMab VEGF by IV infusion every other week in an open-label fashion. These subjects also received 5-FU/leucovorin according to the Roswell

Park regimen (500 mg/m² 5-FU administered by IV push plus 500 mg/m² leucovorin administered as a 2-hour infusion weekly for 6 weeks, with courses repeated every 8 weeks).

As the combination of bolus-IFL + rhuMab VEGF (Arm 2) had not been tested in clinical trials, the initial part of the trial included a real-time assessment of safety. The results of the interim safety analysis were used to decide whether the bolus-IFL + rhuMab VEGF combination (Arm 2) was safe. If the DMC determined that Arm 2 was safe, enrollment in Arm 3 would be discontinued after 100 subjects had been randomized to that arm, and enrollment in Arms 1 and 2 would be continued until a total of 400 subjects per treatment arm had been enrolled. If the DMC determined that Arm 2 was unsafe, enrollment in Arm 2 would be immediately discontinued, and enrollment in Arms 1 and 3 would be continued until a total of 400 subjects per treatment arm were enrolled. Following the interim safety analysis, the DMC notified Genentech that the safety profile of Arm 2 was acceptable. Accordingly, the 5-FU/leucovorin + rhuMab VEGF arm (Arm 3) was closed to further enrollment of new subjects, as specified in the original protocol.

The protocol-specified chemotherapy regimen for Arms 1 and 2 subjects was the bolus-IFL regimen. This regimen was an approved standard first-line treatment for subjects with metastatic colorectal cancer at the time this study was initiated. Two randomized, controlled trials had demonstrated that the combination of irinotecan/5-FU/leucovorin prolongs survival compared with 5-FU/leucovorin alone in the first-line setting.

The protocol-specified chemotherapy regimen for Arm 3 subjects was the Roswell Park regimen of 5-FU/leucovorin. This regimen was selected because it was one of two standard 5-FU/leucovorin regimens used in the United States prior to approval of irinotecan in the first-line setting and because it was the regimen used in Phase II trials of rhuMab VEGF. Treatment assignment was not blinded for subjects randomized to Arm 3 because these subjects did not receive first-line irinotecan.

The primary efficacy outcome measure for this study was duration of survival defined as the time from randomization to death from any cause. All reported deaths were included, whether the death occurred during first- or second-line therapy or following treatment discontinuation. For subjects who had not died at the time of analysis, survival was censored at the date the subject was last known to be alive.

The four secondary efficacy endpoints were

- progression-free survival (PFS) during first-line therapy, defined as the time from randomization to disease progression or death due to any cause during first-line therapy (tumor assessments were performed every 6 weeks);
- objective response, defined as a complete response or partial response according to RECIST determined on two consecutive investigator assessments ≥ 4 weeks apart during first-line therapy;

- duration of objective response during first-line therapy, defined as the time from the first tumor assessment that supported the subject's objective response to the time of disease progression or death due to any cause during first-line therapy;
- time to Deterioration in Quality of Life (QOL) during First-Line Therapy. Time to deterioration in QOL (TDQ) as measured by the Colorectal Cancer Specific Subscale (CCS) was the primary measure of QOL in this study. Deterioration in QOL as measured by the TOI-C (PWB + FWB + CCS) and the total FACT-C score was also examined as secondary analyses.

3.1.1b Statistical Methodologies

The statistical analysis plan was finalized prior to unblinding of study results, and agreements reached between the FDA and Genentech following study unblinding.

Efficacy analyses and formal hypothesis testing was performed only on the two principal treatment arms: Arm 1 (bolus-IFL + placebo) and Arm 2 (bolus-IFL + rhuMAb VEGF). Efficacy analyses were based on the intent-to-treat population, defined as all subjects randomized to treatment, whether or not treatment was received.

For the survival primary endpoint, the stratified log-rank test was used to determine whether survival was prolonged on the bolus-IFL + rhuMAb VEGF arm (Arm 2) compared with the bolus-IFL + placebo arm (Arm 1) as the primary method. The unstratified log-rank test was also provided. Kaplan-Meier methodology was used to estimate median survival time for each treatment arm. Estimation of the hazard ratio of death in Arm 2 relative to Arm 1 was determined using a stratified Cox regression model with an indicator variable for rhuMAb VEGF treatment. The stratification factors were ECOG performance status (0, ≥ 1), number of organ sites with disease (1, > 1), and site of primary tumor (colon, rectum). Stratification factors were determined from data collected on the Case Report Form (CRF), or if unavailable from the CRF, from data entered into the interactive voice response system (IVRS).

The final analysis was planned when 385 deaths had occurred. The Type I error rate for the study was 0.05 (two-sided). An interim analysis of efficacy was scheduled when approximately half this number of deaths had occurred. To control for the Type I error rate for the primary endpoint of duration of survival, the Lan-DeMets implementation of the O'Brien-Fleming α spending function was used.

PFS was formally compared between treatment arms using the stratified log-rank test at the 0.05 level of significance (two-sided). Objective response rates were formally compared between treatment arms using the chi-square test at the two-sided 0.05 level of significance. Duration of objective response was compared between treatment arms using the unstratified log-rank test and Cox model were made for descriptive purposes. The stratified log-rank test was used to formally compare TDQ between the two principal arms of the study.

3.1.1c Patient Disposition, Demographic and Baseline Characteristics

A total of 925 subjects were randomized in this study. Subjects from _____ center were excluded from all analyses due to the allegation of falsification. Two subjects were randomized at _____ center (Subjects 11281 and 11282). Although not explicitly stated, _____ subjects were excluded from all tables, figures, narratives, data listings, and CRFs included in this clinical study report.

Subject status for first- and second-line treatment is presented in Table 4. Overall, 897 subjects (97.2%) received first-line treatment with study drug (rhUMAb VEGF or placebo).

Table 4
Subject Disposition:
Randomized Subjects

	Arm 1 b-IFL + Placebo (n=411)	Arm 2 b-IFL + AVF (n=402)	Arm 3 5-FU/LV + AVF (n=110)	Total (n=923)
Treated with first-line therapy	396 (96.4%)	392 (97.5%)	109 (99.1%)	897 (97.2%)
Completed study	4 (1.0%)	8 (2.0%)	8 (7.3%)	20 (2.2%)
Currently enrolled	33 (8.0%)	71 (17.7%)	3 (2.7%)	107 (11.6%)
Discontinued first-line therapy	359 (87.3%)	313 (77.9%)	98 (89.1%)	770 (83.4%)
Death	13 (3.2%)	14 (3.5%)	7 (6.4%)	34 (3.7%)
Disease progression	265 (64.5%)	201 (50.0%)	71 (64.5%)	537 (58.2%)
Adverse event	27 (6.6%)	31 (7.7%)	11 (10.0%)	69 (7.5%)
Lost to follow-up	2 (0.5%)	1 (0.2%)	0 (0.0%)	3 (0.3%)
Subject's decision	25 (6.1%)	39 (9.7%)	4 (3.6%)	68 (7.4%)
Physician's decision	27 (6.6%)	27 (6.7%)	5 (4.5%)	59 (6.4%)
Not treated with study drug	15 (3.6%)	10 (2.5%)	1 (0.9%)	26 (2.8%)
Discontinued	15 (3.6%)	10 (2.5%)	1 (0.9%)	26 (2.8%)
Disease progression	2 (0.5%)	2 (0.5%)	0 (0.0%)	4 (0.4%)
Adverse event	1 (0.2%)	2 (0.5%)	0 (0.0%)	3 (0.3%)
Physician's decision	3 (0.7%)	3 (0.7%)	0 (0.0%)	6 (0.7%)
Subject's decision	9 (2.2%)	3 (0.7%)	1 (0.9%)	13 (1.4%)
Treated with second-line therapy on study	47 (11.4%)	110 (27.4%)	55 (50.0%)	212 (23.0%)
Completed study	0 (0.0%)	2 (0.5%)	8 (7.3%)	10 (1.1%)
Currently enrolled	5 (1.2%)	34 (8.5%)	2 (1.8%)	41 (4.4%)
Discontinued	42 (10.2%)	74 (18.4%)	45 (40.9%)	161 (17.4%)
Death	3 (0.7%)	2 (0.5%)	2 (1.8%)	7 (0.8%)
Disease progression	33 (8.0%)	56 (13.9%)	30 (27.3%)	119 (12.9%)
Adverse event	1 (0.2%)	5 (1.2%)	6 (5.5%)	12 (1.3%)
Subject's decision	2 (0.5%)	5 (1.2%)	1 (0.9%)	8 (0.9%)
Physician's decision	3 (0.7%)	6 (1.5%)	6 (5.5%)	15 (1.6%)

AVF = rhUMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin;
5-FU/LV = 5-fluorouracil/leucovorin.

Percentages were computed relative to the number of randomized subjects.

Treatment assignment was unblinded for 351 subjects in Arms 1 and 2 (see Table 5). Of these, 343 subjects were unblinded through the IVRS for the following protocol-allowed reasons: completion of the study, disease progression (in order to help select second-line therapy), complete response, and toxicity. Major eligibility exceptions were reported for 100 subjects as shown in Table 6. Major protocol deviations were reported for 31 subjects (3.5%; see Table 7).

Table 5
Treatment Unblinding: Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL+Placebo	Arm 2 b-IFL+AVF	Total
Unblinding through the IVRS			
Complete response	4	7	11
Completed the study	2	7	9
Disease progression	179	133	312
Toxicity	3	6	9
Other	1	1	2
Unblinding at Genentech (adverse events) ^a			
	2	6	8
Total	191	160	351

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; IVRS = interactive voice response system; NA = not applicable.

^a In addition, treatment assignment was unblinded at Genentech for 2 subjects in Arm 2 who were also unblinded through the IVRS.

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Table 6
Major Eligibility Exceptions:
Randomized Subjects

	Arm 1 b-IFL + Placebo (n=411)	Arm 2 b-IFL + AVF (n=402)	Arm 3 5-FU/LV + AVF (n=110)	Total (n=923)
Any	48 (11.7%)	42 (10.4%)	10 (9.1%)	100 (10.8%)
No measurable metastatic lesions	3 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.3%)
Prior chemotherapy for metastatic disease	7 (1.7%)	9 (2.2%)	3 (2.7%)	19 (2.1%)
No informed consent	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Other invasive malignancy within 5 years	7 (1.7%)	2 (0.5%)	1 (0.9%)	10 (1.1%)
Full-dose warfarin at baseline	5 (1.2%)	0 (0.0%)	0 (0.0%)	5 (0.5%)
History of CNS disease including brain tumor/seizure/stroke	4 (1.0%)	6 (1.5%)	0 (0.0%)	10 (1.1%)
Active cardiovascular disease	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
24-hour urine protein >500 mg	5 (1.2%)	2 (0.5%)	2 (1.8%)	9 (1.0%)
ECOG performance status > 1	4 (1.0%)	3 (0.7%)	2 (1.8%)	9 (1.0%)
Screening lab results out of range (clinically significant)	4 (1.0%)	3 (0.7%)	0 (0.0%)	7 (0.8%)
Adjuvant chemotherapy within 11 months before Day 0	9 (2.2%)	8 (2.0%)	4 (3.6%)	21 (2.3%)
Major surgery within 28 days before Day 0	4 (1.0%)	10 (2.5%)	0 (0.0%)	14 (1.5%)
Radiotherapy within 14 days before Day 0	6 (1.5%)	4 (1.0%)	1 (0.9%)	11 (1.2%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; CNS = central nervous system; 5-FU/LV = 5-fluorouracil/leucovorin.

Table 7
Major Protocol Deviations:
Treated Subjects

	Arm 1 b-IFL + Placebo (n=396)	Arm 2 b-IFL + AVF (n=392)	Arm 3 5-FU/LV + AVF (n=109)	Total (n=897)
Any major protocol deviation	10 (2.5%)	14 (3.6%)	7 (6.4%)	31 (3.5%)
Received incorrect study drug (AVF or placebo)	7 (1.8%)	3 (0.8%)	4 (3.7%)	14 (1.6%)
Received a kit not assigned by IVRS	10 (2.5%)	13 (3.3%)	6 (5.5%)	29 (3.2%)
First dose of 5-FU or irinotecan differed from protocol > 10%	0 (0.0%)	1 (0.3%)	1 (0.9%)	2 (0.2%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; 5-FU/LV = 5-fluorouracil/leucovorin; IVRS = interactive voice response system.

Demographic and baseline characteristics were well balanced across Arms 1 and 2 and were typical of patients with metastatic colorectal cancer in the United States as shown in Table 8. Subject age ranged from 21 to 88 years, with an average of 59 years. Sixty percent of subjects were male, and the majority of the subjects were White (80%).

Table 8
Demographic Characteristics:
Randomized Subjects

	Arm 1 b-IFL+Placebo (n=411)	Arm 2 b-IFL+AVF (n=402)	Arm 3 5-FU/LV+AVF (n=110)	Total (n=923)
Age (yr)				
n	411	402	110	923
Mean (SD)	59.2 (11.47)	59.5 (11.29)	59.7 (12.08)	59.4 (11.45)
Median	60.0	60.0	61.5	60.0
Range	21.0–83.0	23.0–86.0	29.0–88.0	21.0–88.0
<40	17 (4.1%)	18 (4.5%)	7 (6.4%)	42 (4.6%)
40–64	253 (61.6%)	254 (63.2%)	56 (50.9%)	563 (61.0%)
≥65	141 (34.3%)	130 (32.3%)	47 (42.7%)	318 (34.5%)
Sex				
n	411	402	110	923
Female	163 (39.7%)	165 (41.0%)	41 (37.3%)	369 (40.0%)
Male	248 (60.3%)	237 (59.0%)	69 (62.7%)	554 (60.0%)
Race/ethnicity				
n	411	402	110	923
American Indian or Alaskan Native	0 (0.0%)	2 (0.5%)	0 (0.0%)	2 (0.2%)
Asian or Pacific Islander	14 (3.4%)	12 (3.0%)	4 (3.6%)	30 (3.3%)
Black	46 (11.2%)	49 (12.2%)	14 (12.7%)	109 (11.8%)
Hispanic	23 (5.6%)	18 (4.5%)	2 (1.8%)	43 (4.7%)
White	328 (79.8%)	317 (78.9%)	90 (81.8%)	735 (79.6%)
Other	0 (0.0%)	4 (1.0%)	0 (0.0%)	4 (0.4%)
Weight (baseline) (kg)				
n	410	402	110	922
Mean (SD)	80.2 (19.57)	79.5 (19.05)	82.3 (23.77)	80.1 (19.89)
Median	78.2	77.8	76.0	78.0
Range	38.9–174.0	36.0–153.0	45.4–195.0	36.0–195.0
Body surface area (baseline) (m²)				
n	405	400	110	915
Mean (SD)	1.9 (0.27)	1.9 (0.26)	2.0 (0.31)	1.9 (0.27)
Median	1.9	1.9	1.9	1.9
Range	1.3–3.0	1.2–2.8	1.4–3.2	1.2–3.2

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin;
5-FU/LV = 5-fluorouracil/leucovorin.

Disease characteristics for all randomized subjects are presented in Table 9. Fifty-seven percent of subjects had a baseline ECOG performance status of 0. Mean duration of metastatic disease was 4 months (range: 1 to 125 months). Seventy-eight percent of subjects had primary tumor in the colon, and 21.9% had primary tumor in the rectum. Baseline disease characteristics were generally similar across the three treatment arms.

Table 9
Disease Characteristics:
Randomized Subjects

	Arm 1 b-IFL+Placebo (n=411)	Arm 2 b-IFL+AVF (n=402)	Arm 3 5-FU/LV+AVF (n=110)	Total (n=923)
ECOG performance status (baseline)				
n	411	401	110	922
0	227 (55.2%)	234 (58.4%)	61 (55.5%)	522 (56.6%)
1	182 (44.3%)	166 (41.4%)	48 (43.6%)	396 (43.0%)
2	2 (0.5%)	1 (0.2%)	1 (0.9%)	4 (0.4%)
Duration of disease (months)				
n	411	401	110	922
Mean (SD)	16 (22.0)	15 (23.2)	16 (22.3)	16 (22.6)
Median	3	3	3	3
Range	1-142	1-170	1-107	1-170
Duration of metastatic disease (months)				
n	411	402	110	923
Mean (SD)	4 (9.2)	4 (9.2)	4 (8.8)	4 (9.1)
Median	2	2	2	2
Range	1-125	1-91	1-70	1-125
<12	386 (93.9%)	374 (93.0%)	103 (93.6%)	863 (93.5%)
≥12	25 (6.1%)	28 (7.0%)	7 (6.4%)	60 (6.5%)
Location of primary tumor				
n	411	402	110	923
Colon	334 (81.3%)	310 (77.1%)	77 (70.0%)	721 (78.1%)
Rectum	77 (18.7%)	92 (22.9%)	33 (30.0%)	202 (21.9%)
Histologic classification				
n	411	402	110	923
Adenocarcinoma	384 (93.4%)	373 (92.8%)	104 (94.5%)	861 (93.3%)
Adenosquamous carcinoma	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Mucinous adenocarcinoma	21 (5.1%)	26 (6.5%)	6 (5.5%)	53 (5.7%)
Signet-ring carcinoma	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Squamous cell carcinoma	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Undifferentiated carcinoma	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Other	2 (0.5%)	2 (0.5%)	0 (0.0%)	4 (0.4%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin;
5-FU/LV = 5-fluorouracil/leucovorin.

A total of 811 subjects (87.9%) had received some prior cancer treatment. Prior cancer therapies were generally similar across treatment arms, although subjects in Arm 3 had fewer surgeries (88% in Arm 1, 87% in Arm 2, and 81% in Arm 3) and more radiotherapy (14% in Arm 1, 15% in Arm 2, and 22% in Arm 3) than subjects in Arms 1 and 2. The commonly used prior cancer therapies included surgery (86.6%) and systemic chemotherapy (25.8%) in the adjuvant setting. Baseline tumor characteristics are presented in Table 10. The number of organ sites with metastatic disease was similar for Arms 1 and 2.

Table 10
Baseline Tumor Assessment:
Randomized Subjects

	Arm 1 b-IFL+Placebo (n=411)	Arm 2 b-IFL+AVF (n=402)	Arm 3 5-FU/LV+AVF (n=110)	Total (n=923)
Number of organ sites with metastases				
n	409	402	110	921
Mean (SD)	2.0 (1.1)	2.0 (1.0)	1.9 (1.1)	2.0 (1.0)
Median	2	2	2	2
Range	1-5	1-6	1-6	1-6
1	159 (38.9%)	147 (36.6%)	48 (43.6%)	354 (38.4%)
>1	252 (61.6%)	255 (63.4%)	62 (56.4%)	569 (61.8%)
Disease sites				
n	409	402	110	921
Bone	8 (2.0%)	5 (1.2%)	2 (1.8%)	15 (1.6%)
Liver	316 (77.3%)	315 (78.4%)	90 (81.8%)	721 (78.3%)
Lung	196 (47.9%)	199 (49.5%)	43 (39.1%)	438 (47.6%)
Lymph nodes	103 (25.2%)	96 (23.9%)	27 (24.5%)	226 (24.5%)
Abdomen	82 (20.0%)	61 (15.2%)	15 (13.6%)	158 (17.2%)
Mediastinum	6 (1.5%)	14 (3.5%)	6 (5.5%)	26 (2.8%)
CNS	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pelvis	42 (10.3%)	36 (9.0%)	13 (11.8%)	91 (9.9%)
Skin/soft tissue	21 (5.1%)	17 (4.2%)	4 (3.6%)	42 (4.6%)
Pleural effusion	19 (4.6%)	12 (3.0%)	2 (1.8%)	33 (3.6%)
Ascites	13 (3.2%)	17 (4.2%)	0 (0.0%)	30 (3.3%)
Other	22 (5.4%)	29 (7.2%)	11 (10.0%)	62 (6.7%)
Predominant metastatic disease type				
n	409	402	110	921
Local disease only	26 (6.4%)	21 (5.2%)	6 (5.5%)	53 (5.8%)
Hepatic without extra-hepatic disease	158 (38.6%)	153 (38.1%)	52 (47.3%)	363 (39.4%)
Extra-hepatic	225 (55.0%)	228 (56.7%)	52 (47.3%)	505 (54.8%)
SLD of target lesions (cm)				
n	408	402	110	920
Mean (SD)	12.9 (8.9)	12.0 (7.7)	12.2 (8.7)	12.4 (8.3)
Median	11	10	9	11
Range	1-72	2-41	2-49	1-72

AVF=rhuMAb VEGF; b-IFL=bolus irinotecan/5-fluorouracil/leucovorin; CNS=central nervous system; 5-FU/LV=5-fluorouracil/leucovorin; SLD=sum of longest diameters.

Note: Two subjects in Arm 1 had >1 metastatic disease site (non-target lesions only) but the number and location of disease sites were not determined.

3.1.1d Results and Conclusions

As shown in Table 11, Median survival was 15.6 months in Arm 1 and 20.3 months in Arm 2. The stratified hazard ratio for death for Arm 2 subjects relative to Arm 1 subjects was 0.660 (95% CI: 0.54, 0.81). Kaplan-Meier curves for duration of survival are shown in Figure 3. Similarly, there is a significant difference between the two arms in PFS and shown in Table 12 and Kaplan-Meier curves for PFS are shown in Figure 4.

Table 11
Duration of Survival:
Randomized Subjects in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=411)	Arm 2 b-IFL + AVF (n=402)
Subjects who died	225	174
Censored observations	186 (45.3%)	228 (56.7%)
Duration of survival ^a (months)		
Median	15.61	20.34
95% CI	(14.29, 16.99)	(18.46, 24.18)
25%–75% percentile	9.23–25.99	11.66–NR
Range	—	
Stratified analysis		
Hazard ratio ^b	NA	0.660
95% CI	NA	(0.54, 0.81)
p-value (log-rank)	NA	<0.0001

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; 5-FU/LV = 5-fluorouracil/leucovorin; NA = not applicable; NR = the specified statistic has not been reached; + indicates a censored value.

^a Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using Simon's method.

^b Relative to Arm 1. Estimated by Cox regression.

Figure 3
Duration of Survival in Study AVF2017g

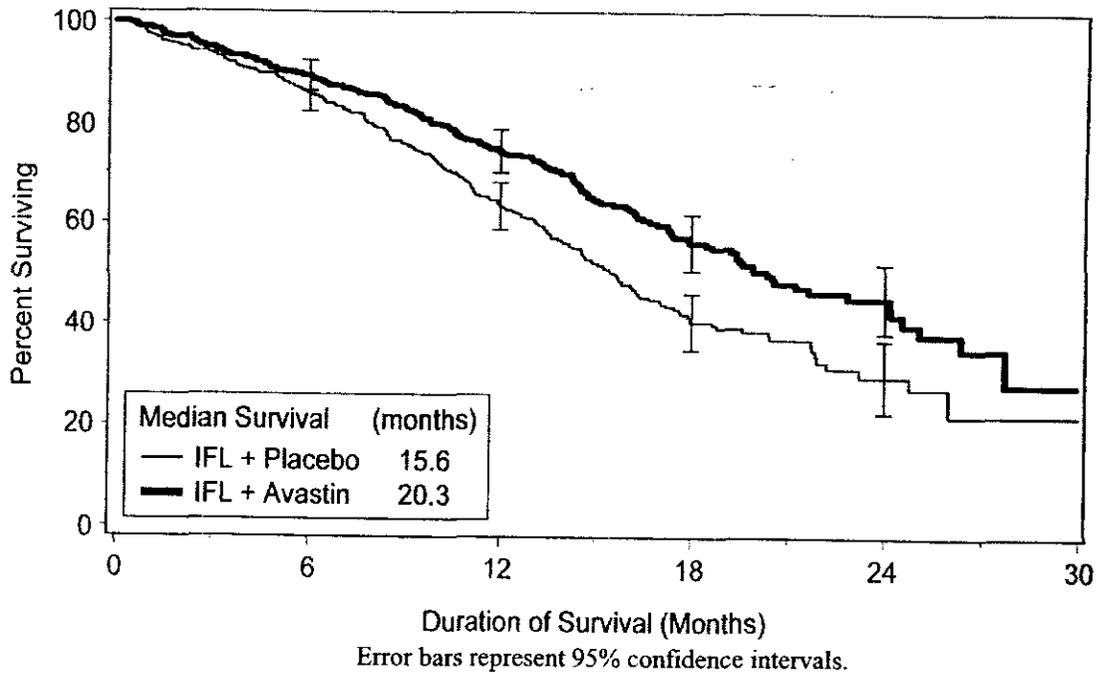


Table 12
Progression-Free Survival during First-Line Therapy:
Randomized Subjects in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=411)	Arm 2 b-IFL + AVF (n=402)
Subjects with an event ^a	284	230
Disease progression	266	215
Death	18	15
Censored observations	127 (30.9%)	172 (42.8%)
Progression-free survival ^b (months)		
Median	6.24	10.55
95% CI	(5.59, 7.66)	(9.03, 11.04)
25%–75% percentile	3.94–10.84	5.55–15.57
Range		
Stratified analysis		
Hazard ratio ^c	NA	0.544
95% CI	NA	(0.45, 0.66)
p-value (log-rank)	NA	<0.0001

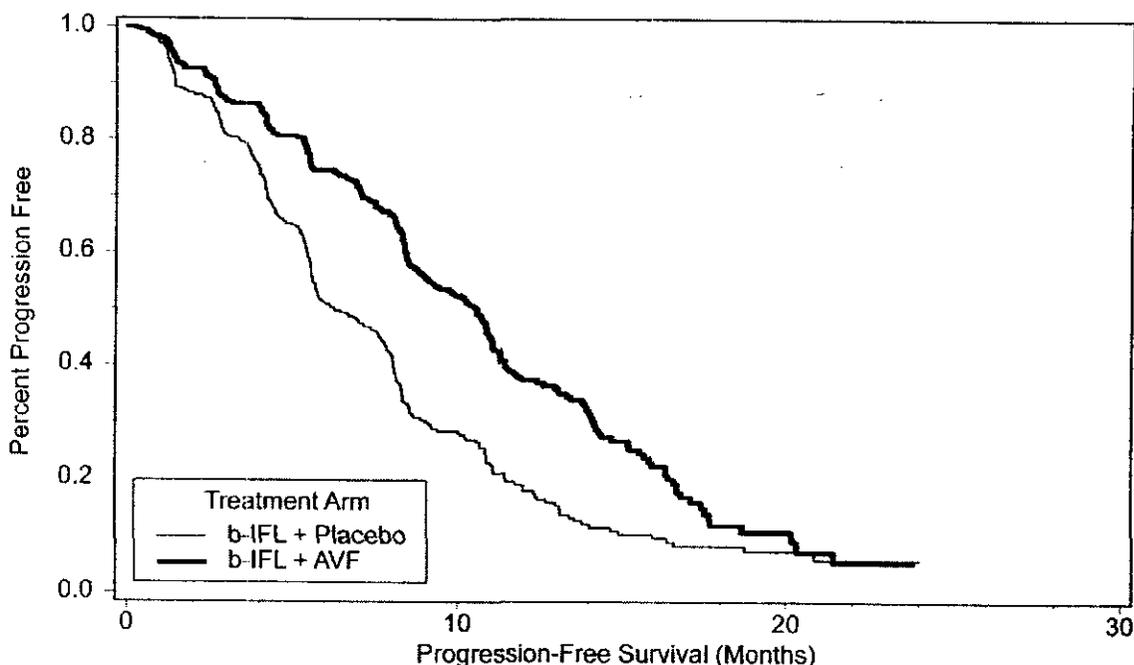
AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; NA = not applicable; . indicates that the specified statistic has not been reached; + indicates a censored value.

^a Earliest contributing event is shown.

^b Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using Simon's method.

^c Relative to Arm 1. Estimated by Cox regression.

Figure 4
Progression-Free Survival during First-Line Therapy



One site (S07396) was identified having problems in tumor progression assessment. Median PFS in the placebo group changed from 6.2 to 6.4 months by excluding 13 patients from this site, but median PFS in bevacizumab arm remains unchanged. The clinical reviewer also identified 66 patients with questionable tumor progression assessments. Again, excluding the 66 patients only resulted in minimal change in median PFS (from 6.2 to 6.3 months) in patients receiving placebo. The problems in tumor progression assessment are unlikely to have any significant impact on PFS analysis.

The objective response rate was statistically significant difference between the two arms ($p=0.0036$) as shown in Table 13 the sponsor provided. The clinical reviewer re-assessed the objective response and found that there was one responder less in each arm, compared to the sponsor's assessment. However, re-analyzing the response data did not change the p-value. The response rates also remain unchanged when they were rounded to integers (179/402, 45% in Arm 2 vs. (142/411, 35% in Arm 1). This discrepancy has no impact on drawing conclusion regarding this endpoint.

Median duration of objective response in Arm 1 was 7.06 months and ranged from 1.3+ to 20.9+ months. Median duration of objective response in Arm 2 was 10.35 months and ranged from 1.1+ to 20.8+ months. Because the determination of duration of objective response was based on a non-randomized subset of subjects, formal hypothesis testing was not performed. However, treatment arms were compared for descriptive purposes ($p=0.0014$; log-rank test).

Table 13
Objective Response during First-Line Therapy:
Randomized Subjects

	Arm 1 b-IFL+Placebo (n=411)	Arm 2 b-IFL+AVF (n=402)
Objective response ^a	143 (34.8%)	180 (44.8%)
95% CI ^b	(30.2%, 39.6%)	(39.9%, 49.8%)
p-value (χ^2)	NA	0.0036
Between-arm difference	NA	10.0%
95% CI ^b	NA	(3.3%, 16.7%)
Best objective response ^c		
Complete response	9 (2.2%)	15 (3.7%)
Partial response	134 (32.6%)	165 (41.0%)

AVF = rhuMab VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin; NA = not applicable.

^a Complete or partial response confirmed ≥ 28 days after initial documentation of response.

^b Based on normal approximation to the binomial distribution.

^c Best objective response was a complete response if a complete response was confirmed with another complete response. Otherwise, best objective response was a partial response.

Baseline FACT-C CCS scores were available for 127 subjects in Arm 1 and for 122 subjects in Arm 2. There was no statistically significant difference in the time to deterioration in CCS score between treatment arms. Median TDQ as measured by CCS scores was 2.73 months in Arm 1 and 2.89 months in Arm 2.

Among the 110 patients enrolled in Arm 3, median overall survival was 18.3 months. The hazard ratio for death in Arm 3 compared to Arm 1 with concurrently enrolled subjects was 0.821 (95% CI: 0.59, 1.15). Median progression-free survival was 8.8 months. The hazard ratio for progression or death in Arm 3 compared with Arm 1 was 0.862 (95% CI: 0.60, 1.24). Overall response rate in Arm 3 was 39% and median duration of response was 8.5 months.

The clinical benefit of AVASTIN, as measured by survival in the two principal arms, was also seen in all subgroups tested (See Section 4 for details).

This large, randomized, double-blind trial demonstrated that the addition of rhuMab VEGF to bolus-IFL chemotherapy improves survival, as reflected in the 34% decrease in the daily risk of death for subjects receiving bolus-IFL + rhuMab VEGF compared with those receiving bolus-IFL alone (hazard ratio = 0.660). Corresponding significant increases in progression-free survival, objective response rate, and duration of response support this finding.

3.1.2 Study AVF0780g

This Phase II, randomized, open-label, multicenter trial was designed to evaluate the preliminary efficacy, safety, and pharmacokinetics of two dose levels of rhuMAb VEGF when combined with 5-FU/leucovorin chemotherapy in subjects with metastatic colorectal cancer. Subjects with previously untreated metastatic colorectal cancer were eligible for enrollment. Following enrollment, approximately 90 subjects (30 subjects per arm) were to be randomized to three treatment arms: one control arm (5-FU/leucovorin chemotherapy alone) and two rhuMAb VEGF (5 mg/kg or 10 mg/kg) plus chemotherapy arms. Chemotherapy was given alone or in combination with rhuMAb VEGF, lasting up to 322 days; a 21-day treatment follow-up period; and a post treatment observation period of varying duration.

The primary efficacy endpoints for this study were time to disease progression and best (confirmed) tumor response rates (CR or PR). The secondary efficacy endpoints were Overall survival, Duration of response, and change in the FACT-C QOL Questionnaire score.

Time to disease progression, duration of response, and survival were evaluated using survival analysis techniques. Kaplan-Meier curves were produced to provide a visual description of how these time-to-event variables compared among the three treatment arms. The log-rank test was used to provide a formal statistical assessment of the differences between treatment arms. Additionally, the Cox proportional hazards model was used to estimate the hazard ratio. An estimate of the best (confirmed) tumor response together with 95% confidence intervals was evaluated for each treatment arm. A two-sided chi-square test was used to compare each rhuMAb VEGF arm with the control arm.

Of the 104 randomized subjects, 102 (98%) received at least one infusion of study-specified treatment. Two subjects who did not receive at least one infusion (Subject 6406 in the control arm and Subject 6014 in the 10 mg/kg arm) discontinued the study prior to treatment because of progressive disease.

Twenty-seven subjects (26%) completed six cycles of the treatment to which they were randomized (4 in the control arm, 14 in the 5 mg/kg arm, and 9 in the 10 mg/kg arm). Table 14 summarizes subject disposition and discontinuation of initial treatment.

Table 14
Subject Disposition and Discontinuation of Initial Treatment

	Control	5 mg/kg	10 mg/kg	Total
Randomized	36	35	33	104
Treated	35	35	32	102
Reason for treatment discontinuation				
Adverse event	2 (6%)	4 (11%)	6 (18%)	12 (11%)
Disease progression	28 (78%) ^a	17 (49%)	15 (46%)	60 (57%)
Sponsor's decision	0	0	1 (3%) ^b	1 (1%)
Noncompliance	1 (3%) ^c	0	0	1 (1%)
Physician decision	0	0	1 (3%) ^d	1 (1%)
Subject decision	1 (3%) ^e	0	1 (3%) ^f	2 (2%)
Total	32 (89%)	21 (60%)	24 (73%)	77 (74%)

^a Twenty subjects from the control arm had progressive disease and crossed over to receive rhuMAb VEGF. Two additional subjects crossed over without an investigator assessment of progressive disease.

^b Subject 6409 got off schedule and completed Cycle 6 in Study AVF0778g.

^c Subject 6153 underwent resection of hepatic metastasis.

^d Subject 6451 developed progressive encephalopathy.

^e Subject 6310 deteriorated and died from progressive disease.

^f Subject 6605 developed gastrointestinal toxicity from 5-FU.

Based on independent review facility (IRF)/investigator assessments, 68 subjects had disease progression; 3 subjects died during the study prior to the IRF/investigator assessment of disease progression. Based on investigator assessments, 75 subjects had disease progression; 2 subjects had died during the study prior to investigator-assessed disease progression. Time to disease progression is summarized by treatment arm in Table 15 and shown in Figures 5 and 6.

Table 15
Time to Disease Progression

Assessment	Control (N=36)	5 mg/kg (N=35)	10 mg/kg (N=33)
IRF/investigator			
Number of progressions	26	22	23
Percent free of progression	28%	37%	30%
Time to progression (months)			
Median (months)	5.2	9.0	7.2
Range (months)		—	
Hazard ratio ^a	—	0.44	0.69
p-value (log rank)	—	0.005	0.217
Investigator only			
Number of progressions	31	24	22
Percent free of progression	14%	31%	33%
Time to progression (months)			
Median (months)	5.4	6.8	8.4
Range (months)		—	
Hazard ratio ^a	—	0.58	0.53
p-value (log rank)	—	0.043	0.027

IRF=independent review facility.

^a Compared with the control arm.

^b Indicates a censored time; subject still responding to therapy.

Figure 5
Progression-Free Estimates Based on IRF/Investigator Assessments
by Treatment Arm

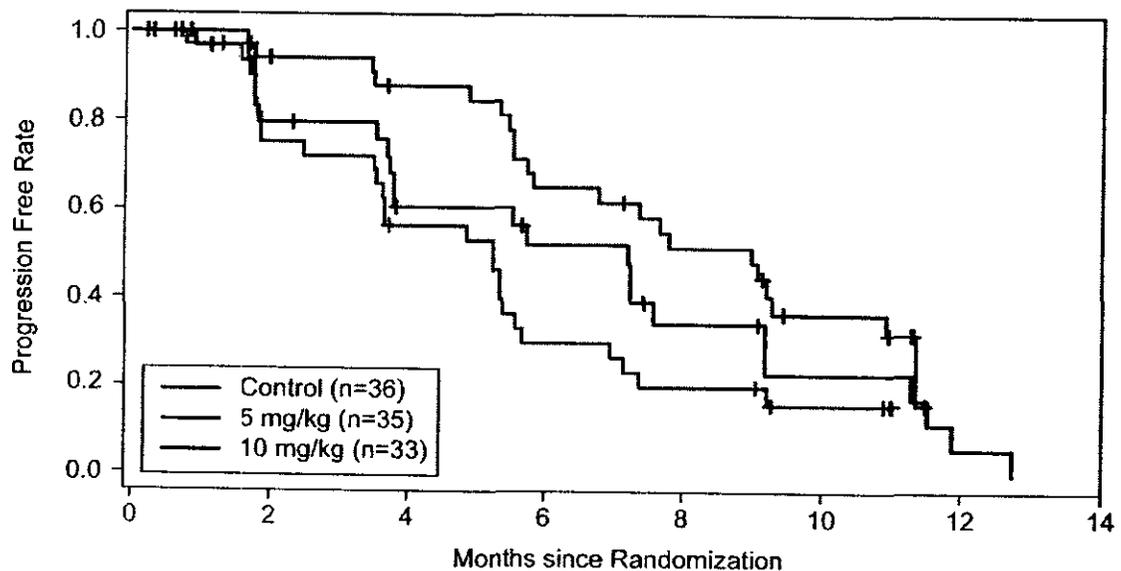
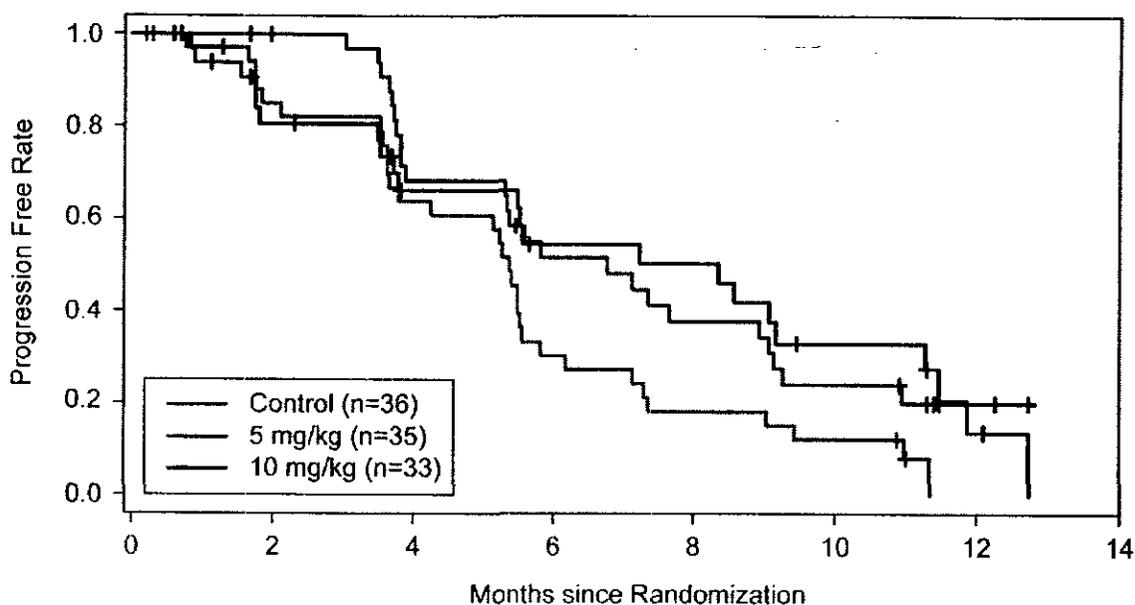


Figure 6
Progression-Free Estimates Based on Investigator Assessments
by Treatment Arm



Overall, there were 28 subjects with a confirmed response (PR or CR) as assessed by IRF/investigator and there were 31 subjects with a confirmed response (PR or CR) as assessed by the investigator. Response rates are summarized by treatment arm in Table 16.

Table 16
Confirmed Response Rates

Assessment	Control (N=36)	5 mg/kg (N=35)	10 mg/kg (N=33)
IRF/investigator			
Response rate	6 (17%)	14 (40%)	8 (24%)
95% CI	(7%, 34%)	(24%, 58%)	(12%, 43%)
p-value (χ^2)	—	0.03	0.43
Investigator only			
Response rate	7 (19%)	12 (34%)	12 (36%)
95% CI	(9%, 37%)	(20%, 52%)	(21%, 55%)
p-value (χ^2)	—	0.16	0.12

IRF=independent review facility.

All 104 randomized subjects were to be followed for survival information for at least 1 year. A summary of survival time by treatment arm is presented in Table 17 and shown in Figure 7.

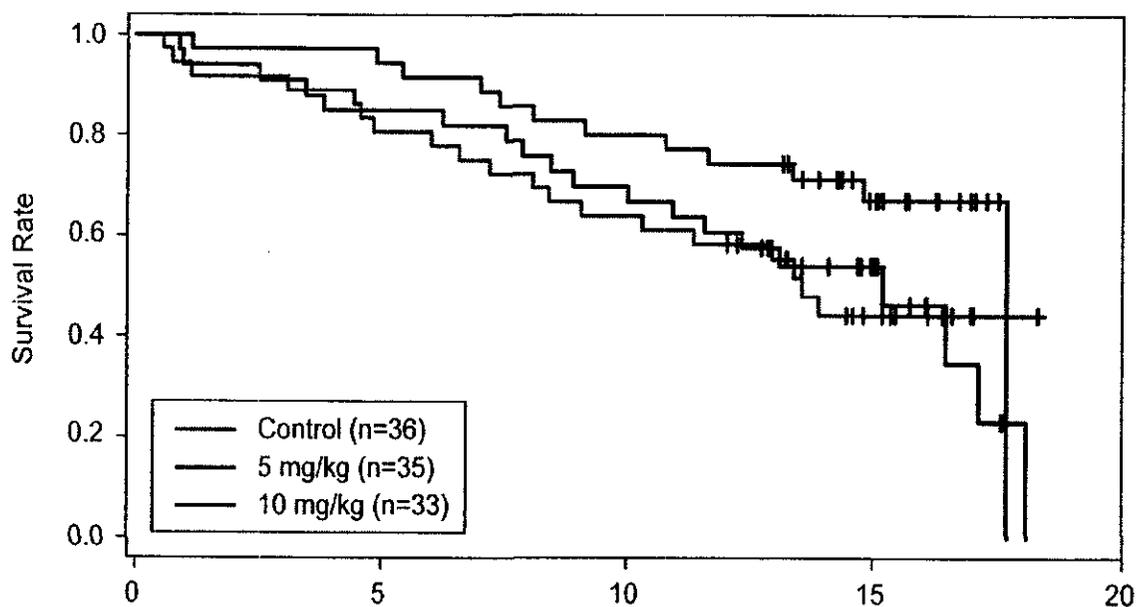
Table 17
Survival Time by Study Treatment

Assessment	Control (N=36)	5 mg/kg (N=35)	10 mg/kg (N=33)
Number of deaths	19	12	19
Percent surviving	47%	66%	42%
Survival time (months)			
Median (months)	13.6	17.7	15.2
Range			
Hazard ratio ^a	—	0.52	1.01
p-value (log rank)	—	0.073	0.978

^a Compared with the control arms.

^b Indicates a censored time; subject still alive.

Figure 7
Survival Time by Treatment Arm



These results indicate that rhuMAb VEGF, in combination with 5-FU/leucovorin chemotherapy, may increase response rates, prolong time to disease progression, and prolong survival compared with 5-FU/leucovorin chemotherapy alone.

3.1.3 An Ongoing Study for Using Bevacizumab as a Single-agent

In an ongoing randomized trial, patients with metastatic colorectal cancer that had progressed following a 5-fluorouracil and irinotecan-based regimen were enrolled into study. Based on the incomplete and unaudited data provided under an IND submission, follow-up information is currently available for 143 patients with 45 deaths in the bevacizumab arm and for 138 patients with 25 deaths in the FOLFOX arm. The median survival times were 191 days for patients who received bevacizumab alone vs. 335 days for those treated with FOLFOX ($p=0.012$, log-rank test). The result implies that patients treated with single-agent bevacizumab may have inferior survival as compared with patients treated with the FOLFOX regimen of 5-fluorouracil, leucovorin and oxaliplatin. However, the results should be interpreted with caution since the data were incomplete and unaudited.

APPEARS THIS WAY
ON ORIGINAL

3.2 Evaluation of Safety

The Summary of Clinical Safety (SCS) includes available safety data on 1032 bevacizumab-treated subjects from Genentech-sponsored studies, including 594 subjects with metastatic colorectal cancer. The other cancer types represented include metastatic breast (n = 310), non-small cell lung (n = 89), (n = 15), sarcoma (n = 10), metastatic renal cell (n = 8), and others (n = 6). The data used to define the safety profile of bevacizumab come primarily from nine Genentech-sponsored studies: AVF0737g, AVF0761g, AVF0778g, AVF0780g, AVF2107g, and AVF2119g (see Table 3).

The safety review will mainly focus on the large randomized study. Study AVF2107g is a large, randomized, double-blind, active-controlled trial in first-line colorectal cancer and provides the most scientifically rigorous data for distinguishing bevacizumab-related toxicities in first-line colorectal cancer from those that are either spontaneous, due to the underlying disease, or due to chemotherapy.

More detailed evaluation of safety can be seen in the medical officer's review.

APPEARS THIS WAY
ON ORIGINAL

3.2.1. Exposure to Study Drug

A total of 396 subjects in Arm 1 and 392 subjects in Arm 2 received study drug (rhUMAb VEGF or placebo). The number of doses of study drug received was higher for subjects in Arm 2 than for those in Arm 1 (see Table 18). The number of doses of concomitant chemotherapy received was also higher for subjects in Arm 2 than for those in Arm 1.

Table 18
Number of Doses Received during First-Line Therapy:
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=396)	Arm 2 b-IFL + AVF (n=392)
Study drug (AVF or placebo)		
n	396	392
Mean (SE)	14.2 (0.5)	18.2 (0.6)
Median	12	18
Range	1–48	1–54
5-FU		
n	396	392
Mean (SE)	18.7 (0.6)	23.9 (0.7)
Median	16	23
Range	1–64	1–65
Leucovorin		
n	396	392
Mean (SE)	18.7 (0.6)	23.9 (0.7)
Median	16	23
Range	1–64	1–65
Irinotecan		
n	396	392
Mean (SE)	18.7 (0.6)	23.7 (0.7)
Median	16	23
Range	1–64	1–65

AVF = rhUMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin.

Dose level reduction was defined as a dose < 85% of the previous dose. The number of subjects with at least one chemotherapy dose level reduction was higher in Arm 2 than in Arm 1 (see Table 19).

Table 19

**Chemotherapy Dose Level Reductions during First-Line Therapy:
Subjects Treated in Arms 1 and 2**

	Arm 1 b-IFL+Placebo (n=396)	Arm 2 b-IFL+AVF (n=392)
5-FU		
Subjects receiving > 1 dose	392	387
Subjects (%) with at least one reduction	268 (68.4%)	312 (80.6%)
Number of dose level reductions		
Mean (SE)	1.9 (0.1)	2.3 (0.1)
Median	2	2
Range	1-6	1-10
Irinotecan		
Subjects receiving > 1 dose	392	387
Subjects (%) with at least one reduction	271 (69.1%)	309 (79.8%)
Number of dose level reductions		
Mean (SE)	1.9 (0.1)	2.2 (0.1)
Median	2	2
Range	1-6	1-10

AVF=rhuMAb VEGF; b-IFL=bolus irinotecan/5-fluorouracil/leucovorin; 5-FU=5-fluorouracil.
Dose level reduction was defined as a dose < 85% of the previous dose.

Dose intensity was calculated for the period of time from the first dose to the last dose received as the amount received over that time period divided by the amount of drug that would have been administered had the protocol-specified first dose been administered at every visit over that time period according to the protocol schedule. Dose intensity percentages for study drug and chemotherapy were slightly lower for subjects in Arm 2 compared with those in Arm 1 (see Table 20).

Table 20
Dose Intensity (%) during First-Line Therapy:
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=396)	Arm 2 b-IFL + AVF (n=392)
Study drug (AVF or placebo)		
n	395	392
Mean (SE)	96.3 (0.5)	94.3 (0.5)
Median	99	97
Range	47–125	43–120
5-FU		
n	390	390
Mean (SE)	79.3 (0.8)	74.3 (0.9)
Median	80	73
Range	31–116	31–111
Leucovorin		
n	390	390
Mean (SE)	97.0 (1.8)	93.1 (1.0)
Median	96	94
Range	50–602	49–387
Irinotecan		
n	390	390
Mean (SE)	78.4 (0.9)	72.7 (1.0)
Median	81	73
Range	30–115	27–110

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin;
5-FU = 5-fluorouracil.

Duration of safety observation was defined as the number of weeks from start of treatment (study drug or chemotherapy) until the last safety assessment. Duration of safety observation was longer for subjects in Arm 2 than for those in Arm 1 (31.1 weeks in Arm 1 and 40.4 weeks in Arm 2; see Table 21), commensurate with longer PFS in Arm 2.

Table 21
Duration of Safety Observation during First-Line Therapy:
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL+Placebo (n=396)	Arm 2 b-IFL+AVF (n=392)
Duration of safety observation (weeks)		
n	396	392
Mean (SE)	31.1 (1.0)	40.4 (1.2)
Median	28	40
Range	1-100	1-103

AVF=rhuMAb VEGF; b-IFL=bolus irinotecan/5-fluorouracil/leucovorin.

The above summary of the exposure to rhuMAb VEGF, placebo, and protocol-specified chemotherapy shows that chemotherapy dose reductions and Chemotherapy dose intensity are comparable between the two arms. Duration of safety observation is longer in Arm 2 compared to Arm 1, reflecting the difference in duration of survival.

3.2.2. Adverse Events

Events occurring during first-line therapy with a $\geq 2\%$ difference between Arm 1 and Arm 2 are presented in Table 22. Overall, 293 subjects (74%) in Arm 1 and 333 subjects (85%) in Arm 2 reported a Grade 3 or 4 adverse event (data were not adjusted for the length of time on treatment). Grade 3 and 4 adverse events that were increased in Arm 2 compared with Arm 1 included deep thrombophlebitis, hypertension, diarrhea, leukopenia, asthenia, abdominal pain, and pain. Grade 3 and 4 adverse events that were reduced in Arm 2 compared with Arm 1 included nausea, vomiting, and hyperglycemia.

Table 22
Grade 3 or 4 Adverse Events during First-Line Therapy by NCI-CTC Grade
(≥2% Difference in Event Rates):
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=396)	Arm 2 b-IFL + AVF (n=392)
Subjects with at least one adverse event	293 (74.0%)	333 (84.9%)
Grade 4	87 (22.0%)	116 (29.6%)
Grade 3	206 (52.0%)	217 (55.4%)
Body as a whole		
Asthenia	28 (7.1%)	35 (8.9%)
Grade 4	3 (0.8%)	2 (0.5%)
Grade 3	25 (6.3%)	33 (8.4%)
Abdominal pain	20 (5.1%)	28 (7.1%)
Grade 4	1 (0.3%)	3 (0.8%)
Grade 3	19 (4.8%)	25 (6.4%)
Pain	12 (3.0%)	20 (5.1%)
Grade 4	0 (0.0%)	1 (0.3%)
Grade 3	12 (3.0%)	19 (4.8%)
Cardiovascular		
Deep thrombophlebitis	25 (6.3%)	35 (8.9%)
Grade 3	25 (6.3%)	35 (8.9%)
Hypertension	9 (2.3%)	43 (11.0%)
Grade 3	9 (2.3%)	43 (11.0%)
Digestive		
Diarrhea	98 (24.7%)	127 (32.4%)
Grade 4	4 (1.0%)	14 (3.6%)
Grade 3	94 (23.7%)	113 (28.8%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin.

Note: Table includes events with rates, either overall or for any grade, ≥2% greater in Arm 2 or 3 vs. Arm 1 or ≥2% greater in Arm 1 vs. Arm 2 or 3. Data are unadjusted for the differential time on treatment.

Table 22 (cont'd)
Grade 3 or 4 Adverse Events during First-Line Therapy by NCI-CTC Grade
($\geq 2\%$ Difference in Event Rates):-
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=396)	Arm 2 b-IFL + AVF (n=392)
Digestive (cont'd)		
Vomiting	41 (10.4%)	30 (7.7%)
Grade 4	2 (0.5%)	1 (0.3%)
Grade 3	39 (9.8%)	29 (7.4%)
Nausea	36 (9.1%)	26 (6.6%)
Grade 3	36 (9.1%)	26 (6.6%)
Hemic/lymphatic		
Leukopenia	123 (31.1%)	145 (37.0%)
Grade 4	31 (7.8%)	47 (12.0%)
Grade 3	92 (23.2%)	98 (25.0%)
Metabolic/nutrition		
Hyperglycemia	17 (4.3%)	9 (2.3%)
Grade 4	4 (1.0%)	1 (0.3%)
Grade 3	13 (3.3%)	8 (2.0%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin.

Note: Data are unadjusted for the differential time on treatment.

Adverse events among subjects occurring with $\geq 10\%$ difference between Arm 1 and either Arm 2 or Arm 3 are presented in Table 23. Events with a higher rate in both Arms 2 and 3 relative to Arm 1 were pain, hypertension, epistaxis, dyspnea, anorexia, stomatitis, taste perversion, rectal hemorrhage, constipation, rhinitis, and lacrimation disorder. Adverse events that occurred more frequently in Arm 3 than Arms 1 and 2 were hypertension, dry skin, skin discoloration, exfoliative dermatitis, and lacrimation disorder. Adverse events that were lower in Arm 3 than in Arms 1 and 2 were leukopenia (54.1% in Arm 1 vs. 56.9% in Arm 2 vs. 11.0% in Arm 3) and alopecia (25.5% vs. 32.4% vs. 5.5%).

Table 23
Adverse Events during First-Line Therapy
 (≥ 10% Difference in Event Rates in Arm 2 or 3 vs. Arm 1):
 Treated Subjects Enrolled in Arm 3 and Concurrently Enrolled Subjects
 in Arms 1 and 2

	Arm 1 b-IFL + Placebo (n=98)	Arm 2 b-IFL+AVF (n=102)	Arm 3 5-FU/LV+AVF (n=109)
Total	98 (100%)	102 (100%)	109 (100%)
Body as a whole			
Pain	34 (34.7%)	51 (50.0%)	43 (39.4%)
Cardiovascular			
Hypertension	14 (14.3%)	22 (21.6%)	37 (33.9%)
Digestive			
Anorexia	29 (29.6%)	44 (43.1%)	37 (33.9%)
Constipation	28 (28.6%)	41 (40.2%)	32 (29.4%)
Stomatitis	13 (13.3%)	24 (23.5%)	19 (17.4%)
Rectal hemorrhage	2 (2.0%)	17 (16.7%)	9 (8.3%)
Hemic/lymphatic			
Leukopenia	53 (54.1%)	58 (56.9%)	12 (11.0%)
Respiratory			
Epistaxis	10 (10.2%)	36 (35.3%)	35 (32.1%)
Dyspnea	15 (15.3%)	26 (25.5%)	27 (24.8%)
Rhinitis	12 (12.2%)	26 (25.5%)	23 (21.1%)
Skin/appendages			
Alopecia	25 (25.5%)	33 (32.4%)	6 (5.5%)
Dry skin	7 (7.1%)	7 (6.9%)	22 (20.2%)
Exfoliative dermatitis	3 (3.1%)	3 (2.9%)	21 (19.3%)
Skin discoloration	3 (3.1%)	2 (2.0%)	17 (15.6%)
Special senses			
Taste perversion	8 (8.2%)	12 (11.8%)	21 (19.3%)
Lacrimation disorder	2 (2.0%)	6 (5.9%)	20 (18.3%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin;
 5-FU/LV = 5-fluorouracil/leucovorin.

Note: Table includes events with rates ≥ 10% greater in Arm 2 or 3 vs. Arm 1 or ≥ 10% greater in Arm 1 vs. Arm 2 or 3. Data are unadjusted for the differential time on treatment.

As shown in Table 24, 214 subjects (54.0%) in Arm 1 and 167 subjects (42.6%) in Arm 2 died during the study or follow-up. The “other” causes of death in Arm 1 were disseminated intravascular coagulation (Subject 12485), pancreatic cancer (Subject 10542), respiratory failure (Subject 11197), and suicide (Subject 13402). The “other” causes of death in Arm 2 were dehydration secondary to draining fistulas in a subject who refused IV hydration (Subject 10708) and volume depletion, with resulting cardiac arrest (Subject 12941).

Table 24
Deaths and Causes of Death:
Subjects Treated in Arms 1 and 2

	Arm 1 b-IFL+Placebo (n=396)	Arm 2 b-IFL+AVF (n=392)
Total deaths	214 (54.0%)	167 (42.6%)
Progressive disease	196 (49.5%)	151 (38.5%)
Bleeding	0 (0.0%)	1 (0.3%)
Cardiac	3 (0.8%)	2 (0.5%)
Infection	6 (1.5%)	5 (1.3%)
Pulmonary embolism	3 (0.8%)	1 (0.3%)
Other	4 (1.0%)	2 (0.5%)
Unknown cause	2 (0.5%)	5 (1.3%)

AVF = rhuMAb VEGF; b-IFL = bolus irinotecan/5-fluorouracil/leucovorin.

Note: Data are unadjusted for the differential time on treatment.

Serious adverse events were reported in 43% of subjects in Arm 1 and 51% of subjects in Arm 2. Serious deep thrombophlebitis occurred at a rate of 5.8% in Arm 1 vs. 8.9% in Arm 2. There were no other serious adverse events with rates that differed by $\geq 2\%$ between arms. The most common serious adverse events during first-line therapy leading to hospitalization among subjects treated in Arms 1 and 2 were diarrhea (9.3% in Arm 1 vs. 8.9% in Arm 2), leukopenia (4.0% vs. 5.6%), intestinal obstruction (4.0% vs. 3.8%), deep thrombophlebitis (2.3% vs. 5.4%), dehydration (3.5% vs. 4.1%), and vomiting (3.5% vs. 3.6%).

In summary, the addition of rhuMAb VEGF to bolus-IFL chemotherapy resulted in a small increase in the chemotherapy-related adverse events such as diarrhea and leukopenia, as well as an increase in the number of chemotherapy dose reductions and a small decrease in chemotherapy dose intensity.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Study AVF2107g is a large, randomized, double-blind, active-controlled trial in first-line colorectal cancer and provides the most scientifically rigorous data for establishing efficacy evidence. The review on findings in special/subgroup populations will focus on this study.

4.1 Gender, Race, Age, and by baseline risk factors

The results by gender, race, age, and baseline risk factor for the primary efficacy endpoint of duration of survival were generally consistent with the results for the randomized population as a whole (see Table 25). There was an overall consistent trend for increased median duration of survival for subjects in Arm 2 compared with those in Arm 1 regardless of baseline risk factor.

There was also an overall consistent trend for increased median PFS for subjects in Arm 2 compared with those in Arm 1 regardless of baseline risk factor. Similarly, there was an overall consistent trend for higher objective response rates for subjects in Arm 2 compared with those in Arm 1 regardless of baseline risk factor.

Table 25
Duration of Survival by Baseline Risk Factor
Randomized Subjects in Arms 1 and 2

Baseline Characteristic	Total n	b-IFL+Placebo		b-IFL+AVF		Hazard Ratio	(95% CI)
		n	Median (mo)	n	Median (mo)		
All Subjects	813	411	15.61	402	20.34	0.67	(0.55 - 0.82)
ECOG Performance Status							
0	461	227	17.87	234	24.18	0.66	(0.49 - 0.88)
≥1	352	184	12.12	168	14.92	0.69	(0.53 - 0.90)
Number of metastatic disease sites							
1	306	159	17.94	147	20.5	0.75	(0.53 - 1.04)
>1	507	252	14.59	255	19.91	0.62	(0.49 - 0.80)
Location of primary tumor							
COLON	644	334	15.7	310	19.52	0.74	(0.59 - 0.92)
RECTUM	169	77	14.92	92	24.15	0.47	(0.30 - 0.73)
Age (years)							
<40	35	17	15.61	18	22.83	0.50	(0.19 - 1.30)
40-64	507	253	15.8	254	19.61	0.71	(0.55 - 0.92)
≥65	271	141	14.92	130	24.15	0.61	(0.43 - 0.87)

(continued to next page)

Table 25 (cont'd)

Baseline Characteristic	Total n	b-IFL+Placebo		b-IFL+AVF		Hazard Ratio	(95% CI)
		n	Median (mo)	n	Median (mo)		
All Subjects	813	411	15.61	402	20.34	0.67	(0.55 - 0.82)
Sex							
FEMALE	328	163	15.7	165	18.66	0.73	(0.54 - 0.99)
MALE	485	248	15.44	237	21.22	0.64	(0.49 - 0.83)
Race							
WHITE	645	328	15.28	317	19.61	0.68	(0.55 - 0.85)
OTHERS	168	83	17.45	85		0.61	(0.38 - 0.98)
Prior adjuvant chemotherapy							
YES	209	113	17.64	96	21.62	0.64	(0.42 - 0.97)
NO	604	298	14.62	306	19.42	0.67	(0.53 - 0.84)
Duration of metastatic disease (months)							
<12	760	386	15.7	374	19.91	0.71	(0.58 - 0.87)
≥12	53	25	14.65	28	24.54	0.29	(0.13 - 0.66)

Baseline Characteristic	Total n	b-IFL+Placebo		b-IFL+AVF		Hazard Ratio	(95% CI)
		n	Median (mo)	n	Median (mo)		
All Subjects	813	411	15.61	402	20.34	0.67	(0.55 - 0.82)
Baseline albumin							
<MEDIAN	305	156	11.2	149	14.32	0.67	(0.51 - 0.89)
>MEDIAN	476	236	21.72	240	24.54	0.66	(0.49 - 0.89)
Baseline alkaline phosphatase							
<MEDIAN	385	195	17.18	190	24.15	0.63	(0.46 - 0.86)
≥MEDIAN	397	197	14	200	19.42	0.69	(0.53 - 0.90)
Baseline LDH							
<MEDIAN	386	189	20.44	197	24.15	0.67	(0.48 - 0.92)
≥MEDIAN	391	200	13.93	191	16.69	0.67	(0.52 - 0.88)

Baseline Characteristic	Total n	b-IFL+Placebo		b-IFL+AVF		Hazard Ratio	(95% CI)
		n	Median (mo)	n	Median (mo)		
All Subjects	813	411	15.61	402	20.34	0.67	(0.55 - 0.82)
Duration of disease (months)							
<12	527	260	14.59	267	18.66	0.72	(0.56 - 0.91)
≥12	285	151	17.02	134	24.15	0.57	(0.40 - 0.82)
SLD of target lesions (cm)							
<MEDIAN	400	199	20.4	201	24.15	0.77	(0.57 - 1.04)
≥MEDIAN	410	209	13.83	201	18.46	0.60	(0.46 - 0.78)
Prior radiotherapy							
YES	119	59	14.92	60	21.62	0.64	(0.38 - 1.09)
NO	694	352	15.64	342	19.91	0.67	(0.54 - 0.84)

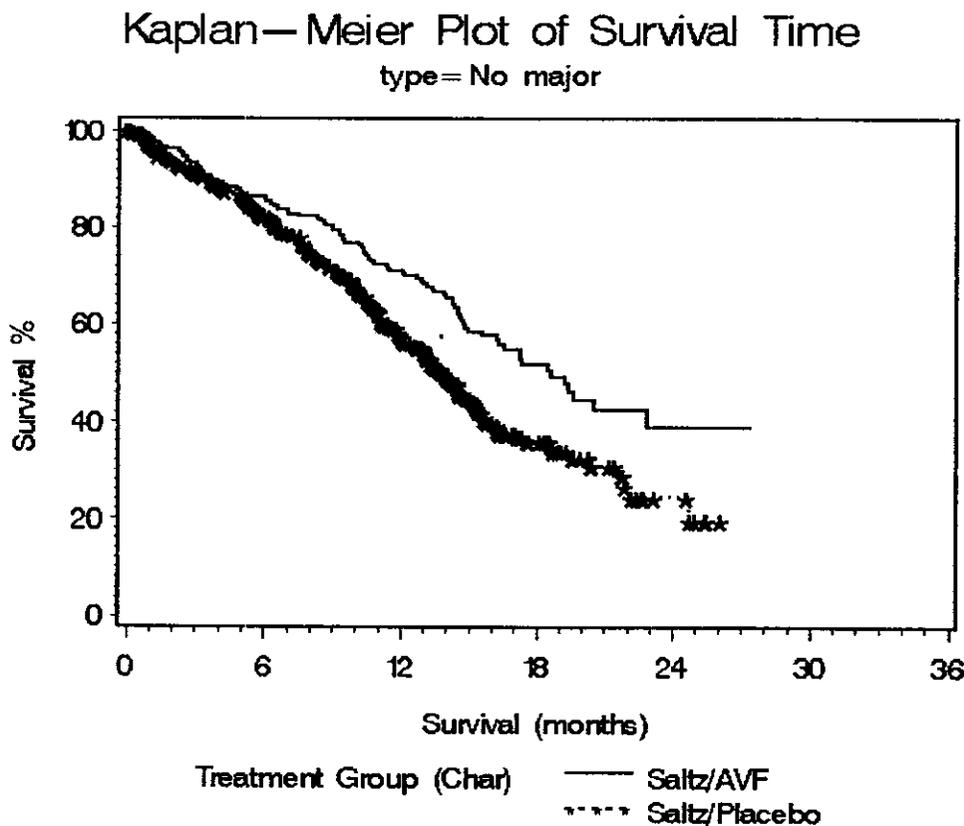
4.2 Other Special Populations

4.2.1 Eligibility and/or major protocol violators

A list of patients with eligibility and/or major protocol violations was provided by the medical reviewer. There was a group of patients who received study chemotherapy drugs 42 days after disease progression. We consider them as having major protocol violations. This reviewer identified the patients from the data sets and added this group of patients into the list of major protocol violations provided by the medical reviewer. Thus, there are four special subgroups in each of which we would like to know if survival benefits are still seen: 1) patients without major protocol and eligibility violations; 2) patients with major protocol and/or eligibility violations; 3) patients without any protocol and eligibility violations; and 4) patients with any protocol and/or eligibility violations.

Kaplan-Meier curves for duration of survival among patients without major protocol and eligibility violations are shown in Figure 8. Survival curves for patients with major protocol and/or eligibility violations are presented in Figure 9.

Figure 8
Subjects without major protocol and eligibility violations

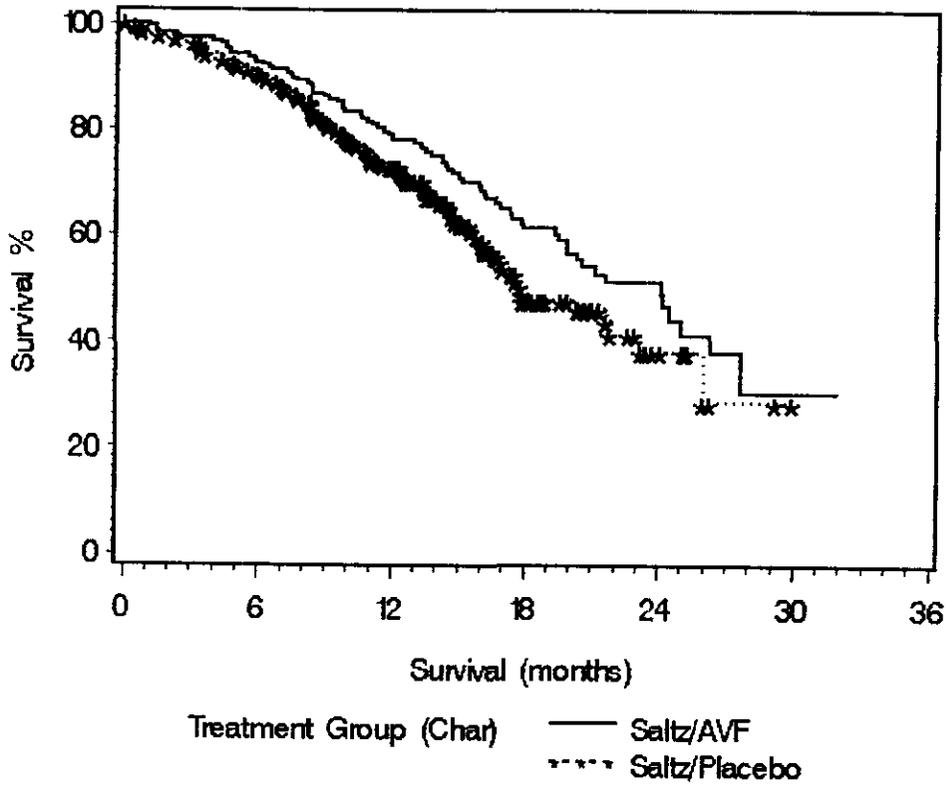


P = 0.0012* (N=450)

* interpretation of the p-value should be taken with caution since this is not a randomized subgroup

Figure 9
Subjects with major protocol and/or eligibility violations

Kaplan—Meier Plot of Survival Time
type= major



P = 0.0879* (N=363)

* interpretation of the p-value should be taken with caution since this is not a randomized subgroup

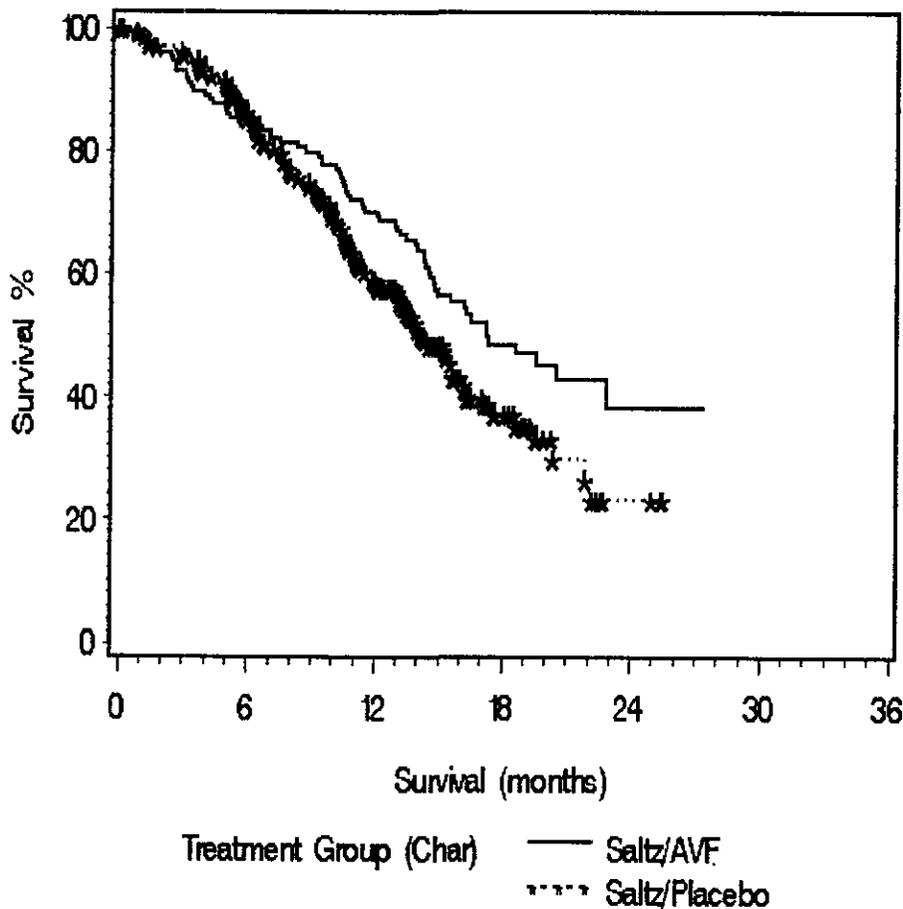
Among patient without any protocol and eligibility violations, Kaplan-Meier curves for duration of survival are shown in Figure 10. Survival curves for patients with any protocol and/or eligibility violations are presented in Figure 11.

As shown in the four graphs, results were generally consistent with the results for the randomized population as a whole. There was an overall consistent trend for increased median duration of survival for subjects treated with bevacizumab compared with those in the placebo group regardless of patients with protocol/eligibility violations or not. Similarly, there was an overall consistent trend for progression free survival for each of the subgroup analyses.

Figure 10
Subjects without any protocol and eligibility violations

Kaplan—Meier Plot of Survival Time

type=No any



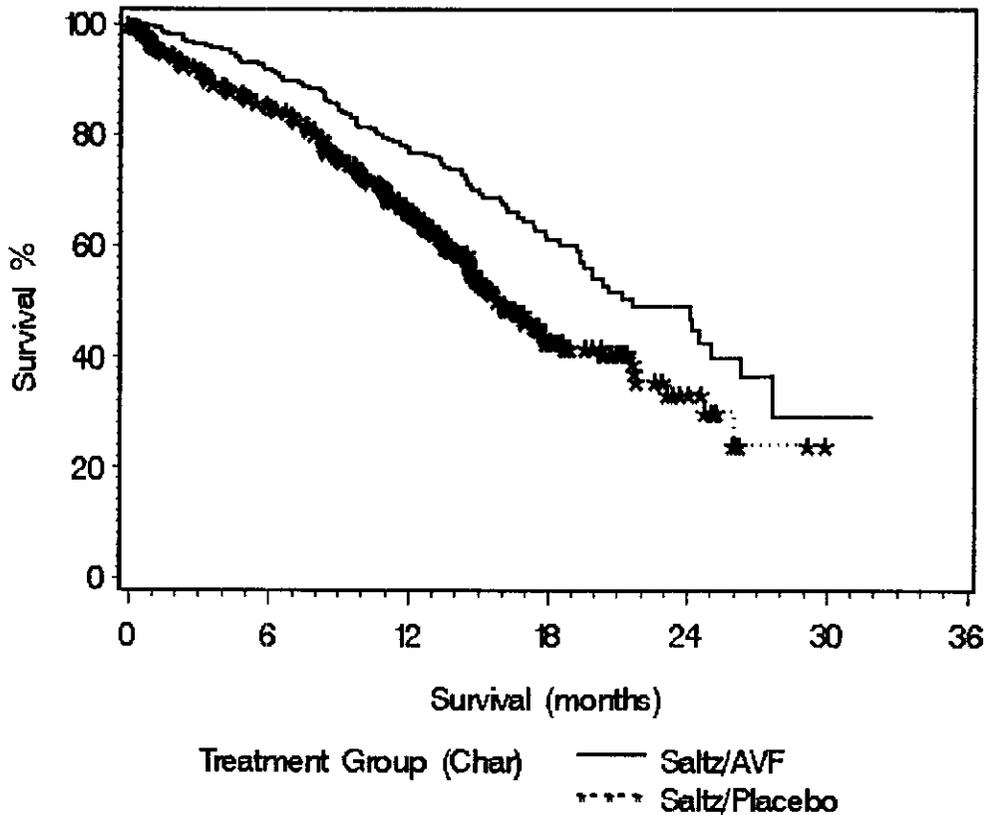
P = 0.0364* (N=301)

* interpretation of the p-value should be taken with caution since this is not a randomized subgroup

Figure 11
Subjects with any protocol and/or eligibility violations

Kaplan—Meier Plot of Survival Time

type= any



P = 0.0009* (N=512)

* interpretation of the p-value should be taken with caution since this is not a randomized subgroup

4.2.2 Investigational Site

Eight hundred and thirteen patients in Arms 1 and 2 were enrolled from 162 investigational sites. Number of patients enrolled per site ranged from 1 to 48 with a median of 5. All sites recruited 17 patients or less except one in which 48 patients were enrolled. Among the 48 patients enrolled in site S02157, the median survival in patients treated with bevacizumab was 20 months, compared to 14 months in the placebo arm. The result is consistent with that for all randomized patients. There may not be sufficient sample size for a meaningful comparison between the two arms in sites with 17 patients or less. It is very unlikely that any one of these sites would have a substantial impact on the overall efficacy results.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Conservation of the overall type I error rate

In the large, randomized, double-blind, Phase III trial (AVF2107g), one arm was dropped in the middle of the trial. There was an interim analysis intended to stop the trial earlier if the efficacy evidence is striking.

As the combination of bolus-IFL + rhuMAb VEGF (Arm 2) had not been tested in clinical trials, the initial part of the trial included a real-time assessment of safety. The results of the interim safety analysis were used to decide whether the bolus-IFL + rhuMAb VEGF combination (Arm 2) was safe. If the DMC determined that Arm 2 was safe, enrollment in Arm 3 would be discontinued after 100 subjects had been randomized to that arm, and enrollment in Arms 1 and 2 would be continued until a total of 400 subjects per treatment arm had been enrolled. If the DMC determined that Arm 2 was unsafe, enrollment in Arm 2 would be immediately discontinued, and enrollment in Arms 1 and 3 would be continued until a total of 400 subjects per treatment arm were enrolled. Following the interim safety analysis, the DMC notified Genentech that the safety profile of Arm 2 was acceptable. Accordingly, the 5-FU/leucovorin + rhuMAb VEGF arm (Arm 3) was closed to further enrollment of new subjects, as specified in the original protocol. Because Arm 3 was dropped based on safety evaluation, it should not have any impact on the overall Type I error rate.

An interim analysis of efficacy was scheduled when approximately half this number of deaths had occurred. To control for the Type I error rate for the primary endpoint of duration of survival, the Lan-DeMets implementation of the O'Brien-Fleming α spending function was used. The α -level for the final analysis is approximately equal to — level not substantially different from 0.05. The actual p-value associated with the chi-square test statistic for the primary analysis is — Thus, the difference between the two arms in overall survival is statistically significant at 0.05 in the final analysis after adjusting for the α spending at the interim analysis.

5.1.2 Potential Biases for Efficacy Evidence

The large, randomized, double-blind, Phase III trial (AVF2107g) demonstrated that the addition of rhuMAb VEGF to bolus-IFL chemotherapy improves survival, as reflected in the 34% decrease in the daily risk of death for subjects receiving bolus-IFL + rhuMAb VEGF compared with those receiving bolus-IFL alone. Corresponding significant increases in progression-free survival, objective response rate, and duration of response support this finding. This reviewer has checked the sponsor's analyses and found that the results agree with what the sponsor has presented.

However, a couple of concerns were raised during the review process 1) there was a substantial number of patients with eligibility and/or protocol violation which may have significant impact on the efficacy results; 2) we were not sure if the difference between the two arms in survival was due to the addition of bevacizumab or due to the less amount of chemotherapy received by patients in the placebo group.

This reviewer re-analyzed the survival endpoint with eligibility and/or protocol violation data and results are presented in Section 4.2.1. As shown from Figures 8-11, there was an overall consistent trend for increased median duration of survival for subjects in Arm 2 (bevacizumab) compared with those in Arm 1 (placebo) regardless of patients with eligibility and/or protocol violations or not. It is unlikely that eligibility and/or protocol violation could have any significant impact on the efficacy results.

From Table 18 in Section 3.2 (Safety Evaluation), one can see that the number of doses of study drug received was higher for subjects in Arm 2 than for those in Arm 1. However, this may be due to the difference between the two arms in length on study and follow-up since patients in the placebo arm were likely to progress and die earlier. As shown in Table 19, the number of subjects with at least one chemotherapy dose level reduction was higher in Arm 2 than in Arm 1. Dose intensity percentages for study drug and chemotherapy were also slightly lower for subjects in Arm 2 compared with those in Arm 1 (see Table 20). These results indicate that patients in the placebo arm did not receive less dosage of chemotherapy agents **per unit of time**, compared to those who were enrolled in the bevacizumab arm. Thus, the difference between the two arms in survival was very unlikely due to the less amount of chemotherapy received by patients in the placebo group.

Therefore, the efficacy evidence remains strong regardless of the concerns.

5.2 Conclusions and Recommendations

The large randomized, double-blind, well-controlled Phase III study demonstrated that the addition of bevacizumab 5 mg/kg every 2 weeks to bolus irinotecan/5-fluorouracil/leucovorin (bolus-IFL) chemotherapy improve survival, time to disease progression, and response rate, compared with those receiving bolus-IFL + placebo. The results from the Phase II randomized trial with 5-FU/leucovorin chemotherapy also support the efficacy findings. It appears that bevacizumab treatment was associated with slightly higher incidence of adverse events. However, the benefits (e.g.: 34% decrease in the hazard of death) outweigh the increase of adverse events due to the addition of bevacizumab.

The efficacy results from the Phase III trial support the claim of using bevacizumab for first-line treatment of patients with metastatic carcinoma of the colon and rectum in combination with bolus-IFL chemotherapy.

