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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Inlyta® / Axitinib (AG-013736)

PROTOCOL NO.: A4061034

PROTOCOL TITLE: A Randomized, Phase 2 Study of FOLFOX or FOLFIRI With AG-013736 or Bevacizumab in Patients With Metastatic Colorectal Cancer After Failure of an Irinotecan or Oxaliplatin-Containing First-Line Regimen

Study Centers: A total of 37 centers took part in the study and enrolled subjects which included 15 in the United States (US), 3 in Canada, 4 in France, 4 in Italy, 3 in Japan, 3 in the Republic of Korea, 3 in Spain, and 2 in Poland.

Study Initiation, Primary Completion and Final Completion Dates:
First Subject First Visit: 14 March 2008
Primary Completion Date: 28 March 2011
Final Completion Date: 12 April 2012

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To demonstrate that the combination of axitinib with either treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan (FOLFIRI) or treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin (FOLFOX) was superior to FOLFIRI or FOLFOX in combination with bevacizumab in prolonging the progression free survival (PFS) in the second-line treatment of subjects with metastatic colorectal cancer (mCRC) after failure of an irinotecan- or oxaliplatin-containing first-line regimen.

Secondary Objectives:

- To compare the overall survival (OS) in subjects randomized to axitinib with either FOLFIRI or FOLFOX versus (vs) that in subjects randomized to FOLFIRI or FOLFOX in combination with bevacizumab.

- To compare the overall response rate (ORR) and duration of response (DR) in subjects randomized to axitinib with either FOLFIRI or FOLFOX vs that in subjects randomized to FOLFIRI or FOLFOX in combination with bevacizumab.

- To evaluate the safety and tolerability of axitinib in combination with either FOLFIRI or FOLFOX.

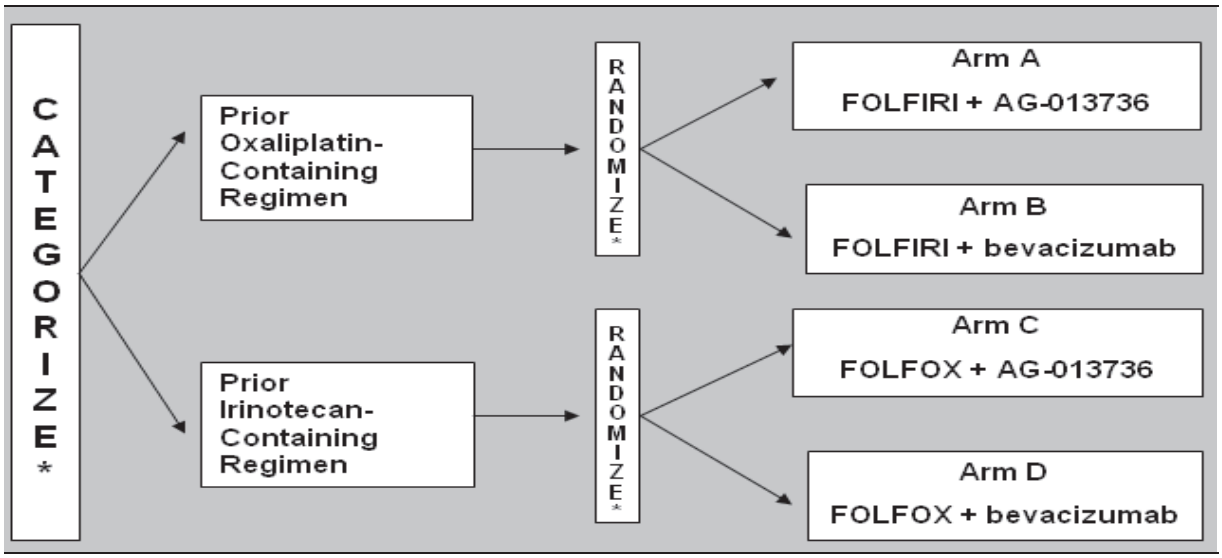
- To evaluate Patient Reported Outcome (PRO) symptom severity and interference using the MD Anderson Symptom Inventory – Diarrhea (MDASI-D).

METHODS

Study Design: This was a multicenter, categorized (by prior treatment), randomized, Phase 2 study in subjects with mCRC after failure of an irinotecan- or oxaliplatin-containing first-line regimen.

Eligible subjects in each of the 2 categories (Figure 1) were stratified by Eastern Cooperative Oncology Group performance status (ECOG PS; 0/1) and by previous bevacizumab treatment (yes/no), and were randomized (1:1 in each category) as summarized in Figure 1. Subjects had assessments for tumor response approximately every 8 weeks. Crossover between treatment arms was not permitted. For the purpose of this study, treatment cycles were defined according to the 2-week FOLFIRI or FOLFOX treatment cycles. Subjects remained on the study until progression of disease, unless unacceptable toxicity or withdrawal of subject consent occurred.

Figure 1. Randomization Scheme to Receive FOLFIRI or FOLFOX



* by previous treatment with oxaliplatin- or irinotecan-containing regimen.
ECOG = Eastern Cooperative Oncology Group performance status; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin.

Table 1 presents the schedule of activities used for this study.

Table 1. Schedule of Activities

Activity	Screening Days –14 to Day 0	Day 1 (Predose) of Each Cycle[a]	Every 8 Weeks, Regardless of Cycle Length	Post Treatment	
				End of Study Treatment / Withdrawal	Follow-Up 28 Days After Last Dose
Informed consent[b]	X				
MD Anderson symptom inventory - diarrhea (MDASI-D)[c]		X		X	
Medical history[d]	X				
Pregnancy test[e] (serum/urine)	Day –3 to 0				
Physical examination[f]	X	X		X	
Weight, temperature, BP[g], pulse	X	X		X	
ECOG PS[h]	X	X, every odd cycles		X	
ECG (12-Lead)[i]	X			X	
Hematology[j]	X	X		X	
Chemistry[k]	X	X		X	
TSH, T_3, T_4[l]	X	Every cycle X 3[l]		X	
Urinalysis[m]	X	X		X	
Safety assessment (adverse events)[n]		Monitored throughout the study			
Concomitant treatment[o]	X	Monitored throughout the study			
Tumor measurements[p]	Day –28 to 0		X		
Brain CT or MRI[q]	X				
Randomization	X				
FOLFIRI or FOLFOX treatment[r]		X			
Axitinib[s]		Twice daily continuously			
Bevacizumab[t]		Every 2 weeks			
Survival[u]		Monthly until at least 12 months after the randomization of the last subject.			
Genotype test for UGT1A1 and other drug metabolizing enzymes/transporters[v]		X[v]			
Exploratory research – blood sample (optional)[w]		X[w]		X[w]	
Exploratory research – archival tumor (optional)[x]		X[x]			
Samples for population pharmacokinetics[y]		X[y]			

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CR = complete response; CT = computed tomography; CTCAE = common terminology criteria for adverse events; ECG = electrocardiogram; ECOG PS = eastern cooperative oncology group performance status; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; Hgb = hemoglobin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PR = partial response; T_3 = tri-iodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; UGT1A1 = uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1; WBC = white blood cell; 5-FU = 5-fluorouracil.

Table 1. Schedule of Activities

a. Cycle length was 2 weeks. Tests and procedures were to be done on schedule, but occasional changes by ±4 days were allowable for holidays, vacations, and other administrative reasons.
b. Informed consent may have been obtained earlier and must have been obtained before any study-specific procedures.
c. The MDASI-D was to be given at Baseline (prior to the start of therapy), Day 1 of the next 4 cycles (up to Cycle 5), and then on Day 1 of every other cycle throughout the rest of the study. It was to be given at the end of study treatment or upon withdrawal.
d. Included history of prior treatments for cancer and use of nicotine products.
e. Subjects of childbearing potential were required to have a negative serum or urine pregnancy test within 3 days before treatment and were required practicing appropriate birth control.
f. Including height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were to be performed.
g. BP was to be taken (2 BP readings, preferably separated by at least 1 hour) with the subject in the seated position after the subjects at quietly for 5 minutes. Subjects randomized to axitinib Arms A and C were to have BP measurements twice daily and were to record results in the subject diary to be collected by the Sponsor.
h. ECOG PS was to assessed on screening, and then on odd cycles.
i. Additional ECGs were to be obtained if clinically indicated.
j. Hgb, WBC, neutrophil count, lymphocyte count, and platelets. If baseline values were obtained within 4 days before Cycle 1 Day 1, repeat hematology was not necessary for Cycle 1 Day 1.
k. Sodium, potassium, chloride, bicarbonate or venous CO_2, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, BUN, creatinine, glucose, and LDH. If baseline values were obtained within 4 days before Cycle 1 Day 1, repeat chemistry was not necessary for Cycle 1 Day 1. Bicarbonate and venous CO_2 were optional for sites in Japan.
l. Thyroid functions tests (TSH, T_3, T_4) on Day 1 of every cycle × 3, then every odd cycle thereafter, and at the end-of-study visit. Subjects receiving axitinib were to be monitored for signs and symptoms of hypothyroidism, such as fatigue, deepening of voice, cold intolerance, constipation, anorexia, periorbital edema, myxedema, or changes in skin or hair. Hypothyroidism was to be treated per standard medical practice to maintain euthyroid state. T_3 test was optional for sites in France.
m. Protein, glucose, and blood. If, during treatment, urine protein was ≥2+ by semi quantitative method (eg, dipstick), then it was to be quantitated by 24-hour urine collection. Dose adjustment may have been required. If baseline values were obtained within 4 days before Cycle 1 Day 1, repeat urinalysis was not necessary for Cycle 1 Day 1.
n. AEs were to be collected through the study period starting at the time written consent was given through at least 28 days after the last dose of study medications. AEs that were serious, suspected to be related to study drug, or considered significant by the Investigator or the Sponsor's medical monitor were to be followed after therapy discontinuation until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator and the Sponsor's medical monitor or his/her designated representative.
o. Was to be collected from Screening to the follow-up visit.
p. Baseline assessments of disease were to be done within 28 days before randomization. Tumor assessments (CT or MRI of chest, abdomen, and pelvis) were to be done every 8 weeks regardless of cycle length. Response (CR/PR) required confirmation at least 4 weeks after the response was noted. For subjects who had not progressed after discontinuing study drug, additional tumor assessments were to be performed approximately every 8 weeks until the subject met criteria for progression or alternate therapy was started.
q. Brain CT or MRI with contrast was to be performed at Screening.
r. Infusion length was 90 minutes for irinotecan (180 mg/m^2) in the FOLFIRI arms (Arms A and B) and 120 minutes for oxaliplatin (85 mg/m^2) in the FOLFOX arms (Arms C and D). In both FOLFOX and FOLFIRI treatment groups, the infusion length was 2 hours for leucovorin. Then 5-FU 400 mg/m^2 bolus was to be given, followed by 5-FU at 2400 mg/m^2 in a 46 to 48 hour infusion. The regimen was to be repeated every 2 weeks.
s. For subjects randomized to Arm A or C. Subjects who tolerated axitinib with no AEs related to axitinib above CTCAE Grade 2 for consecutive 2-week periods were to have their dose increased by 1 dose level, unless BP was >150/90 mm Hg or the subject was receiving antihypertensive medication.
t. For subjects randomized to Arm B or D. Bevacizumab dose was 5 mg/kg every 2 weeks. The initial dose was to be given over 90 minutes, the second dose over 60 minutes, and all subsequent doses over 30 minutes, if prior infusions were tolerated without infusion-associated AEs.
u. All subjects were to be followed for survival at least every month after discontinuation of study treatment until at least 12 months after randomization of the last subject.

Table 1. Schedule of Activities

v. One blood sample (2 mL) was to be collected only on Day 1 of Cycle 1 for genotyping of UGT1A1 and other drug metabolizing enzymes and transporters involved in the disposition of axitinib.
w. Blood sample (optional to site and subject) was to be taken on Cycle 1 Day 1 and at the end of study treatment/withdrawal from all subjects.
x. Archival tumor sample (optional to site and subject) was to be collected on Cycle 1 Day 1 or at any time during the study from all subjects.
y. Two plasma samples (just before and 1 to 2 hours after the morning dose of axitinib) for axitinib were to be obtained each on Cycle 2 Day 1 and Cycle 3 Day 1 only.

Number of Subjects (Planned and Analyzed): Approximately 176 subjects (44 in each of the 4 treatment arms) were planned to be enrolled at multiple sites. A total of 186 subjects were enrolled (46 in the US, 5 in Canada, 17 in Spain, 39 in Poland, 12 in Japan, 33 in Italy, 22 in the Republic of Korea, and 12 in France), of which 171 subjects were randomized (42 in the US, 5 in Canada, 13 in Spain, 39 in Poland, 11 in Japan, 31 in Italy, 20 in the Republic of Korea, and 10 in France), and 168 subjects received treatment.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged ≥18 years (≥20 years in Japan only), with histologically confirmed diagnosis of mCRC, radiographic evidence of failure of 1 prior irinotecan- or oxaliplatin-containing regimen, no prior treatment of mCRC with >1 systemic chemotherapy regimen for metastatic disease, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) and an ECOG PS of 0 or 1 were included in the study.

Study Treatment:

Axitinib: Axitinib dose adjustments, including dose increases or dose reductions were to be based on adverse events (AEs) experienced by the individual subject. Axitinib was to be taken beginning on Day 1 of the study. Doses were taken approximately 12 hours apart. Subjects were to be instructed to take their doses at approximately the same times each day. Subjects were required to be instructed that if they vomited any time after taking a dose, that they must not make it up with an extra dose, but instead resumed subsequent doses as prescribed. Any missed dose may have been taken late up to 3 hours before the next scheduled dose; otherwise, it should be skipped. Axitinib was supplied in 1-mg and 5-mg, film-coated tablets for oral administration.

Bevacizumab: Bevacizumab dose was 5 mg/kg every 2 weeks, just prior to FOLFOX or FOLFIRI. The initial dose was to be given over 90 minutes, the second dose over 60 minutes, and all subsequent doses over 30 minutes, if prior infusions were tolerated without infusion-associated AEs.

FOLFOX (folinic acid [leucovorin], 5-fluorouracil, and oxaliplatin):

- Oxaliplatin 85 mg/m^2 intravenous (IV) was infused over 120 minutes.
- Leucovorin (LV) 400 mg/m^2 (or 200 mg/m^2 of *l*-leucovorin) IV was infused over 2 hours (concurrently with oxaliplatin via separate infusion lines).
- 5-fluorouracil (5-FU) 400 mg/m^2 IV was administered via bolus injection (following LV administration), then 2400 mg/m^2 continuous IV infusion over 46 to 48 hours.

FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan):

- Irinotecan 180 mg/m^2 IV was infused over 90 minutes.
- LV 400 mg/m^2 (or 200 mg/m^2 of *l*-leucovorin) IV was infused over 2 hours (concurrently with irinotecan via separate infusion lines).

- 5-FU 400 mg/m^2 IV was administered via bolus injection (following LV administration), then 2400 mg/m^2 continuous IV infusion over 46 to 48 hours.

Efficacy Endpoints:

Primary Endpoint: PFS defined as the time from randomization to the date of progression or death due any cause, whichever occurs first.

Secondary Endpoints:

- OS defined as the time from randomization to the date of death due to any cause.
- ORR defined as the proportion of randomized subjects with baseline measurable disease and a best response characterized as either a complete response (CR) or partial response (PR) (CR or PR defined according to RECIST).
- DR defined as the time from first documentation of response to the date of progression or death due to any cause, whichever occurs first.
- Overall safety profile characterized by type, frequency, severity as graded using National Cancer Institute Common Terminology Criteria for AEs, version 3.0 and relationship to study therapy of AEs and laboratory abnormalities.
- PRO changes in scores for symptom severity and interference according to the MDASI-D.

Safety Evaluations: AEs, clinical laboratory measurements, physical examinations, electrocardiograms (ECG), and blood pressure (BP) measurements were assessed throughout the study.

Statistical Methods:

Intent-to-treat (ITT) Population: This population (ie, full analysis set [FAS]) included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug according to randomization schedule or received a different drug from that to which they were randomized. This was the primary population for evaluating all efficacy endpoints and subject characteristics.

As-Treated (AT) Population (Safety): The AT population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This was the primary population for evaluating treatment administration/compliance and safety.

Analysis of Efficacy Parameters: Time-to-event endpoints were summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and a 2-sided 95% confidence interval (CI) for each median were provided. In addition, PFS and

OS were compared between the treatment arms using a 1-sided stratified log-rank test with a significance level of 0.15.

Cox proportional hazard models were used to explore the potential influences of the baseline stratification factors on time-to-event endpoints. The estimated hazard ratio (HR) and a 2-sided 95% CI were provided. Additionally, for each treatment arm, the median event time and a 2-sided 95% CI were provided for each level of the stratification factors.

For binary endpoints, point estimates of the rates for each treatment arm and difference of the rates between treatment arms were provided along with the corresponding 2-sided 95% CIs using an exact method based on the F distribution and using a normal approximation for constructing a CI for differences, respectively.

For the stratified analyses, the relative risk ratio estimator was used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation. Treatment arms were compared with a significance level of 0.15 using a 1-sided Pearson χ^2 test for unstratified analyses and Cochran-Mantel-Haenszel (CMH) test for stratified analyses.

Descriptive statistics, including the mean, standard deviation (SD), median, minimum, and maximum values were provided for continuous endpoints. The number and percentage of subjects in each category were provided for categorical variables.

PFS was summarized in the ITT population based on the Investigator's assessment of disease response and progression. Differences in PFS between treatment arms were analyzed by the log rank test (1-sided, $\alpha = 0.15$) stratified for ECOG PS (0 vs 1) and prior treatment with bevacizumab (yes vs no). An unstratified log-rank test (1-sided, $\alpha = 0.15$) and Cox regression model were also used as a secondary, sensitivity check on the primary PFS endpoint. Additionally, for each treatment arm, the median PFS and a 2-sided 95% CI were provided for each level of the stratification variables.

OS was summarized in the ITT population. The 1-year survival probability was estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log (1-year survival probability)] were calculated using a normal approximation and then back transformed to give a CI for the 1-year survival probability itself.

The ORR (CR or PR) was summarized in the ITT population, based on the Investigator's assessment of disease response. The ORR was summarized for each treatment arm, along with the corresponding exact 2-sided 95% CI, using a method based on the F distribution. The relative risk ratio estimator was used to contrast the treatment effects on response rates. A point estimate and a 2-sided 95% CI were calculated using the normal approximation. The CMH test stratified by baseline stratification factors was used to compare ORR between the treatment arms. Additionally, an unstratified test (Pearson χ^2) was used to compare ORR between the treatment arms. The response rate for each treatment arm was summarized for each level of the baseline stratification variables and presented along with the corresponding exact 2-sided 95% CI based on the F distribution method.

DR was summarized for the subgroup of subjects with objective disease response using the Kaplan-Meier method and was displayed graphically, where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median for each treatment arm were provided. The number of subjects with CR or PR may have been small and, therefore, the use of the Kaplan-Meier method to provide reliable estimates may have been limited. As this was the case, descriptive statistics or listings were also provided.

Descriptive statistics were used to summarize study conduct, subject disposition, baseline characteristics, and treatment administration/compliance in the ITT population.

Analysis of Pharmacokinetic Parameters: The plasma concentration data set from this study were to be pooled with data sets from additional axitinib studies conducted in other oncology subject populations. Population PK analysis was to involve mixed effects modeling performed using appropriate software (eg, NONlinear Mixed Effects Modeling).

The intent of this analysis was to establish and build upon a basic population PK model for axitinib and to determine the inter-individual and residual variability in the population (oral) clearance and, if possible, the volume of distribution of the drug. The primary objective of the analysis will be to identify demographic factors (eg, age, body weight, height, ethnicity) that affect the PK of axitinib. A secondary objective will be to screen for relationships with food intake and concomitant medications (drugs known to alter hepatic metabolism and the common concomitant medications) and measures of altered hepatic and renal function (eg, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, serum creatinine). Other covariates that appear to have a relationship in screening may also be assessed for significance.

All subjects treated with axitinib and for whom drug plasma concentration results (from at least 1 visit) were available were to be included in the population analysis. If a subject was removed from the analysis, then a full written justification was to be included in the report as would the procedure for handling missing data. The development of the base model, the subsequent steps leading to the final model, and model validation procedures was to be clearly outlined in the population PK report. Appropriate tests to determine the goodness of fit of the final model to the data were to be performed and documented.

Analysis of Pharmacogenomic Parameters: The UGT1A1 genotype results from this study are included as a listing only, no analyses were performed on these results.

Safety Parameters: Safety population consisted of all subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety.

RESULTS

Subject Disposition and Demography: A total of 37 sites from 8 countries randomized 171 subjects in the study; 168 (98.2%) of 171 randomized subjects received treatment in this study. Table 2 presents disposition of all treatment groups.

Table 2. Subject Evaluation Groups

	Axitinib + FOLFIRI n (%)	Bevacizumab + FOLFIRI n (%)	Axitinib + FOLFOX n (%)	Bevacizumab + FOLFOX n (%)
Number of subjects randomized: 171				
Assigned to study treatment	49	51	36	35
Treated	46	51	36	35
Discontinued	43 (87.8)	50 (98.0)	36 (100.0)	35 (100.0)
Ongoing at date of cutoff	3 (6.1)	1 (2.0)	0	0
Analyzed for safety				
Adverse events	46 (93.9)	51 (100.0)	36 (100.0)	35 (100.0)
Laboratory data	45 (91.8)	50 (98.0)	36 (100.0)	35 (100.0)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; n = number of subjects meeting prespecified criteria.

Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9 present discontinuation details for axitinib, bevacizumab, 5-FU bolus, 5-FU infusion, leucovorin, irinotecan, and oxaliplatin respectively, and Table 10 presents the discontinuations from study for safety analysis set exclusively. Demographic characteristics are reported in Table 11.

Table 3. Discontinuations From Axitinib; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Axitinib + FOLFOX N=36 n (%)
Adverse event	8 (17.4)	6 (16.7)
Subject died	0	1 (2.8)
Other	7 (15.2)	1 (2.8)
Objective progression or relapse	27 (58.7)	24 (66.7)
Global deterioration of health status	2 (4.3)	0
Subject refused continued treatment for reason other than adverse event	2 (4.3)	4 (11.1)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 4. Discontinuations From Bevacizumab; Safety Analysis Set

Primary Reason for Discontinuation	Bevacizumab + FOLFIRI N=51 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Adverse event	3 (5.9)	2 (5.7)
Subject died	3 (5.9)	0
Lost to follow-up	0	1 (2.9)
Other	8 (15.7)	3 (8.6)
Objective progression or relapse	33 (64.7)	26 (74.3)
Subject refused continued treatment for reason other than adverse event	3 (5.9)	3 (8.6)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 5. Discontinuations From 5-FU Bolus; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Adverse event	10 (21.7)	4 (7.8)	3 (8.3)	2 (5.7)
Subject died	1 (2.2)	3 (5.9)	2 (5.6)	0
Lost to follow-up	0	0	0	1 (2.9)
Other	4 (8.7)	9 (17.6)	2 (5.6)	3 (8.6)
Objective progression or relapse	24 (52.2)	31 (60.8)	24 (66.7)	26 (74.3)
Global deterioration of health status	2 (4.3)	0	1 (2.8)	0
Subject refused continued treatment for reason other than adverse event	2 (4.3)	3 (5.9)	4 (11.1)	3 (8.6)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria; 5-FU = 5-fluorouracil.

Table 6. Discontinuations From 5-FU Infusion; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Adverse event	9 (19.6)	3 (5.9)	3 (8.3)	2 (5.7)
Subject died	0	3 (5.9)	2 (5.6)	0
Lost to follow-up	0	0	0	1 (2.9)
Other	5 (10.9)	9 (17.6)	2 (5.6)	3 (8.6)
Objective progression or relapse	24 (52.2)	32 (62.7)	25 (69.4)	26 (74.3)
Global deterioration of health status	3 (6.5)	0	0	0
Subject refused continued treatment for reason other than adverse event	2 (4.3)	3 (5.9)	4 (11.1)	3 (8.6)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria; 5-FU = 5-fluorouracil.

Table 7. Discontinuations From Leucovorin; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Adverse event	8 (17.4)	3 (5.9)	3 (8.3)	2 (5.7)
Subject died	0	3 (5.9)	2 (5.6)	0
Lost to follow-up	0	0	0	1 (2.9)
Other	5 (10.9)	9 (17.6)	2 (5.6)	3 (8.6)
Objective progression or relapse	25 (54.3)	32 (62.7)	25 (69.4)	26 (74.3)
Global deterioration of health status	3 (6.5)	0	0	0
Subject refused continued treatment for reason other than adverse event	2 (4.3)	3 (5.9)	4 (11.1)	3 (8.6)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 8. Discontinuations From Irinotecan; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)
Adverse event	10 (21.7)	3 (5.9)
Subject died	0	3 (5.9)
Other	5 (10.9)	10 (19.6)
Objective progression or relapse	23 (50.0)	31 (60.8)
Global deterioration of health status	3 (6.5)	0
Subject refused continued treatment for reason other than adverse event	2 (4.3)	3 (5.9)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 9. Discontinuations From Oxaliplatin; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Adverse event	9 (25.0)	5 (14.3)
Subject died	2 (5.6)	0
Lost to follow-up	0	1 (2.9)
Other	3 (8.3)	3 (8.6)
Objective progression or relapse	18 (50.0)	23 (65.7)
Subject refused continued treatment for reason other than adverse event	4 (11.1)	3 (8.6)

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 10. Discontinuations From Study; Safety Analysis Set

Primary Reason for Discontinuation	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Subject died	31 (67.4)	31 (60.8)	21 (58.3)	23 (65.7)
Lost to follow-up	1 (2.2)	2 (3.9)	4 (11.1)	5 (14.3)
Other	11 (23.9)	15 (29.4)	10 (27.8)	7 (20.0)
Objective progression or relapse	0	1 (2.0)	0	0
Subject refused continued treatment for reason other than adverse event	0	1 (2.0)	1 (2.8)	0

FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
N = number of subjects; n = number of subjects meeting prespecified criteria.

Table 11. Demographic Characteristics; Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Sex				
Male	31 (63.3)	27 (52.9)	16 (44.4)	24 (68.6)
Female	18 (36.7)	24 (47.1)	20 (55.6)	11 (31.4)
Age (years)				
18-44	5 (10.2)	6 (11.8)	3 (8.3)	1 (2.9)
45-64	30 (61.2)	34 (66.7)	21 (58.3)	22 (62.9)
≥65	14 (28.6)	11 (21.6)	12 (33.3)	12 (34.3)
Median	59	58	58.5	60
Mean	58.6	57.7	58.1	60.5
SD	11.0	10.4	11.1	8.8
Range	24-76	34-80	25-75	41-77
Race				
White	36 (73.5)	41 (80.4)	28 (77.8)	27 (77.1)
Black	1 (2.0)	2 (3.9)	2 (5.6)	0
Asian	11 (22.4)	8 (15.7)	6 (16.7)	7 (20.0)
Other	1 (2.0)	0	0	1 (2.9)
Weight (kg)				
Median	74.38	69.00	70.02	76.00
Mean	74.2	71.3	71.5	75.7
SD	15.2	16.0	19.0	16.8
Range	47-104	41-117	45-126	50-112
Height (cm)				
Median	170.0	167.00	167.50	167.40
Mean	170.2	165.9	166.8	166.9
SD	8.8	9.4	8.8	9.8
Range	154-189	148-186	150-191	146-188
ECOG PS				
0	36 (73.5)	36 (70.6)	24 (66.7)	25 (71.4)
1	13 (26.5)	15 (29.4)	12 (33.3)	10 (28.6)
Prior radiation neoadjuvant therapy				
Yes	2 (4.1)	1 (2.0)	2 (5.6)	2 (5.7)
No	47 (95.9)	50 (98.0)	34 (94.4)	33 (94.3)
Prior radiation adjuvant therapy				
Yes	2 (4.1)	1 (2.0)	1 (2.8)	1 (2.9)
No	47 (95.9)	50 (98.0)	35 (97.2)	34 (97.1)
Prior radiation palliative therapy				
Yes	2 (4.1)	4 (7.8)	1 (2.8)	2 (5.7)
No	47 (95.9)	47 (92.2)	35 (97.2)	33 (94.3)
Prior systemic neoadjuvant therapy				
Yes	1 (2.0)	1 (2.0)	2 (5.6)	2 (5.7)
No	48 (98.0)	50 (98.0)	34 (94.4)	33 (94.3)
Prior systemic adjuvant therapy				
Yes	11 (22.4)	9 (17.6)	9 (25.0)	13 (37.1)
No	38 (77.6)	42 (82.4)	27 (75.0)	22 (62.9)
Prior systemic metastatic therapy				
Yes	43 (87.8)	45 (88.2)	35 (97.2)	30 (85.7)
No	6 (12.2)	6 (11.8)	1 (2.8)	5 (14.3)

Table 11. Demographic Characteristics; Full Analysis Set

ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; SD = standard deviation.

Efficacy Results:

Primary Results: The primary objective of this study was to compare the PFS of subjects with colorectal cancer receiving axitinib with either FOLFIRI or FOLFOX vs bevacizumab with either FOLFIRI or FOLFOX following failure of an irinotecan- or oxaliplatin-containing first-line regimen. Table 12 and Table 13 present a summary of PFS by treatment (stratified analysis and unstratified analysis respectively) for the FAS. Table 14 presents summary of PFS by stratification factors; FAS.

Table 12. Summary of Progression Free Survival (Stratified); Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Number with event	30 (61.2)	38 (74.5)	24 (66.7)	21 (60.0)
Type of event				
Objective progression	28 (57.1)	33 (64.7)	23 (63.9)	21 (60.0)
Death without objective progression	2 (4.1)	5 (9.8)	1 (2.8)	0
Number censored	19 (38.8)	13 (25.5)	12 (33.3)	14 (40.0)
Reason for censorship:				
No baseline or on-study assessments	6 (12.2)	0	0	3 (8.6)
Alive, on study, and progression free at time of analysis	6 (12.2)	8 (15.7)	9 (25.0)	6 (17.1)
At least 1 on-study disease assessment and discontinued treatment before documented PD on study	5 (10.2)	5 (9.8)	2 (5.6)	3 (8.6)
PD occurred after ≥2 consecutive, missed assessments	0	0	0	2 (5.7)
PD occurred after given new antitumor treatment	2 (4.1)	0	1 (2.8)	0
Kaplan-Meier estimates of time to event (months)				
Quartiles [95% CI][a]				
25%	3.75 (1.97, 5.03)	3.65 (2.00, 5.16)	4.01 (1.77, 6.90)	3.84 (2.33, 6.24)
50%	5.72 (4.50, 7.42)	6.87 (4.96, 9.13)	7.59 (5.62, 11.07)	6.44 (5.52, 13.11)
75%	11.30 (7.29, 12.94]	13.47 (8.97, 15.83)	12.42 (9.40, 16.56)	13.11 (6.67, 14.72)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI / axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[b]	1.273		1.041	
95% CI of hazard ratio	0.769, 2.108		0.553, 1.960	
p-Value*	0.8268		0.5498	

*One-sided p-value from the log-rank test stratified by ECOG performance status (0 vs 1) and prior treatment with bevacizumab (yes vs no).
PFS was defined as the first date that criteria for progression was met or the subject died due to any cause - date of randomization +1.
Subjects lacking an evaluation of tumor response after randomization had their event times censored at 1 day. Subjects not experiencing disease progression during the treatment and follow-up periods and who did not die during the treatment period had their event time censored on the last study date that objective tumor assessments verified lack of disease progression.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; PD = progressive disease; PFS = progression free survival; vs = versus.

a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox proportional hazard model stratified by ECOG performance status (0 vs 1) and prior treatment with bevacizumab (yes vs no). A hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of bevacizumab.

Table 13. Summary of Progression Free Survival (Unstratified); Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Number with event	30 (61.2)	38 (74.5)	24 (66.7)	21 (60.0)
Type of event				
Objective progression	28 (57.1)	33 (64.7)	23 (63.9)	21 (60.0)
Death without objective progression	2 (4.1)	5 (9.8)	1 (2.8)	0
Number censored	19 (38.8)	13 (25.5)	12 (33.3)	14 (40.0)
Reason for censorship:				
No baseline or on-study assessments	6 (12.2)	0	0	3 (8.6)
Alive, on study, and progression free at time of analysis	6 (12.2)	8 (15.7)	9 (25.0)	6 (17.1)
At least 1 on-study disease assessment and discontinued treatment before documented PD on study	5 (10.2)	5 (9.8)	2 (5.6)	3 (8.6)
PD occurred after ≥2 consecutive, missed assessments	0	0	0	2 (5.7)
PD occurred after given new antitumor treatment	2 (4.1)	0	1 (2.8)	0
Kaplan-Meier estimates of time to event (months)				
Quartiles [95% CI][a]				
25%	3.75 (1.97, 5.03)	3.65 (2.00, 5.16)	4.01 (1.77, 6.90)	3.84 (2.33, 6.24)
50%	5.72 (4.50, 7.42)	6.87 (4.96, 9.13)	7.59 (5.62, 11.07)	6.44 (5.52, 13.11)
75%	11.30 (7.29, 12.94)	13.47 (8.97, 15.83)	12.42 (9.40, 16.56)	13.11 (6.67, 14.72)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[b]	1.160		0.930	
95% CI of hazard ratio	0.711, 1.892		0.510, 1.697	
p-Value*	0.7244		0.4076	

*p-Value is from 1-sided unstratified log-rank test.
PFS = first date that criteria for progression was met or the subject died due to any cause - date of randomization +1.
Subjects lacking an evaluation of tumor response after randomization had their event times censored at 1 day. Subjects not experiencing disease progression during the treatment and follow-up periods and who did not die during the treatment period had their event time censored on the last study date that objective tumor assessments verified lack of disease progression.
CI = confidence interval; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; PD = progressive disease; PFS = progression free survival; vs = versus.
a. Based on the Brookmeyer and Crowley method.
b. Based on the unstratified Cox proportional hazards model.

Table 14. Summary of Progression Free Survival by Stratification Factors; Full Analysis Set

	Axitinib+FOLFIRI N=49	Bevacizumab+FOLFIRI N=51	Axitinib +FOLFOX N=36	Bevacizumab+FOLFOX N=35
ECOG PS =0/prior treatment without bevacizumab	21	23	14	13
Subject progressed or died	14 (66.7%)	16 (69.6%)	13 (92.9%)	11 (84.6%)
Median PFS (months)[a]	7.4	9.3	7.5	7.6
95% CI of median PFS (months)[b]	(4.0, 12.9)	(5.7, 14.5)	(4.0, 11.1)	(6.4, 14.4)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[c]	1.29		1.52	
95% CI of hazard ratio[c]	(0.62, 2.71)		(0.66, 3.53)	
ECOG PS =0/prior treatment with bevacizumab	13	13	11	11
Subject progressed or died	7 (53.8%)	9 (69.2%)	5 (45.5%)	6 (54.5%)
Median PFS (months)[a]	5.6	6.2	9.4	5.5
95% CI of median PFS (months)[b]	(2.1, 5.9)	(3.8, 7.4)	(5.6, 14.8)	(1.9, 5.6)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[c]	1.75		0.37	
95% CI of hazard ratio[c]	(0.60, 5.09)		(0.09, 1.52)	
ECOG PS =1/prior treatment without bevacizumab	9	8	7	7
Subject progressed or died	4 (44.4%)	8 (100.0%)	4 (57.1%)	2 (28.6%)
Median PFS (months)[a]	7.6	5.2	9.7	6.2
95% CI of median PFS (months)[b]	(3.8, NE)	(1.8, 9.0)	(3.0, NE)	(6.2, NE)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[c]	0.70		0.91	
95% CI of hazard ratio[c]	(0.20, 2.42)		(0.13, 6.53)	
ECOG PS =1/prior treatment with bevacizumab	6	7	4	4
Subject progressed or died	5 (83.3%)	5 (71.4%)	2 (50.0%)	2 (50.0%)
Median PFS (months)[a]	4.5	5.2	6.1	3.8
95% CI of median PFS (months)[b]	(0.5, 11.3)	(2.1, NE)	(1.7, 6.1)	(2.6, NE)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[c]	1.54		1.32	
95% CI of hazard ratio[c]	(0.41, 5.83)		(0.18, 9.53)	

Table 14. Summary of Progression Free Survival by Stratification Factors; Full Analysis Set

PFS = first day that criteria for progression was met or the subject died due to any cause-date of randomization+1.
Subjects lacking an evaluation of tumor response after randomization had their event times censored at 1 day. Subjects not experiencing disease progression during the treatment and follow-up periods and who did not die during the treatment period had their event time censored on the last study date that objective tumor assessments verified lack of disease progression.
CI = confidence interval; ECOG PS = Eastern Cooperative Oncology performance status; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; NE = not estimatable; PFS = progression free survival; vs = versus.

a. Estimated from the Kaplan-Meier Curve.
b. Based on the Brookmeyer and Crowley method.
c. Based on the unstratified Cox proportional hazards model.

Secondary Results:

Table 15, and Table 16 present a summary of OS by treatment (stratified analysis and unstratified analysis respectively) for the FAS.

Table 15. Summary of Overall Survival (Stratified); Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Number of deaths	32 (65.3)	31 (60.8)	21 (58.3)	23 (65.7)
Type of death				
Disease under study	31 (63.3)	29 (56.9)	20 (55.6)	23 (65.7)
Study treatment toxicity	1 (2.0)	0	0	0
Other	1 (2.0)	2 (3.9)	1 (2.8)	0
Number censored	17 (34.7)	20 (39.2)	15 (41.7)	12 (34.3)
Reason for censorship				
In follow-up, alive	16 (32.7)	18 (35.3)	10 (27.8)	7 (20.0)
Subject no longer willing to participate	0	0	1 (2.8)	0
Lost to follow-up	1 (2.0)	2 (3.9)	4 (11.1)	5 (14.3)
Survival probability at Month 12[a] (95% CI)[b]	55.32 (40.34, 67.97)	64.11 (49.44, 75.53)	57.47 (40.09, 71.49)	51.00 (33.85, 65.80)
Kaplan-Meier estimates of time to event (month)				
Quartiles [95% CI][c]				
25%	6.5 (3.9, 10.3)	10.2 (5.6, 12.2)	8.0 (4.5, 11.8)	7.2 (5.6, 10.2)
50%	12.9 (10.2, 16.6)	15.7 (12.1, 23.0)	17.1 (10.1, 23.0)	14.1 (9.0, 16.4)
75%	NE (14.9, NE)	NE (23.0, NE)	23.0 (21.2, 23.0)	NE (14.9, NE)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[d]	1.355		0.689	
95% CI of hazard ratio	0.820, 2.238		0.373, 1.273	
p-Value*	0.8828		0.1159	

* One-sided p-value from the log-rank test stratified by ECOG performance status (0 vs 1) and prior treatment with bevacizumab (yes vs no).
CI = confidence interval; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; NE = not estimatable; vs = versus.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the log [-log (12-month survival probability)] using a normal approximation and back transformation.
c. Based on the Brookmeyer and Crowley method.
d. Based on the Cox proportional hazards model stratified by ECOG performance status (0 vs 1) and prior treatment with bevacizumab (yes vs no).

Table 16. Summary of Overall Survival (Unstratified); Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Number of deaths	32 (65.3)	31 (60.8)	21 (58.3)	23 (65.7)
Type of death				
Disease under study	31 (63.3)	29 (56.9)	20 (55.6)	23 (65.7)
Study treatment toxicity	1 (2.0)	0	0	0
Unknown	0	0	0	0
Other	1 (2.0)	2 (3.9)	1 (2.8)	0
Number censored	17 (34.7)	20 (39.2)	15 (41.7)	12 (34.3)
Reason for censorship				
In follow-up, alive	16 (32.7)	18 (35.3)	10 (27.8)	7 (20.0)
Subject no longer willing to participate	0	0	1 (2.8)	0
Lost to follow-up	1 (2.0)	2 (3.9)	4 (11.1)	5 (14.3)
Survival probability at Month 12[a] (95% CI)[b]	55.32 (40.34, 67.97)	64.11 (49.44, 75.53)	57.47 (40.09, 71.49)	51.00 (33.85, 65.80)
Kaplan-Meier estimates of time to event (month)				
Quartiles [95% CI][c]				
25%	6.5 (3.9, 10.3)	10.2 (5.6, 12.2)	8.0 (4.5, 11.8)	7.2 (5.6, 10.2)
50%	12.9 (10.2, 16.6)	15.7 (12.1, 23.0)	17.1 (10.1, 23.0)	14.1 (9.0, 16.4)
75%	NE (14.9, NE)	NE (23.0, NE)	23.0 (21.2, 23.0)	NE (14.9, NE)
Axitinib + FOLFIRI vs bevacizumab + FOLFIRI/axitinib + FOLFOX vs bevacizumab + FOLFOX				
Hazard ratio[d]	1.318		0.744	
95% CI of hazard ratio	0.803, 2.162		0.407, 1.361	
p-Value*	0.8631		0.1661	

*One-sided p-value from the log-rank test.
CI = confidence interval; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; NE = not estimatable; vs = versus.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the log [-log (12-month survival probability)] using a normal approximation and back transformation.
c. Based on the Brookmeyer and Crowley method.
d. Based on the Cox proportional hazards model.

Table 17 presents summary of OR (CR + PR) by treatment in the axitinib + FOLFIRI arm was 12/49 (24.5%) (95% exact CI [13.3%, 38.9%]) compared with 12/51 (23.5%) (95% exact CI [12.8%, 37.5%]) in the bevacizumab + FOLFIRI arm. The treatment difference (axitinib + FOLFIRI: bevacizumab + FOLFIRI) was 1% (95% CI [-15.8%, 17.7%]) with a 1-sided p-value of 0.4552; FAS.

Table 17. Summary of Best Overall Response by Treatment; Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Complete response (CR)	1 (2.0)	1 (2.0)	0	0
Partial response (PR)	11 (22.4)	11 (21.6)	7 (19.4)	7 (20.0)
Stable disease	15 (30.6)	20 (39.2)	16 (44.4)	15 (42.9)
Progressive disease	11 (22.4)	15 (29.4)	8 (22.2)	8 (22.9)
Indeterminate	11 (22.4)	4 (7.8)	5 (13.9)	5 (14.3)
Overall response[a]	12 (24.5)	12 (23.5)	7 (19.4)	7 (20.0)
95% CI[b]	(13.3, 38.9)	(12.8, 37.5)	(8.2, 36)	(8.4, 36.9)
Treatment comparison: Axitinib + FOLFIRI vs bevacizumab + FOLFIRI (Arm A vs Arm B)/axitinib + FOLFOX vs bevacizumab + FOLFOX (Arm C vs Arm D)				
Treatment difference (%)		1		-0.6
95% CI of difference[c]		-15.8, 17.7		-19.1, 18
p-Value*		0.4552		0.5235

*p-Value was from a 1-sided Pearson chi-square test.
CI = confidence interval; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; RECIST = Response Evaluation Criteria in Solid Tumors; vs = versus.

a. Overall response rate = CR + PR according to RECIST.
b. Exact confidence interval for the overall response rate based on the F-distribution.
c. Calculated based on a normal distribution.

Table 18 shows the summary of the median DR among responders by treatment for the FAS. The median DR in the axitinib + FOLFIRI arm was 7.52 months (95% CI [5.22, not estimatable; NE]) compared with 12.29 months in the bevacizumab + FOLFIRI arm (95% CI [7.39, 12.84]). The median DR in the axitinib + FOLFOX arm was 10.15 months (95% CI [4.17, 12.91]) compared with 10.94 months in the bevacizumab + FOLFOX arm (95% CI [4.53, 12.68]). Table 19 presents the reasons for disease progression in the majority of subjects in each treatment arm. Mean scores for all symptom and functioning scales of the MDASI-D at Baseline for the 4 treatment arms are summarized in Table 20.

Table 18. Summary Duration of Response Among Responders

	Axitinib + FOLFIRI N=12 n (%)	Bevacizumab + FOLFIRI N=12 n (%)	Axitinib + FOLFOX N=7 n (%)	Bevacizumab + FOLFOX N=7 n (%)
Number with event	7 (58.3)	8 (66.7)	4 (57.1)	4 (57.1)
Type of event				
Objective progression	7 (100.0)	7 (87.5)	4 (100.0)	4 (100.0)
Death without objective progression	0	1 (12.5)	0	0
Number censored	5 (41.7)	4 (33.3)	3 (42.9)	3 (42.9)
Reason for censorship				
No baseline or on-study assessment	0	0	0	0
Alive, on study, and progression free at the time of the analysis	2 (40.0)	2 (50.0)	2 (66.7)	3 (100.0)
At least 1 on-study disease assessment and discontinued prior to documented PD on study	3 (60.0)	2 (50.0)	0	0
PD occurred after given new antitumor treatment	0	0	1 (33.3)	0
Kaplan-Meier estimates of time to event (months)				
Quartiles [95% CI][a]				
25%	5.22 (3.71, 7.62)	7.39 (6.47, 12.65)	5.78 (4.17, 12.91)	7.52 (4.53, 10.94)
50%	7.52 (5.22, NE)	12.29 (7.39, 12.84)	10.15 (4.17, 12.91)	10.94 (4.53, 12.68)
75%	NE (7.52, NE)	12.84 (10.22, NE)	12.91 (7.39, 12.91)	12.68 (7.52, 12.68)

Duration of response was the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed, to the first documentation of disease progression or death. Duration of response was censored on the day following the date of the last on-treatment (including 28-day follow-up period) tumor assessment documenting absence of progressive disease.

CI = confidence interval; CR = complete response; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects, n=number of subjects meeting prespecified criteria; NE = not estimatable; PD = progressive disease; PR = partial response.

a. Based on the Brookmeyer and Crowley method.

Table 19. Reason for Disease Progression (RECIST Assessment); Full Analysis Set

	Axitinib + FOLFIRI N=49 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Progressive disease	28 (57.1)	33 (64.7)	23 (63.9)	23 (65.7)
New lesion	13 (26.5)	12 (23.5)	14 (38.9)	10 (28.6)
Progression in target lesion(s)	16 (32.7)	25 (49.0)	14 (38.9)	18 (51.4)
Progression in non-target lesion(s)	20 (40.8)	18 (35.3)	15 (41.7)	16 (45.7)

Only included assessments given within 28 days after last dose of study medication and before taking antitumor treatment.
FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; N = number of subjects; n = number of subjects meeting prespecified criteria; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 20. Summary of Observed Baseline Mean Scores in MDASI-D Endpoints - Evaluable Population

MDASI-D	Axitinib + FOLFIRI (N=49)[a]	Bevacizumab +FOLFIRI (N=51)[a]	Axitinib + FOLFOX (N=36)[a]	Bevacizumab+ FOLFOX (N=35)[a]
Scale/Item Score	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Symptom severity scale[b]	2.1 (1.47)	1.8 (1.47)	1.9 (1.64)	2.0 (1.86)
Pain	2.0 (2.35)	2.2 (2.92)	2.1 (2.65)	1.7 (2.32)
Fatigue	3.0 (2.51)	2.4 (2.78)	2.9 (2.69)	2.9 (3.28)
Nausea	1.0 (1.59)	0.7 (1.97)	1.3 (2.35)	1.3 (2.53)
Disturbed sleep	2.3 (2.74)	2.3 (2.57)	2.4 (2.76)	1.6 (1.84)
Distress	2.9 (2.80)	2.5 (2.75)	2.4 (2.72)	3.5 (3.27)
Shortness of breath	1.7 (2.32)	1.2 (2.22)	1.5 (2.31)	2.2 (2.77)
Remembering things	1.1 (1.53)	1.3 (1.81)	1.6 (2.18)	1.1 (1.50)
Lack of appetite	1.9 (2.61)	1.3 (2.31)	1.6 (2.27)	2.4 (3.06)
Drowsiness	2.2 (2.09)	2.1 (2.86)	2.2 (2.47)	2.6 (2.68)
Dry mouth	2.4 (3.04)	1.2 (1.98)	1.5 (2.31)	2.3 (2.97)
Sadness	2.8 (2.86)	2.2 (2.72)	2.6 (2.84)	3.1 (3.49)
Vomiting	0.7 (1.96)	0.8 (2.10)	1.1 (2.24)	1.0 (2.62)
Numbness or tingling	3.5 (2.78)	3.2 (3.12)	1.9 (2.81)	1.6 (2.46)
Diarrhea	2.0 (2.75)	1.5 (2.49)	1.3 (2.17)	1.1 (1.86)
Symptom interference scale[c]	2.1 (2.04)	1.7 (2.05)	2.4 (2.31)	2.8 (2.90)
General activity	2.1 (2.38)	1.8 (2.88)	2.5 (2.76)	3.3 (3.46)
Mood	2.6 (2.37)	2.1 (2.65)	2.4 (2.55)	3.0 (3.27)
Work	2.3 (2.52)	2.0 (3.05)	2.6 (2.81)	3.1 (3.54)
Relations with other people	1.6 (2.43)	0.7 (1.80)	2.0 (2.38)	2.1 (2.62)
Walking	2.1 (2.50)	1.5 (2.50)	2.3 (2.79)	2.5 (3.23)
Enjoyment of life	2.0 (2.27)	2.2 (3.01)	2.6 (2.70)	2.9 (3.39)

Symptom severity scale was comprised of the following individual items: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness or tingling, and diarrhea. Symptom interference scale was comprised of the following individual items: general activity, mood, work, relations with other people, walking and enjoyment of life. Range of symptom severity scale and symptom interference scale =0 to 10.
FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; MDASI-D = MD Anderson Symptom Inventory-Diarrhea; N = total number of subjects; SD = standard deviation.

a. Due to missing values, the sample size for each scale may not always equal 49 for Axitinib + FOLFIRI, 51 for bevacizumab + FOLFIRI, 36 for Axitinib + FOLFOX, or 35 for bevacizumab + FOLFOX.
b. Interpretation (items and scale scores): A score indicates the severity of the symptom. The lower the symptom score, the less severe the symptom.
c. Interpretation (items and scale scores): The lower the symptom score, the less interference with feeling and function the subject experiences.

MDASI-D: Change From Baseline by Cycle: Based on the mean change scores in cycles with 10 or more subjects completing the MDASI-D (up to and including Cycles 13, 19, 17, and 13 for axitinib + FOLFIRI, bevacizumab + FOLFIRI, axitinib + FOLFOX, and bevacizumab + FOLFOX, respectively), statistically significant increases (worsening) from Baseline in MDASI-D scale scores are given below for each treatment arm. Clinically meaningful increases (defined as a ≥0.98 point mean change from Baseline) were denoted with an asterisk (∗). There were no adjustments for multiple testing.

Axitinib + FOLFIRI:

- MDASI-D Severity scale: Cycles 2, 3, 4, 7, 9*, and 11*
- MDASI-D Interference scale: Cycles 2, 3*, 5*, 9*, and end-of-treatment (EOT)*

Bevacizumab + FOLFIRI:

- MDASI-D Severity scale: None
- MDASI-D Interference scale: Cycle 2 and EOT*

Axitinib + FOLFOX:

- MDASI-D Severity scale: Cycles 2, 5, 7, 11*, 13, 17, and EOT*
- MDASI-D Interference scale: Cycle 13* and EOT*

Bevacizumab + FOLFOX:

- MDASI-D Severity scale: Cycles 9, 13, and EOT
- MDASI-D Interference scale: EOT*

All the clinically meaningful mean score increases were small, none >1.5 on a scale of 0 to 10. No formal statistical comparisons were performed. However, a look at the above results would indicate greater increase in MDASI-D scores (worsening) in the axitinib + FOLFIRI group than the bevacizumab + FOLFIRI group. Similarly the above results appear to indicate more worsening in the axitinib + FOLFOX group than the bevacizumab + FOLFOX group.

Safety Results:

Table 21 and Table 22 present AEs data all causality and treatment related respectively. Table 23 shows serious adverse events (SAEs) that occurred during the study.

The subjects in the axitinib + FOLFIRI arm compared with the bevacizumab + FOLFIRI arm had treatment-related SAEs (13 [28.3%] vs 4 [7.8%], respectively), similarly in the axitinib + FOLFOX arm compared with the bevacizumab + FOLFOX arm had treatment-related SAEs (6 [16.7%] vs 3 [8.6%], respectively).

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI n (%)	Bevacizumab+FOLFIRI n (%)	Axitinib+FOLFOX n (%)	Bevacizumab+FOLFOX n (%)
Number (%) of subjects:				
Evaluable for adverse events	46	51	36	35
With adverse events	45 (97.8)	51 (100.0)	35 (97.2)	33 (94.3)
Blood and lymphatic system disorders	23 (50.0)	32 (62.7)	24 (66.7)	16 (45.7)
Anaemia	6 (13.0)	11 (21.6)	4 (11.1)	5 (14.3)
Leukopenia	6 (13.0)	6 (11.8)	5 (13.9)	2 (5.7)
Lymphopenia	0	0	0	2 (5.7)
Neutropenia	20 (43.5)	27 (52.9)	20 (55.6)	10 (28.6)
Thrombocytopenia	3 (6.5)	4 (7.8)	8 (22.2)	5 (14.3)
Cardiac disorders	1 (2.2)	0	2 (5.6)	3 (8.6)
Left ventricular dysfunction	0	0	0	2 (5.7)
Endocrine disorders	7 (15.2)	0	10 (27.8)	1 (2.9)
Hypothyroidism	7 (15.2)	0	9 (25.0)	1 (2.9)
Eye disorders	4 (8.7)	3 (5.9)	3 (8.3)	4 (11.4)
Eye pain	0	0	0	2 (5.7)
Gastrointestinal disorders	42 (91.3)	44 (86.3)	22 (61.1)	23 (65.7)
Abdominal pain	12 (26.1)	11 (21.6)	7 (19.4)	9 (25.7)
Abdominal pain upper	5 (10.9)	7 (13.7)	1 (2.8)	2 (5.7)
Constipation	7 (15.2)	16 (31.4)	3 (8.3)	10 (28.6)
Diarrhoea	33 (71.7)	25 (49.0)	15 (41.7)	11 (31.4)
Dry mouth	3 (6.5)	1 (2.0)	1 (2.8)	2 (5.7)
Dyspepsia	7 (15.2)	5 (9.8)	1 (2.8)	0
Gastritis	3 (6.5)	2 (3.9)	1 (2.8)	2 (5.7)
Gingivitis	3 (6.5)	2 (3.9)	0	0
Haemorrhoids	4 (8.7)	2 (3.9)	0	0
Nausea	27 (58.7)	30 (58.8)	18 (50.0)	16 (45.7)
Oesophagitis	3 (6.5)	0	0	0
Oral pain	2 (4.3)	1 (2.0)	2 (5.6)	0
Proctalgia	6 (13.0)	2 (3.9)	1 (2.8)	0
Rectal haemorrhage	4 (8.7)	3 (5.9)	0	3 (8.6)
Stomatitis	11 (23.9)	7 (13.7)	9 (25.0)	7 (20.0)
Toothache	0	3 (5.9)	0	1 (2.9)
Vomiting	22 (47.8)	18 (35.3)	12 (33.3)	3 (8.6)

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI n (%)	Bevacizumab+FOLFIRI n (%)	Axitinib+FOLFOX n (%)	Bevacizumab+FOLFOX n (%)
General disorders and administration site conditions	33 (71.7)	33 (64.7)	21 (58.3)	19 (54.3)
Asthenia	14 (30.4)	11 (21.6)	6 (16.7)	6 (17.1)
Chest pain	1 (2.2)	3 (5.9)	1 (2.8)	1 (2.9)
Chills	2 (4.3)	1 (2.0)	2 (5.6)	2 (5.7)
Fatigue	21 (45.7)	18 (35.3)	12 (33.3)	9 (25.7)
Mucosal inflammation	7 (15.2)	11 (21.6)	4 (11.1)	3 (8.6)
Oedema peripheral	7 (15.2)	2 (3.9)	0	1 (2.9)
Pain	0	1 (2.0)	3 (8.3)	1 (2.9)
Pyrexia	5 (10.9)	7 (13.7)	5 (13.9)	3 (8.6)
Disease progression	2 (4.3)	3 (5.9)	0	0
Hepatobiliary disorders	6 (13.0)	3 (5.9)	2 (5.6)	3 (8.6)
Hyperbilirubinaemia	3 (6.5)	1 (2.0)	1 (2.8)	2 (5.7)
Immune system disorders	0	1 (2.0)	6 (16.7)	1 (2.9)
Hypersensitivity	0	1 (2.0)	5 (13.9)	1 (2.9)
Infections and infestations	15 (32.6)	23 (45.1)	8 (22.2)	12 (34.3)
Bronchitis	0	1 (2.0)	0	2 (5.7)
Nasopharyngitis	3 (6.5)	5 (9.8)	0	2 (5.7)
Rhinitis	0	3 (5.9)	0	1 (2.9)
Upper respiratory tract infection	1 (2.2)	3 (5.9)	0	0
Urinary tract infection	3 (6.5)	3 (5.9)	2 (5.6)	1 (2.9)
Viral upper respiratory tract infection	2 (4.3)	3 (5.9)	0	1 (2.9)
Investigations	22 (47.8)	15 (29.4)	14 (38.9)	14 (40.0)
Alanine aminotransferase	1 (2.2)	0	0	3 (8.6)
Alanine aminotransferase increased	3 (6.5)	2 (3.9)	1 (2.8)	2 (5.7)
Aspartate aminotransferase	1 (2.2)	0	0	3 (8.6)
Aspartate aminotransferase increased	2 (4.3)	2 (3.9)	1 (2.8)	2 (5.7)
Blood alkaline phosphatase increased	4 (8.7)	0	0	2 (5.7)
Blood thyroid stimulating hormone increased	4 (8.7)	0	0	0
Breath sounds abnormal	0	0	1 (2.8)	2 (5.7)
Haemoglobin	0	0	1 (2.8)	2 (5.7)
Haemoglobin decreased	3 (6.5)	5 (9.8)	3 (8.3)	0
Neutrophil count	1 (2.2)	0	0	2 (5.7)
Neutrophil count decreased	4 (8.7)	3 (5.9)	3 (8.3)	2 (5.7)

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI n (%)	Bevacizumab+FOLFIRI n (%)	Axitinib+FOLFOX n (%)	Bevacizumab+FOLFOX n (%)
Platelet count	0	0	1 (2.8)	2 (5.7)
Platelet count decreased	2 (4.3)	2 (3.9)	4 (11.1)	3 (8.6)
Weight decreased	13 (28.3)	4 (7.8)	5 (13.9)	2 (5.7)
Metabolism and nutrition disorders	29 (63.0)	20 (39.2)	16 (44.4)	11 (31.4)
Decreased appetite	24 (52.2)	16 (31.4)	13 (36.1)	7 (20.0)
Dehydration	7 (15.2)	1 (2.0)	1 (2.8)	0
Hyperglycaemia	0	1 (2.0)	2 (5.6)	2 (5.7)
Hypoalbuminaemia	2 (4.3)	0	1 (2.8)	0
Hypokalaemia	4 (8.7)	3 (5.9)	3 (8.3)	2 (5.7)
Musculoskeletal and connective tissue disorders	12 (26.1)	16 (31.4)	7 (19.4)	10 (28.6)
Arthralgia	2 (4.3)	1 (2.0)	2 (5.6)	3 (8.6)
Back pain	3 (6.5)	6 (11.8)	2 (5.6)	2 (5.7)
Bone pain	0	3 (5.9)	0	0
Myalgia	0	3 (5.9)	1 (2.8)	1 (2.9)
Nervous system disorders	16 (34.8)	19 (37.3)	18 (50.0)	23 (65.7)
Dizziness	1 (2.2)	3 (5.9)	3 (8.3)	2 (5.7)
Dysgeusia	5 (10.9)	1 (2.0)	3 (8.3)	4 (11.4)
Headache	6 (13.0)	4 (7.8)	7 (19.4)	3 (8.6)
Neuropathy peripheral	3 (6.5)	4 (7.8)	7 (19.4)	16 (45.7)
Paraesthesia	0	2 (3.9)	4 (11.1)	3 (8.6)
Peripheral sensory neuropathy	2 (4.3)	4 (7.8)	4 (11.1)	5 (14.3)
Psychiatric disorders	11 (23.9)	10 (19.6)	6 (16.7)	3 (8.6)
Anxiety	3 (6.5)	3 (5.9)	1 (2.8)	1 (2.9)
Depression	5 (10.9)	3 (5.9)	2 (5.6)	0
Insomnia	3 (6.5)	2 (3.9)	2 (5.6)	3 (8.6)
Renal and urinary disorders	13 (28.3)	5 (9.8)	4 (11.1)	6 (17.1)
Dysuria	2 (4.3)	1 (2.0)	3 (8.3)	4 (11.4)
Proteinuria	8 (17.4)	5 (9.8)	2 (5.6)	3 (8.6)

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI n (%)	Bevacizumab+FOLFIRI n (%)	Axitinib+FOLFOX n (%)	Bevacizumab+FOLFOX n (%)
Respiratory, thoracic and mediastinal disorders	23 (50.0)	24 (47.1)	11 (30.6)	13 (37.1)
Cough	7 (15.2)	5 (9.8)	3 (8.3)	4 (11.4)
Dysphonia	6 (13.0)	2 (3.9)	4 (11.1)	1 (2.9)
Dyspnoea	8 (17.4)	3 (5.9)	4 (11.1)	0
Epistaxis	11 (23.9)	15 (29.4)	4 (11.1)	5 (14.3)
Oropharyngeal pain	2 (4.3)	5 (9.8)	1 (2.8)	1 (2.9)
Skin and subcutaneous tissue disorders	18 (39.1)	17 (33.3)	11 (30.6)	10 (28.6)
Alopecia	6 (13.0)	12 (23.5)	2 (5.6)	0
Dry skin	2 (4.3)	0	1 (2.8)	2 (5.7)
Nail disorder	1 (2.2)	0	1 (2.8)	2 (5.7)
Palmar-plantar erythrodysaesthesia syndrome	8 (17.4)	3 (5.9)	4 (11.1)	2 (5.7)
Pruritus	3 (6.5)	2 (3.9)	4 (11.1)	1 (2.9)
Rash	5 (10.9)	2 (3.9)	3 (8.3)	1 (2.9)
Vascular disorders	19 (41.3)	12 (23.5)	25 (69.4)	10 (28.6)
Hypertension	17 (37.0)	0	24 (66.7)	6 (17.1)
Hypotension	3 (6.5)	0	2 (5.6)	2 (5.7)

Adverse events and Serious adverse events are not separated out.
Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; MedDRA = Medical Dictionary for Regulatory activities; n = number of subjects with adverse events.

Table 22. Treatment-Emergent Treatment-Related Adverse Events (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
Any AEs	45 (97.8)	941	49 (96.1)	639	35 (97.2)	560	30 (85.7)	299
Blood and lymphatic system disorders	21 (45.7)	95	30 (58.8)	115	20 (55.6)	67	11 (31.4)	53
Anaemia	5 (10.9)	7	9 (17.6)	15	2 (5.6)	3	3 (8.6)	5
Leukopenia	5 (10.9)	13	5 (9.8)	14	3 (8.3)	4	2 (5.7)	14
Neutropenia	18 (39.1)	68	26 (51.0)	73	17 (47.2)	46	6 (17.1)	15
Thrombocytopenia	3 (6.5)	6	4 (7.8)	12	8 (22.2)	14	5 (14.3)	12
Cardiac disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (8.6)	4
Left ventricular dysfunction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (5.7)	2
Endocrine disorders	6 (13.0)	10	0 (0.0)	0	8 (22.2)	12	1 (2.9)	1
Hypothyroidism	6 (13.0)	10	0 (0.0)	0	8 (22.2)	12	1 (2.9)	1
Gastrointestinal disorders	40 (87.0)	381	39 (76.5)	282	20 (55.6)	193	18 (51.4)	73
Abdominal pain	6 (13.0)	6	4 (7.8)	6	2 (5.6)	3	1 (2.9)	2
Constipation	1 (2.2)	1	6 (11.8)	7	0 (0.0)	0	5 (14.3)	8
Diarrhoea	31 (67.4)	135	23 (45.1)	71	12 (33.3)	51	6 (17.1)	12
Dyspepsia	4 (8.7)	5	3 (5.9)	3	0 (0.0)	0	0 (0.0)	0
Gingivitis	3 (6.5)	4	2 (3.9)	2	0 (0.0)	0	0 (0.0)	0
Nausea	26 (56.5)	79	28 (54.9)	71	15 (41.7)	62	13 (37.1)	35
Oral pain	2 (4.3)	3	0 (0.0)	0	2 (5.6)	3	0 (0.0)	0
Proctalgia	3 (6.5)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Stomatitis	10 (21.7)	23	6 (11.8)	13	7 (19.4)	21	4 (11.4)	4
Vomiting	21 (45.7)	87	17 (33.3)	93	9 (25.0)	48	2 (5.7)	5
General disorders and administration site conditions	28 (60.9)	126	25 (49.0)	93	17 (47.2)	78	13 (37.1)	32
Asthenia	10 (21.7)	43	10 (19.6)	23	6 (16.7)	10	4 (11.4)	11
Fatigue	19 (41.3)	57	13 (25.5)	34	11 (30.6)	60	7 (20.0)	9
Mucosal inflammation	7 (15.2)	17	11 (21.6)	29	3 (8.3)	4	3 (8.6)	8
Immune system disorders	0 (0.0)	0	1 (2.0)	2	5 (13.9)	8	1 (2.9)	2
Hypersensitivity	0 (0.0)	0	1 (2.0)	2	5 (13.9)	7	1 (2.9)	2

Table 22. Treatment-Emergent Treatment-Related Adverse Events (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
Investigations	15 (32.6)	59	7 (13.7)	24	8 (22.2)	18	8 (22.9)	15
Alanine aminotransferase increased	1 (2.2)	1	0 (0.0)	0	1 (2.8)	1	2 (5.7)	2
Aspartate aminotransferase increased	1 (2.2)	1	0 (0.0)	0	1 (2.8)	1	2 (5.7)	2
Blood thyroid stimulating hormone increased	4 (8.7)	5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Haemoglobin decreased	1 (2.2)	3	3 (5.9)	5	1 (2.8)	1	0 (0.0)	0
Neutrophil count decreased	4 (8.7)	12	3 (5.9)	12	2 (5.6)	3	2 (5.7)	3
Platelet count decreased	2 (4.3)	2	2 (3.9)	3	4 (11.1)	6	1 (2.9)	2
Weight decreased	8 (17.4)	14	1 (2.0)	1	3 (8.3)	5	2 (5.7)	2
Metabolism and nutrition disorders	24 (52.2)	77	14 (27.5)	20	10 (27.8)	34	5 (14.3)	8
Dehydration	7 (15.2)	14	1 (2.0)	1	1 (2.8)	1	0 (0.0)	0
Hyperglycaemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (5.7)	2
Decreased appetite	19 (41.3)	57	13 (25.5)	18	10 (27.8)	32	3 (8.6)	3
Nervous system disorders	12 (26.1)	13	9 (17.6)	9	15 (41.7)	36	21 (60.0)	67
Dizziness	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	2 (5.7)	2
Dysgeusia	5 (10.9)	5	1 (2.0)	1	3 (8.3)	3	4 (11.4)	5
Headache	2 (4.3)	2	0 (0.0)	0	2 (5.6)	2	1 (2.9)	1
Neuropathy peripheral	2 (4.3)	2	2 (3.9)	2	5 (13.9)	8	14 (40.0)	22
Paraesthesia	0 (0.0)	0	2 (3.9)	2	4 (11.1)	7	3 (8.6)	8
Peripheral sensory neuropathy	1 (2.2)	1	2 (3.9)	2	4 (11.1)	11	5 (14.3)	25
Psychiatric disorders	2 (4.3)	3	3 (5.9)	3	2 (5.6)	2	0 (0.0)	0
Insomnia	0 (0.0)	0	1 (2.0)	1	2 (5.6)	2	0 (0.0)	0
Renal and urinary disorders	7 (15.2)	15	4 (7.8)	16	1 (2.8)	3	3 (8.6)	5
Proteinuria	6 (13.0)	14	4 (7.8)	15	1 (2.8)	1	3 (8.6)	4
Respiratory, thoracic and mediastinal disorders	18 (39.1)	36	16 (31.4)	24	8 (22.2)	17	7 (20.0)	9
Dysphonia	4 (8.7)	17	1 (2.0)	1	4 (11.1)	4	0 (0.0)	0
Dyspnoea	3 (6.5)	3	1 (2.0)	1	1 (2.8)	1	0 (0.0)	0
Epistaxis	9 (19.6)	9	13 (25.5)	16	4 (11.1)	6	5 (14.3)	5

Table 22. Treatment-Emergent Treatment-Related Adverse Events (≥5% Threshold)

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
Skin and subcutaneous tissue disorders	16 (34.8)	34	14 (27.5)	27	9 (25.0)	19	6 (17.1)	11
Alopecia	5 (10.9)	5	11 (21.6)	14	1 (2.8)	1	0 (0.0)	0
Nail disorder	1 (2.2)	1	0 (0.0)	0	1 (2.8)	1	2 (5.7)	2
Palmar-plantar erythrodysaesthesia syndrome	7 (15.2)	13	3 (5.9)	9	4 (11.1)	6	2 (5.7)	2
Pruritus	3 (6.5)	3	1 (2.0)	1	3 (8.3)	4	0 (0.0)	0
Rash	3 (6.5)	3	1 (2.0)	1	2 (5.6)	2	1 (2.9)	1
Vascular disorders	17 (37.0)	66	8 (15.7)	11	23 (63.9)	63	7 (20.0)	11
Hypertension	16 (34.8)	64	6 (11.8)	9	23 (63.9)	55	5 (14.3)	7

% = (n/N)∗100.
MedDRA (version 14.0) coding dictionary applied.
AEs and SAEs are not separated out.
AE = adverse event; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; MedDRA = Medical Dictionary for Regulatory activities; N = number of subjects.

Table 23. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
Any SAEs	17 (37.0)	47	9 (17.6)	16	10 (27.8)	15	5 (14.3)	7
Blood and lymphatic system disorders	2 (4.3)	2	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Anaemia	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Febrile neutropenia	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Neutropenia	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Cardiac disorders	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Atrial fibrillation	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Ear and labyrinth disorders	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Otosalpingitis	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastrointestinal disorders	11 (23.9)	21	4 (7.8)	9	3 (8.3)	5	2 (5.7)	2
Abdominal pain	2 (4.3)	2	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Abdominal pain upper	0 (0.0)	0	1 (2.0)	1	1 (2.8)	1	0 (0.0)	0
Colonic obstruction	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Diarrhoea	3 (6.5)	5	2 (3.9)	2	0 (0.0)	0	1 (2.9)	1
Gastrointestinal haemorrhage	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Haematochezia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Ileal ulcer	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Ileus	1 (2.2)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Nausea	2 (4.3)	3	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Oesophagitis	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Rectal perforation	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Stomatitis	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Vomiting	1 (2.2)	2	2 (3.9)	2	1 (2.8)	1	0 (0.0)	0
Anal inflammation	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Subileus	1 (2.2)	1	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Haemorrhagic ascites	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Gastrointestinal ulcer	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Table 23. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
General disorders and administration site conditions	5 (10.9)	8	3 (5.9)	3	3 (8.3)	3	0 (0.0)	0
Asthenia	2 (4.3)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Fatigue	2 (4.3)	3	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Performance status decreased	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
General physical health deterioration	1 (2.2)	1	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Disease progression	2 (4.3)	2	3 (5.9)	3	0 (0.0)	0	0 (0.0)	0
Hepatobiliary disorders	2 (4.3)	2	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Hyperbilirubinaemia	2 (4.3)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hepatic mass	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Infections and infestations	2 (4.3)	2	1 (2.0)	1	2 (5.6)	2	2 (5.7)	2
Cellulitis pharyngeal	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Escherichia sepsis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Pneumonia	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Sepsis	1 (2.2)	1	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Anal abscess	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Lung infection	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Injury, poisoning and procedural complications	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Lumbar vertebral fracture	0 (0.0)	0	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Metabolism and nutrition disorders	5 (10.9)	5	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Dehydration	4 (8.7)	4	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Hypovolaemia	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Musculoskeletal and connective tissue disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Back pain	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Nervous system disorders	1 (2.2)	2	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Cerebral haemorrhage	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Headache	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Peripheral sensory neuropathy	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Psychiatric disorders	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Depression	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Table 23. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term

System Organ Class Preferred Term	Axitinib+FOLFIRI (N=46)		Bevacizumab+FOLFIRI (N=51)		Axitinib+FOLFOX (N=36)		Bevacizumab+FOLFOX (N=35)	
	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events
Renal and urinary disorders	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Renal failure acute	0 (0.0)	0	0 (0.0)	0	1 (2.8)	1	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	2 (4.3)	3	1 (2.0)	1	0 (0.0)	0	1 (2.9)	1
Hypoxia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Pneumothorax	1 (2.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Pulmonary embolism	2 (4.3)	2	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0
Vascular disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1
Hypertension	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.9)	1

%= (n/N)∗100.
MedDRA (version 14.0) coding dictionary applied.
AE = adverse event; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; MedDRA = Medical Dictionary for Regulatory activities; N = number of subjects.

Number and percentage of subjects discontinue the study permanently and temporarily due to AEs are listed in Table 24.

Table 24. Treatment-Emergent Adverse Events (All Causalities and Treatment Related)

	All Causalities				Treatment Related			
	Axitinib +FOLFIRI n (%)	Bevacizumab + FOLFIRI n (%)	Axitinib +FOLFOX n (%)	Bevacizumab +FOLFOX n (%)	Axitinib +FOLFIRI n (%)	Bevacizumab + FOLFIRI n (%)	Axitinib +FOLFOX n (%)	Bevacizumab + FOLFOX n (%)
Subjects evaluable for AEs	46	51	36	35	46	51	36	35
Number of AEs	614	500	369	322	383	288	235	169
Subjects with AEs	45 (97.8)	51 (100.0)	36 (100.0)	33 (94.3)	45 (97.8)	49 (96.1)	35 (97.2)	30 (85.7)
Subjects with serious AEs	17 (37.0)	9 (17.6)	10 (27.8)	5 (14.3)	13 (28.3)	4 (7.8)	6 (16.7)	3 (8.6)
Subjects with Grade 3 or 4 AEs	36 (78.3)	33 (64.7)	23 (63.9)	19 (54.3)	35 (76.1)	31 (60.8)	20 (55.6)	16 (45.7)
Subjects with Grade 5 AEs	3 (6.5)	5 (9.8)	2 (5.6)	1 (2.9)	1 (2.2)	1 (2.0)	1 (2.8)	0
Subjects discontinued from study due to AEs	6 (13.0)	3 (5.9)	5 (13.9)	1 (2.9)	5 (10.9)	0	4 (11.1)	1 (2.9)
Subjects discontinued axitinib/bevacizumab due to AEs	12 (26.1)	7 (13.7)	6 (16.7)	4 (11.4)	8 (17.4)	2 (3.9)	4 (11.1)	3 (8.6)
Subjects discontinued leucovorin due to AEs	11 (23.9)	5 (9.8)	5 (13.9)	2 (5.7)	8 (17.4)	2 (3.9)	3 (8.3)	1 (2.9)
Subjects discontinued 5-FU due to AEs	11 (23.9)	5 (9.8)	5 (13.9)	2 (5.7)	8 (17.4)	2 (3.9)	3 (8.3)	1 (2.9)
Subjects discontinued oxaliplatin/irinotecan due to AEs	12 (26.1)	5 (9.8)	11 (30.6)	6 (17.1)	9 (19.6)	2 (3.9)	9 (25.0)	5 (14.3)
Subjects temporarily discontinued axitinib/bevacizumab due to AEs	32 (69.6)	31 (60.8)	28 (77.8)	19 (54.3)	31 (67.4)	29 (56.9)	27 (75.0)	14 (40.0)
Subjects temporarily discontinued leucovorin due to AEs	33 (71.7)	30 (58.8)	26 (72.2)	19 (54.3)	29 (63.0)	29 (56.9)	24 (66.7)	14 (40.0)
Subjects temporarily discontinued 5-FU due to AEs	35 (76.1)	28 (54.9)	26 (72.2)	19 (54.3)	30 (65.2)	26 (51.0)	24 (66.7)	14 (40.0)
Subjects temporarily discontinued oxaliplatin/irinotecan due to AEs	34 (73.9)	27 (52.9)	26 (72.2)	21 (60.0)	29 (63.0)	26 (51.0)	24 (66.7)	16 (45.7)
Subjects with dose reduction of axitinib/bevacizumab due to AEs	20 (43.5)	4 (7.8)	3 (8.3)	0	19 (41.3)	2 (3.9)	3 (8.3)	0
Subjects with dose reduction of leucovorin due to AEs	12 (26.1)	5 (9.8)	4 (11.1)	1 (2.9)	11 (23.9)	3 (5.9)	4 (11.1)	1 (2.9)
Subjects with dose reduction of 5-FU due to AEs	23 (50.0)	21 (41.2)	9 (25.0)	7 (20.0)	22 (47.8)	18 (35.3)	9 (25.0)	7 (20.0)
Subjects with dose reduction of oxaliplatin/irinotecan due to AEs	26 (56.5)	20 (39.2)	9 (25.0)	10 (28.6)	25 (54.3)	17 (33.3)	9 (25.0)	10 (28.6)

Included data up to 28 days after the last dose of study drug. Except for the number of AEs, subjects were counted only once per treatment in each row.
Serious AEs were according to the Investigator's assessment.
AE = adverse event; FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan; FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin; n = number of subjects meeting prespecified criteria.

Overall, 31 (67.4%) subjects in the axitinib + FOLFIRI arm died; 3 (9.7%) died on-study and 28 (90.3%) died during follow-up. In the bevacizumab + FOLFIRI arm, 31 (60.8%) subjects died; 5 (16.1%) died on-study and 26 (83.9%) died during follow-up. Twenty-one (58.3%) subjects in the axitinib + FOLFOX arm died; 1 (4.8%) died on-study and 20 (95.2%) died during follow-up. In the bevacizumab + FOLFOX arm, 23 (65.7%) subjects died; each of the 23 subjects died during follow-up. Table 25 presents a summary of subject deaths by treatment arm for the updated safety analysis set.

Table 25. Summary of Deaths by Treatment; Safety Analysis Set

	Axitinib + FOLFIRI N=46 n (%)	Bevacizumab + FOLFIRI N=51 n (%)	Axitinib + FOLFOX N=36 n (%)	Bevacizumab + FOLFOX N=35 n (%)
Subjects who died	31 (67.4)	31 (60.8)	21 (58.3)	23 (65.7)
Subjects who died on study[a]	3 (9.7)	5 (16.1)	1 (4.8)	0
Cause of death				
Disease under study	2 (66.7)	3 (60.0)	0	0
Study treatment toxicity	1 (33.3)	0	0	0
Unknown	0	0	0	0
Other	1 (33.3)	2 (40.0)	1 (100.0)	0
Hemorrhage (GI)	0	1 (50.0)	0	0
Intracerebral hemorrhage	0	0	1 (100.0)	0
Sepsis	1 (100.0)	0	0	0
Septicemia	0	1 (50.0)	0	0
Subjects who died during follow-up[b]	28 (90.3)	26 (83.9)	20 (95.2)	23 (100.0)
Cause of death				
Disease under study	28 (100.0)	26 (100.0)	20 (100.0)	23 (100.0)

Note that >1 cause of death for a single subject may have been listed.
FOLFIRI = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan;
FOLFOX = treatment regimen containing folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin;
GI = gastrointestinal; N = number of subjects; n = number of subjects meeting prespecified criteria.
a. On-study deaths were those that occurred after the first dose of study drug and within 28 days after the last dose of study drug.
b. Follow-up deaths were those that occurred >28 days after the last dose of study drug.

CONCLUSIONS:

- Axitinib in combination with either FOLFIRI or FOLFOX compared with bevacizumab in combination with FOLFIRI or FOLFOX did not demonstrate prolonged PFS in the second-line treatment of subjects with mCRC after failure of an irinotecan- or oxaliplatin-containing first-line regimen. The HR for the axitinib + FOLFIRI arm compared with the bevacizumab + FOLFIRI arm was 1.27 (95% CI [0.77, 2.11]). The HR for the axitinib + FOLFOX arm compared with the bevacizumab + FOLFOX was 1.04 (95% CI [0.55, 1.96]).

- The OS results were consistent with the PFS results. No increased OS benefit was observed in the axitinib + FOLFIRI arm compared with the bevacizumab + FOLFIRI arm, with an HR of 1.36 (95% CI [0.82, 2.24]). An increased OS benefit was observed, however, in the axitinib + FOLFOX arm compared with the bevacizumab + FOLFOX arm with an HR of 0.69 (95% CI [0.37, 1.27]).

- The ORR was generally similar for the axitinib and bevacizumab arms. The ORR was 24.5% vs 23.5% for the axitinib + FOLFIRI arm and the bevacizumab + FOLFIRI arm, respectively. An ORR of 19.4% vs 20.0% was observed for the axitinib + FOLFOX arm and the bevacizumab + FOLFOX arm, respectively.

- The median DR was lower in the axitinib + FOLFIRI arm compared with the bevacizumab + FOLFIRI arm (7.5 months vs 12.3 months, respectively). A similar median DR was observed in the axitinib + FOLFOX arm and the bevacizumab + FOLFOX arm (10.2 months vs 10.9 months, respectively).

- There were greater proportions of subjects with dose reduction and temporary drug discontinuation due to AEs in the axitinib arms compared with the bevacizumab arms. A higher incidence of some AEs (eg, diarrhea, fatigue, hypertension) was noted in the axitinib arm when administered with FOLFIRI.

- Baseline mean scores for the MDASI-D severity and interference scales were similar between the axitinib + FOLFIRI and bevacizumab + FOLFIRI and between the axitinib + FOLFOX and bevacizumab + FOLFOX treatment arms. All were relatively small (<3 on a scale of 0 to 10, where 0 indicates no pain and 10 as worst imaginable).

- No formal statistical comparisons of MDASI-D scores were performed to compare the treatment arms. The study results indicate a greater number of increases from baseline (worsening) in the axitinib + FOLFIRI group than the bevacizumab + FOLFIRI group, and similarly in the axitinib + FOLFOX group than the bevacizumab + FOLFOX group. However, all mean score increases in severity and interference were relatively small, with none more than 1.5 points.