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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Sutent® / Sunitinib malate

PROTOCOL NO.: A6181122

PROTOCOL TITLE: A Multicenter, Randomized, Double-Bind, Phase 3 Study of Sunitinib in Metastatic Colorectal Cancer Patients Receiving Irinotecan, 5-Fluorouracil and Leucovorin (FOLFIRI) as First Line Treatment

Study Centers: A total of 124 centers took part in the study and randomized subjects; 9 in Taiwan, 8 in Spain, 7 each in Germany and the Republic of Korea, 6 each in India and the Russian Federation, 5 each in Ukraine, Belgium, Hungary and South Africa, 4 each in Australia, Ireland, Portugal and Thailand, 3 each in Brazil, Bulgaria, Mexico, Serbia, Slovakia, Hong Kong, Poland, Sweden and the United Kingdom (UK), 2 each in Argentina, Austria, Colombia, Norway, Singapore, Canada and the Czech Republic, 1 each in Chile, Bosnia and Herzegovina, Cyprus and Romania.

Study Initiation and Final Completion Dates: 09 July 2007 to 09 March 2010

The study was stopped prematurely.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To demonstrate that the combination of FOLFIRI (irinotecan, 5-fluorouracil [5-FU], and leucovorin) + sunitinib was superior to FOLFIRI + placebo in prolonging the progression-free survival (PFS) in the first-line treatment of subjects with metastatic colorectal cancer (mCRC).

Secondary Objectives:

- To compare the overall survival (OS) in subjects randomized to FOLFIRI + sunitinib and subjects randomized to FOLFIRI + placebo.

- To compare the objective response rate (ORR) and duration of response (DR) in subjects randomized to FOLFIRI + sunitinib and subjects randomized to FOLFIRI + placebo.

- To evaluate the safety and tolerability of sunitinib in combination with FOLFIRI.

- To compare subject-reported symptoms between the 2 treatment arms using MD Anderson Symptom Assessment Inventory of gastrointestinal symptoms (MDASI-GI).

- To compare patient-reported outcomes as measured by the EuroQoL EQ-5D Self-Report Questionnaire (EQ-5D).

METHODS

Study Design: This was a prospective, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-arm, Phase 3 clinical study to evaluate the efficacy and safety of sunitinib versus sunitinib placebo (hereafter referred to as 'placebo') in subjects with mCRC receiving FOLFIRI in the first-line treatment setting.

Subjects were randomized to receive either FOLFIRI + sunitinib (Arm A) or FOLFIRI + placebo (Arm B). Subjects were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0 versus 1), number of organ sites with metastatic disease (1 versus >1), site of primary tumor (colon versus rectum), and prior adjuvant treatment (yes versus no). Treatment was administered in 6-week cycles.

Following radiological documentation of progressive disease (PD) or initiation of subsequent anticancer treatment, subjects were to remain under observation for OS with bi-monthly data collection until the subject was lost to follow-up, withdrew, or was withdrawn from the study.

An external (third party) Independent Reviewer was used to perform tumor assessments during the study for determination of tumor response and progression dates. The Independent Reviewer was blinded to study treatment. An independent third party Data Monitoring Committee (DMC; external to the Sponsor) was also convened to review safety data (received by the Independent Reviewer) periodically, date and reason of deaths, and interim efficacy data.

On 25 June 2009, a recommendation was made by the DMC to the Sponsor to discontinue this study. This recommendation was based on pre-specified futility criteria and that the study was not likely to meet its primary endpoint to demonstrate a statistically significant improvement in PFS. The secondary endpoint of OS was also similar between treatment arms. The recommendation to discontinue the study was not related to safety issues; no new safety issues were identified by the DMC.

The schedule of study activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activities and Forms to be Completed[a]	Screening		Treatment Cycle 1 Onwards (4 Weeks On /2 Weeks Off)						Post-Treatment		
	≤21 D	≤7 D	D1 (-1) (±7)[b]	D8 (±3)	D15 (±3)	D22 (±3)	D29 (±3)	D42	End of Treatment/ Withdrawal[c]	28-D Post Treatment	Survival Follow-Up
Informed consent[d]	X										
Medical/ oncologic history[e]	X										
Physical examination[f]	X		X[g]						X	(X)	
Baseline signs/ symptoms[h]			X								
IVRS registration[i]	X										
Laboratory Studies[j]											
LVEF (ECHO or MUGA)	X	To repeat on study if clinically indicated									
Thyroid function test (TSH)	X	To repeat on study if clinically indicated									
Hematology[k]	X		X[g]	X [C1]	X	X [C1]	X		X	(X)	
Blood chemistry	X		X[g]		X		X		X	(X)	
Coagulation[l]		X	X[g]						X		
CEA		X	X[g]						X	(X)	
Urinalysis[m]	X		X[g,m]						X		
Pregnancy test[n]		X									
12-lead ECG[o]	X						X		X		
Study randomization[p]			X								
FOLFIRI[q]			X	Every 2 weeks							
Sunitinib/placebo[r]			Starting from Day 1 and then daily until D28				OFF sunitinib / placebo from D29 to D42 (2 weeks)				
Tumor assessments											
Sample banking for exploratory research (optional)[s]	X		X [C1]				X [C1]				
Tumor imaging[t]	X		X						X	(X)	(X)
Brain CT or MRI scan[u]	X										
Bone scan[v]	X		X						(X)	(X)	(X)
Other clinical assessments											
ECOG PS, weight, vital signs[w,x,y]	X		X		X[w,x]		X[w,x]		X	(X)	

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Symptom questionnaire (MDASI-GI) and EQ–5D[z]			X						X		
Study drug compliance[aa]							X		X		
Adverse event assessment[bb]			X		X		X		X	X	
Concomitant medications/ treatments[cc]	X		X		X		X		X	X	
Poststudy anticancer treatment										(X)	(X)
Poststudy survival status											X

(X) = if required; C = Cycle; CEA = carcinoembryonic antigen; CR = complete response; CT = computed tomography; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D= EuroQoL Self-Report Questionnaire; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU); ICD = informed consent document; INR = international normalized ratio; IVRS = Interactive Voice Response System; LVEF = left ventricular ejection fraction; MDASI-GI = MD Anderson Symptom Assessment Inventory of gastrointestinal symptoms; MRI = magnetic resonance imaging; MUGA = multigated angiogram; PR = partial response; PS = performance status; PTT = partial thromboplastin time; QTc = corrected QT interval; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone.

a. During treatment, all assessments were to be performed before dosing unless otherwise indicated. Acceptable time windows for performing each assessment were determined for each scheduled treatment day. Cycle lengths could be extended by longer rest periods.

b. Window (±7 days) starting from C2.

c. End-of-study treatment/withdrawal: obtained scheduled assessments if not completed during the last week on study, except for tumor images, which were to be obtained if not performed in the previous 6 weeks.

d. Informed consent was obtained before undergoing any study procedure. The 21-day Screening period started from sign off of the informed consent.

e. Medical/oncology history and demographics included information on prior oncologic history.

f. Physical examination: during Screening and on D1 of each cycle, examination of major body systems was completed, in addition to specific evaluation of cancer-related symptoms. Height was measured at Screening only.

g. Physical examination, hematology, blood chemistry, coagulation, and CEA assessments were not required on C1, D1 if acceptable Screening assessment was performed within 7 days before the start of treatment. CEA results were not required before starting study treatment.

h. Subjects were asked about any signs or symptoms experienced within the 14 days before D1.

i. IVRS was called to register subjects as screened.

j. Laboratory samples were analyzed by local laboratories only.

k. Hematology was to be performed weekly for the first sunitinib/placebo cycle [C1]. Hematology was to be performed from the second sunitinib/placebo cycle, on the first day of every FOLFIRI course, and as clinically indicated.

l. Coagulation (PTT and INR) was not needed on D1 of C1 if acceptable Screening assessment was performed within 7 days before the start of treatment.

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m. Urinalysis was performed using dipsticks. Limited dipstick (protein, pH, specific gravity) were to be repeated on study every 2 cycles, and followed up with 24-hour urine protein spot analysis in cases of positive readout of ≥2+.

n. Pregnancy test (serum or urine) for women of reproductive potential was to be performed within 7 days before the first sunitinib/placebo dose.

o. Three consecutive 12-lead ECGs approximately 2 minutes apart were required at Screening, on D29 of the first 3 cycles, and at study withdrawal, to determine the mean QTc interval. If the mean QTc interval was prolonged (>500 msec), then ECGs were read by a cardiologist at the site for confirmation. In this event, the doses of both FOLFIRI and sunitinib/placebo were withheld until the subject was assessed by a cardiologist. Additional ECGs could be performed as clinically indicated, to include 4 weeks following intrasubject sunitinib dose adjustments.

p. Study randomization number was obtained by calling a central randomization system on D1 of C1. However, for those sites that required extra time to have drug available from the Pharmacy, subjects could be randomized 1 to 2 days before D1 of C1.

q. Treatment with FOLFIRI started on C1, D1 after completing all predose assessments. Subjects received FOLFIRI as infusions of irinotecan and leucovorin on D1 and as a bolus immediately followed by a 46-hour infusion of 5-FU starting on D1 and ending on D2.

r. Treatment with sunitinib/placebo for all cohorts was to start on D1 of C1 and continue for 4 weeks followed by 2 weeks off drug. On D1 (ie, irinotecan administration), sunitinib/placebo was to be administered immediately before the start of the irinotecan infusion.

s. Archival tumor was to be collected at Screening or at any time during the study. Whole blood for germline DNA was to be collected once at Screening or at any time subsequently. Whole blood for RNA was to be collected on C1, D1 and C1 D29.

t. CT or MRI scan was to be performed of the chest, abdomen, pelvis, and other applicable sites to assess disease status at 1) Screening (to avoid undue extra exposure to radiation to repeat baseline scans, scans were accepted if not older than 3 days before the signature of ICD); 2) on or before D1 of every sunitinib/placebo cycle starting from C2; on study, the scans were to be repeated, whenever possible, with a frequency of every 6 weeks ±7 days from the date of the previous scan regardless of cycle extension due to toxicity; 3) if disease progression was suspected; 4) after 4 weeks or more following initial imaging demonstrating either PR or CR to confirm tumor response; 5) at the time of withdrawal from the study (if not done in the previous 6 weeks); and 6) after study drug discontinuation and before starting any new treatment.

u. Brain CT or MRI was to be performed at Screening.

v. Bone scan was only performed at Screening if bone metastases were suspected. Known or treated bone metastases was to be followed by correlative imaging (x-ray, CT, MRI) during the same window period as primary tumor imaging, when disease progression was suspected, at the time of withdrawal from the study (if not done in the previous 6 weeks), after study drug discontinuation, and before starting any new treatment.

w. ECOG performance was assessed at Screening, on D1 of each sunitinib/placebo cycle, and at the end of treatment.

x. Body weight was measured at Screening and on D1 of every FOLFIRI course (prior to the start of infusion) and at the end of sunitinib treatment.

y. Temperature, blood pressure, heart rate, and respiratory rate were to be measured after 5 minutes of rest at Screening, before the start of any treatment on D1 of each FOLFIRI course, and at the end of sunitinib/placebo treatment.

z. Patient-reported outcomes (MDASI-GI symptom and EQ-5D questionnaires) were completed on D1 of the first 3 sunitinib/placebo cycles and, thereafter, on D1 of every odd-numbered cycle (ie, D1 of C5, 7, 9, and so on), and at the end of treatment or withdrawal.

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	≤21 D	≤7 D	D1 (-1) (±7)[b]	D8 (±3)	D15 (±3)	D22 (±3)	D29 (±3)	D42	End of Treatment/ Withdrawal[c]	28-D Post Treatment	Survival Follow-Up

aa. The study drug bottle(s) including any unused capsules was to be returned to the clinic for drug accountability on D29.

bb. Subjects were to be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable", whichever was later. Serious adverse events were to be collected throughout the study period starting at the time written informed consent was given up to at least 28 days after the last dose of study medications.

cc. Concomitant medications and treatments were recorded from 28 days before the start of study treatment, at study entry, and during the study. Once the subject had withdrawn from the study, concomitant medications and treatments were recorded for 28 days, or until all study drug-related toxicities had resolved, whichever was later.

Number of Subjects (Planned and Analyzed): Approximately 360 subjects were planned to be randomized into each treatment arm for a total of 720 subjects. A total of 768 subjects were randomized in the study; 386 subjects were randomized to FOLFIRI + sunitinib (Arm A), of whom 384 received treatment; 382 subjects were randomized to FOLFIRI + placebo (Arm B), of whom 379 subjects received treatment. Of the 386 subjects in Arm A, all subjects were included in the intent-to-treat (ITT) population and 384 subjects were included in the as-treated (AT) population. Of the 382 subjects in Arm B, all subjects were included in the ITT population and 379 subjects were included in the AT population. All randomized subjects were analyzed for efficacy; all randomized subjects who were treated were analyzed for safety.

A total of 768 subjects were randomized in the study (76 each in Taiwan and the Russian Federation, 73 in Ukraine, 68 in Republic of Korea, 48 in Spain, 44 in Poland, 40 in South Africa, 38 in Hungary, 30 in Singapore, 27 in Germany, 23 in India, 21 each in Australia and Sweden, 19 in Serbia, 15 in Slovakia, 14 each in Thailand and Portugal, 13 each in Bulgaria and Belgium, 12 each in Argentina and Mexico, 11 each in Brazil and the UK, 7 in Ireland, 6 each in Cyprus and the Czech Republic, 5 each in Austria, Colombia, Bosnia and Herzegovina and Hong Kong, 4 in Canada, 3 in Norway, 2 in Romania and 1 in Chile).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years with confirmed (histologically or cytologically) colorectal adenocarcinoma with metastatic disease, who had not previously received therapy for metastatic colorectal disease but for whom FOLFIRI treatment was clinically indicated and who had adequate organ function defined by blood test, were eligible for inclusion in the study.

Study Treatment: Sunitinib was supplied as hard gelatin capsules. Placebo (for sunitinib) was supplied as hard gelatin capsules that were size- and color-matched to the sunitinib capsules.

Arm A (FOLFIRI + sunitinib): For Arm A, sunitinib 37.5 mg was administered by mouth (PO) once daily (QD) (in the morning without regards to meals) for 4 consecutive weeks followed by a 2-week rest period to comprise a complete cycle of 6 weeks. Sunitinib was administered in combination with FOLFIRI, 3 courses of FOLFIRI were administered during every 6 week sunitinib cycle. Sunitinib was to be administered immediately prior to the start of the irinotecan infusion, even if there were dose delays.

Arm B (FOLFIRI + placebo): For Arm B, placebo was administered PO QD (in the morning without regards to meals) for 4 consecutive weeks followed by a 2-week rest period to comprise a complete cycle of 6 weeks. Placebo was administered in combination with FOLFIRI, 3 courses of FOLFIRI were administered during every 6 week placebo cycle. Placebo was to be administered immediately prior to the start of the irinotecan infusion, even if there were dose delays.

In both treatment arms, FOLFIRI was administered in the standard fashion: intravenous (IV) irinotecan (180 mg/m²) and levo-leucovorin (200 mg/m² or leucovorin at 400 mg/m^2) immediately followed by 5-FU IV bolus (400 mg/m²) and 5-FU 46-hour continuous IV infusion (2400 mg/m²) every 2 weeks.

Efficacy, Safety and Outcomes Research Endpoints:

Primary Endpoint:

- PFS

Secondary Endpoints:

- OS
- ORR
- DR
- Adverse events (AE)
- Patient-Reported Outcomes

Disease response was categorized using Response Evaluation Criteria in Solid Tumors (RECIST). A central review to document objective disease response and progression during the study was performed by a core laboratory independent from the Sponsor and investigators and blinded with regard to treatment assignment.

Safety Evaluations: Safety evaluations included assessment of AEs, assessment of ECOG PS, clinical laboratory tests (hematology and coagulation analyses, urinalysis, and serum chemistry and electrolyte levels), electrocardiograms (ECGs), vital signs measurements, physical examinations, and left ventricular ejection fraction (LVEF).

Statistical Methods: The ITT population (ie, full analysis population) included all subjects who were randomized, with study drug assignment designated according to initial randomization. The ITT population was the primary population for evaluating all efficacy endpoints and subject characteristics.

The AT population (ie, per-protocol analysis population) included all mCRC subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population was the primary population for evaluating safety.

PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurred first. PFS was summarized in the ITT population based on the assessment of an independent third-party imaging core laboratory using Kaplan-Meier methods. The median event time and corresponding 2-sided 95% confidence interval (CI) for the median was provided for PFS. The hazard ratio and its 95% CIs were estimated. A 1-sided stratified log-rank test was used to compare PFS between the 2 treatment arms.

OS was defined as the time from randomization to the date of death due to any cause. OS was summarized using Kaplan-Meier method. The median event time and 2-sided 95% CI for the median were provided. The hazard ratio and its 95% CI were also estimated.

ORR was defined as the proportion of subjects with a confirmed complete response (CR) or partial response (PR) relative to the number of subjects in the treatment arm. The number and percent of subjects achieving objective response (CR or PR) were summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. A Pearson χ^2 test and Cochran-Mantel-Haenszel test stratified by baseline stratification factors were to be used to compare ORR between the 2 treatment arms. Analyses were performed for ORR in the ITT population based on the results of the central radiological laboratory and also on Investigator assessment.

DR was defined as the time from the first objective documentation of CR or PR that was subsequently confirmed to the first documentation of disease progression or to death due to any cause, whichever occurred first. DR was calculated for the subgroup of subjects with objective disease response. Analyses were performed for DR in the ITT population based on the results of the central radiological laboratory and also on Investigator assessment. DR was summarized using Kaplan-Meier method. The median event time and 2-sided 95% CI for the median were provided.

The MDASI-GI and EQ-5D were scored according to the MDASI scoring manual and the EQ-5D User Guide, respectively. At each assessment time and for each treatment arm, the mean (and 95% CI) and median (and interquartile ranges) of the absolute scores for the MDASI-GI, EQ-5D, and EuroQol EQ-5D visual analog scale (EQ-VAS) and their mean changes from baseline (Cycle 1, Day 1) were estimated. The 5 health status domains of the EQ-5D Index were summarized as the proportion of subjects who reported no problems, some problems, or extreme problems for each domain. Subjects rated their current health state using the EQ-VAS.

Mean changes from baseline for the MDASI-GI and EQ-5D were evaluated within treatments at each cycle using a paired t-test. Changes from baseline were considered statistically significant if the 95% CI did not include 0. A meaningful change from baseline score within treatments was defined as both clinically important and statistically significant. A clinically important difference was defined as 0.98 to 1.2 points based on the MDASI-GI user guide. The EQ-5D manual establishes clinically meaningful changes for the Health Index (0.09 to 0.10 points) and for the VAS (7 to 10 points).

Safety data were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A total of 768 subjects were randomized in the study; 386 subjects were randomized to FOLFIRI + sunitinib (Arm A), of whom 384 received treatment; 382 subjects were randomized to FOLFIRI + placebo (Arm B), of whom 379 subjects received treatment (Table 2). Of the 386 subjects in Arm A, all subjects were included in the ITT population and 384 subjects were included in the AT population. Of the

382 subjects in Arm B, all subjects were included in the ITT population and 379 subjects were included in the AT population.

Table 2. Subject Disposition (Intent-to-Treat Population)

Number of Subjects	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Assigned to study treatment	**386**	**382**
Treated	384	379
Number of subjects withdrawn from sunitinib or placebo	**386 (100.0)**	**382 (100.0)**
Objective progression/relapse	228 (59.1)	211 (55.2)
Global deterioration of health status	10 (2.6)	6 (1.6)
Adverse event	80 (20.7)	40 (10.5)
Subject died	8 (2.1)	3 (0.8)
Protocol violation	4 (1.0)	7 (1.8)
Lost to follow-up	1 (0.3)	1 (0.3)
Subject refused continued treatment for reason other than adverse event	20 (5.2)	36 (9.4)
Other (eg, disease progression, subject discontinued, radiotherapy)	35 (9.1)	78 (20.4)
Number of subjects withdrawn from FOLFIRI	**386 (100.0)**	**382 (100.0)**
Objective progression/relapse	205 (53.1)	215 (56.3)
Global deterioration of health status	12 (3.1)	6 (1.6)
Adverse event	97 (25.1)	45 (11.8)
Subject died	8 (2.1)	4 (1.0)
Protocol violation	4 (1.0)	7 (1.8)
Lost to follow-up	1 (0.3)	1 (0.3)
Subject refused continued treatment for reason other than adverse event	23 (6.0)	43 (11.3)
Other (eg, Chinese traditions festival, suspected vesicular disease, port inserted)	36 (9.3)	61 (16.0)
Number of subjects withdrawn from study	**386 (100.0)**	**382 (100.0)**
Adverse event	4 (1.0)	1 (0.3)
Subject died	163 (42.2)	148 (38.7)
Protocol violation	1 (0.3)	3 (0.8)
Lost to follow-up	23 (6.0)	14 (3.7)
Study terminated by Sponsor	1 (0.3)	1 (0.3)
Subject refused continued treatment for reason other than adverse event	14 (3.6)	19 (5.0)
Other (eg, study terminated, no longer willing to participate)	180 (46.6)	196 (51.3)

FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU); N = number of subjects; n = number of subjects fitting specified criteria.

Demographic and baseline characteristics are presented in Table 3. Overall, the demographic and baseline characteristics were balanced between the 2 treatment arms.

Table 3. Summary of Demographic and Baseline Characteristics (Intent-to-Treat Population)

Variable	FOLFIRI + Sunitinib (Arm A) N=386	FOLFIRI + Placebo (Arm B) N=382
Sex, n (%)		
Male	222 (57.5)	203 (53.1)
Female	164 (42.5)	179 (46.9)
Age, years		
N	386	382
Mean (SD)	58.6 (10.36)	57.6 (10.77)
Median (range)	59.0 (25, 83)	58.0 (25, 82)
Race, n (%)		
White	261 (67.6)	246 (64.4)
Black	6 (1.6)	8 (2.1)
Asian	106 (27.5)	113 (29.6)
Other	13 (3.4)	15 (3.9)
Weight, kg		
N	386	382
Mean (SD)	69.1 (15.68)	68.3 (14.54)
Median (range)	68.0 (34, 121)	67.0 (32, 132)
Height, cm		
N	386	382
Mean (SD)	166.6 (9.61)	165.8 (9.33)
Median (range)	167 (143, 190)	165.0 (139, 190)
CEA, ng/mL		
N	381	372
Mean (SD)	612.8 (2311.07)	388.5 (1457.71)
Median (range)	37.9 (1, 27104)	30.9 (0, 18676)
With the normal range (SD)	74 (19.2)	67 (17.5)
Up to 10 × ULN (SD)	128 (33.2)	151 (39.5)
Between 10 × and 100 × ULN (SD)	108 (28.0)	97 (25.4)
>100 × ULN (SD)	71 (18.4)	55 (14.4)
Stratification Factors		
ECOG performance status, n (%)		
0	212 (54.9)	204 (53.4)
1	174 (45.1)	178 (46.6)
Number of organ sites with metastatic disease, n (%)		
1	127 (32.9)	147 (38.5)
>1	259 (67.1)	234 (61.3)
None	0	1 (0.3)[a]
Site of primary tumor, n (%)		
Colon	237 (61.4)	232 (60.7)
Rectum	149 (38.6)	150 (39.3)
Prior adjuvant treatment, n (%)		
Yes	79 (20.5)	86 (22.5)
No	307 (79.5)	296 (77.5)

Normal textbook range for CEA is 0 to 5 ng/mL.
CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU), N = number of subjects; n = number of subjects fitting specified criteria, SD = standard deviation; ULN = upper limit of normal.
a. This was a protocol violation.

Efficacy Results:

Primary Endpoint: A summary of PFS by treatment based on blinded independent central radiologist assessment (with data up to and including 01 April 2009) and based on Investigator assessment is presented in Table 4. For both treatment arms, the number and percentage of subjects with PFS events were lower based on blinded independent central radiologist review (202 [52.3%] subjects in Arm A and 194 [50.8%] in Arm B had disease progression or death) compared with investigator assessment (286 [74.1%] subjects in Arm A and 267 [69.9%] in Arm B had disease progression or death). Based on the blinded independent central radiologist review, the median PFS in Arm A was 33.6 weeks (95% CI [30.8, 36.6]), and in Arm B was 36.6 weeks (95% CI [32.9, 40.0]).

Table 4. Summary of Progression-Free Survival by Treatment (Intent-to-Treat Population)

PFS Status	PFS Based on Blinded Independent Central Radiologist Assessment[a] FOLFIRI + Sunitinib (Arm A) N=386 n (%)	PFS Based on Blinded Independent Central Radiologist Assessment[a] FOLFIRI + Placebo (Arm B) N=382 n (%)	PFS Based on Investigator Assessment FOLFIRI + Sunitinib (Arm A) N=386 n (%)	PFS Based on Investigator Assessment FOLFIRI + Placebo (Arm B) N=382 n (%)
Number of subjects with progression/death (event)	**202 (52.3)**	**194 (50.8)**	**286 (74.1)**	**267 (69.9)**
Objective progression	153 (39.6)	158 (41.4)	243 (63.0)	238 (62.3)
Death with objective progression	49 (12.7)	36 (9.4)	43 (11.1)	29 (7.6)
Number of subjects without progression/death (censored)	**184 (47.7)**	**188 (49.2)**	**100 (25.9)**	**115 (30.1)**
Reason for censorship				
In follow-up for progression or declared progression by Investigator	53 (13.7)	58 (15.2)	22 (5.7)	29 (7.6)
Withdrew consent for additional follow-up	8 (2.1)	13 (3.4)	13 (3.4)	16 (4.2)
Lost to follow-up	4 (1.0)	5 (1.3)	7 (1.8)	5 (1.3)
Started new treatment without progression	107 (27.7)	105 (27.5)	58 (15.0)	65 (17.0)
Missed >2 consecutive visits	2 (0.5)	2 (0.5)	0	0
No postbaseline assessment	10 (2.6)	5 (1.3)	0	0
Time to progression or death (weeks)				
Quartile (95% CI)				
25%	20.8 (18.4, 23.9)	23.2 (17.9, 24.6)	20.4 (18.7, 23.6)	22.1 (18.1, 24.2)
50%	33.6 (30.8, 36.6)	36.6 (32.9, 40.0)	31.3 (30.1, 34.8)	34.9 (32.1, 37.5)
75%	51.1 (46.0, 54.7)	55.0 (46.4, 62.1)	48.0 (43.6, 50.3)	50.1 (47.7, 55.7)
Range	(1.3, 84.8)	(1.4, 84.5)	(1.3, 103.8)	(1.4, 85.0)
Stratified analysis				
Hazard ratio (sunitinib versus placebo)[b]	1.095		1.179	
95% CI for hazard ratio	0.892, 1.344		0.993, 1.399	
P-value[c]	0.8072		0.9704	
Unstratified analysis				
Hazard ratio (sunitinib versus placebo)[b]	1.103		1.169	
95% CI for hazard ratio	0.905, 1.345		0.989, 1.382	
P-value[d]	0.8359		0.9663	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU); N = number of subjects; n = number of subjects meeting prespecified criteria; PFS = progression free survival.

a. Included data up to and including 01 April 2009.
b. Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of sunitinib; a hazard ratio >1 indicated a reduction in hazard rate in favor of placebo.
c. P-value was from a 1-sided, log-rank test stratified from ECOG performance status (0 versus 1), number of organ sites with disease (1 versus ≥1), site of primary tumor (colon versus rectum), and prior adjuvant therapy (yes versus no).
d. P-value was from a 1-sided, unstratified log-rank test.

Secondary Endpoints:

OS: OS by treatment for the ITT population in which the OS data were censored on the day following the date of the last contact at which the subject was known to be alive is presented in Table 5.

Table 5. Summary of Overall Survival(OS) by Treatment (Intent-to-Treat Population)

Kaplan-Meier Estimate	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Subjects status		
Dead during study	166 (43.0)	148 (38.7)
Alive on study	220 (57.0)	234 (61.3)
Time to Death (Weeks)		
Quartile (95% confidence interval)		
25%	45.3 (39.00, 51.40)	53.4 (44.20, 61.40)
50%	87.9 (75.20, NA)	85.9 (81.10, NA)
75%	NA	NA
Range	(1.30, 91.90)	(1.40, 93.30)
Stratified analysis:		
Hazard ratio (sunitinib versus placebo)[a]	1.171	
95% confidence interval for hazard ratio	0.936, 1.466	
P-value[b]	0.9163	
Unstratified analysis:		
Hazard ratio (sunitinib versus placebo)[a]	1.175	
95% confidence interval for hazard ratio	0.942, 1.467	
P-value[c]	0.9239	

Subjects were censored on the date of the last contact at which the subject was known to be alive.
N = number of subjects; n = number of subjects meeting prespecified criteria; NA = not applicable.

a. Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of sunitinib; a hazard ratio >1 indicated a reduction in hazard rate in favor of placebo.
b. P-value was from a 1-sided, log-rank test stratified for Eastern Cooperative Oncology Group (ECOG) performance status (0 versus. 1), number of organ sites with disease (1 versus. >1), site of primary tumor (colon versus. rectum), and prior adjuvant treatment (yes versus. no).
c. Log-rank test statistic and p-value were from a 1-sided, unstratified log-rank test.

ORR: A summary of ORR by treatment based on blinded independent central radiologist assessment is presented in Table 6.

Table 6. Summary of Objective Response Rate (ORR) by Treatment (Intent-to-Treat Population)

Number(%) of Subjects	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Subjects with Baseline assessment	373 (96.6)	377 (98.7)
Subjects with measurable disease at Baseline	360 (93.3)	357 (93.5)
Best overall response[a]		
Complete response (CR)	0	1 (0.3)
Partial response (PR)	124 (32.1)	127 (33.2)
Stable disease (SD)	200 (51.8)	201 (52.6)
Progressive disease (PD)	25 (6.5)	32 (8.4)
Not evaluable[b]	25 (6.5)	16 (4.2)
Missing	12 (3.1)	5 (1.3)
Objective response (CR + PR)[a]	124 (32.1)	128 (33.5)
95% exact CI	(27.49, 37.04)	(28.79, 38.49)
Treatment difference (sunitinib versus placebo) (%)[a]	-1.384	
95% CI of difference (%)	(-8.025, 5.258)	
P-value[c]	0.6831	

CI = confidence interval; N = number of subjects; n = number of subjects meeting pre-specified criteria.
a. % = (n/N) × 100. Baseline assessment was required for assessment to be included.
b. Including subject died within 30 days and prior to having sufficient evaluations for overall response.
c. P-value was from a Chi-square test.

Based on Investigator assessment, the ORR was 36.8% (95% CI [32.0%, 41.8%]) in Arm A and 38.2% (95% CI [33.3%, 43.3%]) in Arm B. For both treatment arms, the number of subjects with a confirmed objective tumor response was higher based on Investigator assessment compared with the blinded independent central radiologist review.

DR: A summary of DR by treatment based on blinded independent central radiologist assessment is presented in Table 7.

Table 7. Duration of Response (DR) by Treatment (Intent-to-Treat Population)

	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Subjects with a confirmed objective tumor response (N*)	124	128
Subject Status		
Subjects who had disease progression or death due to any cause while on study[a]	42(33.9)	33(25.8)
Subjects who did not progress or die due to any cause while on study	82(66.1)	95(74.2)
Duration of Response (Weeks)		
Quartile (95% CI)		
25%	21.2 (18.80, 26.10)	26.1 (24.10, 31.90)
50%	30.1 (27.10, 37.20)	39.0 (31.90, 49.00)
75%	NA (37.20, NA)	49.0 (NA, NA)
Range	(11.50, 37.20)	(11.10, 49.00)

% = (n/N*)*100, CI = confidence interval; N* = number of randomized subjects with confirmed objective response, N = number of subjects in treatment arm; n=number of subjects; NA = not applicable.
a. On study included treatment plus 28-day follow-up period.

Based on Investigator assessment, the median duration of response in Arm A was 29.9 weeks (95% CI [26.1, 32.9]) compared with 32.6 weeks in Arm B (95% CI [30.1, 38.2]).

Patient-Reported Outcomes: The within treatment change from baseline scores for the MDASI-GI, EQ-5D health state index, and VAS results were evaluated only for cycles where at least 10 subjects in either treatment arm (Cycles 2, 3, 5, 7, 9, 11, and end of treatment) had available data.

Table 8 and Table 9 present the within treatment mean changes from baseline for the MDASI-GI total Symptom Intensity score (sum of 13 MDASI core items: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness or tingling) and the MDASI-GI total Symptom Interference score (sum of 6 MADSI core items: general activity, mood, work, relations with other people, walking, and enjoyment of life), respectively.

Table 8. Summary of MD Anderson Symptom Inventory Core Questionnaire and Additional Gastrointestinal Items (MDASI Core + GI): Change From Baseline Scores by Cycle: Symptom Intensity Scale - Derived Scale Scores[a] (Intent-to-Treat Population)

Change From Baseline Derived Scale Scores[a]	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Cycle 2 Day 1		
N[b]	309	327
Mean (SD)	1.7 (18.90)	0.4 (16.14)
Within-treatment 95% CI	(-0.4, 3.8)	(-1.3, 2.2)
Within-treatment p-value	0.1155	0.6187
Cycle 3 Day 1		
N[b]	265	279
Mean (SD)	0.8 (17.86)	0.9 (17.23)
Within-treatment 95% CI	(-1.4, 2.9)	(-1.1, 3.0)
Within-treatment p-value	0.4757	0.3730
Cycle 5 Day 1		
N[b]	176	188
Mean (SD)	1.0 (17.71)	1.8 (14.98)
Within-treatment 95% CI	(-1.6, 3.7)	(-0.4, 3.9)
Within-treatment p-value	0.4439	0.1073
Cycle 7 Day 1		
N[b]	88	113
Mean (SD)	0.7 (15.53)	2.7 (16.26)
Within-treatment 95% CI	(-2.6, 4.0)	(-0.3, 5.7)
Within-treatment p-value	0.6715	0.0798
Cycle 9 Day 1		
N[b]	41	61
Mean (SD)	0.8 (20.01)	1.2 (17.46)
Within-treatment 95% CI	(-5.6, 7.1)	(-3.3, 5.6)
Within-treatment p-value	0.8077	0.6060
Cycle 11 Day 1		
N[b]	20	26
Mean (SD)	5.0 (17.53)	-2.7 (14.03)
Within-treatment 95% CI	(-3.2, 13.2)	(-8.4, 3.0)
Within-treatment p-value	0.2157	0.3371
End of Treatment		
N[b]	277	271
Mean (SD)	6.8 (20.76)	5.1 (19.01)
Within-treatment 95% CI	(4.4, 9.3)	(2.8, 7.3)
Within-treatment p-value	<0.0001	<0.0001

Items and Scale Scores: A score indicated the intensity of the symptom. The lower the symptom score, the less intense the symptom. Range: Change from Baseline Symptom Intensity Scale = -130 to 130.
CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects; SD = standard deviation.

a. Symptom Intensity Scale = the sum of items 1 to 13 of the MDASI-GI questionnaire. Completed scale required >50% item response on the instrument. If <100% but >50% of the items on a scale were completed, the Symptom Intensity Scale was prorated. Prorated score = [sum of the total items answered] *13/ [Number of items answered]. If ≥2 responses were provided within the same visit, the more severe (higher) response was used.
b. N = the number of subjects completing the item at baseline and at the specified visit.

Table 9. Summary of MD Anderson Symptom Inventory Core Questionnaire and Additional Gastrointestinal Items (MDASI Core + GI): Change From Baseline Scores by Cycle: GI Symptom Interference Scale - Derived Scale Scores[a] (Intent-to-Treat Population)

Change From Baseline Derived Scale Scores[a]	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Cycle 2 Day 1		
N[b]	307	326
Mean (SD)	0.0 (12.42)	-1.3 (11.84)
Within-treatment 95% CI	(-1.4, 1.4)	(-2.6, 0.0)
Within-treatment p-value	0.9993	0.0528
Cycle 3 Day 1		
N[b]	262	277
Mean (SD)	-0.1 (14.02)	-1.7 (12.77)
Within-treatment 95% CI	(-1.8, 1.6)	(-3.2, -0.2)
Within-treatment p-value	0.9382	0.0278
Cycle 5 Day 1		
N[b]	174	187
Mean (SD)	0.2 (13.13)	-1.2 (12.57)
Within-treatment 95% CI	(-1.8, 2.1)	(-3.1, 0.6)
Within-treatment p-value	0.8663	0.1770
Cycle 7 Day 1		
N[b]	86	113
Mean (SD)	-0.5 (11.13)	-0.2 (13.33)
Within-treatment 95% CI	(-2.9, 1.9)	(-2.7, 2.3)
Within-treatment p-value	0.6751	0.8880
Cycle 9 Day 1		
N[b]	40	61
Mean (SD)	2.1 (8.88)	-1.7 (11.45)
Within-treatment 95% CI	(-0.7, 4.9)	(-4.7, 1.2)
Within-treatment p-value	0.1427	0.2404
Cycle 11 Day 1		
N[b]	19	26
Mean (SD)	3.1 (8.88)	-1.0 (13.60)
Within-treatment 95% CI	(-1.2, 7.4)	(-6.5, 4.5)
Within-treatment p-value	0.1449	0.7003
End of Treatment		
N[b]	276	269
Mean (SD)	3.4 (14.52)	1.8 (13.97)
Within-treatment 95% CI	(1.6, 5.1)	(0.2, 3.5)
Within-treatment p-value	0.0002	0.0320

Items and Scale Scores: A score indicated the interference of the symptom. The lower the symptom score, the less interfering the symptom. Range: Change from Baseline Symptom Interference Derived Scale = -60 to 60.
CI = confidence interval; N = number of subjects in treatment arm; n = number of subjects; SD = standard deviation.

a. Symptom Interference Scale = the sum of items 17 to 22 of the MDASI-GI questionnaire. Completed scale required >50% item response on the instrument. If <100% but >50% of the items on a scale were completed, the Symptom Interference Scale was prorated. Prorated score= (sum of the total items answered) *6/ (Number of items answered). If ≥2 responses were provided within the same visit, the more severe (higher) response was used.

b. N = the number of subjects completing the item at baseline and at the specified visit.

Table 10 present the within treatment change from baseline weighted Health State Index Score of the EQ-5D Questionnaire for each treatment arm.

Table 10. EQ-5D Questionnaire: Summary of Weighted Health State Index Score by Treatment - Change From Baseline (Intent-to-Treat Population)

EQ-5D Questionnaire: Weighted Health State Index Score[a] Change From Baseline	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Cycle 2 Day 1		
N[b]	310	328
Mean (SD)	0.02 (0.160)	0.04 (0.141)
Within-treatment 95% CI	(0.00, 0.04)	(0.02, 0.05)
Within-treatment p-value	0.0361	<0.0001
Cycle 3 Day 1		
N[b]	265	279
Mean (SD)	0.02 (0.165)	0.04 (0.155)
Within-treatment 95% CI	(0.00, 0.04)	(0.02, 0.06)
Within-treatment p-value	0.0163	<0.0001
Cycle 5 Day 1		
N[b]	178	189
Mean (SD)	0.02 (0.165)	0.03 (0.143)
Within-treatment 95% CI	(-0.00, 0.05)	(0.01, 0.05)
Within-treatment p-value	0.0716	0.0023
Cycle 7 Day 1		
N[b]	87	115
Mean (SD)	0.03 (0.175)	0.05 (0.137)
Within-treatment 95% CI	(-0.01, 0.06)	(0.02, 0.07)
Within-treatment p-value	0.1672	0.0002
Cycle 9 Day 1		
N[b]	41	61
Mean (SD)	0.00 (0.173)	0.05 (0.108)
Within-treatment 95% CI	(-0.05, 0.05)	(0.02, 0.08)
Within-treatment p-value	0.9999	0.0006
Cycle 11 Day 1		
N[b]	20	26
Mean (SD)	0.01 (0.110)	0.09 (0.107)
Within-treatment 95% CI	(-0.04, 0.06)	(0.05, 0.14)
Within-treatment p-value	0.784	0.0002
End of Treatment		
N[b]	278	271
Mean (SD)	-0.06 (0.207)	-0.02 (0.196)
Within-treatment 95% CI	(-0.08, -0.03)	(-0.04, 0.00)
Within-treatment p-value	<0.0001	0.1223

CI = confidence interval; EQ-5D = EuroQol EQ-5D self-report questionnaire; N = number of subjects in treatment arm; n = number of subjects; NA = not applicable; SD = standard deviation.

a. Calculation of the weighted health state index score was based on a SAS algorithm developed by James Shaw. If ≥2 responses were provided within the same visit, the more severe (higher) response was used. Range: Change from Baseline weighted health state index score = -1.11 to 1.

b. N = number of subjects with a score at Baseline and at the specified visit.

Table 11 presents the within treatment change from baseline VAS scores of the EQ-5D for each treatment arm.

Table 11. EQ-5D Questionnaire: Summary of Visual Analogue Scale (VAS) Score by Treatment - Change From Baseline (Intent-to-Treat Population)

EQ-5D Questionnaire: Visual Analogue Scale (VAS) Score[a] Change From Baseline	FOLFIRI + Sunitinib (Arm A) N=386 n (%)	FOLFIRI + Placebo (Arm B) N=382 n (%)
Cycle 2 Day 1		
N[b]	305	326
Mean (SD)	1.0 (18.30)	3.3 (18.15)
Within-treatment 95% CI	(-1.1, 3.0)	(1.3, 5.3)
Within-treatment p-value	0.3536	0.0011
Cycle 3 Day 1		
N[b]	264	279
Mean (SD)	1.7 (19.23)	4.3 (19.30)
Within-treatment 95% CI	(-0.7, 4.0)	(2.0, 6.6)
Within-treatment p-value	0.1574	0.0003
Cycle 5 Day 1		
N[b]	177	189
Mean (SD)	1.8 (16.08)	6.6 (22.03)
Within-treatment 95% CI	(-0.6, 4.1)	(3.5, 9.8)
Within-treatment p-value	0.1490	<0.0001
Cycle 7 Day 1		
N[b]	86	113
Mean (SD)	3.8 (19.67)	4.3 (20.84)
Within-treatment 95% CI	(-0.4, 8.1)	(0.4, 8.2)
Within-treatment p-value	0.0739	0.0296
Cycle 9 Day 1		
N[b]	41	61
Mean (SD)	-0.9 (16.90)	4.0 (17.45)
Within-treatment 95% CI	(-6.2, 4.5)	(-0.5, 8.5)
Within-treatment p-value	0.7481	0.0784
Cycle 11 Day 1		
N[b]	20	26
Mean (SD)	-1.6 (10.92)	9.0 (15.81)
Within-treatment 95% CI	(-6.7, 3.6)	(2.6, 15.3)
Within-treatment p-value	0.5333	0.0079
End of Treatment		
N[b]	277	272
Mean (SD)	-6.2 (21.16)	-0.9 (20.11)
Within-treatment 95% CI	(-8.7, -3.7)	(-3.3, 1.5)
Within-treatment p-value	<0.0001	0.4849

CI = confidence interval; EQ-5D = EuroQol EQ-5D self-report questionnaire; N = number of subjects in treatment arm; n = number of subjects; NA = not applicable; SD = standard deviation.

a. Change from baseline EQ-5D VAS score ranges from -100 to 100. If ≥2 responses were provided within the same visit, the more severe (lower) response was used.

b. N = the number of subjects with a score at baseline and at the specified visit.

Safety Results: An overall summary of AEs by treatment arm is presented in Table 12. Similar numbers and percentages of subjects in Arm A (382 [99.5%] out of 384 treated

subjects) and Arm B (366 [96.6%] out of 379 treated subjects) experienced AEs. Subjects in Arm A experienced higher numbers and percentages of Grades 3, 4, and 5 AEs as well as higher numbers and percentages of SAEs than in Arm B.

Table 12. Overall Summary of Adverse Events; As-Treated Population

Adverse Event Parameter	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
No. of AEs	9346	6003
No. (%) of subjects		
Subjects with AEs	382 (99.5)	366 (96.6)
Subjects with Grade 3 AEs	334 (87.0)	214 (56.5)
Subjects with Grade 4 AEs	163 (42.4)	79 (20.8)
Subjects with Grade 5 AEs	33 (8.6)	18 (4.7)
Subjects with serious AEs	170 (44.3)	111 (29.3)
Subjects with treatment-related AEs		
Related to study treatment	380 (99.0)	343 (90.5)
Related to sunitinib/placebo, regardless of the relationship to FOLFIRI	308 (80.2)	258 (68.1)
Related to FOLFIRI, regardless of the relationship to sunitinib/placebo	379 (98.7)	342 (90.2)
Related to sunitinib/placebo and FOLFIRI	288 (75.0)	236 (62.3)
Subjects with treatment-related Grade 5 AEs		
Related to study treatment	12 (3.1)	4 (1.1)
Related to sunitinib/placebo, regardless of the relationship to FOLFIRI	8 (2.1)	3 (0.8)
Related to FOLFIRI, regardless of the relationship to sunitinib/placebo	12 (3.1)	4 (1.1)
Related to sunitinib/placebo and FOLFIRI	8 (2.1)	3 (0.8)
Subjects with treatment-related serious AEs		
Related to study treatment	113 (29.4)	63 (16.6)
Related to sunitinib/placebo, regardless of the relationship to FOLFIRI	82 (21.4)	43 (11.3)
Related to FOLFIRI, regardless of the relationship to sunitinib/placebo	101 (26.3)	52 (13.7)
Related to sunitinib/placebo and FOLFIRI	68 (17.7)	32 (8.4)
Subjects permanently discontinued treatment due to AEs – sunitinib/placebo	91 (23.7)	43 (11.3)
Subjects permanently discontinued treatment due to AEs – FOLFIRI	110 (28.6)	50 (13.2)
Subjects with dose reduced due to AEs – sunitinib/placebo	74 (19.3)	18 (4.7)
Subjects with dose reduced due to AEs – FOLFIRI	163 (42.4)	77 (20.3)
Subject with temporary discontinuation due to AEs – sunitinib/placebo	233 (60.7)	131 (34.6)
Subject with temporary discontinuation due to AEs - FOLFIRI	337 (87.8)	235 (62.0)

AE and SAE are not separated out. Treatment-emergent AEs defined as all AEs that occurred on or after the first dose of study treatment were included in this table. Except for the number of AEs, subjects were counted only once per treatment in each cell. Serious AEs were according to Investigator assessment.
AE = adverse event; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU); N = number of subjects, n = number of subjects fitting specified criteria, No. = number; SAE = serious adverse event.

AEs: Summary of Non-serious treatment-emergent AEs (AT population) are presented in Table 13.

Table 13. Summary of Non-Serious Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Any AEs	382 (99.5)	362 (95.5)
Blood and lymphatic system disorders	335 (87.2)	233 (61.5)
Anaemia	120 (31.3)	74 (19.5)
Leukopenia	107 (27.9)	49 (12.9)
Neutropenia	315 (82.0)	188 (49.6)
Thrombocytopenia	129 (33.6)	21 (5.5)
Gastrointestinal disorders	331 (86.2)	292 (77.0)
Abdominal distension	21 (5.5)	26 (6.9)
Abdominal pain	89 (23.2)	73 (19.3)
Abdominal pain upper	43 (11.2)	28 (7.4)
Constipation	89 (23.2)	72 (19.0)
Diarrhoea	247 (64.3)	182 (48.0)
Dyspepsia	45 (11.7)	24 (6.3)
Nausea	190 (49.5)	181 (47.8)
Stomatitis	88 (22.9)	45 (11.9)
Vomiting	144 (37.5)	129 (34.0)
General disorders and administration site conditions	263 (68.5)	221 (58.3)
Asthenia	70 (18.2)	65 (17.2)
Chest pain	28 (7.3)	9 (2.4)
Fatigue	120 (31.3)	93 (24.5)
Mucosal inflammation	87 (22.7)	66 (17.4)
Oedema peripheral	27 (7.0)	26 (6.9)
Pyrexia	67 (17.4)	53 (14.0)
Infections and infestations	121 (31.5)	119 (31.4)
Upper respiratory tract infection	24 (6.3)	20 (5.3)
Investigations	96 (25.0)	66 (17.4)
Alanine aminotransferase increased	23 (6.0)	12 (3.2)
Aspartate aminotransferase increased	22 (5.7)	9 (2.4)
Weight decreased	36 (9.4)	17 (4.5)
Metabolism and nutrition disorders	161 (41.9)	136 (35.9)
Decreased appetite	116 (30.2)	82 (21.6)
Hypokalaemia	40 (10.4)	20 (5.3)
Musculoskeletal and connective tissue disorders	85 (22.1)	74 (19.5)
Back pain	37 (9.6)	32 (8.4)
Nervous system disorders	127 (33.1)	105 (27.7)
Dizziness	29 (7.6)	27 (7.1)
Dysgeusia	30 (7.8)	20 (5.3)
Headache	44 (11.5)	28 (7.4)
Psychiatric disorders	73 (19.0)	70 (18.5)
Insomnia	55 (14.3)	48 (12.7)
Respiratory, thoracic and mediastinal disorders	141 (36.7)	98 (25.9)
Cough	49 (12.8)	41 (10.8)
Dyspnoea	29 (7.6)	15 (4.0)
Epistaxis	48 (12.5)	21 (5.5)
Skin and subcutaneous tissue disorders	212 (55.2)	168 (44.3)
Alopecia	128 (33.3)	121 (31.9)
Palmar-plantar erythrodysaesthesia syndrome	77 (20.1)	26 (6.9)
Rash	41 (10.7)	32 (8.4)
Skin discolouration	22 (5.7)	2 (0.5)
Vascular disorders	84 (21.9)	62 (16.4)
Hypertension	56 (14.6)	19 (5.0)

Treatment-emergent adverse events (AE) defined as all AEs that occurred on or after the first dose of study treatment were included in the table. Except for the number of AEs, subjects are counted only once per treatment in each cell
N = number of subjects, n = number of subjects fitting specified criteria.

Treatment-related AEs (AT-population) are presented in Table 14.

Table 14. Treatment Related AEs by System Organ Class and Preferred Term Experienced by ≥5% of Subjects (As-Treated Population)

System Organ Class and Preferred Term	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Any AEs	380 (99.0)	343 (90.5)
Blood and lymphatic system disorders	341 (88.8)	224 (59.1)
Anaemia	102 (26.6)	61 (16.1)
Febrile neutropenia	28 (7.3)	12 (3.2)
Leukopenia	107 (27.9)	49 (12.9)
Neutropenia	320 (83.3)	189 (49.9)
Thrombocytopenia	132 (34.4)	20 (5.3)
Gastrointestinal disorders	324 (84.4)	276 (72.8)
Abdominal pain	26 (6.8)	34 (9.0)
Abdominal pain upper	22 (5.7)	9 (2.4)
Constipation	35 (9.1)	38 (10.0)
Diarrhoea	241 (62.8)	172 (45.4)
Dyspepsia	36 (9.4)	16 (4.2)
Nausea	186 (48.4)	178 (47.0)
Stomatitis	89 (23.2)	46 (12.1)
Vomiting	137 (35.7)	120 (31.7)
General disorders and administration site conditions	230(59.9)	181(47.8)
Asthenia	64 (16.7)	57 (15.0)
Fatigue	111 (28.9)	80 (21.1)
Mucosal inflammation	84 (21.9)	63 (16.6)
Pyrexia	35 (9.1)	22 (5.8)
Metabolism and nutrition disorders	129 (33.6)	94 (24.8)
Decreased appetite	100 (26.0)	70 (18.5)
Nervous system disorders	94 (24.5)	79 (20.8)
Dysgeusia	27 (7.0)	20 (5.3)
Headache	20 (5.2)	10 (2.6)
Psychiatric disorders	26 (6.8)	23 (6.1)
Insomnia	23 (6.0)	19 (5.0)
Respiratory, thoracic and mediastinal disorders	79 (20.6)	45 (11.9)
Epistaxis	35 (9.1)	15 (4.0)
Skin and subcutaneous tissue disorders	200 (52.1)	154 (40.6)
Alopecia	126 (32.8)	121 (31.9)
Palmar-plantar erythrodysaesthesia syndrome	77 (20.1)	25 (6.6)
Rash	31 (8.1)	23 (6.1)
Skin discolouration	20 (5.2)	1 (0.3)
Vascular disorders	59 (15.4)	38 (10.0)
Hypertension	38 (9.9)	9 (2.4)

Table includes both serious and non-serious AEs, ie, AE and SAE are not separated out. Treatment-emergent AEs defined as all AEs that occurred on or after the first dose of study treatment were included in the table. Except for the number of AEs, subjects were counted only once per treatment in each cell
AE = adverse event; N = number of subjects, n = number of subjects fitting specified criteria; SAE = serious adverse event.

Serious AEs (SAE) by system organ class and preferred term (all causality and treatment-related) (AT population) are presented in Table 15.

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Any AE	170 (44.3)	111 (29.3)	113 (29.4)	63 (16.6)
Blood and lymphatic system disorders	60 (15.6)	18 (4.7)	58 (15.1)	18 (4.7)
Anaemia	9 (2.3)	4 (1.1)	7 (1.8)	3 (0.8)
Febrile neutropenia	25 (6.5)	11 (2.9)	25 (6.5)	11 (2.9)
Granulocytopenia	1 (0.3)	0	1 (0.3)	0
Leukopenia	9 (2.3)	3 (0.8)	9 (2.3)	3 (0.8)
Neutropenia	26 (6.8)	6 (1.6)	23 (6.0)	5 (1.3)
Pancytopenia	2 (0.5)	0	2 (0.5)	0
Thrombocytopenia	13 (3.4)	1 (0.3)	13 (3.4)	1 (0.3)
Cardiac disorders	8 (2.1)	9 (2.4)	5 (1.3)	3 (0.8)
Acute myocardial infarction	1 (0.3)	2 (0.5)	1 (0.3)	0
Atrial fibrillation	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Cardiac arrest	1 (0.3)	0	0	0
Cardiac failure	0	3 (0.8)	0	1 (0.3)
Cardiac failure congestive	1 (0.3)	0	1 (0.3)	0
Cardiopulmonary failure	0	1 (0.3)	0	0
Myocardial infarction	2 (0.5)	0	2 (0.5)	0
Pericardial effusion	0	1 (0.3)	0	0
Ventricular fibrillation	0	1 (0.3)	0	1 (0.3)
Ventricular tachycardia	1 (0.3)	0	0	0
Ear and labyrinth disorders	2 (0.5)	0	1 (0.3)	0
Hearing impaired	1 (0.3)	0	0	0
Vertigo	1 (0.3)	0	1 (0.3)	0
Endocrine disorders	1 (0.3)	0	1 (0.3)	0
Hypothyroidism	1 (0.3)	0	1 (0.3)	0
Eye disorders	0	1 (0.3)	0	1 (0.3)
Pupils unequal	0	1 (0.3)	0	1 (0.3)
Gastrointestinal disorders	67(17.4)	48(12.7)	39 (10.2)	28 (7.4)
Abdominal adhesions	0	1 (0.3)	2 (0.5)	2 (0.5)
Abdominal distension	0	1 (0.3)	0	0
Abdominal pain	7 (1.8)	6 (1.6)	0	0
Abdominal pain lower	0	1 (0.3)	0	0
Abdominal pain upper	1 (0.3)	0	0	0
Acute abdomen	1 (0.3)	0	0	0
Anal fissure	1 (0.3)	0	1 (0.3)	0

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Ascites	2 (0.5)	2 (0.5)	1 (0.3)	0
Colonic obstruction	2 (0.5)	0	1 (0.3)	0
Constipation	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Diarrhoea	23 (6.0)	19 (5.0)	18 (4.7)	16 (4.2)
Diarrhoea haemorrhagic	1 (0.3)	0	1 (0.3)	0
Duodenal ulcer	0	1 (0.3)	0	0
Duodenal ulcer haemorrhage	1 (0.3)	0	1 (0.3)	0
Faecaloma	1 (0.3)	0	0	0
Gastritis	1 (0.3)	2 (0.5)	0	1 (0.3)
Gastritis erosive	0	1 (0.3)	0	1 (0.3)
Gastrointestinal haemorrhage	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)
Gastrointestinal hypomotility	1 (0.3)	0	0	0
Gastrooesophagitis	1 (0.3)	0	1 (0.3)	0
Haematemesis	2 (0.5)	0	1 (0.3)	0
Haematochezia	0	1 (0.3)	0	0
Haemorrhoidal haemorrhage	0	1 (0.3)	0	0
Haemorrhoids	2 (0.5)	0	0	0
Ileus	2 (0.5)	8 (2.1)	1 (0.3)	0
Intestinal ischaemia	0	1 (0.3)	0	0
Intestinal obstruction	8 (2.1)	10 (2.6)	0	1 (0.3)
Intestinal perforation	2 (0.5)	0	1 (0.3)	0
Large intestine perforation	2 (0.5)	0	2 (0.5)	0
Lower gastrointestinal haemorrhage	0	1 (0.3)	0	0
Mechanical ileus	1 (0.3)	0	0	0
Mouth ulceration	1 (0.3)	0	1 (0.3)	0
Nausea	5 (1.3)	4 (1.1)	3 (0.8)	3 (0.8)
Oesophageal ulcer	0	1 (0.3)	0	1 (0.3)
Pancreatitis acute	1 (0.3)	0	1 (0.3)	0
Peritonitis	1 (0.3)	1 (0.3)	1 (0.3)	0
Proctalgia	1 (0.3)	0	0	0
Rectal haemorrhage	7 (1.8)	1 (0.3)	5 (1.3)	0
Small intestinal obstruction	4 (1.0)	2 (0.5)	0	1 (0.3)
Stomatitis	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
Subileus	1 (0.3)	0	0	0
Vomiting	11 (2.9)	11 (2.9)	10 (2.6)	8 (2.1)

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
General disorders and administration site conditions	44(11.5)	26 (6.9)	23 (6.0)	8 (2.1)
Asthenia	3 (0.8)	4 (1.1)	3 (0.8)	3 (0.8)
Catheter related complication	0	1 (0.3)	0	0
Catheter thrombosis	1 (0.3)	0	0	0
Chest pain	2 (0.5)	0	2 (0.5)	0
Chills	1 (0.3)	1 (0.3)	1 (0.3)	0
Death	4 (1.0)	4 (1.1)	1 (0.3)	1 (0.3)
Disease progression	12 (3.1)	3 (0.8)	0	0
Fatigue	4 (1.0)	1 (0.3)	4 (1.0)	1 (0.3)
General physical health deterioration	0	1 (0.3)	0	0
Mucosal inflammation	4 (1.0)	0	3 (0.8)	0
Oedema peripheral	1 (0.3)	1 (0.3)	0	0
Pain	0	1 (0.3)	0	0
Pyrexia	17 (4.4)	12 (3.2)	10 (2.6)	3 (0.8)
Hepatobiliary disorders	4 (1.0)	3 (0.8)	2 (0.5)	1 (0.3)
Cholecystitis	2 (0.5)	0	1 (0.3)	0
Chronic hepatitis	1 (0.3)	0	0	0
Hepatic failure	0	1 (0.3)	0	1 (0.3)
Hepatic pain	0	1 (0.3)	0	0
Hyperbilirubinaemia	1 (0.3)	0	1 (0.3)	0
Jaundice cholestatic	0	1 (0.3)	0	0
Immune system disorders	0	1 (0.3)	0	0
Anaphylactic reaction	0	1 (0.3)	0	0
Infections and infestations	33 (8.6)	25 (6.6)	13 (3.4)	9 (2.4)
Abdominal abscess	0	1 (0.3)	0	0
Abscess	2 (0.5)	0	2 (0.5)	0
Anal abscess	3 (0.8)	1 (0.3)	1 (0.3)	0
Bacterial infection	0	1 (0.3)	0	0
Catheter sepsis	0	1 (0.3)	0	0
Cellulitis	1 (0.3)	0	0	0
Central line infection	4 (1.0)	1 (0.3)	2 (0.5)	0
Cholecystitis infective	1 (0.3)	0	0	0
Cystitis	1 (0.3)	0	0	0
Empyema	1 (0.3)	0	0	0
Escherichia bacteraemia	1 (0.3)	0	0	0

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Gastroenteritis	2 (0.5)	0	1 (0.3)	0
Herpes zoster	1 (0.3)	0	0	0
Implant site cellulitis	1 (0.3)	0	0	0
Infection	2 (0.5)	1 (0.3)	1 (0.3)	0
Liver abscess	1 (0.3)	1 (0.3)	0	1 (0.3)
Lower respiratory tract infection	2 (0.5)	1 (0.3)	0	0
Lung abscess	1 (0.3)	1 (0.3)	0	1 (0.3)
Necrotising fasciitis	1 (0.3)	0	0	0
Neutropenic sepsis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Orchitis	1 (0.3)	0	1 (0.3)	0
Perirectal abscess	0	1 (0.3)	0	0
Peritonitis bacterial	1 (0.3)	0	0	0
Pneumonia	5 (1.3)	7 (1.8)	1 (0.3)	3 (0.8)
Pseudomonal sepsis	0	1 (0.3)	0	1 (0.3)
Pseudomonas pseudomallei infection	0	1 (0.3)	0	1 (0.3)
Retroperitoneal abscess	0	1 (0.3)	0	0
Sepsis	4 (1.0)	3 (0.8)	3 (0.8)	1 (0.3)
Septic shock	1 (0.3)	0	1 (0.3)	0
Subcutaneous abscess	1 (0.3)	0	1 (0.3)	0
Tooth infection	1 (0.3)	0	0	0
Urinary tract infection	2 (0.5)	3 (0.8)	1 (0.3)	2 (0.5)
Urosepsis	0	1 (0.3)	0	0
Injury, poisoning and procedural complications	6 (1.6)	4 (1.1)	3 (0.8)	0
Fall	1 (0.3)	2 (0.5)	1 (0.3)	0
Femoral neck fracture	0	1 (0.3)	0	0
Gastrointestinal stoma complication	0	1 (0.3)	0	0
Overdose	1 (0.3)	0	0	0
Peripancreatic fluid collection	1 (0.3)	0	0	0
Post procedural haemorrhage	2 (0.5)	0	1 (0.3)	0
Stent occlusion	2 (0.5)	0	1 (0.3)	0
Investigations	2 (0.5)	4 (1.1)	1 (0.3)	1 (0.3)
Blood creatinine increased	0	2 (0.5)	0	0
C-reactive protein increased	0	1 (0.3)	0	0
Cardiac stress test abnormal	1 (0.3)	0	0	0
Electrocardiogram ST segment depression	1 (0.3)	0	1 (0.3)	0

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Renal function test abnormal	0	1 (0.3)	0	1 (0.3)
Metabolism and nutrition disorders	12 (3.1)	11 (2.9)	6 (1.6)	5 (1.3)
Decreased appetite	0	1 (0.3)	0	1 (0.3)
Dehydration	5 (1.3)	4 (1.1)	4 (1.0)	3 (0.8)
Diabetes mellitus	1 (0.3)	0	0	0
Diabetic ketoacidosis	1 (0.3)	0	0	0
Electrolyte imbalance	1 (0.3)	0	0	0
Hyperglycaemia	0	3 (0.8)	0	0
Hypochloraemia	0	1 (0.3)	0	1 (0.3)
Hypokalaemia	2 (0.5)	2 (0.5)	1 (0.3)	0
Hyponatraemia	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Tumour lysis syndrome	1 (0.3)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0	0
Monarthritis	1 (0.3)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	2 (0.5)	0	0
Bladder cancer	0	1 (0.3)	0	0
Leukoerythroblastosis	0	1 (0.3)	0	0
Neoplasm malignant	1 (0.3)	0	0	0
Nervous system disorders	7 (1.8)	7 (1.8)	3 (0.8)	5 (1.3)
Amnesia	1 (0.3)	0	1 (0.3)	0
Ataxia	0	1 (0.3)	0	1 (0.3)
Cerebral ischaemia	1 (0.3)	0	1 (0.3)	0
Cerebrovascular accident	0	1 (0.3)	0	1 (0.3)
Convulsion	1 (0.3)	1 (0.3)	0	0
Dizziness	0	2 (0.5)	0	2 (0.5)
Haemorrhage intracranial	0	1 (0.3)	0	0
Headache	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Hemiparesis	0	1 (0.3)	0	0
Ischaemic stroke	0	1 (0.3)	0	1 (0.3)
Syncope	1 (0.3)	0	0	0
Transient ischaemic attack	1 (0.3)	0	0	0
Psychiatric disorders	1 (0.3)	1 (0.3)	0	0
Confusional state	1 (0.3)	0	0	0
Mental status changes	0	1 (0.3)	0	0

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Renal and urinary disorders	9 (2.3)	8 (2.1)	4 (1.0)	2 (0.5)
Anuria	2 (0.5)	0	1 (0.3)	0
Calculus ureteric	0	1 (0.3)	0	0
Haematuria	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Hydronephrosis	3 (0.8)	3 (0.8)	0	0
Hydroureter	1 (0.3)	0	0	0
Renal failure acute	2 (0.5)	0	1 (0.3)	0
Renal impairment	1 (0.3)	2 (0.5)	1 (0.3)	1 (0.3)
Ureteric obstruction	0	1 (0.3)	0	0
Ureteric stenosis	0	1 (0.3)	0	0
Reproductive system and breast disorders	1 (0.3)	0	0	0
Vaginal haemorrhage	1 (0.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	18 (4.7)	16 (4.2)	8 (2.1)	7 (1.8)
Acute respiratory distress syndrome	1 (0.3)	0	0	0
Cough	2 (0.5)	0	0	0
Dyspnoea	2 (0.5)	0	1 (0.3)	0
Epistaxis	2 (0.5)	0	1 (0.3)	0
Haemoptysis	1 (0.3)	0	0	0
Haemothorax	0	1 (0.3)	0	0
Pleural effusion	0	2 (0.5)	0	0
Pleurisy	0	1 (0.3)	0	0
Pneumonia aspiration	1 (0.3)	0	0	0
Pneumothorax	0	5 (1.3)	0	0
Pulmonary embolism	8 (2.1)	8 (2.1)	5 (1.3)	7 (1.8)
Pulmonary oedema	1 (0.3)	0	0	0
Respiratory disorder	1 (0.3)	0	0	0
Respiratory failure	1 (0.3)	0	1 (0.3)	0
Skin and subcutaneous tissue disorders	2 (0.5)	0	2 (0.5)	0
Decubitus ulcer	1 (0.3)	0	1 (0.3)	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	0	1 (0.3)	0
Social circumstances	1 (0.3)	0	0	0
Immobile	1 (0.3)	0	0	0
Surgical and medical procedures	0	1 (0.3)	0	0
Central venous catheter removal	0	1 (0.3)	0	0
Vascular disorders	17 (4.4)	10 (2.6)	10 (2.6)	4 (1.1)

Table 15. Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (As-Treated Population)

System Organ Class and Preferred Term	All-Causalities		Treatment-Related	
	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)	FOLFIRI + Sunitinib (Arm A) N=384 n (%)	FOLFIRI + Placebo (Arm B) N=379 n (%)
Axillary vein thrombosis	1 (0.3)	0	1 (0.3)	0
Circulatory collapse	1 (0.3)	0	0	0
Deep vein thrombosis	6 (1.6)	3 (0.8)	4 (1.0)	1 (0.3)
Embolism	1 (0.3)	0	1 (0.3)	0
Hypertension	2 (0.5)	0	1 (0.3)	0
Hypotension	1 (0.3)	3 (0.8)	0	2 (0.5)
Jugular vein thrombosis	0	2 (0.5)	0	1 (0.3)
Peripheral ischaemia	1 (0.3)	0	0	0
Phlebitis	1 (0.3)	0	1 (0.3)	0
Subclavian vein thrombosis	1 (0.3)	1 (0.3)	0	0
Thrombophlebitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Thrombosis	1 (0.3)	1 (0.3)	1 (0.3)	0

Except for the number of adverse events, subjects were counted only once per treatment in each cell.
N = number of subjects, n = number of subjects fitting specified criteria; SAE = serious adverse event.

Deaths: Summary of deaths by treatment arm for the AT population is presented in Table 16.

Table 16. Summary of Deaths (As-Treated Population)

Summary of Deaths	FOLFIRI + Sunitinib (Arm A) (N=384) n (%)	FOLFIRI + Placebo (Arm B) (N=379) n (%)
Subjects who died	166 (43.2)	148[a] (39.1)
Subjects who died on-study[a,b]	33 (8.6)	17 (4.5)[a]
Disease under study	11 (2.9)	9 (2.4)
Study treatment toxicity	13 (3.4)	2 (0.5)
Unknown	2 (0.5)	1 (0.3)
Other	8 (2.1)	5 (1.3)
Subjects who died during follow-up[c]	133 (34.6)	131 (34.6)
Disease under study	129 (33.6)	124 (32.7)
Study treatment toxicity	1 (0.3)	0
Unknown	1 (0.3)	4 (1.1)
Other	2 (0.5)	4 (1.1)

N = number of subjects; n = number of subjects fitting specified criteria.

a. An additional subject had a Grade 5 adverse event (ie, 18 [4.7%] subjects in Arm B).
b. On-treatment deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug. Subjects may have had >1 cause of death specified.
c. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug. Subjects may have had >1 cause of death specified.

Permanent discontinuations: AEs leading to discontinuation of study treatment or the AT-population are summarized in Table 17.

Table 17. Summary of AEs Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Terms (As-Treated Population)

System Organ Class Preferred Term	Arm A (N=384) n (%)	Arm B (N=379) n (%)
Any AEs	115 (29.9)	54 (14.2)
Blood and lymphatic system disorders	29 (7.6)	3 (0.8)
Anaemia	4 (1.0)	1 (0.3)
Febrile neutropenia	6 (1.6)	1 (0.3)
Granulocytopenia	2 (0.5)	0
Leukopenia	2 (0.5)	0
Neutropenia	13 (3.4)	1 (0.3)
Pancytopenia	1 (0.3)	0
Thrombocytopenia	3 (0.8)	0
Cardiac disorders	7 (1.8)	6 (1.6)
Acute myocardial infarction	1 (0.3)	1 (0.3)
Atrial fibrillation	1 (0.3)	2 (0.5)
Cardiac arrest	1 (0.3)	1 (0.3)
Cardiac failure	0	1 (0.3)
Cardiac failure congestive	1 (0.3)	0
Cardiopulmonary failure	0	1 (0.3)
Left ventricular dysfunction	1 (0.3)	0
Myocardial infarction	2 (0.5)	0
Pericardial effusion	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)
Ear and labyrinth disorders	1 (0.3)	0
Vertigo	1 (0.3)	0
Gastrointestinal disorders	31 (8.1)	18 (4.7)
Abdominal pain	1 (0.3)	1 (0.3)
Abdominal pain lower	1 (0.3)	0
Ascites	2 (0.5)	1 (0.3)
Colonic obstruction	1 (0.3)	0
Diarrhoea	8 (2.1)	2 (0.5)
Dysphagia	1 (0.3)	0
Gastrointestinal haemorrhage	1 (0.3)	0
Gastrointestinal hypomotility	1 (0.3)	0
Gastrooesophagitis	1 (0.3)	0
Ileus	0	1 (0.3)
Intestinal obstruction	3 (0.8)	1 (0.3)
Large intestine perforation	2 (0.5)	0
Mechanical ileus	1 (0.3)	0
Nausea	1 (0.3)	3 (0.8)
Oesophagitis	1 (0.3)	0
Proctalgia	0	1 (0.3)
Rectal haemorrhage	2 (0.5)	0
Reflux oesophagitis	0	1 (0.3)
Retching	0	1 (0.3)
Small intestinal obstruction	1 (0.3)	1 (0.3)
Stomatitis	2 (0.5)	2 (0.5)
Vomiting	4 (1.0)	5 (1.3)
General disorders and administration site conditions	23 (6.0)	7 (1.8)
Asthenia	2 (0.5)	2 (0.5)
Catheter thrombosis	1 (0.3)	0
Chest pain	2 (0.5)	0
Death	1 (0.3)	3 (0.8)
Disease progression	5 (1.3)	0
Fatigue	5 (1.3)	1 (0.3)
General physical health deterioration	3 (0.8)	1 (0.3)
Mucosal inflammation	4 (1.0)	0
Pyrexia	2 (0.5)	0

Table 17. Summary of AEs Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Terms (As-Treated Population)

System Organ Class Preferred Term	Arm A (N=384) n (%)	Arm B (N=379) n (%)
Hepatobiliary disorders	3 (0.8)	2 (0.5)
Hepatotoxicity	1 (0.3)	0
Hyperbilirubinaemia	2 (0.5)	1 (0.3)
Jaundice cholestatic	0	1 (0.3)
Immune system disorders	0	1 (0.3)
Anaphylactic reaction	0	1 (0.3)
Infections and infestations	10 (2.6)	5 (1.3)
Anal abscess	1 (0.3)	0
Fungal infection	1 (0.3)	0
Lower respiratory tract infection	1 (0.3)	0
Neutropenic sepsis	1 (0.3)	1 (0.3)
Orchitis	1 (0.3)	0
Pneumonia	1 (0.3)	3 (0.8)
Retroperitoneal abscess	0	1 (0.3)
Sepsis	2 (0.5)	0
Septic shock	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	0
Therapeutic agent toxicity	1 (0.3)	0
Investigations	2 (0.5)	2 (0.5)
Aspartate aminotransferase increased	1 (0.3)	0
Electrocardiogram ST segment depression	1 (0.3)	0
Renal function test abnormal	0	1 (0.3)
Weight decreased	0	1 (0.3)
Metabolism and nutrition disorders	3 (0.8)	1 (0.3)
Decreased appetite	1 (0.3)	0
Dehydration	1 (0.3)	0
Hypokalaemia	0	1 (0.3)
Tumour lysis syndrome	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0
Neoplasm malignant	1 (0.3)	0
Nervous system disorders	4 (1.0)	5 (1.3)
Cerebral ischaemia	1 (0.3)	0
Cerebrovascular accident	0	1 (0.3)
Convulsion	1 (0.3)	1 (0.3)
Haemorrhage intracranial	0	1 (0.3)
Hemiparesis	0	1 (0.3)
Ischaemic stroke	0	1 (0.3)
Lethargy	1 (0.3)	1 (0.3)
Neuropathy peripheral	1 (0.3)	0
Renal and urinary disorders	4 (1.0)	0
Anuria	1 (0.3)	0
Renal failure acute	2 (0.5)	0
Renal impairment	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	8 (2.1)	5 (1.3)
Acute respiratory distress syndrome	1 (0.3)	0
Haemoptysis	1 (0.3)	0
Pleurisy	0	1 (0.3)
Pulmonary embolism	4 (1.0)	4 (1.1)
Pulmonary oedema	1 (0.3)	0
Respiratory failure	1 (0.3)	0
Skin and subcutaneous tissue disorders	6 (1.6)	0
Hyperhidrosis	1 (0.3)	0
Palmar-plantar erythrodysaesthesia syndrome	4 (1.0)	0
Rash	1 (0.3)	0

Table 17. Summary of AEs Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Terms (As-Treated Population)

System Organ Class Preferred Term	Arm A (N=384) n (%)	Arm B (N=379) n (%)
Skin lesion	1 (0.3)	0
Surgical and medical procedures	1 (0.3)	0
Malignant tumour excision	1 (0.3)	0
Vascular disorders	7 (1.8)	5 (1.3)
Deep vein thrombosis	1 (0.3)	3 (0.8)
Embolism	1 (0.3)	0
Hypertension	2 (0.5)	0
Hypotension	1 (0.3)	1 (0.3)
Jugular vein thrombosis	0	1 (0.3)
Thrombosis	2 (0.5)	0

Treatment-emergent AEs defined as all AEs that occurred on or after the first dose of study treatment were included in the table. Except for the number of adverse events, subjects were counted only once per treatment in each cell.
AE = adverse event; N = number of subjects; n = number of subjects fitting specified criteria.

Temporary Discontinuation: Summary of AEs resulting in dose modification or temporary discontinuation of sunitinib or placebo experienced by ≥3% of subjects by treatment arm (AT-population) is presented in Table 18.

Table 18. Summary of Adverse Events Resulting in Dose Modification or Temporary Discontinuation of Sunitinib/Placebo Experienced by ≥3% of Subjects by Preferred Term (All Causalities); (As-Treated Population)

MedDRA Preferred Term	FOLFIRI + Sunitinib (Arm A) (N=384)		FOLFIRI + Placebo (Arm B) (N=379)	
	n (%)	Number of Events	n (%)	Number of Events
Any AEs	246 (64.1)	863	140 (36.9)	308
Anemia	25 (6.5)	38	10 (2.6)	15
Febrile neutropenia	19 (4.9)	19	5 (1.3)	7
Leukopenia	33 (8.6)	39	11 (2.9)	14
Neutropenia	137 (35.7)	242	46 (12.1)	59
Thrombocytopenia	37 (9.6)	52	1 (0.3)	1
Diarrhea	43 (11.2)	51	20 (5.3)	25
Vomiting	19 (4.9)	22	14 (3.7)	16
Fatigue	18 (4.7)	22	5 (1.3)	5
Pyrexia	17 (4.4)	17	10 (2.6)	12
Mucosal inflammation	14 (3.6)	19	1 (0.3)	1
Palmar-plantar erythrodysesthesia syndrome	24 (6.3)	47	1 (0.3)	3

Treatment-emergent AEs defined as all AEs that occurred on or after the first dose of study treatment were included in this table. Except for the number of AEs, subjects were counted only once per treatment in each cell.
MedDRA (v12.1) coding dictionary applied.
AE = adverse event, FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU), MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects fitting specified criteria.

Summary of AEs resulting in dose modification or temporary discontinuation of FOLFIRI experienced by ≥3% of subjects by treatment arm (AT-population) is presented in Table 19.

Table 19. Summary of Adverse Events Resulting in Dose Modification or Temporary Discontinuation of FOLFIRI Experienced by ≥3% of Subjects by Preferred Term (All Causalities); As-Treated Population

MedDRA Preferred Term	FOLFIRI + Sunitinib (Arm A) (N=384)		FOLFIRI + Placebo (Arm B) (N=379)	
	n (%)	Number of Events	n (%)	Number of Events
Any AE	349 (90.9)	2129	253 (66.8)	866
Anemia	47 (12.2)	77	17 (4.5)	23
Febrile neutropenia	22 (5.7)	25	8 (2.1)	10
Leukopenia	66 (17.2)	131	27 (7.1)	46
Neutropenia	288 (75.0)	1082	143 (37.7)	400
Thrombocytopenia	83 (21.6)	160	5 (1.3)	14
Abdominal pain	13 (3.4)	14	4 (1.1)	6
Diarrhea	72 (18.8)	109	34 (9.0)	41
Nausea	19 (4.9)	19	10 (2.6)	11
Vomiting	24 (6.3)	33	17 (4.5)	18
Fatigue	30 (7.8)	42	11 (2.9)	11
Mucosal inflammation	21 (5.5)	28	3 (0.8)	3
Pyrexia	34 (8.9)	34	19 (5.0)	24
Palmar-plantar erythrodysesthesia syndrome	14 (3.6)	25	3 (0.8)	5

Treatment-emergent AEs defined as all AEs that occurred on or after the first dose of study treatment were included in this table. Except for the number of AEs, subjects were counted only once per treatment in each cell. MedDRA (v12.1) coding dictionary applied.
AE = adverse event; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil (5-FU), MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects fitting specified criteria.

CONCLUSIONS:

- The addition of sunitinib to FOLFIRI did not demonstrate the prespecified improvement in prolonging the PFS in the first-line treatment of subjects with mCRC and the study was stopped prematurely after the second interim analysis due to futility of reaching the primary superiority endpoint. At the final analysis, median PFS was 33.6 weeks (FOLFIRI + sunitinib [Arm A]) versus 36.6 weeks (FOLFIRI + placebo [Arm B]), corresponding to a hazard ratio for PFS of 1.095 (95% CI 0.892, 1.344; p=0.8072) based on the blinded independent central radiologist assessment.

- The OS was similar between the 2 treatment arms, with a median OS of 87.9 weeks (Arm A) versus 85.9 weeks (Arm B) and corresponding hazard ratio of 1.171 (95% CI [0.936, 1.466]) and p-value of 0.9163.

- The ORR was similar between the 2 treatment arms, with an ORR of 32.1% (Arm A) versus 33.5% (Arm B) based on the blinded independent central radiologist assessment.

- The DR was shorter on FOLFIRI + sunitinib than on FOLFIRI + placebo, with a median of 30.1 weeks vs 39.0 weeks, respectively, based on the blinded independent central radiologist assessment.

- The AEs reported in the FOLFIRI + sunitinib arm were generally tolerable and manageable by dosing interruption, dose delay, dose reduction, and/or standard medical therapy, with neutropenia, nausea, diarrhea, and vomiting being the most commonly reported.

- The addition of sunitinib to FOLFIRI for subjects who presented with mCRC did not appear to adversely impact subjects' health-related quality of life or health state utilities as observed within the treatment arms.