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

PROTOCOL NO.: A6181104

PROTOCOL TITLE: A Randomized, Phase 2b Study of Sunitinib Plus oxaliplatin, 5-Fluorouracil and Leucovorin (FOLFOX) Versus Bevacizumab Plus FOLFOX as First-Line Treatment in Patients With Metastatic Colorectal Cancer

Study Center(s): 51 centers took part in the study and randomized subjects; 35 in the United States (US), 7 in Germany, 6 in Japan and 3 in Denmark.

Study Initiation Date and Primary Completion or Final Completion Dates:
First Subject First Visit: 23 April 2008, Last Subject Visit: 06 July 2011, Primary Completion Date: The study was terminated prematurely, based on an interim analysis with a June 2009 data cut-off and additional data analysis with a cut-off date of 01 February 2010 (study did not meet its primary endpoint to demonstrate a statistically significant improvement in progression-free survival (PFS). The cut-off date for this Final Analysis was 01 June 2011.

Phase of Development: Phase 2b

Study Objectives:

Primary Objective: To demonstrate an improvement in PFS in subjects with metastatic colorectal cancer **(**mCRC) treated with sunitinib plus FOLFOX compared with bevacizumab plus FOLFOX in the first-line treatment setting.

Secondary Objectives:

- To compare the overall survival (OS) in subjects with mCRC treated with sunitinib plus FOLFOX versus bevacizumab plus FOLFOX in the first-line treatment setting.
- To compare the objective response rate (ORR) and duration of response (DR) in subjects with mCRC treated with sunitinib plus FOLFOX versus bevacizumab plus FOLFOX in the first-line treatment setting.
- To compare the safety and tolerability of sunitinib plus FOLFOX versus that of the bevacizumab plus FOLFOX combination.
- To compare patient reported outcomes (PROs) of subjects with mCRC treated with sunitinib plus FOLFOX versus bevacizumab plus FOLFOX in the first-line treatment setting.

METHODS

Study Design:

This was a stratified, randomized (1:1 ratio), multicenter, open-label, parallel-group, Phase 2b study comparing the efficacy and safety of sunitinib plus FOLFOX versus bevacizumab plus FOLFOX in the first-line treatment of subjects with mCRC.

Eligible subjects were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), lactate dehydrogenase (LDH) (>1.5 versus ≤1.5 times the upper limit of normal [ULN]), and prior adjuvant treatment (yes versus no). Crossover between treatment arms was not permitted. FOLFOX was administered every 2 weeks using the modified FOLFOX6 (mFOLFOX6) regimen of infusional 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. For Treatment A, sunitinib was administered orally on a 4 weeks on, 2 weeks off dosing regimen (Schedule 4/2) at a starting dose of 37.5 mg daily. For Treatment B, bevacizumab was administered as an intravenous infusion (IV) at a dose of 5 mg/kg every 2 weeks.

Subjects remained on study until disease progression or unacceptable toxicity. However, subjects were allowed to continue treatment as assigned at randomization beyond the time of RECIST-defined progression, at the discretion of the Investigator, if there was evidence of clinical benefit to justify continuation in the study.

Subjects who discontinued oxaliplatin due to oxaliplatin-related toxicity continued therapy with 5-FU /leucovorin plus sunitinib or bevacizumab. Subjects who discontinued treatment with mFOLFOX6 prior to disease progression continued treatment with sunitinib or bevacizumab as assigned at randomization. Subjects who discontinued all treatment prior to disease progression were followed for disease progression until the initiation of a subsequent anticancer therapy in the absence of documented disease progression, or until death, whichever occurred first. Subjects were followed for OS until death.

The schedule of study activities is summarized in Table 1.

Table 1. Schedule of Activities

	Scr	Day 1 of Each Cycle (Cycle = 2 weeks)						Post-Trt		
Protocol Activities and Forms to be Completed[a]	**≤21 Days Prior to Dosing**	**C-1, 7, 13, etc[b] (-1)**	**C-2, 8, 14, etc (-1)**	**C-3, 9, 15, etc (-1)**	**C-4, 10, 16, etc (-1)**	**C-5, 11, 17, etc (-1)**	**C-6, 12, 18, etc (-1)**	**EOT/ Withdrawal[c]**	**Post-Trt[d]**	**Survival F/U**
Baseline Documentation										
Informed consent	X									
Medical/oncological history[e]	X									
Physical examination[f]	X	(X)	X	X	X	X	X	X		
ECOG, body weight, and Vital signs[f]	X	X	X	X	X	X	X	X		
Baseline signs/symptoms		X								
Laboratory studies[g]										
Hematology, blood chemistry	X	(X)	X	X	X	X	X	X		
Coagulation[h]	X									
TSH[h]	X									
CEA[i]	X	(X)	X	X	X	X	X	X		
Urine protein: creatinine ratio[j]	X	(X)		X		X		X		
Pregnancy test[k]	X									
12-lead ECG[l]	X		Cycle 2 only							
MUGA or ECHO scan[m]	X									
Study randomization[n]	X									
Trt Arm A – Sunitinib[o]		X→	X→	off	X→	X→	off			
Trt Arm B – Bevacizumab[p]		X	X	X	X	X	X			
Trt – mFOLFOX6[q]		X	X	X	X	X	X			
Tumor Assessments										
Tumor imaging[r, s]	X	Every 8 weeks for 18 months, then every 12 weeks thereafter						X	(X)	
Bone scan[t]	(X)	Same as above, if bone metastases are present at screening						(X)	(X)	
Brain CT or MRI scan[u]	X	(X)						(X)		
Other Clinical Assessments										
Adverse events[v]	X	X	X	X	X	X	X	X	X	
Concomitant medications/treatments[w]	X	X	X	X	X	X	X	X	X	
Study drug compliance[x]				X			X	X		
Post-study survival status[y]										X
Sample banking for exploratory research[z]	(X)	(X)	(X)							
Patient Reported Outcomes										
FACT-C + FACT & GOG-Ntx[aa]		X			X			X		

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( )=if applicable
C=cycle, CEA=Carcinoembryonic antigen, CT=computed tomography, ECG=electrocardiogram, ECHO=echocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, FACT-C=Functional Assessment of Cancer Treatment–Colorectal, FACT & GOG-Ntx=Functional Assessment of Cancer Treatment–Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity, F/U=Follow-up, mFOLFOX6=modified FOLFOX6, MRI=magnetic resonance imaging, MUGA=multiple gated acquisition, PD=Progressive disease, QTc=corrected QT interval, Scr=screening, Trt=treatment, TSH=thyroid-stimulating hormone.

a. Schedule of Assessments: All assessments were performed prior to dosing with study medications unless otherwise indicated. Each cycle was 2-weeks in duration. Subjects discontinuing all treatment prior to disease progression (PD) returned to the clinic at 8-week intervals for disease assessments.

b. Day 1 Cycle 1 Assessments: Physical examination and laboratory assessments needed not be obtained on Day 1 if Screening assessments had been performed within 7-days prior to the start of treatment.

c. EOT/Withdrawal: These assessments did not need to be completed if they were performed within the previous 2-weeks on study (within the last 8-weeks for tumor assessments).

d. Post-Treatment F/U: Subjects discontinuing all treatment prior to PD were followed for tumor assessments until PD, until the initiation of a subsequent anticancer therapy in the absence of documented PD, or until death, whichever occurred first. Subjects were evaluated for safety up to 28-days after the last dose of study treatment. Adverse events were followed up until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Refer to the protocol for specific guidelines.

e. Medical/Oncological History: Included oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.

f. Physical Examination: Examination of major body systems, ECOG performance status, body weight, height (at Screening only), and vital signs. Body weight was recorded prior to each treatment with mFOLFOX6 or bevacizumab. Post-treatment physical examinations were for the purpose of disease assessment and safety F/U (vital signs and body weight were not required).

g. Laboratory Studies: All laboratory assessments were performed by a central laboratory, with the exception of the pregnancy test.

h. Coagulation and TSH: Collected at screening, then as clinically indicated thereafter.

i. CEA: Collected at screening, at the start of each new cycle, and at the EOT/withdrawal visit.

j. Urine Protein:Creatinine Ratio: Collected at screening, at the start of study treatment, every 2 cycles thereafter, and at the EOT/withdrawal visit.

k. Pregnancy Test: Serum or urine test were performed for all women of childbearing potential at the local laboratory.

l. ECG: Three consecutive 12-lead ECGs approximately 2 minutes apart at screening and on Cycle 2 Day 1 to determine the mean QTc interval. If the mean QTc interval was prolonged (>500 msec), the ECGs was overread by a cardiologist at the site for confirmation. Additional ECGs were performed as clinically indicated, including after intrasubject dose adjustments.

m. MUGA or ECHO Scan: Were performed at screening and as clinically indicated thereafter.

n. Study Randomization: Subject number and treatment assignment were obtained via centralized randomization.

o. Study Trt Arm A (sunitinib): Treatment with sunitinib occured in 6-week intervals: 4 weeks on, 2 weeks off, overlapping with three 2-week cycles of mFOLFOX6.

p. Study Trt Arm B (bevacizumab): Subjects received bevacizumab as 90 minutes infusions every 2 weeks after completion of the oxaliplatin, leucovorin, and bolus 5-FU infusions. If the 90-minute infusion was well tolerated, all subsequent infusions were administered over 60- and then 30-minute infusions, or as per Investigator’s clinical practice.

q. Study Treatment (mFOLFOX6): Subjects received mFOLFOX6 as short infusions of oxaliplatin and leucovorin, and a bolus of 5-FU on Day 1 followed by infusional 5-FU throughout Days 1 and 2 of each 2-week cycle. If oxaliplatin was discontinued because of oxaliplatin-related toxicity, treatment with 5-FU/leucovorin and either sunitinib or bevacizumab wascontinued on the same schedule. If all treatment with mFOLFOX6 were discontinued prior to PD, treatment with sunitinib or bevacizumab was continued on the same schedule until PD.

r. Allowable window for tumor assessment imaging studies ±7 days. Prestudy tumor assessment was performed up to 4 weeks prior to enrollment.

s. Tumor Imaging: CT or MRI scans of the chest, abdomen and pelvis and any other applicable sites of disease at screening, every 8 weeks (±1 week) independent of cycle length for 18 months, then every 12 weeks thereafter, whenever

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disease progression is suspected, to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the EOT/withdrawal visit. Note that tumor imaging continued on this calendar schedule regardless of any delays in dosing. All imaging studies indicating response or disease progression were objectively verified by an independent third-party core imaging laboratory as described in the protocol.

t. Bone Scan: Was only performed at screening if bone metastases were suspected. Known or treated bone metastases were followed with repeat scans on the same days when tumor imaging was performed.

u. Brain Scan: Was Required at screening to confirm eligibility. Repeat brain scans were required on study if new metastases were suspected.

v. Adverse Events: Subjects were followed for adverse events from the first day of study treatment until at least 28 days after the last dose of study treatment, 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 monitored and reported from the time the subject provides informed consent as described in the protocol.

w. Concomitant Medications/Treatments: Concomitant medications and treatments were recorded from 30 days prior to the start of study treatment, during the study, and up to 28 days after the last dose of study treatment.

x. Study Drug Compliance: Sunitinib drug compliance was performed every 3 cycles, starting with Cycle 3, and at the EOT/withdrawal visit.

y. Post-Study Survival Status: After discontinuation of study treatment, follow-up survival information, including follow-up surgery, radiation, and/or systemic therapy, were collected by clinic visit or telephone contact every 2 months until death.

z. Sample Banking for Exploratory Research (optional): Please refer to the Molecular Profiling Supplement in the protocol for details.

aa. FACT-C and FACT&GOG-Ntx questionnaires: Self-administered at the clinic PRIOR to dosing or other clinical activities on Cycle 1 Day 1, every 3 cycles thereafter (eg, Cycle 4 Day 1, Cycle 7 Day 1, etc), and at the EOT/withdrawal.

Number of Subjects (Planned and Analyzed):

A total sample size of approximately 290 subjects (145 subjects per treatment arm) was planned for this multi-center study conducted in the US, Germany, Denmark, and Japan. The full analysis (FA) population of 191 subjects included all subjects who were randomized, and the per protocol (PP) population of 189 subjects included all randomized subjects that did receive at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects had histologically or cytologically confirmed adenocarcinoma of the colon or rectum, with locally advanced or documented metastatic disease, evidence of unidimensionally measurable disease, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), and age of 18 years or older, ECOG performance status of 0 or 1.

Excluded were subjects with previous treatment with sunitinib, bevacizumab, or any other systemic therapy for locally advanced or mCRC; ≤6 months since completion of adjuvant chemotherapy to documentation of recurrent disease, known dihydropyrimidine dehydrogenase deficiency or severe hypersensitivity reaction to 5-FU, history of or ongoing cardiac disease, cerebrovascular accident or transient ischemic attack ≤6 months prior to

study drug administration, and history of or known brain metastases, spinal cord compression, or carcinomatous meningitis.

Study Treatment:

All subjects received treatment with FOLFOX. FOLFOX was administered every 2 weeks (ie, cycle) using the mFOLFOX6 regimen consisting of oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 (or 200 mg/m^2 of l-leucovorin) as a 2-hour IV infusion followed by an IV bolus of 5-FU 400 mg/m^2 and an infusion of 5-FU 2,400 mg/m^2 over 46 hours.

Treatment A: Sunitinib was self-administered on an outpatient basis, once daily in the morning without regard to meals, except on the days when the mFOLFOX6 regimen was administered. On those days, sunitinib was taken in clinic immediately before the start of the chemotherapy infusion. Sunitinib was administered orally on a 4 weeks on, 2 weeks off intermittent dosing regimen (Schedule 4/2), at a starting dose of 37.5 mg daily, with the opportunity to dose escalate to 50 mg on Schedule 4/2, at the Investigator's discretion, and overlapping with 3 cycles of mFOLFOX6. Dose reductions of sunitinib based on CTCAE grades were predefined in the protocol.

Treatment B: Bevacizumab was administered as IV at a dose of 5 mg/kg over 30-90 minutes every 2 weeks.

Efficacy Endpoints:

Primary Endpoint:

- PFS.

Secondary Endpoints:

- OS and 1- and 2-year survival rates.
- Objective response rate (ORR) and duration of response (DR).

Safety Endpoints:

- Type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities.
- Other Safety Measures included Physical Examination, Vital Signs, Electrocardiogram, MUGA scan or ECHO, and ECOG Performance Status Scale.
- Patient Reported Outcomes (PROs) of health-related quality of life and colorectal cancer-related symptoms, assessed by the self-administered questionnaires Functional Assessment of Cancer Treatment-Colorectal (FACT-C) and the Functional Assessment of Cancer Treatment-Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity (FACT&GOG-Ntx) neuropathy sub-scale.

Statistical Methods:

The determination of antitumor efficacy was based on objective tumor assessments made according to the RECIST system of unidimensional evaluation and assessed by an independent core imaging laboratory.

Time-to-Event Endpoints: For the purpose of endpoint definitions, the term "on-study" included the period of study treatment plus 28 days following the last dose.

Primary Endpoint:

PFS was defined as the time from randomization to first documentation of objective tumor progression, or to death on-study due to any cause, whichever occurred first. PFS was summarized in the FA population using Kaplan-Meier methods and displayed graphically where appropriate. The median time-to-event for PFS with hazard ratio and 2-sided 95% confidence interval (CI) was estimated. For PFS in the PP population, a stratified log-rank test (1-sided, α=0.05) based on randomization stratification factors was used to compare PFS between the 2 treatment arms.

Secondary Endpoints:

OS was defined as the time from randomization to date of death due to any cause.

ORR and DR: ORR was defined as the percent of subjects with confirmed complete response (CR) or partial response (PR) according to RECIST, relative to the FA population. Confirmed responses were those that persisted on repeat imaging study ≥4 weeks after initial documentation of response. Designation of best response of stable disease (SD) required the criteria to be met at least 8 weeks after randomization. DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of tumor progression or death due to any cause. DR was only calculated for the subgroup of subjects with objective response.

Safety Evaluations:

Assessment of AEs and serious AEs (SAEs) included type, incidence, severity (graded by the NCI CTCAE, Version 3.0), timing, seriousness, and relatedness; and laboratory abnormalities. The PP population was the primary population for evaluating safety.

Baseline tumor-related signs and symptoms were recorded as AEs during the trial if they worsen in severity or increase in frequency. Progression of the malignancy under study (including signs and symptoms of progression) was not reported as a SAE unless the outcome was fatal during the study or within the safety-reporting period. Hospitalization due to signs and symptoms of disease progression were not reported as SAE. If the malignancy had a fatal outcome during the study or within the safety reporting period, then the event leading to death was recorded as an SAE with CTC Grade 5.

Other Safety Measures and PROs were analyzed using descriptive statistical methods and change from baseline calculations.

RESULTS

Subject Disposition and Demography: Of the 191 subjects in the study, 96 were randomized to the sunitinib treatment arm and 95 to the bevacizumab treatment arm (Table 2). Because the study did not meet its primary endpoint and was closed early, the number of subjects that withdrew from the study in each arm was 100%. Most subjects (≥15% per treatment arm) withdrew due to objective progression or relapse (49.0% on sunitinib, 43.2% on bevacizumab), refusal to continue treatment not due to AE (21.1% on bevacizumab), and study termination (16.7% on sunitinib). Most subjects were white (69.1%; 64.4% male and 35.6% female). The mean age of subjects was 59.9 years (SD: 10.06 years) distribution of age, weight, and height was comparable for both treatment groups. Slightly more Asians (21.9% versus 12.6 %) were assigned to sunitinib compared with bevacizumab.

Table 2. Subject Evaluation Groups

Number (%) of Subjects	Sunitinib +mFOLFOX6	Bevacizumab +mFOLFOX6	Total
Randomized	96 (100)	95 (100)	191(100.0)
Withdrawals	96 (100)	95 (100)	
Primary reason for withdrawal from study[a]			
Objective progression or relapse	47 (49.0)	41 (43.2)	88 (46.1)
Global deterioration of health status	6 (6.3)	2 (2.1)	8 (4.2)
Adverse event	14 (14.6)	10 (10.5)	24 (12.6)
Subject died	1 (1.0)	4 (4.2)	5 (2.6)
Lost to follow-up	0	0	0
Withdrawn due to pregnancy	0	0	0
Study terminated by sponsor	16 (16.7)	3 (3.2)	19 (9.9)
Subject refused continued treatment for reason other than adverse event	4 (4.2)	20 (21.1)	24 (12.6)
Other	7 (7.3)	14 (14.7)	21 (11.0)

a. The study did not meet its primary endpoint and was closed early. Therefore, the number of subjects that withdrew from the study in each arm was 100%.

Efficacy Results:

Primary Evaluation: The study did not meet its primary endpoint and was closed early.

PFS: Overall 27 (28.1%) subjects on sunitinib had either objective progression (24 subjects [25.0%]) or death without objective progression (3 subjects, [3.1%]) and 13 (13.7%) subjects on bevacizumab had either objective progression (10 subjects, [10.5%]) or death without objective progression (3 subjects, [3.2%]) (Table 3).

Table 3. Progression Free Survival - Full Analysis Set

	Sunitinib + mFOLFOX6 N=96 n (%)	Bevacizumab + mFOLFOX6 N=95 n (%)
Number of subjects with event n (%)	27 (28.1)	13 (13.7)
Type of Progression		
Objective progression	24 (25.0)	10 (10.5)
Death without objective progression	3 (3.1)	3 (3.2)
Number censored	69 (71.9)	82 (86.3)
Reason for censorship		
In follow-up for progression or declared progression by Investigator	55 (57.3)	56 (58.9)
Withdrew consent for additional follow-up	4 (4.2)	17 (17.9)
Lost to follow-up	1 (1.0)	0 (0.0)
After the 28-day of the last dose	4 (4.2)	2 (2.1)
Started new treatment without progression	5 (5.2)	7 (7.4)
Kaplan-Meier estimate of time to event (Weeks) Quartiles (95% CI)[a]		
25%	25.8 (25.1, 40.0)	41.6 (32.3, 67.0)
50%	40.5 (39.5, 44.2)	67.0 (41.6, 67.0)
75%	48.3 (40.6, --)	67.0 (--, --)
Range	(8.3, 48.3)	(8.0, 67.0)
Stratified Analysis:		
Hazard Ratio (Sunitinib versus Bevacizumab)[b]		2.705
95% Confidence Interval for Hazard Ratio		1.3, 5.8
P-value[c]		0.9963
Unstratified Analysis:		
Hazard Ratio (Sunitinib versus Bevacizumab)[b]		2.4
95% Confidence Interval for Hazard Ratio		1.2, 4.7
P-value[d]		0.9949

ECOG=Eastern Cooperative Oncology Group, LDH=lactate dehydrogenase, N=number of subjects per treatment group, n=number of subjects with observation, ULN=upper limit of normal

a. Based on the Brookmeyer and Crowley method.

b. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate favor of Sunitinib + mFOLFOX6; a hazard ratio >1 indicates a reduction in hazard rate in favor of bevacizumab + mFOLFOX6.

c. P-value is from a 1-sided, log-rank test stratified for ECOG Performance Status (0 versus 1), Baseline LDH: >1.5 versus ≤1.5 × ULN, and Prior Adjuvant Treatment (yes versus no).

d. P-value is from a 1-sided, unstratified log-rank test.

Secondary Evaluations:

OS: The OS curve was not mature at the time of analysis and OS could not be determined for both arms of the study (see Table 4).

Table 4. Overall Survival - Full Analysis Set

	Sunitinib + mFOLFOX6 N=96 n (%)	Bevacizumab + mFOLFOX6 N=95 n (%)
Patients Status [n (%)]		
Dead	26 (27.1)	15 (15.8)
Alive	70 (72.9)	80 (84.2)
Time to Death (Weeks)		
Quartile (95% Confidence Interval)		
25%	57.4 (44.00, --)	(50.10, --)
50%	84.3 (84.30, --)	(--, --)
75%	(84.30, --)	(--, --)
Range	(8.30, 84.30)	(9.80, 70.90)
Stratified Analysis:		
Hazard Ratio (Sunitinib versus bevacizumab)[a]		1.618
95% Confidence Interval for Hazard Ratio		0.845, 3.096
P-value[b]		0.9289
Unstratified Analysis:		
Hazard Ratio (Sunitinib versus bevacizumab)[a]		1.608
95% Confidence Interval for Hazard Ratio		0.851, 3.038
P-value[c]		0.9303

N=number of subjects per treatment group, n=number of subjects with observation

a. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of SUNITINIB + mFOLFOX6; a hazard ratio >1 indicates a reduction in hazard rate in favor of BEVACIZUMAB + mFOLFOX6

b. P-value was from a 1-sided, log-rank test stratified for ECOG Performance Status (0 versus 1), Baseline LDH: >1.5 vs. <=1.5 x ULN. and Prior Adjuvant Treatment (yes versus no)

c. Log-rank test statistic and p-value are from a 1-sided, unstratified log-rank test

ORR: One subject (1.0%) had a complete response in the sunitinib arm of the study, 39 subjects (40.6%) had partial response, and 43 subjects (44.8%) had stable disease (Table 5).

Table 5. Overall Objective Response Rate – Full Analysis Set

	Sunitinib + mFOLFOX6 N=96 n (%)	Bevacizumab + mFOLFOX6 N=95 n (%)
Subjects with baseline assessment n (%)	91 (94.8)	90 (94.7)
Subjects with measurable disease at baseline n (%)	91 (94.8)	90 (94.7)
Best overall response n (%)[a]		
Complete response (CR)	1 (1.0)	1 (1.1)
Partial response (PR)	39 (40.6)	35 (36.8)
Stable disease (SD)	43 (44.8)	53 (55.8)
Progressive disease (PD)	3 (3.1)	1 (1.1)
Indeterminate	0 (0.0)	0 (0.0)
Not evaluable[b]	0 (0.0)	0 (0.0)
Missing	5 (5.2)	0 (0.0)
Objective response (rate) (CR + PR), n (%)[a]	40 (41.7)	36 (37.9)
95% exact confidence interval (%)[b]	(33.6,54.8)	(29.8,50.9)
Treatment Difference (Sunitinib versus bevacizumab) (%)[a]		3.956
95% Confidence Interval of Difference (%)		(-10.4, 18.3)
P-value[c]		0.5898

N=number of subjects per treatment group, n=number of subjects with response.
a. % = (n/N) × 100. Baseline assessment is 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 is from a Chi-square test

Safety Results:

Overview of Safety Results: Safety was analyzed for the per-protocol population, which consisted of 96 subjects in the sunitinib arm and 93 subjects in the bevacizumab arm of the study (total=189 subjects). At the time of this analysis, all subjects in both treatment arms had treatment-emergent AEs.

Twenty-four subjects (12.6%) prematurely discontinued study drug treatment due to AEs (14 discontinuations were associated with sunitinib and 10 discontinuations were associated with bevacizumab). Eight subjects (4.2%) died within 28 days of last dose of study drug (5 [5.2%] sunitinib arm, 3 [3.2%] bevacizumab arm) including 1 subject (1.0%) with a cause of death (left ventricular systolic dysfunction) related to treatment according to the Investigator in the sunitinib arm. Sixty-six subjects (34.9%) had SAEs (36 [37.4%] in the sunitinib arm and 30 [32.3] in the bevacizumab arm). Thirty 33 subjects (17.5%) had SAEs that the Investigator and the sponsor judged to be treatment-related: 18 (18.8%) in the sunitinib arm and 15 (16.1%) in the bevacizumab arm.

There were 18 subjects (9.6%) with a shift in platelet results from Grade ≤2 at baseline to Grade ≥3 post baseline: 17 (17.9%) in the sunitinib arm and 1 (1.1%) in the bevacizumab arm. There were 86 subjects (45.7%) with shifts in neutrophil results from Grade ≤2 at baseline to Grade ≥3 post baseline: 53 (55.8%) in the sunitinib arm and 33 (35.5%) in the bevacizumab arm.

Non-Serious Treatment-Emergent Adverse Events: Summary of non-serious treatment-emergent AEs experienced by ≥5% of subjects is summarized in Table 6.

Table 6. Summary of Non-Serious Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects

System Organ Class Preferred Term	Sunitinib + mFOLFOX6 N=96	Bevacizumab + mFOLFOX6 N=93	Total (N=189)
		n (%)	
Any AE	96(100.0)	93 (100.0)	189(100.0)
Blood and lymphatic system disorders	71 (74.0)	47 (50.5)	118 (62.4)
Anaemia	27 (28.1)	26 (28.0)	53 (28.0)
Leukopenia	21 (21.9)	11 (11.8)	32 (16.9)
Neutropenia	67 (69.8)	33 (35.5)	100 (52.9)
Thrombocytopenia	50 (52.1)	19 (20.4)	69 (36.5)
Eye disorders	19 (19.8)	13 (14.0)	32 (16.9)
Lacrimation increased	5 (5.2)	5 (5.4)	10 (5.3)
Vision blurred	6 (6.3)	3 (3.2)	9 (4.8)
Gastrointestinal disorders	92 (95.8)	87 (93.5)	179 (94.7)
Abdominal distension	6 (6.3)	5 (5.4)	11 (5.8)
Abdominal pain	20 (20.8)	21 (22.6)	41 (21.7)
Abdominal pain lower	1 (1.0)	5 (5.4)	6 (3.2)
Abdominal pain upper	6 (6.3)	7 (7.5)	13 (6.9)
Cheilitis	4 (4.2)	5 (5.4)	9 (4.8)
Constipation	22 (22.9)	30 (32.3)	52 (27.5)
Diarrhoea	66 (68.8)	49 (52.7)	115 (60.8)
Dry mouth	11 (11.5)	5 (5.4)	16 (8.5)
Dyspepsia	17 (17.7)	7 (7.5)	24 (12.7)
Dysphagia	4 (4.2)	7 (7.5)	11 (5.8)
Flatulence	5 (5.2)	7 (7.5)	12 (6.3)
Gastrooesophageal reflux disease	11 (11.5)	7 (7.5)	18 (9.5)
Haemorrhoids	0 (0.0)	5 (5.4)	5 (2.6)
Nausea	62 (64.6)	57 (61.3)	119 (63.0)
Oral pain	6 (6.3)	5 (5.4)	11 (5.8)
Proctalgia	5 (5.2)	2 (2.2)	7 (3.7)
Rectal haemorrhage	3 (3.1)	5 (5.4)	8 (4.2)
Stomatitis	31 (32.3)	26 (28.0)	57 (30.2)
Vomiting	33 (34.4)	33 (35.5)	66 (34.9)
General disorders and administration site conditions	77 (80.2)	77 (82.8)	154 (81.5)
Asthenia	8 (8.3)	11 (11.8)	19 (10.1)
Chest pain	2 (2.1)	10 (10.8)	12 (6.3)
Chills	2 (2.1)	6 (6.5)	8 (4.2)
Fatigue	65 (67.7)	62 (66.7)	127 (67.2)
Mucosal inflammation	12 (12.5)	21 (22.6)	33 (17.5)
Oedema peripheral	11 (11.5)	5 (5.4)	16 (8.5)
Pain	7 (7.3)	9 (9.7)	16 (8.5)
Pyrexia	21 (21.9)	22 (23.7)	43 (22.8)
Immune system disorders	7 (7.3)	6 (6.5)	13 (6.9)
Hypersensitivity	2 (2.1)	5 (5.4)	7 (3.7)

Table 6. Summary of Non-Serious Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects

System Organ Class Preferred Term	Sunitinib + mFOLFOX6 N=96	Bevacizumab + mFOLFOX6 N=93	Total (N=189)
		n (%)	
Infections and infestations	35 (36.5)	44 (47.3)	79 (41.8)
Nasopharyngitis	4 (4.2)	9 (9.7)	13 (6.9)
Rhinitis	0 (0.0)	7 (7.5)	7 (3.7)
Upper respiratory tract infection	4 (4.2)	6 (6.5)	10 (5.3)
Urinary tract infection	10 (10.4)	3 (3.2)	13 (6.9)
Injury, poisoning and procedural complications	20 (20.8)	11 (11.8)	31 (16.4)
Contusion	5 (5.2)	1 (1.1)	6 (3.2)
Investigations	53 (55.2)	39 (41.9)	92 (48.7)
Blood alkaline phosphatase increased	5 (5.2)	5 (5.4)	10 (5.3)
Blood potassium decreased	5 (5.2)	1 (1.1)	6 (3.2)
Haemoglobin decreased	6 (6.3)	2 (2.2)	8 (4.2)
Neutrophil count decreased	19 (19.8)	8 (8.6)	27 (14.3)
Platelet count decreased	17 (17.7)	0 (0.0)	17 (9.0)
Weight decreased	19 (19.8)	16 (17.2)	35 (18.5)
White blood cell count decreased	13 (13.5)	5 (5.4)	18 (9.5)
Metabolism and nutrition disorders	49 (51.0)	48 (51.6)	97 (51.3)
Decreased appetite	32 (33.3)	36 (38.7)	68 (36.0)
Dehydration	11 (11.5)	6 (6.5)	17 (9.0)
Hyperglycaemia	3 (3.1)	6 (6.5)	9 (4.8)
Hypocalcaemia	5 (5.2)	2 (2.2)	7 (3.7)
Hypokalaemia	18 (18.8)	10 (10.8)	28 (14.8)
Hypomagnesaemia	5 (5.2)	2 (2.2)	7 (3.7)
Musculoskeletal and connective tissue disorders	35 (36.5)	37 (39.8)	72 (38.1)
Arthralgia	5 (5.2)	7 (7.5)	12 (6.3)
Back pain	13 (13.5)	8 (8.6)	21 (11.1)
Bone pain	4 (4.2)	7 (7.5)	11 (5.8)
Musculoskeletal pain	6 (6.3)	6 (6.5)	12 (6.3)
Myalgia	4 (4.2)	8 (8.6)	12 (6.3)
Pain in extremity	8 (8.3)	10 (10.8)	18 (9.5)
Nervous system disorders	81 (84.4)	88 (94.6)	169 (89.4)
Dizziness	14 (14.6)	16 (17.2)	30 (15.9)
Dysgeusia	31 (32.3)	21 (22.6)	52 (27.5)
Headache	14 (14.6)	22 (23.7)	36 (19.0)
Hyperaesthesia	7 (7.3)	8 (8.6)	15 (7.9)
Hypoaesthesia	5 (5.2)	5 (5.4)	10 (5.3)
Neuropathy peripheral	39 (40.6)	37 (39.8)	76 (40.2)
Paraesthesia	6 (6.3)	14 (15.1)	20 (10.6)
Peripheral sensory neuropathy	29 (30.2)	33 (35.5)	62 (32.8)
Polyneuropathy	0 (0.0)	5 (5.4)	5 (2.6)

Table 6. Summary of Non-Serious Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects

System Organ Class Preferred Term	Sunitinib + mFOLFOX6 N=96	Bevacizumab + mFOLFOX6 N=93	Total (N=189)
		n (%)	
Psychiatric disorders	27 (28.1)	36 (38.7)	63 (33.3)
Anxiety	5 (5.2)	13 (14.0)	18 (9.5)
Depression	6 (6.3)	11 (11.8)	17 (9.0)
Insomnia	16 (16.7)	20 (21.5)	36 (19.0)
Renal and urinary disorders	14 (14.6)	15 (16.1)	29 (15.3)
Proteinuria	3 (3.1)	5 (5.4)	8 (4.2)
Respiratory, thoracic and mediastinal disorders	57 (59.4)	59 (63.4)	116 (61.4)
Cough	15 (15.6)	16 (17.2)	31 (16.4)
Dysphonia	2 (2.1)	11 (11.8)	13 (6.9)
Dyspnoea	16 (16.7)	14 (15.1)	30 (15.9)
Dyspnoea exertional	6 (6.3)	4 (4.3)	10 (5.3)
Epistaxis	22 (22.9)	30 (32.3)	52 (27.5)
Hiccups	10 (10.4)	7 (7.5)	17 (9.0)
Oropharyngeal pain	7 (7.3)	8 (8.6)	15 (7.9)
Rhinorrhoea	3 (3.1)	5 (5.4)	8 (4.2)
Skin and subcutaneous tissue disorders	57 (59.4)	64 (68.8)	121 (64.0)
Alopecia	17 (17.7)	24 (25.8)	41 (21.7)
Dry skin	9 (9.4)	5 (5.4)	14 (7.4)
Hyperhidrosis	3 (3.1)	5 (5.4)	8 (4.2)
Palmar-plantar erythrodysaesthesia syndrome	26 (27.1)	15 (16.1)	41 (21.7)
Pruritus	7 (7.3)	9 (9.7)	16 (8.5)
Rash	20 (20.8)	16 (17.2)	36 (19.0)
Skin discolouration	9 (9.4)	5 (5.4)	14 (7.4)
Skin hyperpigmentation	2 (2.1)	8 (8.6)	10 (5.3)
Yellow skin	9 (9.4)	0 (0.0)	9 (4.8)
Vascular disorders	29 (30.2)	29 (31.2)	58 (30.7)
Hypertension	19 (19.8)	21 (22.6)	40 (21.2)
Hypotension	2 (2.1)	6 (6.5)	8 (4.2)

Except for the number of AEs, subjects are counted only once per treatment in each cell.
SAE was excluded from this table.
AE=adverse event, N=number of subjects per treatment group, n=number of subjects with observation, SAE=serious adverse event

Treatment-related AEs Grades 3-4 are summarized in Table 7. Eight subjects (4.2%) reported Grade 5 AEs: 5 (5.2%) for the sunitinib arm and 3 (3.2%) for the bevacizumab arm.

Table 7. Summary of Treatment-Related AEs with Maximum Grade of 3, 4, and 5 and ≥5% of Subjects - Related to Study Treatment [a]

	Sunitinib + mFOLFOX6 N=96			
Preferred Term	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Neutropenia	33(34.4)	16(16.7)	0 (0.0)	49(51.0)
Thrombocytopenia	16(16.7)	7 (7.3)	0 (0.0)	23(24.0)
Neutrophil count decreased	9 (9.4)	9 (9.4)	0 (0.0)	18(18.8)
Platelet count decreased	11(11.5)	1 (1.0)	0 (0.0)	12(12.5)
Leukopenia	9 (9.4)	1 (1.0)	0 (0.0)	10(10.4)
Peripheral sensory neuropathy	9 (9.4)	1 (1.0)	0 (0.0)	10(10.4)
Fatigue	9 (9.4)	0 (0.0)	0 (0.0)	9 (9.4)
White blood cell count decreased	7 (7.3)	2 (2.1)	0 (0.0)	9 (9.4)
Diarrhoea	6 (6.3)	1 (1.0)	0 (0.0)	7 (7.3)
Neuropathy peripheral	6 (6.3)	0 (0.0)	0 (0.0)	6 (6.3)
Febrile neutropenia	2 (2.1)	3 (3.1)	0 (0.0)	5 (5.2)
Palmar-plantar erythrodysaesthesia syndrome	5 (5.2)	0 (0.0)	0 (0.0)	5 (5.2)

	Bevacizumab + mFOLFOX6 N=93			
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Neutropenia	12(12.9)	6 (6.5)	0 (0.0)	18(19.4)
Diarrhoea	7 (7.5)	0 (0.0)	0 (0.0)	7 (7.5)
Peripheral sensory neuropathy	7 (7.5)	0 (0.0)	0 (0.0)	7 (7.5)
Fatigue	6 (6.5)	0 (0.0)	0 (0.0)	6 (6.5)
Neuropathy peripheral	6 (6.5)	0 (0.0)	0 (0.0)	6 (6.5)
Leukopenia	5 (5.4)	0 (0.0)	0 (0.0)	5 (5.4)

MedDRA (version 13.1) coding dictionary applied.
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.
AE=adverse event, N=number of subjects per treatment group, n=number of subjects with observation, SAE=serious adverse event
a. AE/SAE results are not separated out.

Serious Adverse Events: SAE experienced by ≥5% of subjects is summarized in Table 8.

Table 8. Serious Adverse Events Experienced by ≥5% of Subjects

System Organ Class Preferred Term	Sunitinib + mFOLFOX6 N=96	Bevacizumab + mFOLFOX6 N=93	Total (N=189)
		n (%)	
Any SAE	36 (37.5)	30 (32.3)	66 (34.9)
Blood and lymphatic system disorders	9 (9.4)	0 (0.0)	9 (4.8)
Febrile neutropenia	5 (5.2)	0 (0.0)	5 (2.6)
Metabolism and nutrition disorders	5 (5.2)	3 (3.2)	8 (4.2)
Dehydration	5 (5.2)	2 (2.2)	7 (3.7)
Any SAE	36 (37.5)	30 (32.3)	66 (34.9)

Except for the number of adverse events, subjects are counted only once per treatment in each cell.
AE=adverse event, N=number of subjects per treatment group, n=number of subjects with observation, SAE=serious adverse event

Other Serious Adverse Events: Within 28 days post last dose of study drug 66 (34.9%) subjects had SAEs (36 [37.5%] on sunitinib and 30 [32.3%] on bevacizumab, including the 8 subjects (4.2%) with fatal SAEs that died. The most common SAEs (occurring in ≥5 [5%] subjects in the sunitinib treatment group), which were not related to disease progression, were dehydration in both treatment groups (5 subjects on sunitinib and 2 subjects on bevacizumab), and febrile neutropenia only in the sunitinib group.

Deaths: Eight subjects (4.2%) died within 28 days of last dose of study drug: 5 (5.2%) in the sunitinib arm and 3 (3.2%) in the bevacizumab arm (Table 9).

Table 9. Deaths Occurring within 28 Days of Last Dose of Study Drug

Serial Number	Gender (M/F) /Age (years)/Race (W, B, A, O)	Days Since Last dose	Treatment Arm	Cause of Death
1	F/56/W	385	Sunitinib	Study Disease
2	M/46/W	18	Sunitinib	Other (aspirated fecal material)
3	F/64/A	5	Sunitinib	Left ventricular systolic dysfunction
4	F/72/A	28	Sunitinib	Other (pulmonary hypertension)
5	M/63/W	3	Sunitinib	Study Disease
6	M/60/W	20	Bevacizumab	Study Disease
7	M/71/W	66	Bevacizumab	Study Disease
8	M/61/W	2	Bevacizumab	Study Disease

A=Asian, AE=adverse event, B=black, F=female, M=male, O=other, W=white

Clinical Laboratory Evaluation:

In the sunitinib arm, 22 (23.2%) Grade 4 hematology abnormalities and in the bevacizumab arm 11 (11.8%) Grade 4 hematology abnormalities were observed, with neutropenia being the most frequent Grade 3-4 event in both arms. There were 6 (6.3%) Grade 4 chemistry laboratory abnormalities in the sunitinib arm and 3 (3.2%) Grade 4 chemistry laboratory abnormalities in the bevacizumab arm. Electrolyte changes (for

sunitinib) and glucose changes (for bevacizumab) were the most frequently reported Grade 3-4 abnormalities.

PRO Evaluation: From baseline to Cycle 4 Day 1, no clinically meaningful and statistically significant differences in FACT-C subscales or FACT-GOG/Ntx neurotoxicity subscale were observed between treatment groups.

CONCLUSIONS:

- The safety profile of sunitinib was acceptable and manageable, as AEs were generally similar to those reported in other studies of single-agent sunitinib and/or normally reported by subjects with advanced mCRC.
- The majority (4 out of 7; 57.1%) of mean baseline FACT-C scores and all mean baseline FACT-GOG/Ntx and FACT-G scores were similar between treatment groups.
- No overall conclusions can be drawn between treatments with respect to the mean change from baseline in FACT-C and the FACT-GOG/Ntx scores since the study was stopped early due to futility.
- ORR was 41.7 % for the sunitinib arm and 37.9% for the bevacizumab arm.
- The median time of PFS for sunitinib was 40.5 weeks. The median time of PFS for bevacizumab was 67.0 weeks. Therefore no PFS advantage was observed in the sunitinib arm of the study versus the bevacizumab arm.
- Median OS could not be determined for this report as the OS data was not mature at the time of analysis.