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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: N/A

PROTOCOL NO.: A6181049

PROTOCOL TITLE: A Phase-1 Study of SU11248 in Combination With FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) in Patients With Metastatic Colorectal Cancer

Study Centers: Three centers in Spain and 3 centers in the United Kingdom (1 further center in Spain did not randomize subjects).

Study Initiation and Completion Dates: 17 October 2005 to 20 August 2008

Phase of Development: Phase 1

Study Objectives:

Primary:

- To assess the Maximum Tolerated Dose (MTD) and overall safety and tolerability of sunitinib (SU011248) in combination with FOLFIRI.

Secondary:

- To assess the plasma pharmacokinetic (PK) parameters of SU011248 (and its metabolite SU012662), irinotecan (and its metabolite SN-38) and 5-FU when these drugs were coadministered.

- To assess preliminary anti-tumor activity of sunitinib and FOLFIRI when given in combination.

METHODS

Study Design: This was a Phase 1, open-label dose-escalation, multicenter study of the multitargeted tyrosine kinase inhibitor sunitinib given in combination with FOLFIRI for subjects who had not received prior chemotherapy or immunotherapy for metastatic CRC. Subjects were treated for a maximum of 12 cycles of FOLFIRI. The duration of each cycle

was 2 weeks, giving a maximum duration of FOLFIRI treatment on the study of 24 weeks. The number of subjects to be enrolled was dependent on the toxicity observed.

Number of Subjects (Planned and Analyzed): It was originally anticipated that a total of approximately 36 subjects would be enrolled in this study, 37 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion: The main diagnostic and inclusion criteria were histologically confirmed diagnosis of adenocarcinoma of the rectum or colon; metastatic disease, not amenable to curative surgery or radiation therapy; evidence of unidimensionally measurable disease as per Response Evaluation Criteria In Solid Tumors (RECIST); male or female subjects, 18 years of age or older; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; life expectancy of ≥12 weeks; >6 months since completion of any adjuvant 5-FU (± oxaliplatin) chemotherapy; and no prior pelvic radiotherapy.

Study Treatment: This was an open-label study without randomization. Sunitinib was given concomitantly either continuously (Schedule continuous daily dosing [CDD]) throughout all cycles of FOLFIRI treatment or as a 4 weeks on/2 weeks off (Schedule 4/2) regimen, coinciding with the start of Cycles 1, 4, 7, and 10. Sunitinib was added to FOLFIRI in escalating doses in serial subject cohorts. Sunitinib was initially given orally at 37.5 mg/day on Schedule 4/2 with the option to dose escalate in successive cohorts to 50 mg/day on Schedule 4/2 or to 37.5 or 25 mg/day on Schedule CDD, depending on tolerability. Doses of sunitinib below 25 mg were not given. Sunitinib was added to FOLFIRI in escalating doses in serial subject cohorts as shown in Table S1.

To allow PK assessments to be made, the administration of sunitinib in Cycle 1 was delayed, such that it began on Day 3 and continued through until either Day 2 of Cycle 3 (Schedule 4/2) or until the end of Cycle 12 (Schedule CDD).

After a protocol amendment was implemented, additional cohorts were opened for CDD of sunitinib initially at 37.5 mg and later to 25 mg.

Table S1. Available Dose Levels

Dose Level	Sunitinib (mg)	Sunitinib dispensed as
-1 (4/2 regimen)	25	1 x 25 mg capsule
1 (4/2 regimen)	37.5	3 x 12.5 mg capsules
2 (4/2 regimen)	50	1 x 50 mg capsule
-1 (continuous regimen)	25	1 x 25 mg capsule
1 (continuous regimen)	37.5	3 x 12.5 mg capsules

Subjects in these cohorts started sunitinib on Day 3 and continued until Day 2 of Cycle 3. This 2-day delay permitted acquisition of PK data.

For PK studies, the administration of sunitinib was delayed for the first 2 days of Cycle 1 for patients in all 3 cohorts. During Cycle 1, sunitinib dosing began on Day 3 and continued through until Day 2 of Cycle 3. This schedule permitted the acquisition of PK data when FOLFIRI was administered alone (Cycle 1 Day 1), when sunitinib was administered alone at

steady state (Cycle 1 Day 14), and when sunitinib was given in combination with FOLFIRI (Cycle 3 Day 1).

Pharmacokinetic Evaluations: PK assessments were to be completed on all subjects enrolled during the dose-finding phase of the study prior to the definition of the MTD. PK assessments were to be completed on at least 6 evaluable subjects in the expansion groups for both Schedules 4/2 and CDD. Full PK profiles were measured for irinotecan (and its metabolite SN-38), 5-FU, and SU011248 (and its metabolite SU012662). Samples were drawn from the arm not receiving chemotherapy.

Plasma SU011248, SU012662, irinotecan, SN-38, and 5-FU concentrations were measured using validated methods. Prior to analysis of samples, the assay sensitivity, accuracy, and reproducibility were determined.

PK parameter values were calculated for each subject by noncompartmental analysis of concentration-time data using WinNonlin version 4.1. Nominal sample collection time was used for SU011248, its metabolite (SU012662), irinotecan, its active metabolite (SN-38), and 5-FU. Summary descriptives of plasma concentrations by nominal time and PK parameters are presented only for paired observations with respect to each analyte. In the case where the dose for 1 of the paired observations was different than the other observation, dose correction to the intended dose was performed (correction factor: intended dose/actual dose).

For the computation of steady state AUC_{24} (ie, AUC_{TAU}), in the events where the concentration value at 24 hours was missing, the steady state plasma concentration at time zero for the mentioned cycle was used as the concentration value at the nominal time 24 hours. If concentration at time 0 hours was missing, C0, the value assigned was the minimum value between dosing time and tau.

Summary descriptions and figures for dose-corrected PK parameters and for all dose levels combined were presented for paired observations. Dose correction to the MTD, 37.5 mg of SU011248 plus 180 mg/m^2 of irinotecan, plus 2800 mg/m^2 of 5-FU, was performed.

Individual subject trough plasma concentrations were summarized per schedule, cycle and study day. Due to potential dose changes throughout the study in different subjects, the observed trough concentrations were dose-corrected to the starting dose (ie, reference dose) where appropriate. Dose-corrected trough plasma concentrations were summarized by schedule, cycle and study day and determined as the observed values times the reference dose (37.5 mg) divided by the actual dose. Linear plots of individual predose and trough and box plots of mean and dose corrected mean values of SU011248, its metabolite, and total drug trough are provided by schedule, cycle and study day.

All concentrations which were below the limits of quantitation (BLQ) were set to zero prior to computation of descriptive statistics (BLQ values were excluded from the calculations of geometric means and the associated 95% CIs).

Efficacy Evaluations: The determination of antitumor efficacy was based on objective tumor assessments made according to the RECIST system of unidimensional evaluation. A

minor modification was adopted to accommodate standard practice use of spiral computerized tomography (CT) scan with a reconstruction interval up to 8 mm. In the event that spiral CT scan was used to assess tumors, the minimum lesion size qualifying as measurable was twice the reconstruction interval used and at least 10 mm. The CT scans were to be performed with contrast agents unless contraindicated for medical reasons. The same imaging modality was to be used throughout the study to measure disease. Tumor evaluation by positron emission tomography scan or by ultrasound could not substitute for CT or magnetic resonance imaging (MRI) scans.

Antitumor activity was assessed through radiological tumor assessments conducted at screening, at the end of every full sunitinib treatment period (ie at the end of every third FOLFIRI cycle), whenever disease progression was suspected (eg symptomatic deterioration), to confirm a partial response (PR) or complete response (CR) (at least 4 weeks after initial documentation of response), and at the time of withdrawal from the study (if not done in the previous 6 weeks). Assessments could have included CT scans, MRI scans, bone scans and others as required. Assessment of response was made using RECIST. Confirmation of response by RECIST required repeat imaging studies ≥4 weeks after the initial documentation of response. All subjects' files and radiological images were to be available for CRF source verification. Copies of all images were to be made available for review by the sponsor.

Safety Evaluations: Safety evaluations included clinical monitoring, physical examinations, vital signs (heart rate, blood pressure, body temperature and respiration rate), 12-lead ECGs, adverse events (AEs), safety laboratory tests and Eastern Cooperative Oncology Group (ECOG) performance status.

Statistical Methods: The following populations were defined in the statistical analysis plan:

- **Intent-to-Treat (ITT) Population** - This population included all subjects enrolled in the study who received at least 1 dose of study medication.

- **'Evaluable' Set for PK Analyses** - The evaluable PK data set included subjects who received study drug and completed sufficient plasma collections for PK evaluation. If subjects incompleted PK collections, the pharmacokineticist evaluated these data on a case-by-case basis to determine if the data were sufficient for PK evaluation.

- **Safety Population** - The safety population included all subjects enrolled in the study who received at least 1 dose of study medication.

Pharmacokinetics: For all calculations, figures and estimation of individual PK parameters, all concentrations assayed as BLQ were set to zero. In log-linear plots these values were not presented. Descriptive statistics (n, mean, standard deviation [SDev], percentage of coefficients of variation (CV), median, minimum, maximum) of plasma concentrations for irinotecan, SN-38, 5-FU, SU011248, SU012662 and total drug (SU011248 + SU012662) were presented for full PK profiling days by schedule, treatment group, study day and nominal time. Plasma trough concentrations were presented in a similar fashion. No correction was made for differences in molecular weights between SU011248 and SU012662

prior to summarization of total drug (SU011248 + SU012662) concentration data since the differences are negligible.

Linear and semi-log plots of individual and mean plasma concentrations by nominal time for irinotecan, SN-38, 5-FU, SU011248, SU012662 and total drug (SU011248 + SU012662) were prepared for PK sampling days (separately by schedule and treatment group). Similar plots were prepared for each individual subject plasma concentrations.

Plasma PK parameters were estimated using noncompartmental analysis and actual collection times and listed and summarized by schedule, treatment group, and study day using descriptive statistics (eg, n, mean, SDev, %CV, median, minimum, maximum, and geometric mean and its associated 95% CI). PK parameters with 0 values were excluded from the calculation of geometric mean and confidence intervals. Comparisons of PK parameters between treatments are illustrated via graphical presentations.

Efficacy: The set of subjects analyzed for objective response included all subjects with measurable disease at baseline, subjects receiving at least 1 dose of study medication and at least 1 on-study tumor assessment carried out by the investigator. The number of subjects achieving CR, PR, stable disease (SD), or progressive disease (PD, according to RECIST) as their best response while on therapy, were tabulated by cohort and tumor type.

Safety: For each cohort, DLTs were summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Frequencies of subjects experiencing at least 1 AE are displayed by body system and preferred term according to MedDRA terminology. Additional subcategories were based on event intensity, such as CTC severity grade and by maximum CTC grade group (Grade 1-2 versus Grade 3-5), and relationship to study drug. The number and percentage of subjects who experienced any AE, treatment related AE, SAE and treatment related SAE were summarized. Subject deaths were summarized by presenting the number and percentage of subjects for each cause of death. Subjects who died were also listed.

Hematology and serum chemistry were summarized for baseline, treatment visits and change from baseline, as appropriate.

Vital signs (eg, pulse rate, blood pressure) data were summarized and presented.

Individual subject ECG data listings were generated. Changes from baseline (defined as the screening value, or the last value on or before the start of dosing) in QTcF (Fridericia correction) and other ECG parameters, as appropriate, were calculated to describe and display the frequency of subjects who experienced QTc interval prolongation, displayed by category according to CTCAE v3.0 severity grades 1-5.

All medications received during the treatment period were considered as concomitant medications and were coded by World Health Organization (WHO) medical dictionary; subjects who received concomitant medications are listed.

SAE presentations were derived from a separate, centralized, AE monitoring database that was continuously updated based on rapidly communicated reports from the investigators to

the sponsor. The clinical study database was based on information provided from the CRFs. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

RESULTS

Subject Disposition and Demography: A total of 37 subjects with metastatic CRC were assigned to study treatment (enrolled) and treated (Table S2.). Twelve subjects completed the study (ie, had 12 cycles of FOLFIRI therapy in combination with sunitinib) and 25 subjects discontinued. Note that following a protocol amendment, additional cohorts were added for CDD of sunitinib, thus the number of subjects was greater than planned.

One additional subject was enrolled to receive sunitinib 25 mg/day on Schedule CDD with FOLFIRI in order to ensure that a minimum number of PK evaluable samples were collected, because 1 subject had missed PK sampling.

Table S2. Subject Evaluation Groups

	Sunitinib 37.5 mg/day Schedule 4/2 + FOLFIRI	**Sunitinib 50 mg/day Schedule 4/2 + FOLFIRI**	**Sunitinib 25 mg/day CDD + FOLFIRI**	**Sunitinib 37.5 mg/day CDD + FOLFIRI**
Number of Subjects Assigned to Treatment 37				
Treated	21	6	7	3
Completed	9	0	3	0
Discontinued	12	6	4	3
Subject Died	0	1	0	0
Related to Study Drug	8	3	1	2
Adverse event	4	2	1	2
Lack of efficacy	4	1	0	0
Not Related to Study Drug	4	2	3	1
Adverse event	1	0	2	1
Lost to follow-up	0	1	0	0
Other	3	0	1	0
Subject no longer willing to participate in study	0	1	0	0
Analyzed for Efficacy				
Objective Response	19	6	7	3
Analyzed for Safety				
Adverse events	21	6	7	3
Laboratory data	21	6	7	3
Analyzed for Pharmacokinetics	21	6	7	3

CDD = continuous daily dosing

Demographic and baseline characteristics were similar across the treatment groups. The study population consisted of 20 male and 17 female subjects aged between 39-78 years; 33 subjects were White, 2 subjects were Black, and 2 subjects were Asian.

Twenty-three (62.2%) subjects had ECOG performance status 0 at baseline, 14 (37.8%) subjects had ECOG performance status 1. Twenty-five (67.6%) subjects had more than 1 involved disease site, with liver (24 [64.9%] subjects) and lung (19 [51.4%] subjects) being the most common involved disease sites.

All subjects had a confirmed primary diagnosis of CRC. The time from initial diagnosis ranged from 0-5.2 years. Previous therapies for the disease under study included chemotherapy in 11 (29.7%) subjects, radiotherapy in 1 (2.7%) subject, and cancer surgery in 27 (73.0%) subjects.

Efficacy Results: Thirty-five subjects had measurable disease at baseline (Table S3.) and had at least 1 on-study tumor assessment by the investigator.

- Sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI: 11 (57.9%) subjects (95% CI: 33.5%, 79.7%) had an objective response (1 [5.3%] subject achieved CR; 10 [52.6%] subjects achieved PR), and 7 (36.8%) subjects maintained SD with an average duration of 17 weeks.

- Sunitinib 50 mg/day on Schedule 4/2 with FOLFIRI: All 6 (100%) subjects maintained SD with an average duration of 13 weeks.

- Sunitinib 25 mg/day on Schedule CDD with FOLFIRI: 2 (28.6%) subjects (95% CI: 3.7%, 71.0%) had an objective response (both PR), and 5 (71.4%) subjects maintained SD with an average duration of 20 weeks.

- Sunitinib 37.5 mg/day on Schedule CDD with FOLFIRI: All 3 (100%) subjects maintained SD with an average duration of 11 weeks.

Table S3. Summary of Best Overall Tumor Response as Determined by the Investigator (ITT)

	Sunitinib 37.5 mg/day Schedule 4/2 + FOLFIRI (N=21)	Sunitinib 50 mg/day Schedule 4/2 + FOLFIRI (N=6)	Sunitinib 25 mg/day CDD + FOLFIRI (N=7)	Sunitinib 37.5 mg/day CDD + FOLFIRI (N=3)
Number of subjects (%):				
Subjects with Baseline Assessment	21 (100.0)	6 (100.0)	7 (100.0)	3 (100.0)
Subjects with Measurable Disease at Baseline and a Response Assessment by the Investigator	19 (90.5)	6 (100.0)	7 (100.0)	3 (100.0)
Best Overall Response (%) [a]				
Complete Response (CR)	1 (5.3)	0	0	0
Partial Response (PR)	10 (52.6)	0	2 (28.6)	0
Stable Disease (SD)	7 (36.8)	6 (100.0)	5 (71.4)	3 (100.0)
Progressive Disease (PD)	1 (5.3)	0	0	0
Not Evaluable (NE)	0	0	0	0
Objective Response (CR+PR)[a]	11 (57.9)	0	2 (28.6)	0
95% CI	(33.5, 79.7)		(3.7, 71.0)	

CI = confidence interval; N = number of subjects; ITT = intent-to-treat; CDD = continuous daily dosing
[a]The denominator is the number of subjects with measurable disease at baseline and a response assessment made by the investigator.

Pharmacokinetic Results: Due to the low tolerability of dose level 1 on the CDD schedule, only 1 paired observation was available for PK evaluations. Therefore, descriptive statistics for the PK parameters at this dose level could not be calculated.

SU011248, SU012662, and Total Drug Pharmacokinetics: For subjects on sunitinib Schedule 4/2 at dose levels 1 and 2, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to sunitinib alone) were 0.92 and 1.19, for SU011248 C_{max}, and 0.92 and 1.11 for SU011248 AUC_{24}; 1.23 and 1.13 for SU012662 C_{max}, and 1.20 and 1.10 for SU012662 AUC_{24}; 0.98 and 1.17 for total drug C_{max}, and 0.99 and 1.10 for total drug AUC_{24}. For all dose levels combined, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to sunitinib alone) of C_{max} and AUC_{24} were 1.01 and 0.99 for SU011248, 1.19 and 1.16 for SU012662, and 1.04 and 1.03 for total drug. For subjects on the CDD schedule of SU011248 at dose level -1, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to sunitinib alone) of C_{max} and AUC_{24} were 1.16 and 1.12 for SU011248, 1.12 and 1.06 for SU012662 and 1.13 and 1.08 for total drug. For all dose levels combined, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to sunitinib alone) of C_{max} and AUC_{24} were 1.13 and 1.06 for SU011248, 0.83 and 1.11 for SU012662, and 1.11 and 1.03 for total drug.

Following intermittent dosing of sunitinib (daily for 4 consecutive weeks followed by a 2-week off-treatment period), dose-corrected (reference dose is the intended dose) trough values (Day 1 of Cycles 5, 8, and 11) for SU011248, its metabolite, and total drug were within 39.0-44.4 ng/mL, 8.26-9.64 ng/mL, and 47.3-54.0 ng/mL, respectively, for dose level 1 on Schedule 4/2. On the CDD schedule, there was insufficient trough PK data available due to the poor tolerability of sunitinib on this dose schedule in combination with FOLFIRI.

Pharmacokinetics of Irinotecan: For subjects on schedule 4/2 at dose levels 1 and 2, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to FOLFIRI alone) were 1.25, and 1.57 for irinotecan C_{max} and 1.26 and 1.34 for irinotecan AUC_{inf}; 0.90 and 1.09 for SN-38 C_{max} and 1.25 and 1.61 for SN-38 AUC_{24}. In all dose levels combined, the respective geometric mean ratios were 1.34 for irinotecan C_{max} and 1.28 for irinotecan AUC_{inf} and 0.96 for SN-38 C_{max} and 1.35 for SN-38 AUC_{24}. For subjects on CDD schedule at dose level -1, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to FOLFIRI alone) were 1.01 for irinotecan C_{max} and 1.15 for irinotecan AUC_{inf} and 0.78 for SN-38 C_{max} and 1.04 for SN-38 AUC_{24}. In all dose levels combined, the respective geometric mean ratios were 1.01 for irinotecan C_{max} and 1.23 for irinotecan AUC_{inf} and 0.83 for SN-38 C_{max} and 1.11 for SN-38 AUC_{24}.

Pharmacokinetics of 5-FU: For subjects under schedule 4/2 at dose levels 1 and 2, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to FOLFIRI alone) were 1.34 and 1.17 for C_{ss}, and 0.75 and 0.83 CL_{ss}. In all dose levels combined, the respective geometric mean ratios of C_{ss} and CL_{ss} were 1.25 and 0.79. For subjects under CDD schedule at dose level -1, the respective geometric mean ratios (ie, sunitinib + FOLFIRI to FOLFIRI alone) of C_{ss} and CL_{ss} were 1.15 and 0.87. In all dose levels combined, the respective geometric mean ratios of C_{ss} and Cl_{ss} were 1.33 and 0.74.

Safety Results: There were a total of 493 AEs reported, with all 37 subjects experiencing at least 1 AE (Table S4). A total of 251 AEs in 37 subjects were considered related to study drug(s) by the investigator. Most AEs were mild to moderate in severity (Grades 1 or 2). Diarrhea and nausea were the most common non-hematologic AEs (>70% of subjects at 37.5 mg/day on Schedule 4/2. The most common hematologic abnormality was neutropenia, anemia, followed by thrombocytopenia.

The MTD of sunitinib given in combination with FOLFIRI was 37.5 mg/day on Schedule 4/2. No DLTs were reported in the 6 subjects treated with sunitinib 37.5mg/day on Schedule 4/2 with FOLFIRI. The other treatment groups (summarized below) each had 2 out of 3 to 6 subjects experience DLTs. The most commonly reported DLT was neutropenia.

- Sunitinib 50 mg/day on Schedule 4/2 with FOLFIRI: 2 subjects experienced DLTs; 1 of these subjects had her dose stopped temporarily, and the other subject had a dose reduction.

- Sunitinib 25 mg/day on Schedule CDD with FOLFIRI: 2 subjects experienced DLTs, both of whom had their dose stopped temporarily.

- Sunitinib 37.5 mg/day on Schedule CDD with FOLFIRI: 2 subjects experienced DLTs; 1 of these subjects had her dose stopped temporarily, and the other subject had a dose reduction prior to permanent discontinuation.

Table S4. Summary of Treatment-Related Adverse Events

	Sunitinib 37.5 mg/day Schedule 4/2 + FOLFIRI	**Sunitinib 50 mg/day Schedule 4/2 + FOLFIRI**	**Sunitinib 25 mg/day CDD + FOLFIRI**	**Sunitinib 37.5 mg/day CDD + FOLFIRI**
Number of Subjects:				
Subjects Evaluable for AEs	**21**	**6**	**7**	**3**
Number of AEs	**266**	**86**	**107**	**34**
Treatment-Related	133	55	52	11
Subjects with AEs	**21**	**6**	**7**	**3**
Treatment-Related	21	6	7	3
Subjects with SAEs	**10**	**4**	**3**	**2**
Treatment-Related	4	4	1	2
Subjects with Grade 3 or 4 AEs	**15**	**6**	**7**	**3**
Treatment-Related	11	6	6	3
Subjects with Grade 5 AEs	**0**	**1**	**0**	**0**
Treatment-Related	0	0	0	0
Subjects discontinued due to AEs	**5**	**3**	**3**	**3**
Treatment-Related	4	2	1	2
Subjects with dose reduction due to AEs	**3**	**2**	**0**	**1**
Treatment-Related	2	2	0	1
Subjects with temporary discontinuation due to AEs	**18**	**6**	**6**	**2**
Treatment-Related	15	5	6	2

AEs = adverse events; SAEs = serious adverse events; CDD = continuous daily dosing

Diarrhea and lethargy were the most common non-hematologic AEs of Grade 3 or 4. All 3 subjects (100%) treated with sunitinib 37.5 mg/day on Schedule CDD in combination with FOLFIRI had treatment-related Grade ≥3 neutropenia compared to approximately 50% of subjects on 37.5 mg/day Schedule 4/2 with FOLFIRI, and approximately 85% of subjects in the other 2 cohorts. Two subjects experienced Grade ≥3 thrombocytopenia on the 37.5 mg/day and 50 mg/day Schedule 4/2 with FOLFIRI, and only 1 subject experienced Grade ≥3 thrombocytopenia when treated with sunitinib 37.5 mg/day on Schedule CDD in combination with FOLFIRI. Three subjects experienced Grade ≥3 febrile neutropenia on the 37.5 mg/day and 50 mg/day Schedule 4/2 with FOLFIRI, and only 1 subject experienced Grade ≥3 febrile neutropenia when treated with sunitinib 25 mg/day on Schedule CDD in combination with FOLFIRI. Two subjects had Grade ≥3 anemia on the 37.5 mg/day Schedule 4/2 with FOLFIRI.

The frequency and type of sunitinib-related AEs was similar to that observed for all causality treatment-emergent AEs. Comparison of treatment-related AEs in Cycles 1-3, the primary

DLT reporting period, with treatment-related AEs in later cycles did not reveal evidence of cumulative treatment-related AEs in subjects from all cohorts.

Of 37 subjects, a total of 14 subjects were discontinued from the study due to AEs. Nine discontinuations were due to treatment-related AEs. Seven discontinuations were due to SAEs. The most common reason for discontinuation was treatment-related neutropenia (6 subjects).

- Sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI: 18 (86%) subjects temporarily discontinued sunitinib due to AEs; 3 subjects had dose reductions due to AEs. The most common AE leading to dose reductions or temporary discontinuations was neutropenia; other AEs included nausea, diarrhea, lethargy, joint abscess, thrombocytopenia, fatigue, infection and pyrexia.

- Sunitinib 50 mg/day on Schedule 4/2 with FOLFIRI: 6 (100%) subjects temporarily discontinued sunitinib due to AEs; 2 subjects had dose reductions due to AEs. The most common AE leading to dose reductions or temporary discontinuations was neutropenia; other AEs included nausea, diarrhea, thrombocytopenia, abdominal pain and pyrexia.

- Sunitinib 25 mg/day on Schedule CDD with FOLFIRI: 6 (86%) subjects temporarily discontinued sunitinib due to AEs; no subjects had dose reductions due to AEs. The most common AE leading to temporary discontinuations was neutropenia; other AEs included nausea, diarrhea and pyrexia.

- Sunitinib 37.5 mg/day on Schedule CDD with FOLFIRI: 2 (67%) subjects temporarily discontinued sunitinib due to AEs; 1 subject had dose reductions due to AEs. The most common AE leading to dose reductions or temporary discontinuations was neutropenia; other AEs included nausea, anemia, lethargy, diarrhea and pyrexia.

There were a total of 6 deaths during the follow-up period. No treatment-related deaths were reported. All deaths were of subjects on Schedule 4/2.

Of the 21 subjects treated with sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI who had follow-up visits, 5 deaths (23.8%) were reported during the follow-up period. All of these deaths were reported more than 28 days after the last dose of study drug and were not considered related to study drug by the investigator.

Of the 5 subjects treated with sunitinib 50 mg/day on Schedule 4/2 with FOLFIRI, who had follow-up visits, 1 subject died of fever and infection.

- Sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI: A total of 19 SAEs were reported in 10 subjects; 6 SAEs were study drug related. Two subjects experienced SAEs categorized as Grade 1 (nausea, vomiting and pyrexia), 4 subjects as Grade 2 (increased blood creatinine, abdominal pain, vomiting, syncope, stomatitis, hyperglycaemia), 4 subjects as Grade 3 (febrile neutropenia, dehydration, vomiting), and 5 subjects as Grade 4 (depression, neutropenic sepsis,febrile neutropenia, neutropenia). All SAEs were resolved.

- Sunitinib 50 mg/day on Schedule 4/2 with FOLFIRI: A total of 11 SAEs were reported in 4 subjects; 6 SAEs were study drug related. Two subjects experienced SAEs categorized as Grade 1 (drug interaction and periorbital oedema), 1 subject as Grade 2 (stomatitis), 2 subjects as Grade 3 (diarrhea and abdominal pain), and 3 subjects as Grade 4 (febrile neutropenia and neutropenia). All SAEs were resolved during the study with the exception of 1 ongoing SAE (abdominal pain) for a 43-year-old female subject. She also experienced an SAE (infection) which was categorized as Grade 5. This subject died of fever and infection at follow-up.

- Sunitinib 25 mg/day on Schedule CDD with FOLFIRI: A total of 3 SAEs were reported in 3 subjects; 1 SAE was study drug related. All subjects experienced SAEs categorized as Grade 3 (catheter related infection, febrile neutropenia and infection), which were resolved.

- Sunitinib 37.5 mg/day on Schedule CDD with FOLFIRI: A total of 6 SAEs were reported in 2 subjects; 5 SAEs were study drug related. Two subjects experienced SAEs categorized as Grade 3 (axillary vein thrombosis, jugular vein thrombosis and rectal haemorrhage) and 1 subject had Grade 4 neutropenia. All of these SAEs were resolved.

The most common hematologic abnormality was neutropenia, followed by low hemoglobin. Approximately 50% of subjects had Grade 3 or 4 neutropenia.

Most subjects experienced a shift in absolute neutrophils and WBC.

Grade 3 chemistry abnormalities were reported for 6 out of 27 subjects on the sunitinib 37.5 mg or 50 mg/day on Schedule 4/2 with FOLFIRI, of which 2 subjects experienced Grade 4 chemistry abnormalities. One subject on sunitinib 25 mg/day on Schedule CDD with FOLFIRI experienced Grade 3 chemistry abnormalities. No other shifts in blood chemistry parameters were experienced.

- Sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI: Changes in ECOG performance status compared to baseline were observed in 14 of 21 subjects: 7 subjects (33.3%) with an ECOG performance status of 0 at baseline experienced a maximum decline to an ECOG performance status of 1 or greater during the study. The number of subjects with ECOG performance status 1 increased from 7 subjects (33.3%) to 11 subjects (52.4%). Two subjects (9.5%) experienced a decline to ECOG performance status 2, and 1 subject (4.8%) experienced a decline to an ECOG performance status of 3 during the study.

- Sunitinib 50 mg/day Schedule 4/2 with FOLFIRI: Changes in ECOG performance status compared to baseline were observed in 2 of 6 subjects: 2 subjects (33.3%) with an ECOG performance status of 0 at baseline experienced a maximum decline to an ECOG performance status of 1 during the study.

- Sunitinib 25 mg/day on Schedule CDD with FOLFIRI: Changes in ECOG performance status compared to baseline were observed in 3 of 7 subjects: 3 subjects (42.9%) with an ECOG performance status of 0 at baseline experienced a maximum decline to an ECOG

performance status of 1, and 2 subjects (28.6%) experienced a maximum decline to an ECOG performance status of 2 during the study.

- Sunitinib 37.5 mg/day on Schedule CDD with FOLFIRI: Changes in ECOG performance status compared to baseline were observed in 2 of 3 subjects: 1 subject (33.3%) with an ECOG performance status of 0 at baseline experienced a maximum decline to an ECOG performance status of 1, and 1 subject (33.3%) experienced a maximum decline to an ECOG performance status of 2 during the study.

No subjects had systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg.

The mean QTc interval was similar to baseline when measured on Day 1 of Cycle 3 and at the end of treatment.

One subject on sunitinib 37.5 mg/day on Schedule 4/2 with FOLFIRI, who had a QTc interval within the normal range (390, 412, 390 sec) at baseline, had a maximum on-study Grade 3/4 QTc interval of 460, 510, 440 sec on Day 36.

CONCLUSIONS:

- The MTD of sunitinib was 37.5 mg/day on Schedule 4/2 in combination with FOLFIRI in metastatic CRC subjects. The most commonly reported DLT was neutropenia.

- The overall AE and laboratory profile of this combination in subjects with metastatic CRC was generally acceptable and clinically manageable at the MTD. The most common Grade 3/4 AEs of neutropenia and diarrhea were adequately controlled with standard medical management.

- There were no clinically significant changes in the PK of SU011248, irinotecan, or 5-FU when these drugs were combined, indicating a lack of PK drug-drug interaction between these drugs when co-administered.

- There was evidence of antitumor activity with this combination in metastatic CRC subjects, with 11 of 19 (58%) subjects at the MTD achieving an objective response.