CESAR

Central European Society for Anticancer Drug Research-E W I V

CLINICAL STUDY REPORT

(Preliminary / Part on Safety only)

A prospective angiogenic imaging study with DCE-MRI and DCE-USI in patients with colorectal cancer

Study protocol No:	**CESAR C-II-005 / EUDRACT 2008-001515-37**
Document status:	**Final**
Investigational product:	Sutent® (Sunitinib)
Sponsor	CESAR Central European Society for Anticancer Drug Research-EWIV Hanglüssgasse 4/1-3, A-1150 Vienna, Austria
Study Chairman:	Priv.-Doz Dr. Klaus Mross Tumor Biology Center Dept. Medical Oncology, Breisacherstrasse 117 D-79106 Freiburg i.Br., Germany phone: +49-761 206 1802, fax: +49-761 206 1832 email: mross@tumorbio.uni-freiburg.de
Development phase:	Phase II
Study initiation date:	28-Aug-2008 (first patient in)
Study termination date:	06-Sep-2010 (last patient out)
CESAR Central Office (Sponsor Signatory)	Dr. Berta Moritz Hanglüssgasse 4/1-3, A-1150 Vienna, Austria phone: +43 1 522 30 9312, fax: +43 1 522 30 93 14 email: berta.moritz@cesar.or.at

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

Date of the report: 20 September 2011

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASR	Annual Safety Report
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BF	Blood flow
CBC	Complete Blood Count
CCO	CESAR Central Office
CR	Complete Response
CRC	Colorectal cancer
CRF	Case Report/Record Form
CRO	Contract Research Organization
CPT	Irinotecan, CPT-11, Campto®
CT	Computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DCE-MRI	Dynamic-Contrast-Enhanced Magnetic Resonance Imaging
DCE-USI	Dynamic-Contrast-Enhanced Ultrasound Imaging
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FOLFIRI	5-FU + Folinic Acid + Irinotecan
FOLFOX	5-FU + Folinic Acid + Oxaliplatin
GCP	Good Clinical Practice
iAUC60	Initial area under the curve (60 sec)
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ITT	Intent-to-Treat
K_{trans}	Transfer constant
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
N_R	Number of patients recruited
N_S	Number of patients evaluable according to study protocol
OS	Overall Survival
PD	Progressive Disease
PFS	Progression free survival
PFS12	Progression Free for at 12 Weeks
PPP	Per-Protocol-Population
PR	Partial Response
Pt-ID	patient-identification
PV BD	pharmacovigilance database
QT prolongation	Prolongation of the QT interval (measure of the time between the start of the Q wave and the end of the T wave)
SAE	Serious Adverse Event

List of abbreviations (cont'd)

SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SP	Safety Population
SUSAR	Serious Unexpected Suspected Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour-Node-Metastasis
TSH	Thyroid Stimulating Hormone
TTF	Time-to-treatment failure
TTP	Time-to-progression
TVP	Tumor vessel permeability
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Count

1. Introduction

The CESAR Study C-II-005 was initiated to evaluate whether the addition of sunitinib to FOLFIRI results in a significant reduction of tumor vessel permeability (TVP) and blood flow (BF) measured by DCE-MRI and DCE-USI on liver metastases in patients with colorectal cancer.

The clinical part of the study started on 28 Aug 2008 (first patient in) and ended on 06 Sep 2010 (last patient out). The study was closed on 12 Jul 2010 upon decision of the Sponsor, since the recruitment target had been reached. All patients had stopped treatment at this time.

The clinical database was closed End January 2011 and transferred for statistical analyses on 03 Feb 2011. The Statistical Analysis Plan (SAP) was finalized on 28 Jan 2011. The final biometrical report is not yet available. This report represents an abbreviated report based on the draft biometrical analysis report[1] on 29 Aug 2011 and focuses on safety. The report will be updated after the final biometrical analysis report becomes available which is expected for October/November 2011.

2. Ethics and Regulatory

This study was performed in compliance with ICH guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki for biomedical research involving human subjects.

2.1. Informed Consent Form of Trial Subjects

In obtaining and documenting informed consent, the investigator did comply with the applicable regulatory requirements and adhere to ICH guideline for GCP and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the investigator or an authorized physician gave the subject oral and written information about the trial in a form that the subject can read and understand and a signed and dated Informed Consent Form was obtained. In addition, the written informed consent was signed by the person who conducted the informed consent process.

The original Informed Consent Form (ICF) was updated as follows:

ICF	Date	Document(s)	Reason for change
Original	28-Mar- 2008		
1st change	02-Sep- 2008	New ICF	FOLFIRI Schedule simplified
2nd change	02-Sep- 2009	New ICF and Addition to ICF	List of side effects updated due to changes in SmPC (addition of: fatigue, depression, problems

[1] Please note that the biometrical analysis report uses the RandomNo according to the nomenclature in the clinical database. In this report, the term Pt-ID (patient-identification) is used instead.

			to fall asleep, QTc prolongations)
3rd change	29-Mar-2010	New ICF and Addition to ICF	Fistula formation added to side effects (due to change in SmPC).

All document versions were submitted to the ECs, and implemented only following favorable opinion by the ECs.

Patients that were receiving treatment on study when new safety information became available were informed by their treating physician and asked to sign the respective Addition to ICF.

2.2. Independent Ethics Committees

Prior to commencement of the trial, the protocol, any amendments, Subject Information/Informed Consent Form, any other written information to be provided to the subject, Investigator's Brochure (IB), information about payments and compensation available to subjects, the investigator's current CV and other documentation evidencing qualifications, and other documents as required were submitted to the IEC in Freiburg, acting as Leading Ethics Committee ("federführende Ethikkommission") and to the ECs concerned. Written favorable opinion was obtained from the IEC on 26-May-2008.

All protocol amendment, and changes to the Informed Consent were submitted (or notified, in case of non-substantial protocol amendments) to the ECs. Two Annual Safety Reports were also submitted.

2.3. Regulatory Authorities

The Regulatory Authority in Germany, the BfArM, received the Clinical Trial application with all documents required on 24 Apr 2008 and granted approval to conduct the clinical study on 11 Jun 2008.

The original protocol was dated 25 Mar 2008. The following protocol amendments were made:

Amendment	Protocol version	date	Description
1	1.1	28-Jul-2008	Only Sunitinib in its commercial presentation will be used, as agreed upon with BfArM. Clarified that no additional radiation exposure than in clinical routine.
2	1.2	16-Sep-2008	Use a simplified FOLFIRI regimen
3	1.3	18-Nov-2008	Change in the study schedule with regard to the time-points for the evaluations of DCE-MRI and DCE-USI (from baseline, 4, 10, 12 weeks to baseline, 2,4,6 weeks)
4	2.0		Inclusion "Fistula" in in Section on Sunitinib adverse reactions. Main responsibility for study statistics transferred from Dr. Lutz Edler (Abteilung Biostatistik C060, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany) to Dr. Iris Burkholder (StaBiL

			Statistische und Biometrische Lösungen, Pistorstr. 7, D- 66482 Zweibrücken, Germany)

Amendment 3 was classified as „non-substantial amendment“ by the Sponsor and submitted to the BfArM together with the ASR. The BfArM noted that this constitutes a substantial amendment. The Sponsor provided a rationale on 29-Sep-2009, outlining that the changes in the time-point for measurements of DCE-MRI and DCE-USI did not influence the statistical assumptions in sample size calculation. BfArM granted approval on 18 Oct 2009.

Amendment 4 was submitted on 01 Apr 2010 and approval was granted on 20 Apr 2010.

2.4. Insurance

All subjects participating in this clinical trial were insured via HDI-Gerling Industrie Versicherung AG, Überseering 10a, 22297 Hamburg under the policy number 70-006620454-2.

3. Investigators and Study Administrative Structure

This clinical study was initiated by PD Dr. Klaus Mross, Freiburg and sponsored by the CESAR (Central European Society of Anticancer drug Research - EWIV). The CESAR is a scientific non-profit organization with the aim to foster research and development of novel drugs and therapies in Oncology. CESAR has the sole responsibility for design, conduct, recording and reporting of the study and is the owner of the clinical data generated.

The study was conducted in 4 centers in Germany:

Site 01
Priv.-Doz Dr. Klaus Mross
Tumor Biology Center
Dept. Medical Oncology, Breisacherstrasse 117
D-79106 Freiburg i.Br., Germany

Site 02
Prof. Dr. Max Scheulen
Innere Univ.-Klinik u. Poliklinik Tumorforschung
Hufelandstrasse 55, D-45122 Essen

Site 03
PD Dr. Dirk Strumberg
Marienhospital
Abt. Hämatologie & Onkologie
Hölkekampring 40, D-44625 Herne

Site 04
PD Dr. Richard Fischer
Medizinische Universitätsklinik der Albert-Ludwigs-Universität Freiburg
Abt. Gastroenterologie
Hugstetterstr. 55, D-79106 Freiburg

In addition, two MRT application centers in the departments of radiology of the University Hospital in Freiburg and in Essen were included:

Dr. Martin Büchert
Magnetic Resonance Development and Application Center
Radiologische Klinik der Universitätsklinik der Albert-Ludwigs-Universität Freiburg, Hugstetterstr. 55
D-79106 Freiburg

and
Dr. Dr. Jörg Stattaus
Radiologische Klinik der Universitätsklinik Essen
Hufelandstr. 55, D-45122 Essen

DCE-measurements were performed at the Radiology in Freiburg for sites 01 and 04, and in Essen for sites 02 and 03. Data were centrally evaluated by Dr. Büchert in Freiburg.

It was the original plan to centrally evaluate all DCE-USI data in Freiburg by Dr. Jan Arends, Tumor Biology Center. Due to incompatibility in data generated in Freiburg and Essen, this could not be done. Therefore these findings are not included in the biometrical analysis.

Serum biomarkers (VEGF and soluble VEGF-receptors 2 and 3) and pharmacokinetics were analyzed at ProQinase GmbH, Breisacher Str. 117, 79106 and evaluated in the Department of Clinical Pharmacy, Universitätsklinik Bonn, Prof. Dr. Ulrich Jaehde, An der Immenburg 4, 53121 Bonn.

Project management was done by the CESAR Central Office (CCO), Hanglüssgasse 4/1-3, 1150 Vienna, Austria. Data Management and Monitoring was performed by iOMEDICO AG, Hanferstr. 28, D-79108 Freiburg.

The statistical evaluation was originally to be performed by Dr. Lutz Edler, CESAR's Biostatistics (CBS) at the Deutsches Krebsforschungszentrum Heidelberg. Main responsibility for study statistics were transferred to Dr. Iris Burkholder (StaBiL Statistische und Biometrische Lösungen, Pistorstr. 7, D- 66482 Zweibrücken, Germany) in 2010, following the retirement of Dr. Edler at the DKFZ.

4. Study Objectives

The primary objective of this study was to evaluate whether the addition of sunitinib to FOLFIRI resulted in a significant reduction of tumor vessel permeability (TVP) and blood flow (BF) measured by DCE-MRI and DCE-USI on liver metastases.

Secondary objectives were antitumor response, time to progression (TTP), effect on pharmacokinetics of sunitinib and biomarkers (VEGF und soluble VEGF-receptor) and drug/treatment safety.

5. Investigational Plan

5.1. Overall Study Design and Plan-Description

Colorectal cancer shows coexpression of VEGF and PDGF: thus sunitinib, blocking both VEGFR and PDGFR, might be active in treating colorectal carcinoma.

No data with angiogenic imaging techniques have been available when combining FOLFIRI and sunitinib in metastatic colorectal cancer. Dynamic-Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) has become a standard procedure to evaluate antiangiogenic procedures. Dynamic-Contrast-Enhanced Ultrasound Imaging (DCE-USI) is available as new technique since contrast-enhancing drugs have been introduced 3 years ago. The technique has been successfully introduced recently into clinical antiangiogenic research. As liver metastasis are optimal for such research program and liver metastasis are the main site of metastasis in colorectal cancer, this clinical research program was focusing in the antiangiogenic imaging evaluation using liver metastasis as main target of the imaging studies. Besides the implemented imaging procedures common tumor response criteria as well as the common toxicity criteria and some antiangiogenic biomarkers measured in blood samples were to be used to correlate response data with DCE-MRI and DCE-USI data as well as with biomarkers.

This was an open label single arm prospective multicenter study. Patients with colorectal cancer with liver metastasis were eligible for the trial. It was planned to recruit (N-recruited) NR=22 patients into the study with the aim of 20 patients treated according to the study protocol (Ns = 20)

The primary objective of this study was to evaluate whether the addition of sunitinib to FOLFIRI resulted in a significant reduction of tumor vessel permeability (TVP) and blood flow (BF) measured by DCE-MRI and DCE-USI on liver metastases.

Secondary objectives were antitumor response, time to progression (TTP), effect on pharmacokinetics of sunitinib and biomarkers (VEGF und soluble VEGF-receptor) and drug/treatment safety.

One therapy cycle was defined as 6 weeks. Patients were to receive sunitinib 37,5 mg/d in cycles of 6 weeks with a 4 weeks on / 2 weeks off schedule, added to FOLFIRI (*L*-Folinic Acid 200 mg/m² 2h day 1 & 2, 5-FU 400 mg/m² bolus day 1 & 2, 5-FU 2400 mg/m² over 46 h infusion day 1 & 2 and irinotecan 180 mg/m² 1h day 1 (all intravenously) every 2 weeks.

All patients had to visit the study center sites at regular time intervals, for determination of the safety laboratory parameters, recording of AEs and the predefined investigations as outlined in the flow chart. An assessment of tumor response were to be performed at baseline, 6 and 12 weeks after start of treatment

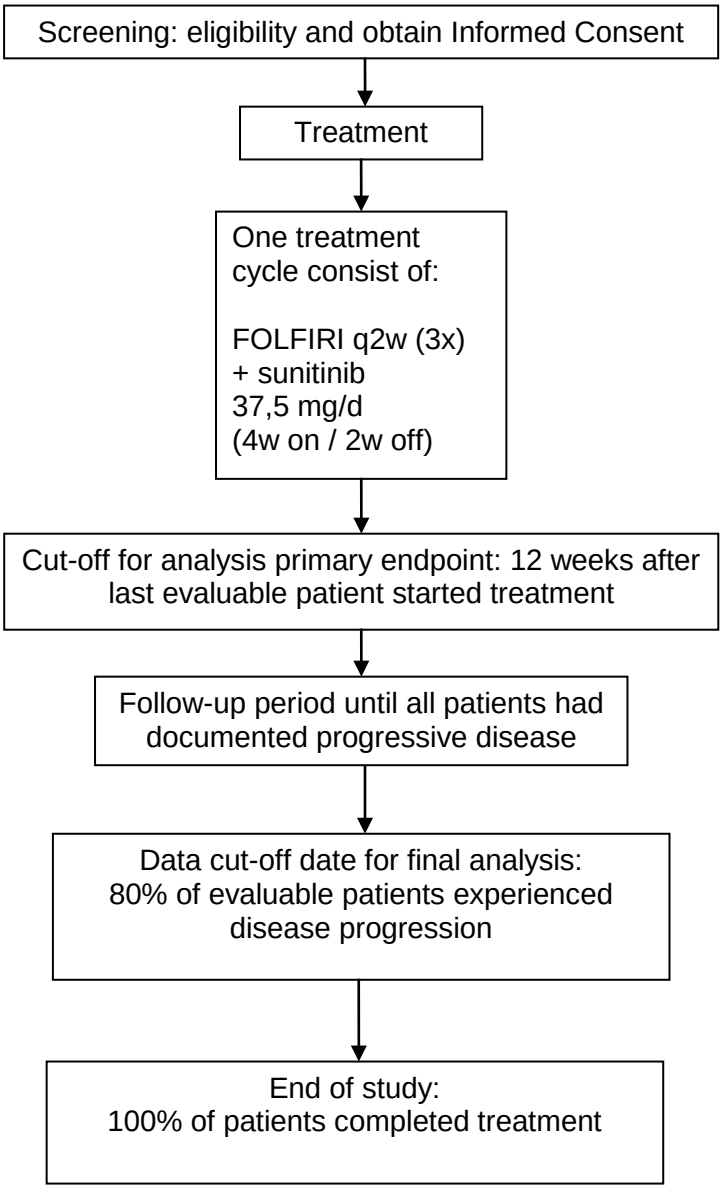
and every 12 weeks thereafter. Tumor response was to be assessed by using the RECIST criteria 1.0.

The trial was to be performed by investigators specialized in the treatment of colorectal cancer having experience with DCE-MRI and DCE-USI. The tumor assessment which was required for deciding the continuation of a patient's trial participation was to be performed at the investigators site. The safety laboratory investigations were also to be performed at the investigators site. Additionally laboratory investigations were allowed by the local oncologist / general physician if indicated.

Patients were to receive therapy until disease progression or intolerable toxicity whichever came first.

In case of tumor progression, treatment on study ended for all patients. Patients could receive further treatment according to best local practice, possible treatments were eg. 2nd line: irinotecan + erbitux followed by 3rd line FOLFOX or XELOX +/- Avastin or vice versa.

Figure 1 illustrates the study design:



Since the established date for data cut-off for final analysis was not yet reached when all patients completed treatment, due to a higher number of early withdrawals, the cut-off date was the date of study closure (06 Sep 2010).

Study Assessments were:

Activity Assessment:

Tumor vessel permeability (TVP) and blood flow (BF) will be determined by dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI and additionally with dynamic-contrast-enhanced ultrasound imaging (DCE-USI). DCE-MRI and DCE-USI will be performed at baseline and in week 4, 10 and 12 after start of treatment.

Efficacy Assessments:

Tumor Assessment, according to RECIST criteria: at baseline, 6 and 12 weeks after start of treatment and every 12 weeks thereafter until disease progression.

Pharmacokinetics and Biomarkers:

Plasma concentrations of sunitinib and its metabolite SU12662 and biomarkers (VEGF und soluble VEGF-receptors 2 and 3) are measured at baseline and at 9 time-points during the first 17 weeks of treatment.

Safety Assessments:

Medical history: at baseline

Physical Examination: Complete physical exam at baseline and end of treatment visit; Interim physical examinations including ECOG score, vital signs, weight and brief review of systems and physical examination of pertinent organ systems: every 2 weeks during treatment.
ECG: at baseline and at the end of treatment visit.

Hematology – Complete Blood Cell Count (CBC): prior to each administration of FOLFIRI

Chemistry comprising sodium, potassium, chloride, calcium, Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), Lactate Dehydrogenase (LDH), gamma-GT (GGT), alkaline phosphatase (AP), bilirubin, albumin, total protein, glucose, creatinine: at baseline, every 2 weeks during the treatment and at the end of treatment visit.

Coagulation comprising Prothrombin Time (PT) or PT-INR, and activated Partial Thromboplastin Time (aPTT): at baseline, every 6 weeks during the treatment and at the end of treatment visit.

Thyroid function comprising Thyroid Stimulating Hormone (TSH), T3 (total) and T4 (total): at baseline, every 6 weeks during the treatment and at the end of treatment visit.

Pregnancy test: Urine or serum pregnancy test, if applicable (i.e. in female patients of child-bearing potential): within one week prior to the start of treatment and at the end of treatment visit.

Monitoring and recording all adverse events (AE): continuously

5.2. Selection of Study Population

Patients with colorectal cancer and liver metastasis intended to receive first-line FOLFIRI chemotherapy were enrolled in the study.

Inclusion Criteria

(1) Adult males and females: over 18 years of age.

(2) Patients with histologically or cytologically confirmed colorectal cancer who will receive their first palliative treatment.

(3) Patients who have at least one measurable hepatic lesion of 2 cm or more in the MRI evaluable according to RECIST criteria.

(4) ECOG 0 or 1.

(5) Signed written informed consent.

(6) White blood cell count (WBC) $\geq$ 4x10*9/L with neutrophils $\geq$ 1.5 x 10*9/L, platelet count $\geq$ 100x10*9/L, hemoglobin $\geq$ 5.6 mmol/L (10 g/dL).

(7) Total bilirubin $\leq$ 2 x upper limit of normal.

(8) AST and ALT $\leq$ 2.5 x upper limit of normal, or $\leq$ 5 x upper limit of normal in case of liver metastases.

(9) Serum creatinine $\leq$ 1.5 x upper limit of normal or creatinine clearance > 60 ml/min.

(10) Normal ECG without QT prolongation.

Exclusion Criteria

(11) Resectable liver metastasis

(12) Adjuvant therapy with FOLFOX or 5-FU / Capecitabine =< 6 months prior to treatment on study or any previous palliative chemotherapy.

(13) Any contraindication for FOLFIRI chemotherapy regimen.

(14) Any investigational drug within the 30 days before inclusion.

(15) Prior use of sunitinib or other multitarget tyrosine kinase inhibitors or VEGF pathway directed treatments like bevacizumab.

(16) Known or suspected allergy or hypersensitivity reaction to any of the components of study treatments.

(17) Pregnancy (absence to be confirmed by beta-hCG test) or lactation period.

(18) Men or women of child-bearing potential who are sexually active and unwilling to use a medically acceptable method of contraception during the trial.

(19) Clinically symptomatic brain or meningeal metastasis (known or suspected).

(20) Cardiac arrhythmias requiring anti-arhythmics (excluding beta blockers or digoxin).

(21) History of any of the following cardiac events within the past 6 months:

- myocardial infarction (including severe/unstable angina),
- coronary/peripheral artery bypass graft,
- congestive heart failure (CHF),
- cerebrovascular accident or transient ischemic attack,
- pulmonary embolism.

(22) History of clinically significant bleeding within the past 6 months, including gross hemoptysis or haematuria, or underlying coagulopathy.

(23) History of peptic ulcer disease, deep vein thrombosis, or other significant thromboembolic event within the past 6 months.

(24) Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 90 mm Hg despite the use of $\geq$ 3 anti-hypertensive drugs.

(25) Acute or sub-acute intestinal occlusion or history of inflammatory bowel disease or chronic diarrhea.

(26) Previous malignancy (other than colorectal cancer) in the last 5 years except basal cell cancer of the skin, pre-invasive cancer of the cervix or superficial bladder tumor [Ta, Tis and T1].

(27) History of organ allograft.

(28) Treatment with potent CYP3A4 inhibitor within 7 days of sunitinib/placebo dosing or with potent CYP3A4 inducer within 12 days of sunitinib/placebo dosing.

(29) Prior full field radiotherapy $\leq$ 4 weeks, or limited field radiotherapy, $\leq$ to 2 weeks prior to study enrollment; or previous radiation treatment >30% of the bone marrow.

(30) Major surgical procedure, open biopsy or significant traumatic injury within 4 weeks before starting treatment; anticipation of need for major surgical procedure (e.g., impending bowel obstruction) during the course of the study.

(31) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment, unless affected area has been removed surgically.

(32) Significant disease which, in the investigator's opinion would exclude the patient from the study.

(33) Patients with seizure and epileptic disorder or other conditions requiring medication such as phenytoin, carbamazepin, phenobarbital.

(34) Patients requiring long-term cortisone therapy.

(35) Patients requiring oral anticoagulation treatment (marcoumar).

(36) Known alcohol or drug abuse.

(37) Medical or psychological conditions that would not permit the patient to complete the study or sign informed consent.

In version 2.0 of the protocol, the following exclusion criterion was added:

(38) Current fistula formation.

5.3. Study Treatments

Treatments consisted of Sunitinib 37.5 mg/d (Sutent®) in cycles of 6 weeks with a 4 weeks on / 2 week off schedule, added to FOLFIRI therapy given every two weeks.

FOLFIRI[2] is a combination chemotherapy consisting of *L*-folinic acid (FA)[*] 200 mg/m² in 250 ml NaCl 0.9% given as 2 h infusion at day 1 of every 14 days. After FA, 5-fluoruracil (5-FU) 400 mg/m² in 50 ml NaCl 0.9% was given as bolus injection at day 1. 5-FU 2400 mg/m² in 250 ml NaCl 0.9% was given as continuous infusion over 46 hours at day 1 and 2. On day 1, irinotecan (CPT-11) was given at 180 mg/m² in 250 ml NaCl 0.9% as 1 h infusion. The FOLFIRI application needed totally 48 hours with continuous infusion, 1 and 2 h infusions and bolus injections.

The following dose modification schemes were provided in the protocol:

> "Any hematological toxicity CTCAE grade ≥ 3 in case of duration of neutropenia > 7 days or neutropenic fever or CTCAE grade 4 thrombocytopenia or anemia, will lead to a dose reduction of Sunitinib to 25 mg/day.
>
> If haematological toxicities as described above continue, withhold sunitib until toxicity is grade $\leq$ 1 or has returned to baseline, then resume sunitinib at dose of 25 mg/day. If haematological toxicities recur, decrease FOLFIRI (Irinotecan 30 – 35 % 5-FU 30-35%).
>
> If toxicity recurs with grade ≥ 3 in case of duration of neutropenia > 7 days or neutropenic fever or CTCAE grade 4 thrombocytopenia or anemia, this will be considered intolerable toxicity.
>
> If any non-hematological toxicity CTCAE grade 3 or 4 (except for fever, chills and flulike symptoms or alopecia; liver transaminase elevations, hyperuricemia or hypophosphatemia without clinical symptoms; inadequately treated diarrhea, nausea and vomiting and tolerable rash) occurs, and no dose reduction due to

[2] FOLFIRI is the standard therapy for first-line mCRC. FOLFIRI, however, can, be given in different regimen. The regimen used here is the same as used in the Phase I study to evaluate safety and tolerability of FOLFIRI in combination with sunitinib.

[*] instead of 200 mg/m² *L*-folinic acid, 400 mg/m² racemic folinic acid could be used.

hematological toxicity has been done or is done simultaneously, one of the following dose reductions will be performed, depending on the suspected causality of the occurring toxicity:

- Sunitinib: decrease to 25 mg/d or withhold dose until toxicity is grade $\leq$ 1 or has returned to baseline, then resume treatment at the same dose level. If toxicity recurs with grade 3 severity, reduce the dose to 25 mg/d.
- Irintoecan: decrease by 33% (30-35%)
- 5-FU: decrease by 33% (30-35%).

If symptoms do not improve, the original dose of the drug that has been reduced should be restarted, and one of the other compounds reduced instead.

In case of grade 3 and 4 dermatological toxicities, consider to first withhold sunitinib for 1 week, and restart with 25 mg/day following recovery. If no improvement is seen, restart sunitinib and reduce 5-FU by 33% (30-35%).

It will be considered intolerable toxicity if:

- more than 4 weeks treatment interruption (of either sunitinib or FOLFIRI) due to unresolved toxicity would be required;
- dose reduction of sunitinib to < 25 mg/d would be required;
- hematological toxicity (grade ≥ 3 in case of duration of neutropenia > 7 days or neutropenic fever or CTCAE grade 4 thrombocytopenia or anemia) recurs following reduction to 25 mg and withholding sunitinib until toxicity have resolved.

If intolerable toxicity occurs, treatment on study should be stopped."

6. Statistical Methods: Determination of Sample Size

The CESAR Study C-II-005 was initiated to evaluate whether the addition of sunitinib to FOLFIRI results in a significant reduction of tumor vessel permeability (TVP) and blood flow (BF) measured by DCE-MRI and DCE-USI on liver metastases in patients with colorectal cancer.
The assessment of the primary endpoint of DCE-MRI was planned at baseline and in weeks 4, 10 and 12. Amendment 3 of the study protocol implemented a change in the study schedule with regard to the time-points for the evaluation of DCE-MRI. According to the new schedule, TVP and BF was determined at baseline, 2, 4 and 6 weeks after start of treatment.

The study was designed as an open-label, single arm, prospective, multicenter phase II study and planned such that two statistical hypothesis tests on the two differences (D) ΔiAUC and Δ K_{trans} can be tested in two one-sided statistical tests at the multiple significance level alpha=0.05 (two tests performed at the nominal level of 0.025). Formally:

H_0: D=0, i.e. no change within 6 weeks

versus

H_1: D<0, i.e. reduction within 6 weeks

will be tested for D=ΔiAUC and ΔK_{trans}, respectively.
The sample size was planned as of 22 patients to achieve a power of at least 80% in iAUC.

7. Study Patients

7.1. Disposition of Subjects

The clinical part of the study started on 28-Aug-2008 (first patient in) and ended on 06-Sep-2010 (last patient out). Altogether 28 patients were recruited by 4 institutions. The number of recruited patients per center is given in Table 1.

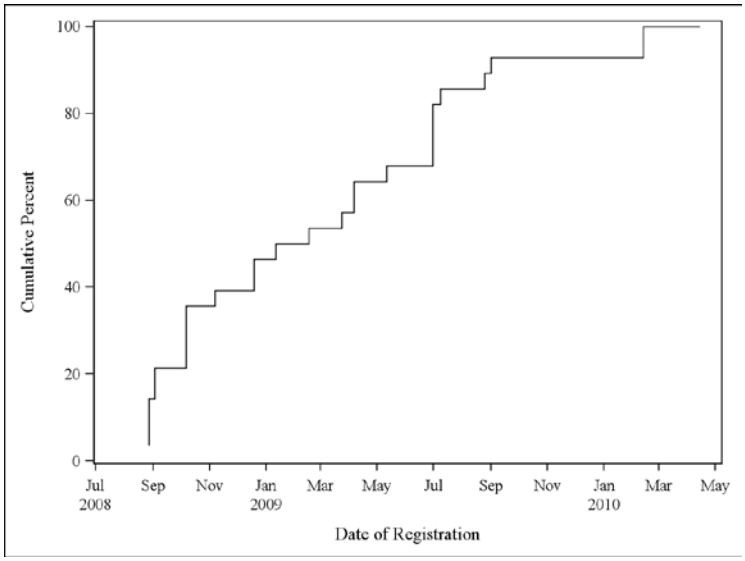
Table 1: Number of recruited patients per center

		Total n (%)	*Pt-ID. coded as*
Recruiting by center	Fischer, Freiburg	9 (32%)	0401 ≤ Pt-ID.≤ 0409
	Mross, Freiburg	6 (21%)	0101 ≤ Pt-ID. ≤ 0107
	Scheulen, Essen	10 (36%)	0201 ≤ Pt-ID.≤ 0210
	Strumberg, Herne	3 (11%)	0301 ≤ Pt-ID. ≤ 0303

Note: Calculation of percentages based on the number of screened patients (N=28)
Source: Table 1.1.

A total of 28 patients was screened -. The total number of patients by recruiting time is illustrated in Figure 2.

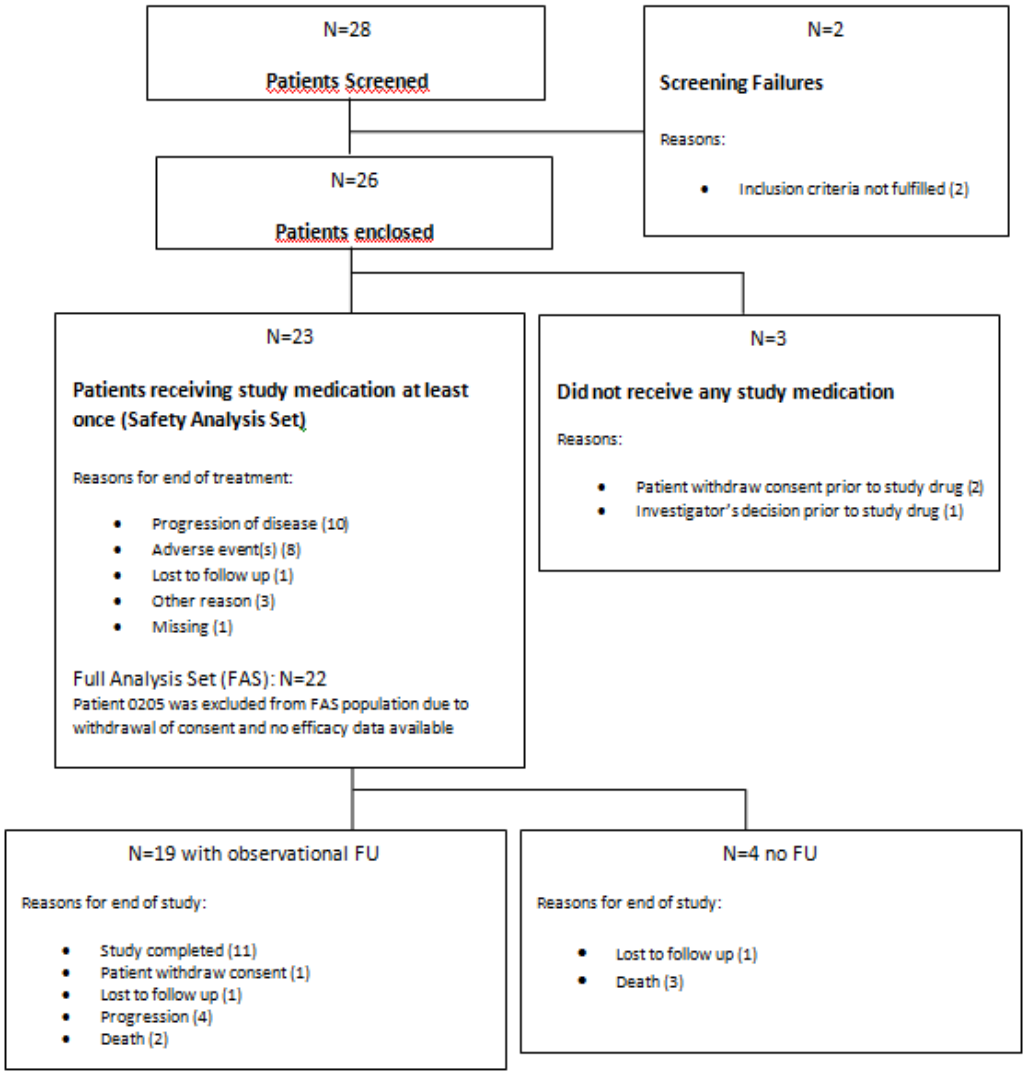
Figure 2: Number of patients by recruiting time



Note: Calculation of percentages based on the number of screened patients (N=28)

Out of the 26 enclosed patients, 3 (12%) did not receive any study medication, while 23 (88%) received at least once the study treatment. Figure 3 shows the progress of the study.

Figure 3: Patient Disposition



Out of the 26 enrolled patients, 23 patients (88%) started the treatment. The treatment on study was ended due to disease progression in 10 patients, and due to an adverse event in 8 patients (see Section 8.3). In 1 case, patient was lost to follow-up, and 1 patient withdrew informed consent. Other reasons for end of treatment (in 3 patients) were:

- Explorative Laparotomy with left-lateraler Liver Resection (pt-ID 0202)
- Tumor response: Hemihepatectomy right OP (pt-ID 0204)
- Investigator´s Decision: Risk of rectal bleeding (pt-ID 0206)[3].

[3] This patient had earlier developed melaena, considered as related to Sunitinib, and leading to temporal interruption of Sunitinib.

For patient 0301 end for treatment on study was disease progression. At the same , 2 AEs (Astenia, possibly related und Hyperbilirubinaemia, not related) were reported as leading to discontinuation of Sunitinib. The study site provided the following statement on the sequence of events:

> "The patient presented on 9 Jan 2009 with asthenia II°, most likely related to sunitinib since it is a well known adverse event. In detail, our patient reported problems walking her dog; she could only walk slowly and felt insecure when walking due to frailty. We therefore decided to pause treatment with sunitinib, a reevaluation in terms of continuation or cessation of treatment was scheduled for the following week.
> However, only four days (13 Jan) later, the patient presented with a worsened general condition and a clearly visible jaundice. Hospitalization was needed in order to quickly assess the reason (which was progression of the disease in a very rapid and massive way) and to assess possibilities of ameliorating the jaundice (which unfortunately could not be done in the end). A CT scan on the 14 Jan revealed not only metastatic destruction of the liver, but also an obstruction of the small intestine in the context of a suspected peritoneal carcinomatosis. Best supportive palliative care was given, she died on 28 Jan 2009[4]."

The study was closed after all 23 patients had completed treatment. Out of the 26 enclosed patients, 11 (42%) patients terminated the study due to study closure by the sponsor, and 15 (58%) patients had already terminated the study prematurely. The reasons for end of study are summarized in Table 2.

Table 2: Reasons for end of study

			Total n (%)
Reasons for end of study	**Before start of treatment**	Patient withdrew consent prior to study drug	2 (8%)
		Investigator's decision prior to study drug	1 (4%)
	After completion of treatment	Patient lost to follow-up	2 (8%)
		Patient withdrew consent	1 (4%)
		Progression	4 (15%)
		Patient died	5 (19%)
		Study closed	11 (42%)

Note: Calculation of percentages based on the number of enrolled patients (N=26)

7.2. Protocol Deviations

The following major protocol deviations to the eligibility criteria occurred in all patients enclosed into the study:

[4] See also section 8.6, Death cases

- No hepatic lesions in two patients
    - patient receiving at least once study medication: 0205
    - patient not receiving study medication: 0209
- The number of white blood cells was lower than 4x10*9\L in one patient
    - patient receiving at least once study medication: 0105
- Hemoglobin was lower than 10 g\dL in two patients
    - patient receiving at least once study medication: 0401
    - patient not receiving study medication: 0209

Patients 0205, 0105 and 0401 were included in the Safety Analysis set, but excluded from the Per Protocol set of patients. Patients 0105 and 0401 were included in the Full Analysis Set, patient 0205 was excluded from the Full Analysis Set, since he withdrew informed consent early and did not have any efficacy data. The patient 0209 was not included in any Analysis Set as he did not receive the study medication at least once.

8. Safety

8.1. Extent of Exposure

The total cumulative dose per patient and medication was summarized using descriptive statistics over the whole treatment period in Table 3.

Table 3: Cumulative doses (SAS)

		FA (in mg)	*5-FU bolus (in mg)*	*5-FU cont. (in mg)*	*CPT (in mg)*	*Sunitinib (in mg)*
Total dose over all cycles	N	23	23	23	23	23
	Mean	3703.0	7163.4	42568	3134.0	2913.0
	SD	2286.49	4641.80	27895.6	2027.62	1754.96
	Median	3180.0	6300.0	36000	2700.0	2512.5
	Min	420.0	840.0	5000.0	370.0	600.0
	Max	8360.7	16250	97500	6889.7	6075.0

Note: SD=Standard deviation, Min=minimum, Max=maximum

The length of a cycle was defined as 6 weeks. The number of active patients at the beginning of each cycle is summarized in Table 4.

Table 4: Active patients per cycle

		Total n (%)
Cycle number	**1**	23 (88.5%)
	2	18 (69.2%)
	3	16 (46.2%)
	4	12 (46.2%)
	5	7 (26.9%)
	6	6 (23.1%)
	7	3 (11.5%)
	8	2 (7.7%)

Note: Calculation of percentages based on the number of -enrolled patients (N=26)

Time under treatment was calculated from first intake to last intake of study medication. Median time under treatment was 18.4 weeks (range: 2.3-50.7 weeks).

8.2. Adverse Events

Altogether 412 AEs occurred in the SAS, 164 of them were not related/unlikely to any of the the study medications, whereas 247 the relation to study drug was assessed as definite, probable or possible (suspected AE); relation to study medication was not assessable in one patient. All 23 patients of the SAS had at least one AE under study and 21 patients had at least one suspected AE.

For the 247 suspected AEs, relation to study drug was assessed to be definite in 18 AEs, probable in 30 AEs and possible in 199 AEs.

AEs classified as having a definite causal relationship to study medication were leucopenia, neutropenia, fatigue, hypertension, paraesthesia, anal ulcer, mucosal inflammation, melaena, constipation, vomiting and nausea, each one occurring in one patient only. Some events occurred more than once in one patient (leucopenia [6], fatigue [2] and vomiting [2], resulting in a total of 18 AEs in 11 patients.

Adverse events CTC Grade 3 and CTC Grade 4 with maximum suspected causal relationship to study medication are provided in Table 5. CTC Grade 4 suspected adverse events were bone marrow failure (1), leucopenia (2), neutropenia (4) and pulmonary embolism (1).

Table 5: Adverse events CTC 3 and CTC 4 with suspected causal relationship to study medication

System Organ Class	***Preferred Term***	***Relation***	*CTC 3 n[1] (%)*	*CTC 4 n[1] (%)*
Blood and lymphatic system disorders	Anaemia	possible	1 (4 %)	
	Bone marrow failure	probable		1 (4 %)
	Leukopenia	possible	2 (9 %)	2 (9 %)
		probable	1 (4 %)	
	Neutropenia	definite		1 (4 %)
		possible	4 (17 %)	3 (13 %)
		probable	1 (4 %)	
	Thrombocytopenia	possible	1 (4 %)	
Gastrointestinal disorders	Gastritis	possible	1 (4 %)	
	Melaena	definite	1 (4 %)	
	Stomatitis	possible	3 (13 %)	
General disorders and administration site conditions	Ulcer[2]	possible	1 (4 %)	
Infections and infestations	Infected skin ulcer[3]	possible	1 (4 %)	
Investigations	C-reactive protein increased	possible	1 (4 %)	
Nervous system disorders	Loss of consciousness	possible	1 (4 %)	
	Paraesthesia	definite	1 (4 %)	
	Syncope	possible	1 (4 %)	
	Transient ischaemic attack	possible	1 (4 %)	
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	possible		1 (4 %)
Skin and subcutaneous tissue disorders	Hyperkeratosis	possible	1 (4 %)	
Vascular disorders	Hypertension	possible	2 (9 %)	

[1] Number of patients experiencing AE. Calculation of percentages based on number of patients in SAS (N=22)

[2] Pt 0407, SAE Case 025: The treating physician described a possible causal relationship to FOLFIRI.

[3] Pt 0302 SAE Case 010: reported as SUSAR

8.3. Dose Modifications/Interruptions

At least one dose modification for FA occurred in 3 patients (13%) due to hematological toxicity (Pt-ID 0105, 0406 and 0407). At least one dose modification for 5-FU bolus was recorded in 4 patients (17%) due to hematological toxicity (Pt-ID 0105, 0403, 0406, 0407). Dose of 5-FU continuous was modified at least once in 6

patients (26%). The reason for modification in 5FU continuous was hematological toxicity in 5 patients and investigator's decision in 1 patient. Modification of CPT was observed in 7 patients (30%) due to hematological toxicity (6 patients) and non-hematological toxicity (1 patient).

A total of 36 treatment modifications in Sunitinib were documented (28 dose modifications and 8 dose interruptions). At least one dose modification in Sunitinib occurred in 10 patients (44%) due to toxicity. At least one dose interruption was documented for 6 patients (26%). Reasons for treatment interruption were toxicity (3 patients) and patient's wish (1 patient). In two patients treatment was interrupted twice: in one patient due to toxicity and patient's wish and in one patient due to patient's wish and investigator's decision. Hematological and non-hematological toxicities leading to dose modifications or treatment interruptions are provided in table 6.

Table 6: Hematological and non-hematological toxicities leading to dose modifications or treatment interruptions in individual patients, occurring at least once

Pt-ID	Hematological toxicity	Non-hematological toxicity
0101		Palmar-plantar erythrodysaesthesia syndrome / Anal Ulcer
0104	Thrombocytopenia / Bone marrow failure	Pulmonary embolism
0105	Leukopenia / Neutropenia	Diarrhea
0106	Leukopenia* / Neutropenia*	
0201	Neutropenia	Stomatitis
0203	Neutropenia	
0204	Neutropenia	Palmar-plantar erythrodysaesthesia syndrome
0206		Melaena[+]
0301	Leukopenia	
0303	Leukopenia	
0401	Anemia	Mucosal inflammation
0403	Leukopenia	
0404	Leukopenia	
0406	Leukopenia / Neutropenia	Viral pneumonia

* occurred after cycle 1. Pt received no further treatment due to disease progression

[+] treatment interruption due to melaena. Pt was then taken off-treatment due to risc of rectal bleeding

8.4. Adverse Events leading to Discontinuation of Treatment with Sunitinib

In 8 patients, treatment on study was stopped due to an adverse event (see table 7).

Table 7: Adverse events leading to discontinuation of Sunitinib*

Pt-ID	Adverse event	Causal relationship	Highest CTC-grade
0101	Anal ulcer[+]	definite	2
0104	Palmar-plantar erythrodysaesthesia syndrome / Mucosal inflammation	possible	2
0105	Leukopenia / Neutropenia	possible	3
0210	General physical health deterioration	possible	2
	Lower gastrointestinal haemorrhage	not related	5
0302	Infected skin ulcer – SUSAR	possible	3
0406	Leukopenia	definite	3
0407	Polyneuropathy	possible	2
0408	Paraesthesia	definite	3

* In contrast to Listing 3.1.6.2. of the biometrical analysis report, table 6 does not contain AEs for pt 0206, since end of treatment was “risk of rectal bleeding” and AEs for pt 0301, since end of treatment was disease progression (please see section 7.1. for details)

[+] Anal wound ulceration was getting better upon temporal interruption. Patient had stopped Sutent medication for 4 days; after re-intake of sunitinib for 1 day wound opened again and treatment was stopped definitively.

8.5. Serious adverse events:

A total of 27 serious adverse events occurred during the study, as reported in the EDC system. All of those were reported in expedited manner to CESAR’s Medical Safety Desk. Table 8 lists all SAES and provides the reconciliation between the EDC system and the pharmacovigilance database (PV DB).

Tables 9 and 10 are based on the information in the pharmacovigilance database and were already previously reported in the Annual Safety Reports in 2009 and 2010.

There were 12 SSARs (Causal relationship suspected), 11 out of these were expected. One event (infected ulcer) has been classified by the Investigator as suspected side effects of Sunitinib. This reaction is not described in the SmPC, and was event has been reported as SUSAR:

Case No.	Site	Pt no	Arm	Date SAE onset	Event	Causality Sun./FOLFIRI	Expected-ness	Outcome	Comment
010	03	03-02	N/A	04.05.2009	infected ulcus left lower leg	Y/N	No - SUSAR	Rec. 08.06.09	

Case Narrative:

The patient, a 64-year old male with a colorectal adenocarcinoma is participating since October 2008 in clinical study C-II-005 (EUDRACT 2008-001515-37), receiving standard FOLFIRI therapy in combination with Sunitinib (Sutent®). Sunitinib is given daily (37.5 mg dose) for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks. On 20 April 2009, the patient took the last dose of Sunitinib prior to a 2-week rest period. The patient presented on 04 May 2009 in the context of a regular visit at the clinic with a 3x3 cm ulcus cruris on the left lower leg. The patient indicated that he had slipped on the staircase causing a wound that did not heal subsequently. Upon presentation, the left lower leg was warm, red, painful and showing several blisters (clinical aspect like erysipelas, deep soft tissue infection). Inflammation markers were elevated and the smear test showed Oxacillin-sensitive S. aureus. The patient was hospitalized on the same day (04 May 2009). The investigator indicated later that the condition was severe, in part because the patient did not consult the physician in time, but just showed the wound at the next regular visit. Sunitinib therapy was permanently discontinued and the patient taken "off study" due to this adverse event.
Duplex sonography revealed chronic venous insufficiency Stadium III according to Widmer (ulcus cruris). The patient received the following antibiotic therapy: Clindamycin 3 x 600 mg, start 04 May, end 15 May 2009; Ceftriaxon 1 x 2 g i.v., start 04 May 2009, end 08 May 2009; and Flucloxacillin 2 x 500 mg, start 07 May, end 14 May 2009 [Flucoxacillin was started based on results of smear test]. With antibiotic treatment and and daily wound care, the patient improved and was discharged on 18 May 2009. At the latest visit on 08 June 2009, the wound has clearly improved, although not yet healed completely ("recovered with sequelae"). The patient received further treatment with FOLFIRI outside of this clinical study.
Medical history includes arterial hypertension, gonarthrosis, psoriasis and benign hyperplasia of the prostate. Concomitant medications were Enalapril, Atenolol (both for hypertension) and Pantozol (ulcus prophyaxis for medication with Fortecortin as antiemetic treatment prior to chemotherapy).
In the initial SAE report from the site on 04 May 2009, no causality assessment was provided. In the Follow-up report on 16 June 2009, this adverse event was classified as possibly related to sunitinib by the investigator. Since this adverse reaction is not described in the SmPC, this event is therefore reported as SUSAR.

Table 8: Listing of all SAEs based on the data in the clinical database and reconciliation clinical database and the pharmacovigilance database (PV DB).

Obs	*Pt-ID*	*AE No*	*Begin*	*End*	*SOC*	*PT*	*Relation*	*CTC-grade*	*SAE in PV DB*	*Comment*
1	0102	11	11FEB2009	12FEB2009	Nervous system disorders	Presyncope	not related	3	Case 008	Reported as Vasovagal episode
2	0104	1	05JAN2009	13JAN2009	Infections and infestations	Febrile infection	not related	2	Case 002	
3	0104	2	14JAN2009	28JAN2009	Gastrointestinal disorders	Stomatitis	possible	3	Case 004	
4	0104	3	16JAN2009	26JAN2009	Blood and lymphatic system disorders	Bone marrow failure	probable	4	Case 005	Reported as Myelosuppression
5	0104	14	05FEB2009	31MAR2009	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	possible	4	Case 007	
6	0104	21	04MAR2009	06MAR2009	Gastrointestinal disorders	Abdominal pain	possible	3	Case 009	
7	0104	22	06MAR2009	11MAR2009	Gastrointestinal disorders	Stomatitis	possible	3	Case 009	
8	0104	40	07MAY2009	18MAY2009	Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	possible	2	Case 011	Reported as hand-foot-skin reaction
9	0105	6	26JUL2009	12AUG2009	Gastrointestinal disorders	Stomatitis	possible	2	Case 015	
10	0105	7	29JUL2009	08AUG2009	Gastrointestinal disorders	Diarrhoea	possible	2	Case 015	

Obs	*Pt-ID*	*AE No*	*Begin*	*End*	*SOC*	*PT*	*Relation*	*CTC-grade*	*SAE in PV DB*	*Comment*
11	0105	8	30JUL2009	03AUG2009	Blood and lymphatic system disorders	Leukopenia	possible	4	Case 015	
12	0203	10	27SEP2009	01OCT2009	Hepatobiliary disorders	Jaundice	not related	2	Case 020	
13	0205	1	10JUL2009	24JUL2009	General disorders and administration site conditions	Pyrexia	unlikely	2	Case 014	
14	0206	1	11SEP2009	17SEP2009	Gastrointestinal disorders	Melaena	definite	3	Case 017	
15	0208	7	24MAR2010	01MAR2010	Blood and lymphatic system disorders	Thrombocytopenia	possible	2	Case 021	
16	0208	11	24MAR2010	07MAY2010	General disorders and administration site conditions	General physical health deterioration	not related	3	Case 021	
17	0210	3	08JUN2010	21JUN2010	General disorders and administration site conditions	General physical health deterioration	possible	2	Case 023	The treating physician explained that the general deterioration was per se not related, but was accompanied with stomatitis and diarrhea that were considered as possible related.
18	0210	6	14JUN2010	21JUN2010	Gastrointestinal disorders	Lower gastrointestinal haemorrhage	not related	5	Case 024	

Obs	*Pt-ID*	*AE No*	*Begin*	*End*	*SOC*	*PT*	*Relation*	*CTC-grade*	*SAE in PV DB*	*Comment*
19	0301	4	13JAN2009		Hepatobiliary disorders	Hyperbilirubinaemia	not related	4	Case 003	The patient died on 28 Jan 2009 on disease progression and hyperbilrubinemia classified as CTC 5.
20	0302	1	22JAN2009	29JAN2009	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	not related	4	Case 006	
21	0302	3	04MAY2009	18MAY2009	Infections and infestations	Infected skin ulcer	possible	3	Case 010	Reported as SUSAR
22	0401	8	23NOV2008	26NOV2008	Gastrointestinal disorders	Abdominal pain	unlikely	2	Case 001	
23	0401	29	08JUN2009	09JUN2009	Blood and lymphatic system disorders	Anaemia	possible	4	Case 013	
24	0401	30	05JUN2009	09JUN2009	Gastrointestinal disorders	Abdominal pain	not related	3	Case 012	
25	0404	6	29JUL2009	26AUG2009	Nervous system disorders	Spinal cord compression	not related	3	Case 016	Reported as compression of myelom by metastases
26	0407	3	02JUN2009	24SEP2009	General disorders and administration site conditions	Ulcer	possible	3	Case 025	The treating physician described a possible causal relationship to FOLFIRI.
27	0407	8	14SEP2009	19SEP2009	Nervous system disorders	Transient ischaemic attack	possible	3	Case 018	TIA might have been caused by hypertension.

Table 9: A line listing of all suspected serious adverse reactions (including all SUSARs), based on the PV-DB.

Country / Site / Case No.	Pat No / Age / Sex	Event/Reaction (MedDRA)	System organ Class (SOC)	Onset Date	Treatment start Date	Treatment Stop Date	Outcome
Germany/01/004	**01-04/60/M**	STOMATITIS	Gastrointestinal disorders	14.01.2009	22.05.2008		Recovered (28.01.09)
Germany/01/005	**01-04/60/M**	LEUKOPENIA, NEUTROPENIA, THROMBOCYTOPENIA	Blood and lymphatic system disorders	16.01.2009	22.05.2008		Recovered (21.01.09)
Germany/01/007	**01-04/60/M**	PULMONARY EMBOLISM	Respiratory, thoracic and mediastinal disorders	05.02.2009	22.05.2008		Recovered (31.03.09)
Germany/01/009	**01-04/60/M**	ABDOMINAL CRAMPS	Gastrointestinal disorders	04.03.2009	22.05.2008		Recovered (11.03.09)
Germany/03/010	**03-02/64/M**	INFECTED SKIN ULCER	Infections and infestations	04.05.2009	10.11.2008	20.04.2009	Recovered (08.06.09)
Germany/01/011	**01-04/60/M**	HAND-AND-FOOT SYNDROME	Skin and subcutaneous tissue disorders	07.05.2009	22.05.2008		Recovered (18.05.09)
Germany/04/013	**04-01/55/M**	ANEMIA	Blood and lymphatic system disorders	08.06.2009	17.09.2008	25.05.2009	Recovered (09.06.09)
Germany/01/015	**01-05/54/F**	LEUCOPENIA	Blood and lymphatic system disorders	29.07.2009	10.07.2009		Recovered (12.08.2009)
Germany/02/017	**02-06/72/M**	MELAENA	Gastrointestinal disorders	11.09.2009	02.09.2009	22.09.2009	Recovered (17.09.2009)
Germany/04/018	**04-07/71/F**	TRANSIENT ISCHAEMIC ATTACK	Nervous system disorders	14.09.2009	18.05.2009	24.08.2009	Recovered (19.09.2009)
Germany/02/021	**02-08/84/F**	LEUCOPENIA	Blood and lymphatic system disorders	25.03.2009	03.03.2010	24.03.2010	Recovered (NK.03.2010)
Germany/02/023	**02-10/67/M**	STOMATITIS	Gastrointestinal disorders	08.06.2010	11.05.2010	07.06.2010	Ongoing (tumor related Death 21.06.2010)

Please note: If there is more than one reaction, the case is listed under the most serious adverse reaction (sign, symptom or diagnosis) based on CTC AE 3.0 Grading.

Table 10: An aggregate summary tabulation of suspected serious adverse reactions, based on the PV-DB.

Primary SOC	Event/Reaction (MedDRA)	Sum (Trial)
Blood and lymphatic system disorders	LEUKOPENIA	3
	THROMBOCYTOPENIA	2
	NEUTROPENIA	2
	ANEMIA	1
All		***8***
Gastrointestinal disorders	STOMATITIS	4
	ABDOMINAL CRAMPS	1
	DIARRHOEA	2
	MELAENA	1
	NAUSEA	1
All		***9***
Infections and infestations	INFECTED SKIN ULCER	1
All		***1***
Respiratory, thoracic and mediastinal disorders	PULMONARY EMBOLISM	1
All		***1***
Skin and subcutaneous tissue disorders	HAND-AND-FOOT SYNDROME	1
All		***1***
General disorders and administration site conditions	MUCOSITIS	1
All		***1***
Nervous system disorders	TRANSIENT ISCHAEMIC ATTACK	1
All		***1***

8.6. Death Cases

Two death cases occurred after the patient had stopped treatment on study, but within 28 days of last intake of Sunitinib:

> Patient 0210 was a 67 year old male starting treatment on study on 11 May 2010, but was discontinued on 07 June 2010 due to general condition worsening. The patient was hospitalized on that day due to general condition worsening CTC 2, Stomatitis CTC 3 and Diarrhoea CTC 2. Stomatitis and Diarrhoea were seen as possible related to Sunitinib and FOLFIRI, the worsening of the general condition was attributed to the underlying disease. The patient developed lower gastrointestinal bleeding on 14 Jun 2010 (seen as unrelated to study medication), and underwent an emergency abdomino-perineale rectum amputation. The patient eventually died on 21 Jun 2011 due to tumor related complications.
> (the underlying SAEs have been reported and were recorded as cases 023 and 024 in the Sponsor's Pharmacovigilance Database)

> Patient 0301 was a 44 year old female starting treatment on study on 09 Sep2008, and stopped treatment on 08 Jan 2009, due to disease progression. The patient presented on 13 Jan 2009 with deterioration of her general condition, jaundice, and increase of abdominal pain. Due to asthenia, sunitib had already been interrupted previously. On 22 Jan 2009, the patient was hospitalized in the palliative unit to adjust pain medication. The patient received hydromorphon and amtriptylin. During hospitalization, general condition deteriorated with signs of infection and increase in liver enzymes. On 28 Jan 2009, the patient became somnolent and pain therapy was switched to continous intravenous pain therapy. The patient died on 28 Jan 2009 at 23:50, due to tumour progression and hyperbilirubinemia.
> (the underlying SAE has been reported and were recorded as case 003 in the Sponsor's Pharmacovigilance Database)

The other 3 patients died between months to 1 year after end of treatment, patient 0303 und 0401 due to their underlying disease. It should be noted that for patient 0302, the reason of death was indicated as "toxicity": this patient received sunitib and FOLFIRI in this study, then developed an infected skin ulcer (ulcus cruris on the left lower leg) that was assessed as possibly related to subitinib (reported as SUSAR, Case 010). The patient discontinued Sunitib and was treated first with FOLFIRI, and subsequently, upon disease progression with FOLFOX. Since death occurred 4 months after end of treatment on study, the Sponsor contacted the treating physician who indicated that "the patient died at home, according to his family on a thromboembolic event, details are not known, and the event seemed to be of a sudden nature. I cannot see any relationship to study medication, but rather as a consequence of the chronic venous insufficiency that might also have placed a role in the development of the ulcus cruris."

9. Conclusion

An open label, single arm, prospective, multicenter phase II study was performed to evaluate the antiangiogenic effects of sunitinib in addition to 5-FU, folinic acid and irinotecan (FOLFIRI) as 1st line therapy in patients with colorectal cancer and liver metastases. Between August 2008 and September 2010, a total of 28 were recruited for treatment.
Out of the 28 recruited patients, 5 did not receive any study medication. Therefore a total of 23 patients were evaluable for safety (SAS). Time under treatment was calculated from first intake to last intake of study medication. Median time under treatment was 18.4 weeks (range: 2.3-50.7 weeks).

Efficacy not included in this report.

Safety:

Altogether 412 AEs occurred in the SAS, 164 of them were not related/unlikely to any of the study medications, whereas 247 the relation to study drug was assessed as definite, probable or possible (suspected AE); relation to study medication was not assessable in one patient. All 23 patients of the SAS had at least one AE under study and 21 patients had at least one suspected AE. Out of the 247 suspected AEs, relation to study drug was assessed to be definite in 18 AEs, probable in 30 AEs and possible in 199 AEs. A total of 27 AEs in 13 patients were classified as Serious Adverse Events.

A total of 27 serious adverse events occurred during the study, as reported in the EDC system. There were 12 SSARs (Causal relationship suspected), 11 out of these were expected. One event (infected ulcer) has been classified by the Investigator as suspected side effects of Sunitinib. This reaction is not described in the SmPC, and was event has been reported as SUSAR.

During the study, 5 deaths (22%) were documented. Two death cases occurred after the patient had stopped treatment on study, but within 28 days of last intake of Sunitinib, the other 3 patients died between months to 1 year after end of treatment. None of them is related to treatment on study: four patients died on their underlying disease; one patient with an underlying chronic venous insufficiency died 4 months after treatment on study probably on a thromboembolic event.

As summary, the AE profile is as expected for this type of clinical study.

CLINICAL STUDY REPORT

(Preliminary / Part on Safety only)

A prospective angiogenic imaging study with DCE-MRI and DCE-USI in patients with colorectal cancer

Appendices

CESAR

Central European Society for Anticancer Drug Research-E W I V

CLINICAL STUDY REPORT

(Preliminary / Part on Safety only)

A prospective angiogenic imaging study with DCE-MRI and DCE-USI in patients with colorectal cancer

Date of the report: 20 September 2011

Signature Page

Prepared by: _____ 20 Sep 2011

Berta Moritz, PhD
CESAR, Dir. Clinical Affairs

Date

Approved by: _____ 20.9.11

Klaus Mross, MD
Study Chair

Date

Registration

Report data [Page 1/8]	
Eudract No. (1/11)	**2008-001515-37**
Study name (2/11)	**C-II-005 FOLFIRI + Sut in mCRC**
Sponsor No. (3/11)	**C-II-005**
SAE No. (4/11)	**FOLFIRISUT-23**
Initial report date (5/11)	**10**/**06**/20**10** [day/month/year]
Type of report (6/11)	**Follow-Up**
Additional documents (7/11)	_____ _____ _____
Date last change (export relevant) (8/11)	**29**/**07**/20**10** [day/month/year]
Date last change (9/11)	**29**/**07**/20**10** [day/month/year]
Date of last EVWEB import (10/11)	__/__/20__ [day/month/year]
Report source (11/11)	_____ _____ _____

Demographics [Page 2/8]	
Subject ID (1/7)	**02** / **10** [Site No./Subject No.]
Patient initials (2/7)	**X** / **X** [first/last name]
Patient date of birth (3/7)	**26**/**07**/**1942** [day/month/year]
Sex of patient (4/7)	**male**
Body height (5/7)	**170** cm
Body weight (6/7)	**60** kg
Treatment Arm (7/7)	**Single Arm** In blinded studies only: Please provide randomization code: _____

Case [Page 3/8]	
Type of event (1/9)	**SSAR**
Seriousness criteria (2/9)	**[x] Fatal** [ ] Life threatening **[x] Prolonging or requiring hospitalisation** [ ] Resulting in persistent significant disabillity / incapacity [ ] Congenital anomaly / birth defect [ ] Other if other, please specify: _____
Relationship to Study Drug - Investigator (3/9)	**Suspected**
Case description (4/9)	**since 8.6.2010 hospitalization due to general condition worsening Death date 21.06.2010**
Reporter comment (5/9)	**General condition worsening - is seen as not suspected to study drug Stomatitis and Diarrhoe are seen as susptected to study drug and folfiri**
Death information	
Death date (6/9)	**21/06/2010** [day/month/year]
Death cause (7/9)	**tumor related complication**
MedDRA10 Coding Code: Term:	 **10066921** **Tumor related complication**
Autopsy (8/9)	**no**

Study site [Page 4/8]	
Name of reporter (1/4)	First name: **Irene** Last name: **Lauff**
Profession (2/4)	**Other health professional**
City (3/4)	**Essen**, Post code: _____
Country (4/4)	**Germany**

Reactions

Reaction [Page 5/8] - Table

Instance-no: 1 (Reaction)	
Description of adverse reaction (1/4)	**general condition worsening CTC2**
MedDRA10 Coding Code: Term:	 **10057364** **Reduced general condition**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**08/06/2010** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Ongoing**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 2 (Reaction)	
Description of adverse reaction (1/4)	**Stomatitis G3**
MedDRA10 Coding Code: Term:	 **10042128** **Stomatitis**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**08/06/2010** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Ongoing**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 3 (Reaction)	
Description of adverse reaction (1/4)	**Diarrhoe CTC 2**
MedDRA10 Coding Code: Term:	 **10012735** **Diarrhoea**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**08/06/2010** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Ongoing**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 4 (Reaction)	
Description of adverse reaction (1/4)	_____
MedDRA10 Coding Code: Term:	
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	__/__/____ [day/month/year] __:__ [hour/minute]

Outcome (4/4)	_____
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Study medications / Concomitant medication / Non-drug therapies

Medication [Page 6/8] - Table

Instance-no: 1 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Irinotecan**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **180** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Suspected**
SAE relationship - sponsor (9/17)	**Suspected** Comment: **suspected together with sutent for stomatitis and diarrhoe**
Expectedness (10/17)	**Expected** Comment: _____ _____ _____
Instance-no: 2 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Folinic Acid**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **400** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Suspected**
SAE relationship - sponsor (9/17)	**Suspected** Comment: **suspected together with sutent for stomatitis and diarrhoe**
Expectedness (10/17)	**Expected** Comment: _____ _____ _____

Instance-no: 3 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Fluorouracil**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **2800** Unit: **mg/m^2 bol/cont.inf** Frequency: **day 1 & 2 ev. 2weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Suspected**
SAE relationship - sponsor (9/17)	**Suspected** Comment: **suspected together with sutent for stomatitis and diarrhoe**
Expectedness (10/17)	**Expected** Comment: _____ _____ _____

Instance-no: 4 (Medication)	
Type of Medication (1/17)	**Study medication**
Preparation / Non-drug treatment (2/17)	**Sunitinib**
Indication (3/17)	**Metastatic colorectal cancer**
Batch No. (4/17)	_____
Dosage (5/17)	Dose: **37.5** Unit: **mg** Frequency: **od 4w on/2w off**
Route (6/17)	**Oral**
Start (7/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
Action taken with study drug (8/17)	**Permanently discontinued**
Last administration (9/17)	**07/06/2010** [day/month/year]
Last treatment prior to SAE onset (10/17)	**07/06/2010** [day/month/year] __:__ [hour/minute] or interval between last treatment prior to SAE and SAE onset: __._ _____
SAE relationship - investigator (11/17)	**Suspected**
SAE relationship - sponsor (12/17)	**Suspected** Comment: **suspected for Stomatitis and Diarrhea**
Expectedness (13/17)	**Expected** Comment: _____ _____ _____

Instance-no: 5 (Medication)	
Type of Medication (1/17)	_____
Preparation / Non-drug treatment (2/17)	_____
Dosage (3/17)	Dose: __.__ Unit: _____ Frequency: _____
Route (4/17)	_____
Start (5/17)	__/__/____ [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (6/17)	__/__/____ [day/month/year] or [ ] Ongoing
SAE relationship - investigator (7/17)	_____
SAE relationship - sponsor (8/17)	_____ Comment: _____ _____ _____

Relevant tests

Test [Page 7/8] - Table

Instance-no: 1 (Relevant test)	
Test name (1/3)	_____
MedDRA10 Coding Code: Term:	
Date performed (2/3)	__/__/____ [day/month/year]
Result (3/3)	_____ Unit: _____ if applicable: normal range lower limit: ____.__, upper limit: ____.__

Relevant medical history

History [Page 8/8] - Table

Instance-no: 1 (Medical History)	
Disease / Surgery (1/3)	_____
MedDRA10 Coding Code: Term:	
Start (2/3)	__/__/____ [day/month/year]
End (3/3)	__/__/____ [day/month/year] or [ ] Ongoing

Registration

Report data [Page 1/8]	
Eudract No. (1/11)	**2008-001515-37**
Study name (2/11)	**C-II-005 FOLFIRI + Sut in mCRC**
Sponsor No. (3/11)	**C-II-005**
SAE No. (4/11)	**FOLFIRISUT-24**
Initial report date (5/11)	**19**/**07**/20**10** [day/month/year]
Type of report (6/11)	**Follow-Up**
Additional documents (7/11)	_____ _____ _____
Date last change (export relevant) (8/11)	**29**/**07**/20**10** [day/month/year]
Date last change (9/11)	**29**/**07**/20**10** [day/month/year]
Date of last EVWEB import (10/11)	__/__/20__ [day/month/year]
Report source (11/11)	_____ _____ _____

Demographics [Page 2/8]	
Subject ID (1/7)	**02** / **10** [Site No./Subject No.]
Patient initials (2/7)	**X** / **X** [first/last name]
Patient date of birth (3/7)	**26**/**07**/**1942** [day/month/year]
Sex of patient (4/7)	**male**
Body height (5/7)	**170** cm
Body weight (6/7)	**60** kg
Treatment Arm (7/7)	**Single Arm** In blinded studies only: Please provide randomization code: _____

Case [Page 3/8]	
Type of event (1/9)	**SAE**
Seriousness criteria (2/9)	**[x] Fatal** [ ] Life threatening **[x] Prolonging or requiring hospitalisation** [ ] Resulting in persistent significant disabillity / incapacity [ ] Congenital anomaly / birth defect [ ] Other if other, please specify: _____
Relationship to Study Drug - Investigator (3/9)	**Not suspected**
Case description (4/9)	**since 08.06.2010 hospitalization due to general condition worsening (SAE 23) emergency laparotomy, abdomino-perineale rectum amputation at 14.06.2010. On 22 Jan 2009, the patient was hospitalized in the palliative unit to adjust pain medication. The patient received hydromorphon and amtriptylin. During hospitalization, general condition deteriorated with signs of infection and increase in liver enzymes. On 28 Jan 2009, the patient became somnolent and pain therapy was switched to continous intravenous pain therapy. The patient died on 28 Jan 2009 at 23:50, due to tumour progression and hyperbilirubinemia.**
Reporter comment (5/9)	_____ _____ _____ _____ _____
Death information	
Death date (6/9)	**21/06/2010** [day/month/year]
Death cause (7/9)	**tumor related complication**
MedDRA10 Coding Code: Term:	 **10066921** **Tumor related complication**
Autopsy (8/9)	**no**

Study site [Page 4/8]	
Name of reporter (1/4)	First name: **Irene** Last name: **Lauff**
Profession (2/4)	**Other health professional**
City (3/4)	**Essen**, Post code: _____
Country (4/4)	**Germany**

Reactions

Reaction [Page 5/8] - Table

Instance-no: 1 (Reaction)	
Description of adverse reaction (1/4)	**lower gastrointestinal bleeding**
MedDRA10 Coding Code: Term:	 **10051746** **Lower gastrointestinal hemorrhage**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**14/06/2010** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Death**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 2 (Reaction)	
Description of adverse reaction (1/4)	_____
MedDRA10 Coding Code: Term:	
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	__/__/____ [day/month/year] __:__ [hour/minute]

Outcome (4/4)	_____
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Study medications / Concomitant medication / Non-drug therapies

Medication [Page 6/8] - Table

Instance-no: 1 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Irinotecan**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **180** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 2 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Folinic Acid**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **400** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 3 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Fluorouracil**
Indication (3/17)	**metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **2800** Unit: **mg/m^2 bol/cont.inf** Frequency: **day 1 & 2 ev. 2weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**26/05/2010** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 4 (Medication)	
Type of Medication (1/17)	**Study medication**
Preparation / Non-drug treatment (2/17)	**Sunitinib**
Indication (3/17)	**Metastatic colorectal cancer**
Batch No. (4/17)	_____
Dosage (5/17)	Dose: **37.5** Unit: **mg** Frequency: **od 4w on/2w off**
Route (6/17)	**Oral**
Start (7/17)	**11/05/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
Action taken with study drug (8/17)	**Permanently discontinued**
Last administration (9/17)	**07/06/2010** [day/month/year]
Last treatment prior to SAE onset (10/17)	**07/06/2010** [day/month/year] __:__ [hour/minute] or interval between last treatment prior to SAE and SAE onset: __._ _____
SAE relationship - investigator (11/17)	**Not suspected**
SAE relationship - sponsor (12/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 5 (Medication)	
Type of Medication (1/17)	**SAE treatment**
Preparation / Non-drug treatment (2/17)	**abdomino-perineale rectum amputation**
Dosage (3/17)	Dose: __.__ Unit: _____ Frequency: _____
Start (4/17)	**14/06/2010** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (5/17)	**14/06/2010** [day/month/year] or [ ] Ongoing

Instance-no: 6 (Medication)	
Type of Medication (1/17)	_____
Preparation / Non-drug treatment (2/17)	_____
Dosage (3/17)	Dose: __.__ Unit: _____ Frequency: _____
Route (4/17)	_____
Start (5/17)	__/__/____ [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (6/17)	__/__/____ [day/month/year] or [ ] Ongoing
SAE relationship - investigator (7/17)	_____
SAE relationship - sponsor (8/17)	_____ Comment: _____ _____ _____

Relevant tests

Test [Page 7/8] - Table

Instance-no: 1 (Relevant test)	
Test name (1/3)	_____
MedDRA10 Coding Code: Term:	
Date performed (2/3)	__/__/____ [day/month/year]
Result (3/3)	_____ Unit: _____ if applicable: normal range lower limit: ____.__, upper limit: ____.__

Relevant medical history

History [Page 8/8] - Table

Instance-no: 1 (Medical History)	
Disease / Surgery (1/3)	**rectum carcinom**
MedDRA10 Coding Code: Term:	 **10007464** **Carcinoma rectum**
Start (2/3)	__/**04**/**2010** [day/month/year]
End (3/3)	__/__/____ [day/month/year] or **[x] Ongoing**

Instance-no: 2 (Medical History)	
Disease / Surgery (1/3)	_____
MedDRA10 Coding Code: Term:	
Start (2/3)	__/__/____ [day/month/year]
End (3/3)	__/__/____ [day/month/year] or [ ] Ongoing

Registration

Report data [Page 1/8]	
Eudract No. (1/11)	**2008-001515-37**
Study name (2/11)	**C-II-005 FOLFIRI + Sut in mCRC**
Sponsor No. (3/11)	**C-II-005**
SAE No. (4/11)	**FOLFIRISUT-3**
Initial report date (5/11)	**13**/**01**/20**09** [day/month/year]
Type of report (6/11)	**Follow-Up**
Additional documents (7/11)	_____ _____ _____
Date last change (export relevant) (8/11)	**02**/**03**/20**09** [day/month/year]
Date last change (9/11)	**02**/**03**/20**09** [day/month/year]
Date of last EVWEB import (10/11)	__/__/20__ [day/month/year]
Report source (11/11)	_____ _____ _____

Demographics [Page 2/8]	
Subject ID (1/7)	**03** / **1** [Site No./Subject No.]
Patient initials (2/7)	**B** / **R** [first/last name]
Patient date of birth (3/7)	**25**/**12**/**1964** [day/month/year]
Sex of patient (4/7)	**female**
Body height (5/7)	**181** cm
Body weight (6/7)	**65** kg
Treatment Arm (7/7)	**Single Arm** In blinded studies only: Please provide randomization code: _____

Case [Page 3/8]	
Type of event (1/9)	**SAE**
Seriousness criteria (2/9)	**[x] Fatal** [ ] Life threatening **[x] Prolonging or requiring hospitalisation** [ ] Resulting in persistent significant disabillity / incapacity [ ] Congenital anomaly / birth defect [ ] Other if other, please specify: _____
Relationship to Study Drug - Investigator (3/9)	**Not suspected**
Case description (4/9)	**The patient presented on 13 Jan 2009 with deterioration of her general condition, jaundice, and increase of abdominal pain. Due to asthenia, sunitib had already been interrupted previously. On 22 Jan 2009, the patient was hospitalized in the palliative unit to adjust pain medication. The patient received hydromorphon and amtriptylin. During hospitalization, general condition deteriorated with signs of infection and increase in liver enzymes. On 28 Jan 2009, the patient became somnolent and pain therapy was switched to continous intravenous pain therapy. died on 28 Jan 2009 at 23:50, due to tumour progression and hyperbilirubinemia.**
Reporter comment (5/9)	_____ _____ _____ _____ _____
Death information	
Death date (6/9)	**28/01/2009** [day/month/year]
Death cause (7/9)	**tumour progression, hyperbilirubinema Grade V**
MedDRA10 Coding Code: Term:	 **10053563;10020582** **Tumor progression;Hyperbilirubinemia**
Autopsy (8/9)	**no**

Study site [Page 4/8]	
Name of reporter (1/4)	First name: **Beate** Last name: **Schultheiss**
Profession (2/4)	**Physician**
City (3/4)	**Herne**, Post code: _____
Country (4/4)	**Germany**

Reactions

Reaction [Page 5/8] - Table

Instance-no: 1 (Reaction)	
Description of adverse reaction (1/4)	**hyperbilirubinemia CTC 3 - 5**
MedDRA10 Coding Code: Term:	 **10020582** **Hyperbilirubinemia**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**13/01/2009** [day/month/year] **08:00** [hour/minute]

Outcome (4/4)	**Death**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 2 (Reaction)	
Description of adverse reaction (1/4)	**Asthenia grade 2**
MedDRA10 Coding Code: Term:	 **10003549** **Asthenia**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**09/01/2009** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Death**
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 3 (Reaction)	
Description of adverse reaction (1/4)	**Abdominal pain Grade 2**
MedDRA10 Coding Code: Term:	 **10000081** **Abdominal pain**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**13/01/2009** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Recovered / resolved**
	if recovered, please provide date of recovery:
	22/01/2009 [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Instance-no: 4 (Reaction)	
Description of adverse reaction (1/4)	_____
MedDRA10 Coding Code: Term:	
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	__/__/____ [day/month/year] __:__ [hour/minute]

Outcome (4/4)	_____
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Study medications / Concomitant medication / Non-drug therapies

Medication [Page 6/8] - Table

Instance-no: 1 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Irinotecan**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **180** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**09/09/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 2 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Folinic Acid**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **200** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**09/09/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 3 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Fluorouracil**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **2800** Unit: **mg/m^2 bol/cont.inf** Frequency: **day 1 & 2 ev. 2weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**09/09/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 4 (Medication)	
Type of Medication (1/17)	**Study medication**
Preparation / Non-drug treatment (2/17)	**Sunitinib**
Indication (3/17)	**Metastatic colorectal cancer**
Batch No. (4/17)	_____
Dosage (5/17)	Dose: **37.5** Unit: **mg** Frequency: **od 4w on/2w off**
Route (6/17)	**Oral**
Start (7/17)	**09/09/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
Action taken with study drug (8/17)	**Permanently discontinued**
Last administration (9/17)	**08/01/2009** [day/month/year]
Last treatment prior to SAE onset (10/17)	**08/01/2009** [day/month/year] __:__ [hour/minute] or interval between last treatment prior to SAE and SAE onset: __._ _____
SAE relationship - investigator (11/17)	**Not suspected**
SAE relationship - sponsor (12/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 5 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**metamizole tablets**
Indication (3/17)	**Pain**
MedDRA10 Coding Code: Term:	 **10033371** **Pain**
Dosage (4/17)	Dose: **500** Unit: **mg** Frequency: _____
Route (5/17)	**Oral**
Start (6/17)	**23/12/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**22/01/2009** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 6 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**macrogole**
Indication (3/17)	**obstipation**
MedDRA10 Coding Code: Term:	 **10029932** **Obstipation**
Dosage (4/17)	Dose: __.__ Unit: _____ Frequency: **as needed**
Route (5/17)	**Oral**
Start (6/17)	**16/12/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	**22/01/2009** [day/month/year] or [ ] Ongoing
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 7 (Medication)	
Type of Medication (1/17)	_____
Preparation / Non-drug treatment (2/17)	_____
Dosage (3/17)	Dose: __.__ Unit: _____ Frequency: _____
Route (4/17)	_____
Start (5/17)	__/__/____ [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (6/17)	__/__/____ [day/month/year] or [ ] Ongoing
SAE relationship - investigator (7/17)	_____
SAE relationship - sponsor (8/17)	_____ Comment: _____ _____ _____

Relevant tests

Test [Page 7/8] - Table

Instance-no: 1 (Relevant test)	
Test name (1/3)	_____
MedDRA10 Coding Code: Term:	
Date performed (2/3)	__/__/____ [day/month/year]
Result (3/3)	_____ Unit: _____ if applicable: normal range lower limit: ____.__, upper limit: ____.__

Relevant medical history

History [Page 8/8] - Table

Instance-no: 1 (Medical History)	
Disease / Surgery (1/3)	_____
MedDRA10 Coding Code: Term:	
Start (2/3)	__/__/____ [day/month/year]
End (3/3)	__/__/____ [day/month/year] or [ ] Ongoing

Registration

Report data [Page 1/8]	
Eudract No. (1/11)	**2008-001515-37**
Study name (2/11)	**C-II-005 FOLFIRI + Sut in mCRC**
Sponsor No. (3/11)	**C-II-005**
SAE No. (4/11)	**FOLFIRISUT-10**
Initial report date (5/11)	**04**/**05**/20**09** [day/month/year]
Type of report (6/11)	**Follow-Up**
Additional documents (7/11)	_____ _____ _____
Date last change (export relevant) (8/11)	**16**/**06**/20**09** [day/month/year]
Date last change (9/11)	**16**/**06**/20**09** [day/month/year]
Date of last EVWEB import (10/11)	__/__/20__ [day/month/year]
Report source (11/11)	_____ _____ _____

Demographics [Page 2/8]	
Subject ID (1/7)	**03** / **2** [Site No./Subject No.]
Patient initials (2/7)	**H** / **W** [first/last name]
Patient date of birth (3/7)	**26**/**03**/**1945** [day/month/year]
Sex of patient (4/7)	**male**
Body height (5/7)	**170** cm
Body weight (6/7)	**106** kg
Treatment Arm (7/7)	**Single Arm** In blinded studies only: Please provide randomization code: _____

Case [Page 3/8]	
Type of event (1/9)	**SUSAR**
Seriousness criteria (2/9)	[ ] Fatal [ ] Life threatening **[x] Prolonging or requiring hospitalisation** [ ] Resulting in persistent significant disabillity / incapacity [ ] Congenital anomaly / birth defect [ ] Other if other, please specify: _____
Expedited criteria (3/9)	**no**
Relationship to Study Drug - Investigator (4/9)	**Suspected**
Case description (5/9)	**The patient, a 64-year old male with a colorectal adenocarcinoma is participating since October 2008 in clinical study C-II-005 (EUDRACT 2008-001515-37), receiving standard FOLFIRI therapy in combination with Sunitinib (Sutent®). Sunitinib is given daily (37.5 mg dose) for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks. On 20 April 2009, the patient took the last dose of Sunitinib prior to a 2-week rest period. The patient presented on 04 May 2009 in the context of a regular visit at the clinic with a 3x3 cm ulcus cruris on the left lower leg. The patient indicated that he had slipped on the staircase causing a wound that did not heal subsequently. Upon presentation, the left lower leg was warm, red, painful and showing several blisters (clinical aspect like erysipelas, deep soft tissue infection). Inflammation markers were elevated and the smear test showed Oxacillin-sensitive S. aureus. The patient was hospitalized on the same day (04 May 2009). The investigator indicated later that the condition was severe, in part because the patient did not consult the physician in time, but just showed the wound at the next regular visit. Sunitinib therapy was permanently discontinued and the patient taken "off study" due to this adverse event. Duplex sonography revealed chronic venous insufficiency Stadium III according to Widmer (ulcus cruris). The patient received the following antibiotic therapy: Clindamycin 3 x 600 mg, start 04 May, end 15 May 2009; Ceftriaxon 1 x 2 g i.v., start 04 May 2009, end 08 May 2009; and Flucloxacillin 2 x 500 mg, start 07 May, end 14 May 2009 [Flucoxacillin was started based on results of smear test]. With antibiotic treatment and and daily wound care, the patient improved and was discharged on 18 May 2009. At the latest visit on 08 June 2009, the wound has clearly improved, although not yet healed completely ("recovered with sequelae"). The patient received further treatment with FOLFIRI outside of this clinical study. Medical history includes arterial hypertension, gonarthrosis, psoriasis and benign hyperplasia of the prostate. Concomitant medications were Enalapril, Atenolol (both for hypertension) and Pantozol (ulcus prophyaxis for medication with Fortecortin as antiemetic treatment prior to chemotherapy). In the initial SAE report from the site on 04 May 2009, no causality assessment was provided. In the Follow-up report on 16 June 2009, this adverse event was classified as possibly related to sunitinib by the investigator. Since this adverse reaction is not described in the SmPC, this event is therefore reported as SUSAR. Based on the current information, the risk-benefit analysis for this clinical study remains unchanged.**
Reporter comment (6/9)	_____ _____ _____ _____ _____
Death information	
Death date (7/9)	__/__/____ [day/month/year]
Death cause (8/9)	_____
MedDRA10 Coding Code: Term:	
Autopsy (9/9)	___

Study site [Page 4/8]	
Name of reporter (1/4)	First name: **Beate** Last name: **Schultheiss**
Profession (2/4)	**Physician**
City (3/4)	**Herne**, Post code: _____
Country (4/4)	**Germany**

Reactions

Reaction [Page 5/8] - Table

Instance-no: 1 (Reaction)	
Description of adverse reaction (1/4)	**infected ulcus left lower leg**
MedDRA10 Coding Code: Term:	 **10021784** **Infected skin ulcer**
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	**04/05/2009** [day/month/year] __:__ [hour/minute]

Outcome (4/4)	**Recovered with sequelae**
	if recovered, please provide date of recovery:
	08/06/2009 [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	wound not yet completely healed

Instance-no: 2 (Reaction)	
Description of adverse reaction (1/4)	_____
MedDRA10 Coding Code: Term:	
Term highlighted (2/4)	_____
Onset date / onset time (3/4)	__/__/____ [day/month/year] __:__ [hour/minute]

Outcome (4/4)	_____
	if recovered, please provide date of recovery:
	__/__/____ [day/month/year] __:__ [hour/minute]
	if recovered with sequelae, please provide details:
	_____
	_____
	_____

Study medications / Concomitant medication / Non-drug therapies

Medication [Page 6/8] - Table

Instance-no: 1 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Irinotecan**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **180** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**10/11/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 2 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Folinic Acid**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **200** Unit: **mg/m^2** Frequency: **day 1 every 2 weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**10/11/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____
Instance-no: 3 (Medication)	
Type of Medication (1/17)	**Concomitant medication**
Preparation / Non-drug treatment (2/17)	**Fluorouracil**
Indication (3/17)	**Metastatic colorectal cancer**
MedDRA10 Coding Code: Term:	 **10052362** **Metastatic colorectal cancer**
Dosage (4/17)	Dose: **2800** Unit: **mg/m^2 bol/cont.inf** Frequency: **day 1 & 2 ev. 2weeks**
Route (5/17)	**Intravenous (not otherwise specified)**
Start (6/17)	**10/11/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (7/17)	__/__/____ [day/month/year] or **[x] Ongoing**
SAE relationship - investigator (8/17)	**Not suspected**
SAE relationship - sponsor (9/17)	**Not suspected** Comment: _____ _____ _____

Instance-no: 4 (Medication)	
Type of Medication (1/17)	**Study medication**
Preparation / Non-drug treatment (2/17)	**Sunitinib**
Indication (3/17)	**Metastatic colorectal cancer**
Batch No. (4/17)	_____
Dosage (5/17)	Dose: **37.5** Unit: **mg** Frequency: **od 4w on/2w off**
Route (6/17)	**Oral**
Start (7/17)	**10/11/2008** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
Action taken with study drug (8/17)	**Permanently discontinued**
Last administration (9/17)	**20/04/2009** [day/month/year]
Last treatment prior to SAE onset (10/17)	**20/04/2009** [day/month/year] __:__ [hour/minute] or interval between last treatment prior to SAE and SAE onset: __._ _____
SAE relationship - investigator (11/17)	**Suspected**
SAE relationship - sponsor (12/17)	**Suspected** Comment: _____ _____ _____
Expectedness (13/17)	**Unexpected** Comment: _____ _____ _____
Instance-no: 5 (Medication)	
Type of Medication (1/17)	**SAE treatment**
Preparation / Non-drug treatment (2/17)	**Clindamycin**
Dosage (3/17)	Dose: **3** Unit: **mg** Frequency: _____
Start (4/17)	**04/05/2009** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (5/17)	**15/05/2009** [day/month/year] or [ ] Ongoing
Instance-no: 6 (Medication)	
Type of Medication (1/17)	**SAE treatment**
Preparation / Non-drug treatment (2/17)	**Ceftriaxon**
Dosage (3/17)	Dose: **1** Unit: **g** Frequency: _____
Start (4/17)	**04/05/2009** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (5/17)	**08/05/2009** [day/month/year] or [ ] Ongoing
Instance-no: 7 (Medication)	
Type of Medication (1/17)	**SAE treatment**
Preparation / Non-drug treatment (2/17)	**Flucloxacillin**
Dosage (3/17)	Dose: **1000** Unit: **mg** Frequency: _____
Start (4/17)	**07/05/2009** [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (5/17)	**14/05/2009** [day/month/year] or [ ] Ongoing
Instance-no: 8 (Medication)	
Type of Medication (1/17)	_____
Preparation / Non-drug treatment (2/17)	_____
Dosage (3/17)	Dose: __.__ Unit: _____ Frequency: _____
Route (4/17)	_____
Start (5/17)	__/__/____ [day/month/year] __:__ [hour/minute] [ ] N/A, SAE prior to study medication
End (6/17)	__/__/____ [day/month/year] or [ ] Ongoing
SAE relationship - investigator (7/17)	_____
SAE relationship - sponsor (8/17)	_____ Comment: _____ _____ _____

Relevant tests

Test [Page 7/8] - Table

Instance-no: 1 (Relevant test)	
Test name (1/3)	**Duplex sonography**
MedDRA10 Coding Code: Term:	 **10013596** **Doppler ultrasound**
Date performed (2/3)	__/__/____ [day/month/year]
Result (3/3)	**chronic venous insuffic Widmer III (ulcus cruris** Unit: _____ if applicable: normal range lower limit: ____.__, upper limit: ____.__
Instance-no: 2 (Relevant test)	
Test name (1/3)	_____
MedDRA10 Coding Code: Term:	
Date performed (2/3)	__/__/____ [day/month/year]
Result (3/3)	_____ Unit: _____ if applicable: normal range lower limit: ____.__, upper limit: ____.__

Relevant medical history

History [Page 8/8] - Table

Instance-no: 1 (Medical History)	
Disease / Surgery (1/3)	_____
MedDRA10 Coding Code: Term:	
Start (2/3)	__/__/____ [day/month/year]
End (3/3)	__/__/____ [day/month/year] or [ ] Ongoing