Biometrical Report

CESAR C-II-005/ EUDRACT 2008-001515-37

A prospective angiogenic imaging study with DCE-MRI and DCE-UCI in patients with colorectal cancer and liver metastases receiving sunitinib in addition to 5-FU, folinic acid and irinotecan (FOLFIRI) as 1st line therapy.

Protocol

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28.07.2008	Version 1.1	1st amendment
16.09.2008	Version 1.2	2nd amendment
18.11.2008	Version 1.3	3rd amendment
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SAP

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Biometrical Report

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Summary

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. Due to withdrawal of consent before start of treatment or deviations to in-/exclusion criteria, 6 patients were not included in the Full Analysis Set. The primary endpoints were the change of tumor vessel permeability and blood flow measured as K_{trans} (transfer constant) and iAUC60 (initial area under the time-concentration curve defined over the first 60 seconds post enhancement) evaluated with DCE-MRI. FAS analysis of **primary endpoint was based only on data of 10 patients** due to missing DCE-MRI assessments at baseline and/or 6 weeks. Confirmatory statistical analysis of the changes ΔK_{trans} and ΔiAUC60 from baseline to 6 weeks was performed using two one-sided paired t-tests for continuous data at the multiple significance level of 5% (two tests performed at the nominal level of 0.025). The null hypotheses of no change within 6 weeks cannot be rejected at a 2.5% significance level for K_{trans} (p=0.22) and for iAUC (p=0.28). The one-sided 97.5% confidence intervals (CI) for the change within 6 weeks of K_{trans} was [-Inf, 1.20] and of iAUC [-Inf, 2.56]. This means that at a level 97.5% probability it can be stated that the two parameters increase at maximum by 1.2 and 2.6 units respectively, in concordance with the non-significant outcome of the respective hypotheses tests. At time of analysis 12 of the 22 patients of the FAS (54.5%) were in progressive disease. The median TTP was 48.0 weeks (n=12, 95%CI: 26.6-inf weeks). Best overall response could be determined in 17 patients and was assessed as PR in 8 patients (47.1%, 95%-CI: [23.0, 72.2%]) and in 9 patients as SD (52.9%, 95%-CI: [27.8-77.0 %]).

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). 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. 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. During the study, 5 deaths (22%) were documented. The reason for death was in 4 patients the underlying malignant disease and in one patient toxicity. This patient with toxicity was treated after end of study treatment with FOLFORI and thereafter with FOLFOX. The death occurred approximately 4 months after end of treatment on study and was not related to the study medication.

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3. Abbreviations and Definitions

AE	Adverse event
ALT	Alanine Aminotransferase
AP	Alkaline phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BF	Blood flow
BMI	Body Mass Index
CI	Confidence interval
CR	Complete Remission
DCE-MRI	Dynamic-Contrast-Enhanced Magnetic Resonance Imaging
DCE-USI	Dynamic-Contrast-Enhanced Ultrasound Imaging
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FOLFIRI	5-FU+Folinic Acid+Irinotecan
GGT	Gamma-GT
iAUC60	Initial area under the curve (60sec)
ITT	Intention-To-Treat
K_{trans}	Transfer constant
LD	Longest Diameter
LDH	Lactate dehydrogenase (LDH)
MedDRA	Medica Dictionary for Regulatory Activities
OR	Objective Response
ORR	Objective Response Rate
PD	Progressive Disease
PPS	Per Protocol Set
PR	Partial Remission
PT	Prothrombin Time
PT	Preferred Term (MedDRA)
PT-INR	International Ration of PT
RBC	Red Blood Count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
SOC	System Organ Class
TSH	Thyroid Stimulating Hormone
TTP	Time to progression
TVP	Tumor vessel permeability
WBC	White Blood Count

4 Preliminaries and Methods

This biometrical report is based on the results of statistical evaluation of the study data available from IOMedico, Freiburg, by 03-Feb-2011 at StaBiL. The statistical evaluation was performed from February to June 2011. Data listings and tables enclosed as appendices are part of this report. In a data check in November 2012 it was observed that the iAUC data underlying the Biometric Report dated on 16-Dec-2011 had been incorrectly imported into the data sets used for that first evaluation of the study data. Therefore, all analyses on the iAUC data were reconsidered and re-performed in November 2012. The outcome of that revised biometric analysis was used to update the Biometric Report as 2.0 Version.

4.1 Design of the study and Statistical Analysis Plan

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.

4.2 Data handling and statistical analyses

The data was obtained in form of an ACCESS data base from the CRO IOMedico, Freiburg, by 03-Feb-2011. From this data base, relevant information for statistical analysis was extracted and transformed into *SAS* original data sets by StaBiL. These *SAS* original data sets provided the base for

SAS analysis data sets. All data corrections and results of data merging were documented in the *SAS* analysis programs. All data corrections were also specified and listed in the corresponding chapters of this report. The biometric analysis reported here was based on these *SAS* analysis data sets and the *SAS* analysis programs. All *SAS* programs and *SAS* analysis data sets were stored at StaBiL. Biometric analyses were performed according to the Standard Operating Procedures (SOPs) of CESAR-EWIV valid at time of data base closure using the statistical package *SAS* for Windows Version 9.2 (SAS Institute Inc., North Carolina).

4.3 Changes to analyses specified in the statistical analysis plan

The Statistical Analysis Plan (SAP) defined the statistical analyses for all study evaluations. Changes of the statistical analyses planned in the protocol were stated in the SAP version Final1 dated 28-Jan-2011.

The statistical analysis performed for this report deviates in the following points from those planned in the SAP:

- Due to the small number of patients in the per protocol set (PPS), all analyses were only performed on the full analysis set (FAS).

- Since a QTc prolongation was not recorded on the CRF, an abnormal ECG was not considered as major or minor protocol deviation to the inclusion criterion 10: “Normal ECG without QT prolongation” (Study protocol Version 1.3, 18Nov2008, p. 27).

- According to the protocol, the tumor assessment at baseline should be performed within 14 days before start of treatment. In agreement with the principal sponsor of this study and since RECIST allows a baseline evaluation window of maximum 4 weeks before the beginning of treatment, the deviation in baseline assessment visit window leads not to the exclusion of the full analysis set.

- Adverse events were coded using terminology of MedDRA (Medical Dictionary for Regulatory Activities) and were summarized on the level of System Organ Classes (SOC) and Preferred Terms (PT).

5 Study Patients

5.1 Disposition of patients

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.

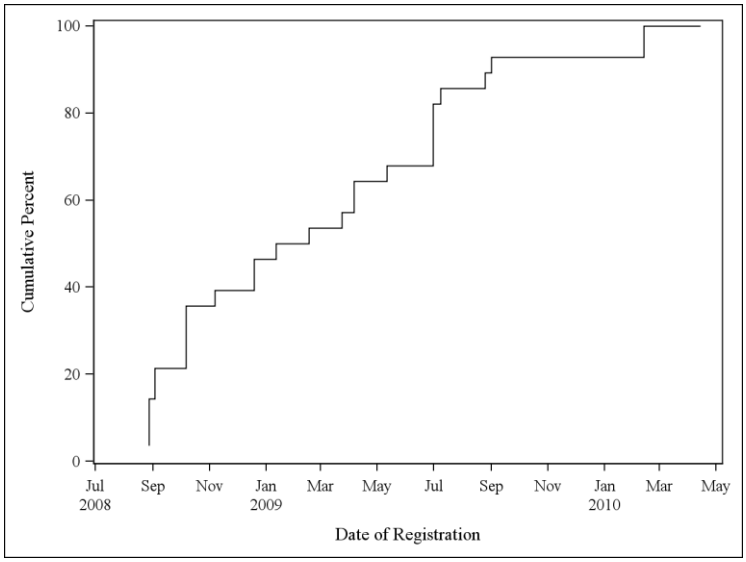
Table 1: Number of recruited patients per center

		Total n (%)	*RandomNo. coded as*
Recruiting by center	Fischer, Freiburg	9 (32%)	0401 ≤ RandomNo.≤ 0409
	Mross, Freiburg	6 (21%)	0101 ≤ RandomNo. ≤ 0107
	Scheulen, Essen	10 (36%)	0201 ≤ RandomNo.≤ 0210
	Strumberg, Herne	3 (11%)	0301 ≤ RandomNo. ≤ 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 and randomized to treatment. The total number of patients by recruiting time is illustrated in Figure 1.

Figure 1: Number of patients by recruiting time

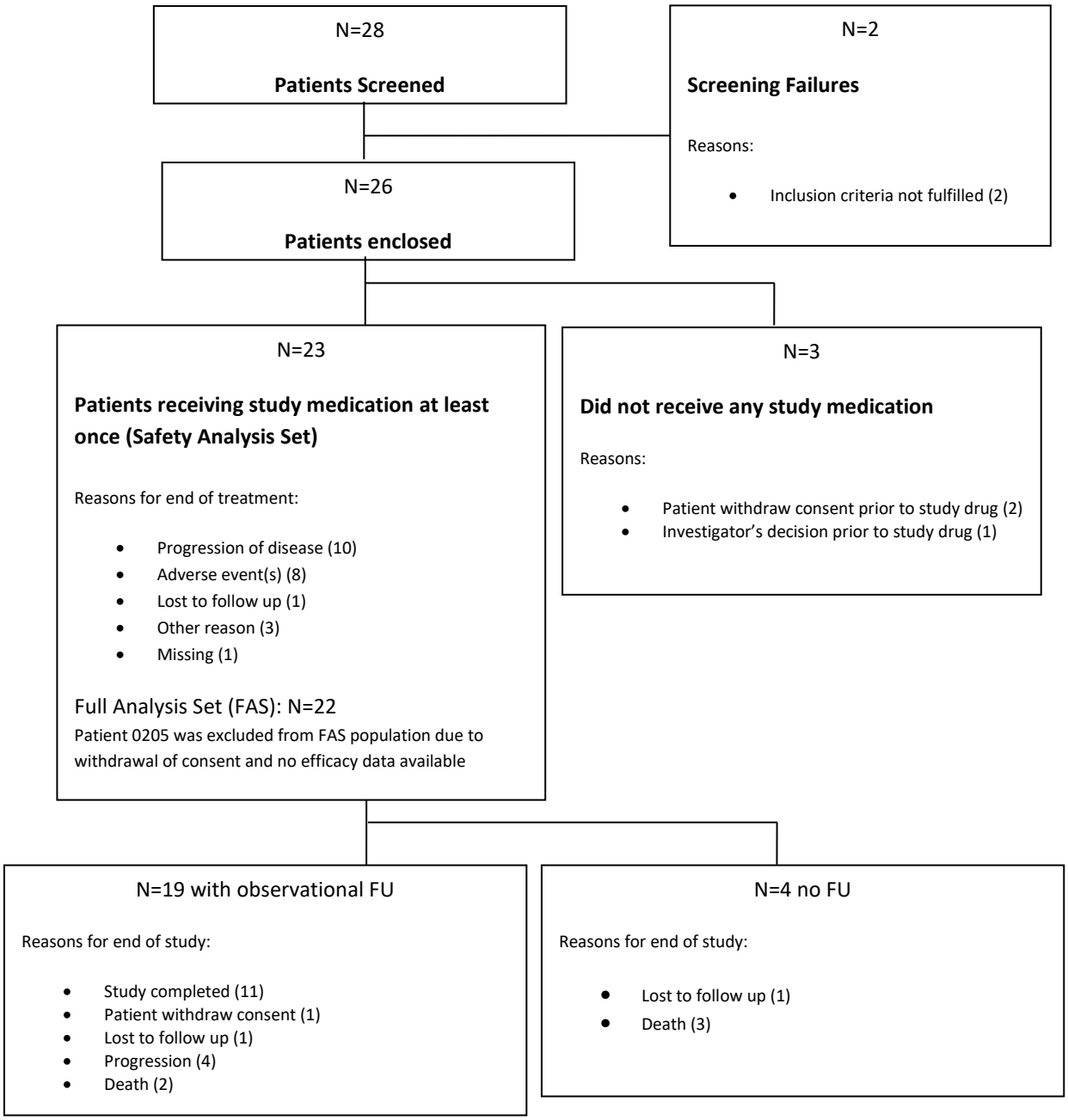


Note: Calculation of percentages based on the number of screened patients (N=28)
Source: Figure 1.2

An individual listing of recruitment information can be found in Appendix Listing 1.1.

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 2 shows the progress of the study.

Figure 2: Patient Disposition



A summary table of patients' disposition is given in Appendix Table 1.2.

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 2.

Table 2: 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 enclosed patients (N=26)
Source: Table 1.3.

Out of the 26 enclosed patients, 15 (58%) patients terminated the study prematurely whereas 11 (42%) patients terminated the study due to study closure. The reasons for end of study are summarized in Table 3.

Table 3: Reasons for end of study

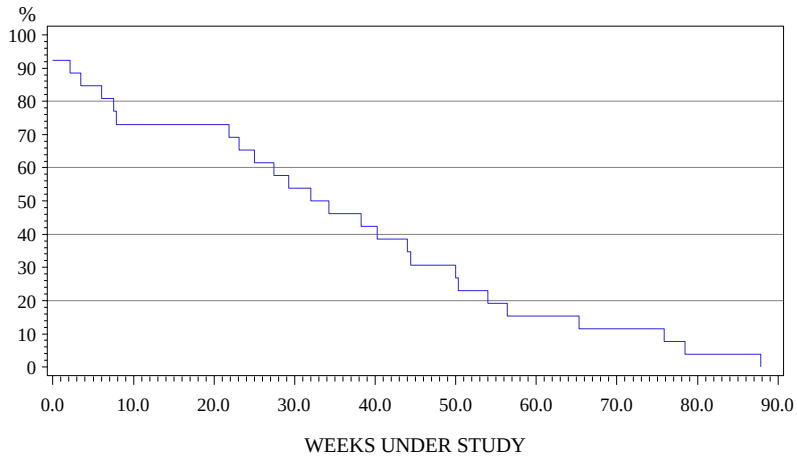
			Total n (%)
Reasons for end of study	**Before start of treatment**	Patient withdrew consent prior to study drug	2 (8%)
		Investigator's decision prior to study drug	1 (4%)
	After start of treatment	Patient lost to follow-up	2 (8%)
		Patient withdrew consent	1 (4%)
		Progression	4 (15%)
		Patient died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

Note: Calculation of percentages based on the number of enclosed patients (N=26)
Source: Table 1.5.

An individual listing of all withdrawals and reasons for end of study is given in Appendix Listing 1.3.

The time under study was calculated from Date of Registration until Date of End of study for all enclosed patients. Figure 3 shows the distribution function of time under study.

Figure 3: Distribution function of time under study



Median time under study was 33.1 weeks (range 0 - 87.9 weeks). Summary statistics for the time under study in weeks is given in Table 4.

Table 4: Summary statistics of time under study

		Total n(%)
Time under study (in weeks)	n	26
	Mean	34.8
	SD	25.39
	Median	33.1
	Min	0.0
	Max	87.9

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.4.

The individual patient data on trial participation together with the information on start and end of treatment are provided in Appendix Listing 1.2.

5.2 Protocol Deviations

5.2.1 Inclusion and exclusion criteria

Protocol deviations were defined in SAP prior to database closure and were classified as minor and major protocol deviation. Minor protocol deviations from the protocol did not have any impact on the planned analyses respective on the analysis populations whereas major protocol deviations resulted in the exclusion from the PPS.

A summary of major and minor protocol deviations is given in Table 5.

Table 5: Major and minor protocol deviations from in-exclusion criteria

		Criteria Fulfilled Total n(%)	*Assessment not done Total n(%)*	*Criteria not Fulfilled Total n(%)*
Minor criteria	(4): ECOG 0 or 1	27 (96.4%)	1 (3.6%)	--
	(7): bilirubin lower than 2 x ULN	27 (96.4%)	1 (3.6%)	--
	(8): AST, ALT lower than 5 x ULN	27 (96.4%)	1 (3.6%)	--
	(9): Creatinine lower than 1.5 x ULN	27 (96.4%)	1 (3.6%)	--
Major criteria	(1): over 18 years	28 (100%)	--	--
	(2): colorectal cancer	27 (96.4%)	1 (3.6%)	--
	(3): measurable hepatic lesion > 2cm	24 (85.7%)	2 (7.1%)	2 (7.1%)
	(5): Informed consent	28 (100%)	--	--
	(6): White blood cell count (WBC) greater than 4x10*9\L with neutrophils greater than 1.5 x 10*9\L,platelet count greater than 100x10*9\L, hemoglobin greater than 5.6 mmol\L (10 g\dL)	24 (85.7%)	1 (3.6%)	3 (10.7%)
	(17): Pregnancy[a]	4 (14.3%)	24 (85.7%)	--

[a] Assessment was to be performed only in females of child-bearing potential.
Note: Calculation of percentages based on the number of screened patients (N=28)
Source: Table 1.6.

No minor protocol deviations occurred. **At least one major protocol deviation was observed in 4 patients (1.4%).**

The following major protocol deviations occurred:

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

All deviations from in- and exclusion criteria are shown in Appendix Listing 1.4.

5.2.2 Study medication

To define the PPS, the study medication should be administered according to the protocol for at least 6 weeks. A summary of protocol conform administration of study medication until 6 weeks is given in Table 6. Please note that according to the study protocol, Sunitinib was noted as study medication whereas FOLFIRI was considered as background therapy, details are provided for study medication and background therapy.

Table 6: Administration of study medication until week 6

	Total n (%)
Protocol conform administration of	
Sunitinib	20 (71.4%)
FA bolus	18 (64.3%)
5-FU bolus	18 (64.3%)
5-FU continuous	17 (60.7%)
CPT-11	18 (64.3%)
all study medication	17 (60.7%)

Note: Calculation of percentages based on the number of screened patients (N=28)
Source: Table 1.7.

Five patients did not receive any study medication (RandomNo. 0103, 0207, 0209, 0402 and 0405). **A total of 17 patients (61%) was treated according to protocol until week 6.**

Individual patient data of administration of study medication until week 6 are presented in Appendix Listing 1.5-1.9. Data of all non-protocol conform treated patients until week 6 are provided in Appendix Listing 1.10.

5.2.3 DCE-MRI examination

To define the PPS, valid measurements of K_{trans} and iAUC should be available at least at baseline and at week 6 with a time window deviation of no more than 7 days at each of the two times. A summary of valid DCE-MRI measurements is given in Table 7.

Table 7: Valid K_{trans} and iAUC measurement at baseline and week 6

	Total *n (%)*
Valid K_{trans} measurement	10 (35.7%)
Valid iAUC measurement	10 (35.7%)
Valid time window at week 6	9 (32.1%)

Note: Calculation of percentages based on the number of screened patients (N=28)
Source: Table 1.8.

At total of 10 patients (36%) had available K_{trans} and iAUC measurements at baseline and at week 6. In one patient (RandomNr. 0303) the 6 week DCE-MRI measurement was performed 56 days after the baseline measurement and therefore was outside the permitted time window (35-49 days). Nevertheless this value was included in the FAS analysis.

The individual listing of DCE-MRI measurement at baseline and at week 6 is presented in Appendix Listing 1.11.

6 Data sets analyzed

Three populations were defined in the SAP for the statistical analyses of this study.

6.1 Full analysis set (FAS)

According to the ITT principle, the FAS population consists of all patients included into the study irrespective whether any protocol violation was present at the time of treatment start or during treatment on study or whether the patient withdraw consent or was taken off-study at any time after treatment start.

Not included are patients

- who withdraw informed consent before start of treatment or
- about whom it becomes known that major in/exclusion criteria were violated which would have excluded them from study treatment when known at start of treatment.

The FAS of this study consists of N=22 patients. The following 6 patients were excluded from the FAS:

RandomNo.	Reason
0103	Inclusion criteria not fulfilled (investigators decision)
0205	Patient withdrew consent
0207	Patient withdrew consent prior to study drug
0209	Investigator's decision prior to study drug
0402	Patient withdrew consent prior to study drug
0405	Inclusion criteria not fulfilled (investigators decision)

The baseline characteristics of all patients excluded from the FAS are given in Appendix Listing 1.12.

6.2 Per protocol set (PPS)

The PPS population consists of all patients who were eligible for the study according to the in/exclusion criteria and who received the study treatment according to the protocol for at least 6 weeks. Since the PPS will only be used to evaluate the robustness of the results of analysis of primary endpoints based on FAS, eligibility to the PPS requires only adherence to the imaging dates of DCE-MRI. In contrast to the study protocol, adherence to the imaging dates of DCE-USI will not be necessary to be eligible to the PPS.

The PPS of this study consists of N=7 patients. The following 21 patients were excluded from the PPS:

RandomNo.	Reason
0101	Only baseline DCE-MRI measurement
0102	Only DCE-MRI baseline measurement
0103	Inclusion criteria not fulfilled (investigators decision)
0105	Major Criteria no fulfilled (WBC=3.5 10*9/L)
0202	No DCE-MRI baseline measurement
0203	No DCE-MRI measurements (wrong position)
0205	Patient withdrew consent
0206	No DCE-MRI measurements
0207	Patient withdrew consent prior to study drug
0208	No 6w DCE-MRI measurement
0209	Investigator's decision prior to study drug
0210	Major Criteria no fulfilled (No target lesion) No 6w DCE-MRI measurement
0301	No 6w DCE-MRI measurement
0302	No 6w DCE-MRI measurement
0303	6w DCE-MRI measurement not in time window (56 days)
0401	Major Criteria no fulfilled (Hemoglobin=9.1 g/dl)No 6w measurement
0402	Patient withdrew consent prior to study drug
0403	No 6w DCE-MRI measurement
0405	Inclusion criteria not fulfilled (investigators decision)
0406	No 6w DCE-MRI measurement
0407	No therapy at w5

The baseline characteristics of all patients excluded from the PPS are given in Appendix Listing 1.13.

6.3 Safety analysis set (SAS)

The SAS consists of all patients who received the study medication at least once.

The SAS of this study consists of N=23 patients. The following 5 patients were excluded from the SAS:

RandomNo.	Reason
0103	Inclusion criteria not fulfilled (investigators decision)
0207	Patient withdrew consent prior to study drug
0209	Investigator's decision prior to study drug
0402	Patient withdrew consent prior to study drug
0405	Inclusion criteria not fulfilled (investigators decision)

The baseline characteristics of all patients excluded from the SAS are given in Appendix Listing 1.14.

Individual patient data on the in-/exclusion to the data sets analyzed are provided in Appendix Table 1.9.

7 Baseline characteristics

All 22 patients of the FAS were characterized according to demography, tumoranamnesis, previous and concomitant diseases, prior medical therapies and baseline laboratory parameters.

7.1 Demographic data

Demographic data of the 22 patients of the FAS were collected at the beginning of the study. The age was calculated as difference between date of birth and date of consent. 13 patients (59%) were male and 9 patients were female (41%). The analyzed population aged between 33.4-85.1 years (range), the average age was 62.3 ± 11.24 years and the median age was 62.5 years. The average weight was 78.9 ± 15.07 kg, the average height was 170.5 ± 8.77 cm and the average BMI.

Table 8: Demographic data (FAS)

		Total n(%)
Gender	Male	13 (59 %)
	Female	9 (41 %)
Age (years)	n	22
	Mean	62.3
	SD	11.24
	Median	62.5
	Min	33.4
	Max	85.1
Weight (kg)	n	21
	Mean	78.9
	SD	15.07

		Total n(%)
	Median	75.0
	Min	57.0
	Max	106.0
Height (cm)	n	22
	Mean	170.5
	SD	8.77
	Median	172.0
	Min	149.0
	Max	184.0
BMI	n	21
	Mean	27.0
	SD	5.29
	Median	26.0
	Min	19.3
	Max	39.3

Note: Calculation of percentages based on the number of patients in FAS (N=22)
Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.10.

Individual patient demographic data are provided in Appendix Listing 1.15.

7.2 Vital signs/Performance Status/ Physical examination

Summary statistics were calculated for systolic and diastolic blood pressure, pulse rate and temperature at baseline. ECOG Scale, physical examination and ECG results were summarized by percentages.

14 patients of FAS (64%) had ECOG 0 and 8 (36%) ECOG 1. Summary of vital signs and physical examination are presented in Table 9.

Table 9: Physical examination (FAS)

		Total n(%)
Systolic blood pressure (mmHG)	N	22
	Mean	128.6
	SD	13.70
	Median	127.0
	Min	110.0
	Max	160.0
Diastolic blood pressure (mmHG)	N	22
	Mean	76.3
	SD	10.37
	Median	75.5
	Min	60.0
	Max	100.0
Pulse (beats\min)	N	22
	Mean	74.0
	SD	12.75
	Median	76.0
	Min	52.0
	Max	100.0
Temperature (°Celcius)	N	21
	Mean	36.2
	SD	0.32
	Median	36.2
	Min	35.4
	Max	36.9
ECOG Scale	0	14 (64 %)
	1	8 (36 %)

		Total n(%)
Pathological findings in physical examination	No	18 (82 %)
	Yes	4 (18 %)
ECG result	Missing	2 (9 %)
	Normal	13 (59 %)
	Abnormal, but not clinically relevant	7 (32 %)
Chest examination result	Normal	7 (32 %)
	tumor finding	10 (45 %)
	other finding	5 (23 %)

Note: Calculation of percentages based on the number of patients in FAS (N=22)
Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.11.

It should be noted that in 7 cases, the ECG was recorded as abnormal, and in all cases the investigator has classified these changes as clinically not significant and provided a brief explanation that can be found in Appendix Listing 1.16.2. The Sponsor, together with the Study Chair, therefore decided that these findings do not represent a deviation of Inclusion criterion " (10) normal ECG without QTc prolongation".

Pathological findings in physical examination were not specified. Other findings in chest examination were:

- scarred changes in lung (RandomNo. 0104)
- granulomatous (RandomNo. 0206)
- emphysem, pericardial effusion (RandomNo. 0301)
- enlarged lymph nodes (RandomNo. 0408, 0409).

Individual patient data on physical examination at baseline are provided in Appendix Listing 1.16.1.

7.3 Tumoranamnesis

Tumor was in 13 patients (59%) located at rectum and in 9 patients at colon (41%, see Appendix Table 1.12). Summary statistics of time between date of initial diagnosis and date of informed consent for the study, time between occurrence of organ metastasis and initial diagnosis and time between liver metastasis and initial diagnosis in weeks are provided in Table 10.

Table 10: Time since initial diagnosis, organ and liver metastases (FAS)

Time between initial diagnosis and informed consent (weeks)	n	22
	Mean	27.9
	SD	43.98
	Median	6.4
	Min	1.0
	Max	173.3
Time between initial diagnosis and organ metastasis (weeks)	n	22
	Mean	13.2
	SD	25.66
	Median	0.8
	Min	0.0
	Max	96.0
Time between initial diagnosis and liver metastasis (weeks)	n	22
	Mean	18.2
	SD	30.79
	Median	0.8
	Min	0.0
	Max	96.0

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.13.

Individual data on tumoranamnesis is provided in Appendix Listing 1.17.

According to study protocol, tumor lesions at baseline were classified using RECIST criteria (Therasse, 2000) as

- measurable if they can be accurately measured in at least one dimension as ≥ 20mm in conventional techniques or as ≥ 10mm with spinal CT;
- non-measurable if they were small lesions (longest diameter <20mm in conventional techniques or <10mm in spinal CT) as well as bone lesions, leptomeningeal disease, ascites, pleural/pericard effusions, lymphangitits, cutis/pulmonis, inflammatory breast disease, abdominal masses and cystic lesions.

All measurable lesions up to 10 lesions were identified as target lesions. Non-measurable lesions and measurable lesions analyzed beyond the maximum of 10 measurable lesions -even if listed as target lesions - were considered as non-target lesions.

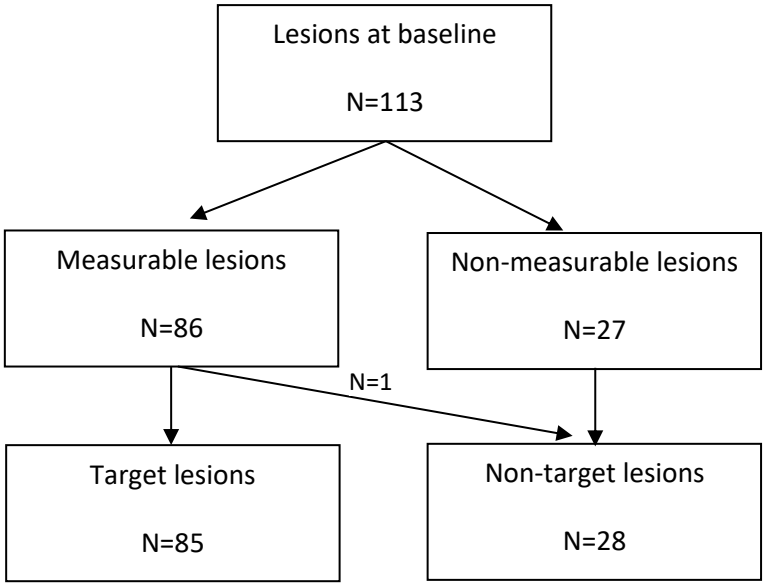
According to the study protocol, the tumor assessment at baseline should have been performed within 14 days before start of treatment, whereas according to RECIST the baseline evaluations should be performed never more than 4 weeks (28 days) before the beginning of treatment. The following evaluation window deviations were observed:

RandomNo.	Start of Treatment	Date of tumor assessment	Difference (in days)
0202	26.03.2009	10.03.2009	16
0206	02.09.2009	18.08.2009	15
0302	10.11.2008	29.09.2008	42
0303	18.11.2008	27.10.2008	22
0409	03.08.2009	15.07.2009	19

In agreement with the principal sponsor of this study, the deviation in baseline assessment visit window leads not to the exclusion of the full analysis set.

A total of 113 lesions were observed at baseline in the FAS. One lesion (LesionNo. 4 of RandomNo. 0401) was assessed as target lesion. This lesion was measurable but the longest diameter was only 7 mm in spiral CT scan. According to RECIST this lesion has be classified as non-target lesion. A characterization of baseline lesion is presented in Figure 4.

Figure 4: Characterization of baseline lesions in FAS (N= 23)



The localization of all n= 133 tumor lesions at baseline as well as the localization of all target (n=85) and non-target lesions (n=28) is presented in Table 11.

Table 11: Localization of tumor lesions at baseline (FAS)

		All lesions Total n(% of 113)	*Target lesions Total n(% of 85)*	*Non-target lesions Total n(% of 28)*
Tumor localisations at baseline	bone	3 (3 %)		3 (11 %)
	breast	1 (1 %)		1 (4 %)
	liver	63 (56 %)	58 (68 %)	5 (18 %)
	lung	26 (23 %)	18 (21 %)	8 (29 %)
	lymph nodes	16 (14 %)	6 (7 %)	10 (36 %)
	other	2 (2 %)	2 (2 %)	
	soft tissue	2 (2 %)	1 (1 %)	1 (4 %)

Note: Calculation of percentages based on number of baseline lesions
Source: Table 1.14.

One patient had one solitary lesion and 21 patients had multiple lesions at baseline. One patient (RandomNo. 0210) had no target but only non-target lesions. The number of lesions per patient ranged from 1 to 10 lesions (see Table 12). The median number of lesion per patient was 4.5 lesions.

Table 12: Frequency of lesions at baseline per patient (FAS)

		All lesions Total n(%)
Frequency of lesions per patient at baseline	1	1 (5 %)
	2	2 (9 %)
	3	2 (9 %)
	4	6 (27 %)
	5	3 (14 %)
	6	2 (9 %)
	7	1 (5 %)
	8	2 (9 %)
	9	2 (9 %)
	10	1 (5 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Source: Table 1.15.

The sum of the longest diameter (LD) for all target lesions was calculated per patient. Table 13 gives summary statistics for the sum of LD of baseline target lesions. Since one patient had no target lesions, these calculation were based on n=21 patients of the FAS.

Table 13: Sum of longest diameters of baseline target lesions (FAS)

sum of longest diameter (in mm)	n	21
	Mean	154.9
	SD	77.52
	Median	148.0
	Min	24.0
	Max	358.0

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.16.

Individual tumor lesion characteristics at baseline are presented in a by-lesion tabular listing in Appendix Listing 1.18.

7.4 Previous and concomitant diseases

Diseases occurring before study entry were divided in concomitant diseases and previous diseases. Concomitant diseases were present at start of treatment and persisting some time or totally during treatment with study medication. Previous diseases were not persisting at start of treatment. If begin and/or end of disease was not specified, the disease was analyzed as concomitant disease. Classification was according NCI-CTC v3.0 guidelines.

A total of 12 previous and 111 concomitant diseases were recorded in the FAS. Twenty patients (91%) had at least one previous or concomitant disease. Previous and concomitant diseases are summarized in Table 14.

Table 14: Summary of previous and concomitant diseases (FAS)

		Total n(%)
At least one previous or concomitant disease	no	2 (9 %)
	yes	20 (91 %)
At least one previous disease	no	12 (55 %)
	yes	10 (45 %)
At least one concomitant disease	no	2 (9 %)
	yes	20 (91 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Source: Table 1.17.

Twelve patients (55%) had no previous diseases, whereas in 10 patients (45%) a total of 12 previous diseases were recorded. Table 15 presents the frequency by affected organ systems.

Table 15: Previous diseases by CTC organ system (FAS)

CTC Organ	*Total n(%)*
CARDIAC GENERAL	1 (5 %)
DERMATOLOGY/SKIN	1 (5 %)

CTC Organ	*Total n(%)*
ENDOCRINE	1 (5 %)
GASTROINTESTINAL	2 (9 %)
HEMORRHAGE/BLEEDING	1 (5 %)
MUSCULOSKELETAL/SOFT TISSUE	2 (9 %)
RENAL/GENITOURINARY	1 (5 %)
SEXUAL/REPRODUCTIVE FUNCTION	1 (5 %)
SURGERY/INTRA-OPERATIVE INJURY	1 (5 %)
VASCULAR	1 (5 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Note: A patient with more than one previous disease within a CTC organ system was counted once
Source: Table 1.18.

A previous disease could occur repeatedly in a patient at different times, respectively in different time windows and with different CTC-grades. Table 16 shows the different previous diseases with the maximal CTC-grade (CTC1, CTC2, CTC3, CTC4) if occurred repeatedly per patient, respectively, with its single CTC-grade if occurred only once in one patients.

Table 16: Previous diseases by CTC symptoms and maximum CTC-grade (FAS)

CTC Organ	*CTC Symptom*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
CARDIAC GENERAL	**Cardiac ischemia/infarction**	1 (5 %)				1 (5 %)
DERMATOLOGY/SKIN	**Dermatology/Skin - Other (Specify, __)**	1 (5 %)	1 (5 %)			
ENDOCRINE	**Thyroid function, low (hypothyroidism)**	1 (5 %)	1 (5 %)			
GASTROINTESTINAL	**Gastrointestinal - Other (Specify, __)**	1 (5 %)		1 (5 %)		
	Mucositis/stomatitis (functional/symptomatic) - Oral cavity	1 (5 %)			1 (5 %)	

CTC Organ	*CTC Symptom*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
HEMORRHAGE/BLEEDING	**Hemorrhage, GI - Colon**	1 (5 %)		1 (5 %)		
MUSCULOSKELETAL/SOFT TISSUE	**Fracture**	1 (5 %)			1 (5 %)	
	Musculoskeletal/Soft Tissue - Other (Specify, __)	1 (5 %)	1 (5 %)			
RENAL/GENITOURINARY	**Stricture/stenosis (including anastomotic), GU - Prostate**	1 (5 %)	1 (5 %)			
SEXUAL/REPRODUCTIVE FUNCTION	**Sexual/Reproductive Function - Other (Specify, __)**	1 (5 %)		1 (5 %)		
SURGERY/INTRA-OPERATIVE INJURY	**Intra-operative injury - Hepatobiliary/Pancreas - Gallbladder**	1 (5 %)			1 (5 %)	
VASCULAR	**Thrombosis/thrombus/embolism**	1 (5 %)			1 (5 %)	

Note: Calculation of percentages based on number of patients in FAS (N=22)
Note: A patient with more than one previous disease within a CTC symptom was counted once with maximum CTC-grade
Source: Table 1.19.

A by-patient tabular listing of all previous diseases is provided in Appendix Listing 1.19.

In 20 patients (91%) at least on concomitant disease was observed and a total of 111 concomitant diseases were recorded. Table 17 summarizes the concomitant diseases by CTC organ system.

Table 17: Concomitant diseases by CTC organ system (FAS)

CTC Organ	*Total n(%)*
ALLERGY/IMMUNOLOGY	4 (18 %)

CTC Organ	*Total n(%)*
AUDITORY/EAR	1 (5 %)
CARDIAC ARRHYTHMIA	3 (14 %)
CARDIAC GENERAL	13 (59 %)
CONSTITUTIONAL SYMPTOMS	8 (36 %)
DERMATOLOGY/SKIN	5 (23 %)
ENDOCRINE	4 (18 %)
GASTROINTESTINAL	9 (41 %)
HEMORRHAGE/BLEEDING	2 (9 %)
INFECTION	2 (9 %)
LYMPHATICS	1 (5 %)
METABOLIC/LABORATORY	3 (14 %)
MUSCULOSKELETAL/SOFT TISSUE	6 (27 %)
NEUROLOGY	5 (23 %)
OCULAR/VISUAL	3 (14 %)
PAIN	6 (27 %)
PULMONARY/UPPER RESPIRATORY	1 (5 %)
RENAL/GENITOURINARY	4 (18 %)
SURGERY/INTRA-OPERATIVE INJURY	2 (9 %)
VASCULAR	1 (5 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Note: A patient with more than one concomitant disease within a CTC organ system was counted once
Source: Table 1.20.

A concomitant disease could occur repeatedly in a patient at different times, respectively in different time windows and with different CTC-grades. Table 18 shows the different concomitant diseases with the maximal CTC-grade reported if symptom occurred in more than 10% of the patients. A complete table for all symptoms recorded is provided in Appendix Table 1.21.

Table 18: Concomitant diseases by CTC symptoms and maximum CTC-grade (FAS)

CTC Organ	*CTC Symptom*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
CARDIAC GENERAL	**Hypertension**	11 (50 %)	7 (32 %)	3 (14 %)	1 (5 %)	

CTC Organ	*CTC Symptom*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
CONSTITUTIONAL SYMPTOMS	**Constitutional Symptoms - Other (Specify, __)**	3 (14 %)	1 (5 %)	2 (9 %)		
	Fatigue (asthenia, lethargy, malaise)	3 (14 %)	3 (14 %)			
	Insomnia	5 (23 %)	2 (9 %)	3 (14 %)		
GASTROINTESTINAL	**Gastritis (including bile reflux gastritis)**	3 (14 %)	2 (9 %)	1 (5 %)		
	Gastrointestinal - Other (Specify, __)	3 (14 %)	2 (9 %)	1 (5 %)		
MUSCULOSKELETAL /SOFT TISSUE	**Musculoskeletal/Soft Tissue - Other (Specify, __)**	4 (18 %)	4 (18 %)			
OCULAR/VISUAL	**Ocular/Visual - Other (Specify, __)**	3 (14 %)		2 (9 %)		1 (5 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Note: A patient with more than one concomitant disease within a CTC symptom was counted once with maximum CTC-grade
Source: Table 1.21.

A by-patient tabular listing of all concomitant diseases is provided in Appendix Listing 1.20.

7.5 Prior medical therapies

Previous treatments for cancer were recorded as previous systemic anticancer therapy, radiotherapy and previous anticancer surgery.

Seven patients (32%) had received no previous therapies at all, whereas 15 patients (68%) had received at least one. Among those, 4 patients (18%) were pretreated with systemic anticancer therapy, radiotherapy and anticancer surgery, 1 patient (5%) received systemic anticancer therapy and anticancer surgery and 10 patients (45%) were only pretreated with anticancer surgery. Summary of prior medical therapies is presented in Table 19.

Table 19: Previous medical therapies (FAS)

		Total n(%)
Previous systemic therapy	no	17 (77 %)
	yes	5 (23 %)
Previous radiotherapy	no	18 (82 %)
	yes	4 (18 %)
Previous surgical therapy	no	7 (32 %)
	yes	15 (68 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Source: Table 1.22.

Information on previous systemic anticancer therapies, radiotherapy and anticancer surgery is provided in Appendix Listing 1.21-1.23.

7.6 Laboratory

Laboratory evaluations were performed at baseline and during the intake of study medication and consisted of

- Hematology (hemoglobin, hematocrit, platelets, RBC, WBC, neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Clinical chemistry (sodium, potassium, chloride, calcium, AST, ALT, LDH, Gamma-GT (GGT), AP, bilirubin, albumin, total protein, glucose, creatinine)
- Coagulation/Thyroid parameters (PT, PT-INR, aPTT, TSH, total T3, free T3, total T4, free T4).

Due to the use of different units of laboratory parameters among participating study centers, allowed by the documentation system, some parameters had to be converted into a conventionally used unit. Hematological parameters (e.g. neutrophils, lymphocytes, monocytes, basophils and eosinophils) were recorded in two units either '/nL' or '%'. Those could not be converted into each other and summary statistics were calculated separately for '/nL' and '%'.

Different units were used for the following laboratory parameters:

Parameter	Unit	Other unit used	Conversion
Neutrophils	/nL	%	No conversion
Lymphocytes	/nL	%	No conversion
Monocytes	/nL	%	No conversion
Basophils	/nL	%	No conversion
Eosinophils	/nL	%	No conversion
Hematocrit	%	L/L	100 L/L
TSH	µU/mL	mU/L	mU/L
TSH	µU/mL	µIU/mL	µIU/mL
TSH	µU/mL	mIU/L	mIU/L
Total T3	ng/mL	nmol/L	0.649 ng/mL
Total T4	µg/dL	nmol/L	0.0777 nmol/L
Free T4	ng/dL	pmol/L	0.0777 pmol/L

Two laboratory values measured at baseline were corrected or deleted from the analysis:

RandomNo.	Parameter	Value	Conversion
0202	Hematocrit	0.397 %	39.7%
0208	Total T3	88 nmol/L	deleted

According to the study protocol, baseline laboratory screening should be performed within 7 days prior to start of treatment. The following laboratory window deviations were observed:

RandomNo.	Start of Treatment	Date of laboratory	Difference (in days)
0301	09.09.2008	28.08.2008	12
0302	10.11.2008	28.10.2008	13
0303	18.11.2008	07.11.2008	11
0401	17.09.2008	09.09.2008	8

Nevertheless those values were not deleted from the analyses. Statistical summary statistics were calculated for the FAS when measurements were available at baseline (see Table 20). Deviations from the number of FAS (N=22) are due to missing values parameter in some patients.

Table 20: Laboratory parameters at baseline (FAS)

	Parameter	*Unit*	*n*	*mean*	*std*	*median*	*min*	*max*
Hematology	Hemoglobin	g\dL	22	12.2	1.84	12.4	9.1	17.3
	Hematocrit	%	22	36.7	4.87	36.7	28.5	50.4
	Platelets	\nL	22	339.2	124.99	351.5	153.0	609.0
	RBC	\pL	22	4.2	0.56	4.2	3.5	5.4
	WBC	\nL	22	8.4	3.16	8.6	3.5	16.1
	Neutrophils	/nL	12	5.6	2.81	5.7	1.8	12.5

	Parameter	*Unit*	*n*	*mean*	*std*	*median*	*min*	*max*
	Neutrophils	%	10	73.0	6.90	72.7	61.9	84.0
	Lymphocytes	/nL	7	1.6	0.36	1.4	1.3	2.2
	Lymphocytes	%	15	18.3	8.17	18.4	6.0	39.0
	Monocytes	/nL	7	0.9	0.52	0.8	0.4	1.9
	Monocytes	%	15	7.0	1.67	7.0	2.8	10.0
	Basophils	/nL	7	0.0	0.02	0.0	0.0	0.1
	Basophils	%	15	0.7	0.36	1.0	0.0	1.0
	Eosinophils	/nL	7	0.3	0.25	0.2	0.0	0.7
	Eosinophils	%	15	3.3	1.86	3.0	1.0	6.5
Clinical Chemistry	Sodium	mmol\L	22	138.5	3.73	139.5	127.0	143.0
	Potassium	mmol\L	22	4.4	0.51	4.4	3.1	5.2
	Chloride	mmol\L	22	102.2	4.87	102.5	89.0	109.0
	Calcium	mmol\L	22	2.3	0.15	2.3	1.9	2.6
	AST	U\L	22	51.7	35.04	38.0	12.0	132.0
	ALT	U\L	22	35.6	34.55	25.0	7.0	167.0
	LDH	U\L	21	471.8	320.98	347.0	136.0	1250.0
	gamma-GT	U\L	22	302.6	396.46	112.5	23.0	1146.0
	AP	U\L	22	211.1	217.98	100.0	50.0	906.0
	Bilirubin	mg\dL	22	0.5	0.28	0.4	0.1	1.5
	Albumin	g\dL	22	3.9	0.42	3.9	2.9	4.4
	Total protein	g\dL	22	7.0	0.50	7.1	6.2	7.9
	Glucose	mg\dL	22	96.6	12.32	94.0	80.0	124.0
	Creatinine	mg\dL	22	0.8	0.22	0.7	0.5	1.4
Coagulation/Tyroid	PT	%	9	105.4	13.14	109.0	83.0	120.0
	PT-INR	INR	5	1.0	0.07	1.0	0.9	1.1
	aPTT	sec	20	30.0	3.97	30.0	24.0	38.0
	TSH	µU/mL	19	1.8	1.49	1.5	0.1	5.6
	Total T3	ng\mL	11	1.1	0.25	1.1	0.8	1.6
	Free T3	pmol\L	7	3.9	1.11	4.1	2.4	5.5
	Total T4	µg/dL	9	9.5	1.79	8.6	8.3	13.4
	Free T4	ng/dL	10	1.2	0.08	1.2	1.1	1.3

Parameter	*Unit*	*n*	*mean*	*std*	*median*	*min*	*max*

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 1.23.

An individual listing of baseline laboratory parameters is provided in Appendix Listing 1.24.

8 Primary efficacy endpoints

As quantitative primary endpoints, the vascular permeability (K_{trans}) and the initial area under the contrast enhanced curve (iAUC60) were analyzed only on the FAS, due to the small number of patients in PPS.

According to study protocol, one hepatic lesion per patient was analyzed by DCE-MRI assessment. Additionally, it was documented if the examined hepatic lesion was a lesion which was followed by RECIST. A total of 21 hepatic lesions were defined at baseline in the FAS for DCE-MRI assessment. In one patient, no lesion was defined for DCE-MRI measurement (RandomNo. 0206), since no baseline measurements were performed for this patient. Seven lesions (32%) were also followed according to RECIST, whereas 14 lesions (64%) were not followed according to RECIST and no lesion was defined for one patient (5%). The localisation of the hepatic lesions is presented in Table 21.

Table 21: Examined hepatic lesions (FAS)

		Total n(%)
RECIST lesion	No lesion defined	1 (5 %)
	no	14 (64 %)
	yes	7 (32 %)
Localisation of hepatic lesion	No lesion defined	1 (5 %)
	Leber S4a	1 (5 %)
	hepatic segment VII	1 (5 %)
	left hepatic lobe, segment II	3 (14 %)
	left hepatic lobe, segment II/III	1 (5 %)
	left hepatic lobe, segment III	1 (5 %)
	left hepatic lobe, segment IV	1 (5 %)
	right hepatic lobe, segment V	3 (14 %)
	right hepatic lobe, segment V/VII	1 (5 %)

		Total n(%)
	right hepatic lobe, segment VI	2 (9 %)
	right hepatic lobe, segment VI /	2 (9 %)
	right hepatic lobe, segment VII	1 (5 %)
	right hepatic lobe, segment VIII	4 (18 %)

Note: Calculation of percentages based on number of patients in FAS (N=22)
Source: Table 2.1.

DCE-MRI assessments were performed at baseline, at the end of week 2, 4 and 6. Summary statistics were calculated for K_{trans} and iAUC separately for each assessment time point as well as for the difference between baseline and 6 weeks measurement in Table 22.

Table 22: K_{trans} and iAUC measurements (FAS)

		K_{trans}	*iAUC*
Baseline	n	19	19
	Mean	2.4	12.9
	SD	2.35	5.97
	Median	1.6	10.8
	Min	0.5	6.7
	Max	10.0	29.4
Cycle 1 - Week 2	n	12	12
	Mean	1.3	10.2
	SD	1.20	8.02
	Median	1.0	6.7
	Min	0.1	1.2
	Max	3.7	26.1
Cycle 1 - Week 4	n	16	16
	Mean	1.7	11.2
	SD	1.18	8.31
	Median	1.4	7.2
	Min	0.1	1.9
	Max	3.8	27.2

		K_{trans}	*iAUC*
Cycle 1 - Week 6	n	11	11
	Mean	2.3	11.5
	SD	1.53	6.53
	Median	3.1	10.4
	Min	0.4	3.8
	Max	4.0	26.7
Cycle 2 - Week 10	n	2	2
	Mean	0.7	6.9
	SD	0.28	1.02
	Median	0.7	6.9
	Min	0.5	6.2
	Max	0.9	7.7
Cycle 2 - Week 10			
	Mean	0.7	6.9
	SD	0.28	1.02
	Median	0.7	6.9
	Min	0.5	6.2
	Max	0.9	7.7
Difference between baseline and week 2			
	Mean	-0.8	-1.2
	SD	1.28	6.70
	Median	-0.9	-3.3
	Min	-2.7	-9.6
	Max	1.4	10.2
Difference between baseline and week 4			
	Mean	-1.0	-0.9
	SD	1.95	6.94
	Median	-0.5	-1.4

	K_{trans}	*iAUC*
Min	-6.3	-7.7
Max	2.0	17.5

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 2.2.

The distribution of K_{trans} and iAUC measurements are visualized graphically by side-by side box-and whiskers plots in Figure 5 and 6. The upper respective the lower edge of the box displays the third respective the first quartile. The line inside the box represents the median whereas the mean is marked by a diamond. The whiskers are drawn from the upper respective from the lower edge of the box to the largest respective to the lowest observed value within 1.5 times the interquartile range (third minus first quartile) above the third quartile respective below the first quartile. Observations outside this range are marked with a non-filled circle.

Figure 5: Boxplot for K_{trans} (FAS)

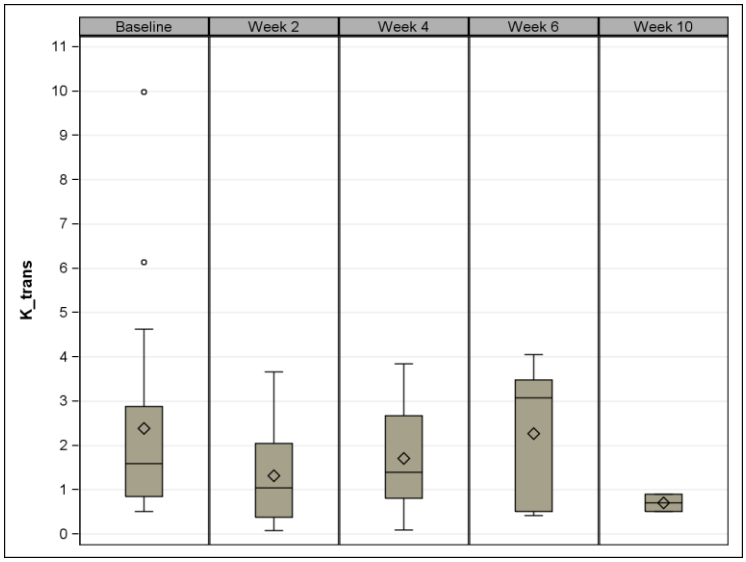
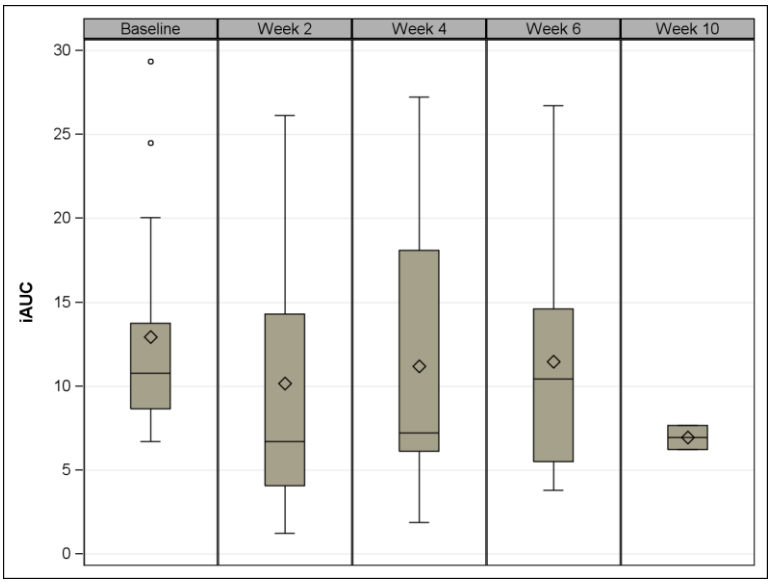


Figure 6: Boxplot for iAUC (FAS)



All baseline assessments were performed within the planned time window of 7 days prior to start of study drug. All measurements at week 6 were performed as planned at the end of week 6 with the exception of one patient (RandomNo. 0106). For this patient the DCE-MRI assessment was performed at the first day of week 6. This value was included in this analysis.

Changes Δ K_{trans} and ΔiAUC60 from baseline to 6 weeks in DCE-MRI examination were the primary endpoints. Normality of the differences between baseline and 6 week assessment was tested using Shapiro-Wilk test at the 5% level of significance. The null hypotheses that the data follow a normal distribution cannot be rejected at a 5% significance level for Δ K_{trans} (p=0.2714) and ΔiAUC60 (p=0.5493). Therefore confirmatory statistical analysis of the changes Δ K_{trans} and ΔiAUC60 from baseline to 6 weeks was performed using two one-sided paired t-tests for continuous data at the multiple significance level of 5% (two tests performed at the nominal level of 0.025). The testing results as well as the one-sided 97.5% confidence intervals are presented in Table 23.

Table 23: Confirmatory tests (FAS)

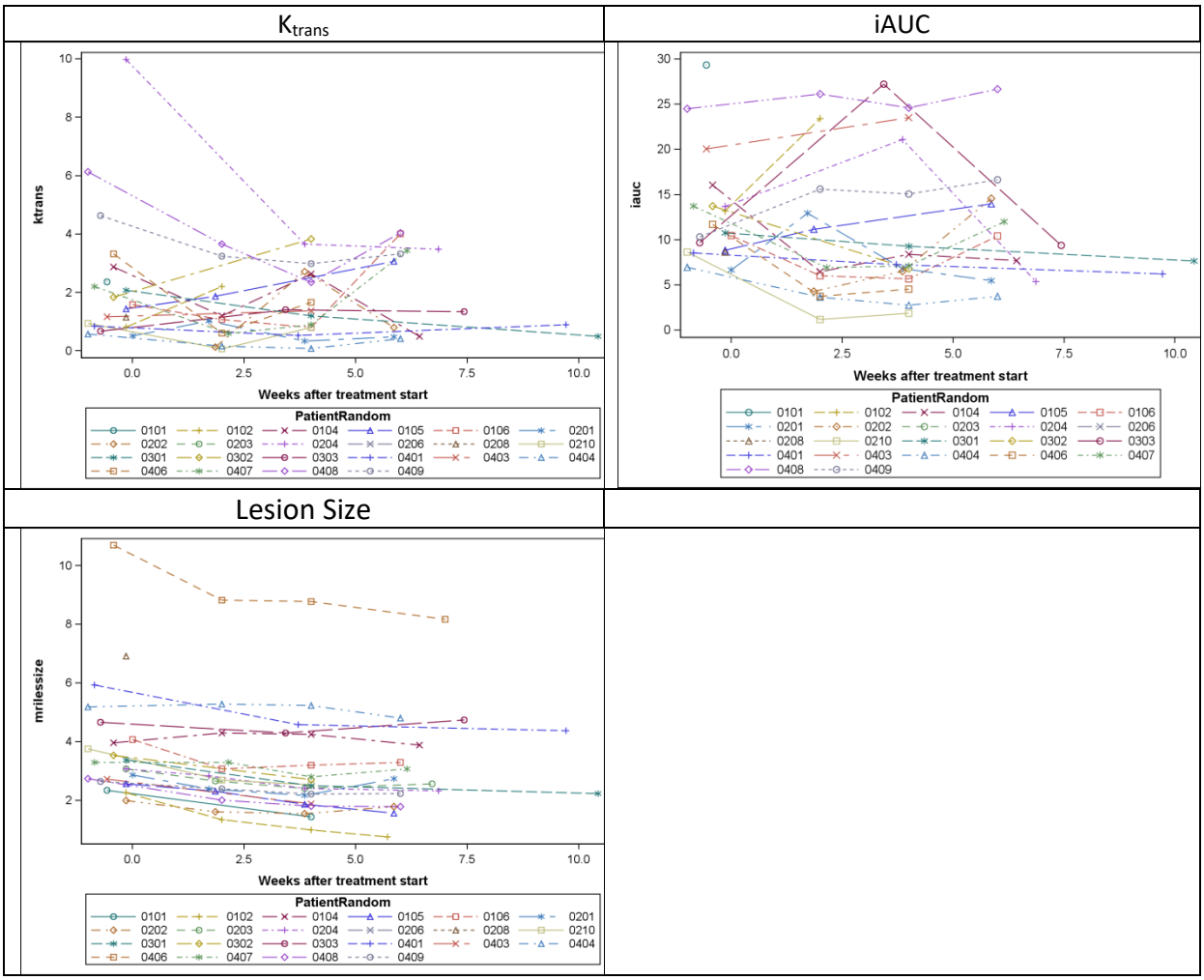
	T	*DF*	*p*	*one-sided 97.5% CI*
ktrans	-0.79	9	0.22	[-Inf. , 1.20]
iauc	-0.61	9	0.28	[-Inf. , 2.56]

Note: T=paired t-test statistic, DF=Degree of freedoms
Source: Table 2.3.

The null hypotheses of no change within 6 weeks cannot be rejected at a 2.5% significance level for K_{trans} (p=0.22) and for iAUC (p=0.28). The one-sided 97.5% confidence intervals (CI) for the change within 6 weeks of K_{trans} was [-Inf, 1.20] and of iAUC [-Inf, 2.56). This means that at a level 97.5% probability it can be stated that the two parameters increase at maximum by 1.2 and 2.6 units respectively, in concordance with the non-significant outcome of the respective hypotheses tests.

Additionally, the time course of K_{trans} and iAUC was visualized per patient in Figure 7.

Figure 7: Time couse of K_{trans}, iAUC and Lesion Size (FAS)



Individual data on DCE-MRI assessment together with the date of first and last intake of Sunitinib in the corresponding cycle are provided in Appendix Listing 2.1.

9 Time-to Progression (TTP)

TTP was defined as the time in days from date of the first study medication to the date of the occurrence of progression assessed according to RECIST or to the individual termination of the study (censored observation) whatever occurs first. If the reason of the event responsible for the individual patient's study termination is not related to disease progression TTP will be analyzed as censored failure time. If it cannot be excluded that the reason of the event responsible for individual patient's study termination is related to disease progression TTP is analyzed as censored failure time lasting from the date of first study medication until the last date under study conditions when the patient was confirmed to be progression free.

In two patients (RandomNo. 0301, 0303) not all target lesion measured at baseline were assessed in the course of the study. In one patient (RandomNo. 0301) three target lesions were measured at baseline and at Cycle 2 – Week 7. Out of these 3 target lesions, one lesion was not assessed after Cycle 2- Week 7 (LesionNo. 2, max. diameter at baseline and Cycle 2- Week 7: 13 mm). In one other patient (RandomNo. 0303) four target lesions were defined at baseline and out of these 4 lesions one lesion was not assessed in later visits (LesionNo. 0, max. diameter at baseline: 43 cm). In agreement with the principal sponsor of this study, response assessment according to RECIST was based for these two patients only on lesions which were measured at all visits.

At time of analysis 12 of the 22 patients of the FAS (54.5%) were in progressive disease. The median TTP was 48.0 weeks (95%CI: 26.6-inf weeks). The upper limit of the 95%CI could not be determined due to low number of events. The 12, 24, 36 48 weeks rates without progression are provided in Table 24.

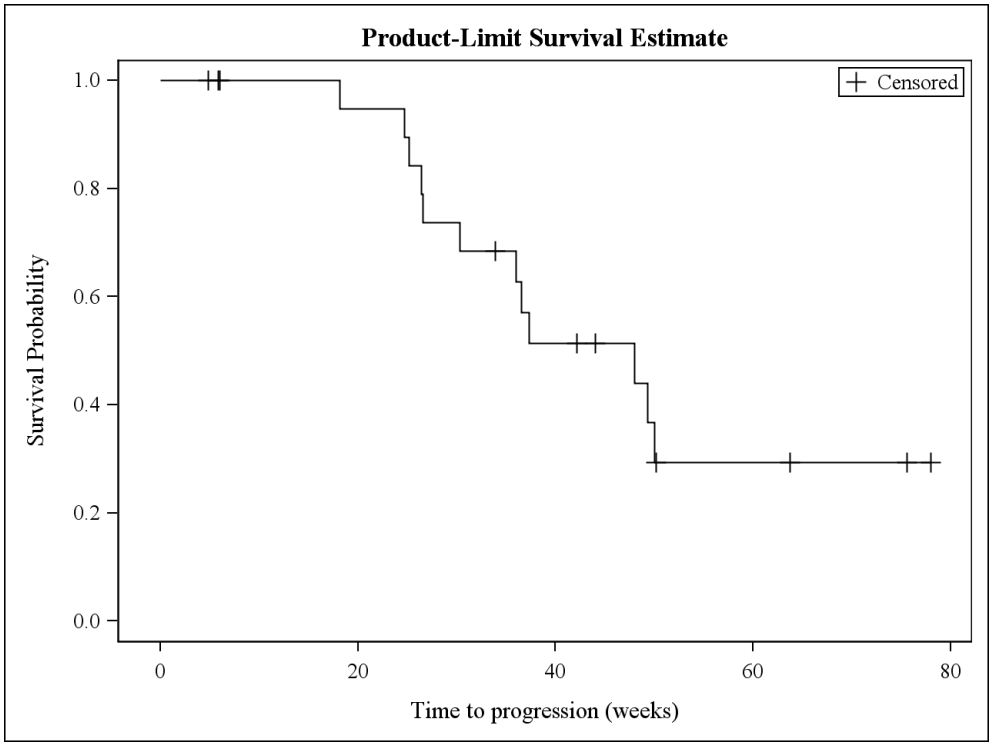
Table 24: Kaplan-Meier estimates for TTP (FAS)

Weeks	*Progression-free rate*	*95% confidence interval*
12	100.00%	--
24	94.74%	[68.12, 99.24]
36	62.72%	[37.25, 80.22]
48	43.98%	[20.50, 65.34]

Source: Table 2.4.

Figure 8 shows the Kaplan-Meier curve for TTP.

Figure 8: Kaplan-Meier Curve for TTP (FAS)



Due to the small number of data, no further analysis of time to progression (e.g. Cox regression) was performed.

Individual data on TTP together with the information on end of treatment and end of study are provided in Appendix Listing 2.2.

10 Objective response

According to study protocol and SAP, evaluable for response were only patients who were at least 8 weeks under treatment according to the protocol and for whom at least one staging was performed within 8-12 weeks after start of treatment or who experienced PD by 8 - 24 weeks. In agreement with the principal sponsor, the interval for which at least one staging should be performed was enlarged to 8-17 weeks.

Out of the 22 patients of the FAS, the time between first and last intake of study medication was lower than 8 weeks in 5 patients (RandomNo. 0106, 0206, 0208, 0210, 0408). Best overall response over the treatment course was determined according to RECIST by using individual information on tumor lesion measurement. Individual lesion assessment information is provided in Appendix Listing 2.3. Individual response assessment according to RECIST together with the summarized diameters during the study course and with the investigators assessment is given in Appendix Listing 2.4

Out of the 17 evaluable patients evaluable for best objective response, 8 patients had PR (47.1%) and 9 patients had SD (52.9%, see table 25).

Table 25: Best response over treatment course

Best RECIST response over treatment	N (out of 17)	Response Rate	95%-CI
CR	--	--	--
PR	8	47.1%	[23.0, 72.2%]
SD	9	52.9%	[27.8-77.0 %]
PD	--	--	--

Response assessment was compared for each visit with the investigators assessment. Individual Inconsistencies between the response assessment and the investigators assessment are presented in Appendix Table 2.5.

Logistic regression was performed for best overall response in order to examine influence of K_{trans} and iAUC measured using DCE-MRI. This analysis could be performed only on N=9 patients (N=11 patients with valid K_{trans} and iAUC measurement at week 6, but RandomNo. 0106 and 0408 were not evaluable for best overall response). Logistic regression for best overall response including ΔK_{trans} and ΔiAUC as covariates was based only on N=8 patients as one patient had no reliable baseline measurements (RandomNo. 0202). Results of both logistic regressions are presented in Table 26.

Table 26: Logistic regression for OR including K_{trans} and iAUC at week 6 (model 1) resp. including ΔK_{trans} and ΔiAUC (model 2)

	Parameter	Estimate	Standard Error	Wald Chi-Square	p	OR [95-CI]
Model 1:	Intercept	-0.5377	1.9851	0.0734	0.7864	
	K_{trans}	1.1525	0.8843	1.6986	0.1925	3.166 [0.560, 17.917]

	iAUC	-0.1882	0.2610	0.5198	0.4709	0.828 [0.497, 1.382]
Model 2:	Intercept	0.4567	1.2637	0.1306	0.7178	
	ΔK_{trans}	1.3675	1.2672	1.1644	0.2805	3.925 [0.327, 47.051]
	ΔiAUC	-0.6643	0.5059	1.7242	0.1891	0.515 [0.191, 1.387]

Source: Table 2.6

The predictive power of tumor vessel permeability and blood flow was evaluated by using MRI measurement at week 6. The percentage change of K_{trans} was calculated as difference between baseline and 6 week measurement divided by the baseline measurement. The percentage change was dichotomized using 40% change as cut-off value, since a change in K_{trans}≥40% is considered in literature to represent some evidence to correlate with disease response. The resulting contingency table for best overall response and dichotomized percentage change is presented in Table 27.

Table 27: Contingency table for best overall response and percentage change in K_{trans}

		PR	*SD*	*Total*
	< 40%	3	2	5
	≥ 40%	1	2	3
Total		4	4	8

Note: PR= partial remission, SD=stable disease
Source: Table 2.7

The K_{trans} reduction of the 4 patients with PR were (1.14, -0.28, -0.28, -0.65) and of the 4 patients with SD (0.98, 0.56, -0.05, -0.83).

Sensitivity is defined by the percentage of patients with PR and percentage change in K_{trans} between baseline and week 6 ≥ 40% within all patients classified as PR. Therefore, sensitivity is 25% [95%-CI: 0.63-80.59%]. Specificity is defined by the percentage of patient with SD and percentage change in K_{trans} between baseline and week 6 < 40% within all patients classified as SD. Therefore, specificity is 50% [95%-CI: 6.76-93.24%].

Since no cut-off value for iAUC is available, this parameter was planned to be analyzed as continuous variable. Due to the small number of evaluable patients (N=8) this analysis was not performed.

The iAUC change from baseline of the 4 patients with PR were (0.61, 0.58, -0.46, -0.61) and of the 4 patients with SD (-0.03, -0. 13, -0.18,-0.52).

Individual data on best overall response together with the covariates are presented in Appendix Listings 2.5.

11 Safety Analysis

All safety analyses were based on the SAS.

11.1 Study Medication

Study medication consisted of Sunitinib, administered 37.5mg once daily for 4 weeks followed by 2 weeks of rest, and the background medication FOLIFIRI with200 mg/m^2 L-folinic acid (FA) at day 1 of every 14 days, 5 fluoruracil (5-FU) 400mg/m^2 as bolus at day 1 and 2400 mg/m^2 continuously given at day 1 and 2 and Irinotecan (CPT-11) 180 mg/m^2 at day 1.

Two patients (0208, 0210) received 400mg/m^2 racemic Folinic Acid instead of 200mg/m^2 L-Folinic Acid and therefore administered dose was corrected by factor 0.5 for both patients.

The total cumulative dose per patient and medication was summarized using descriptive statistics over the whole treatment period in Table 28.

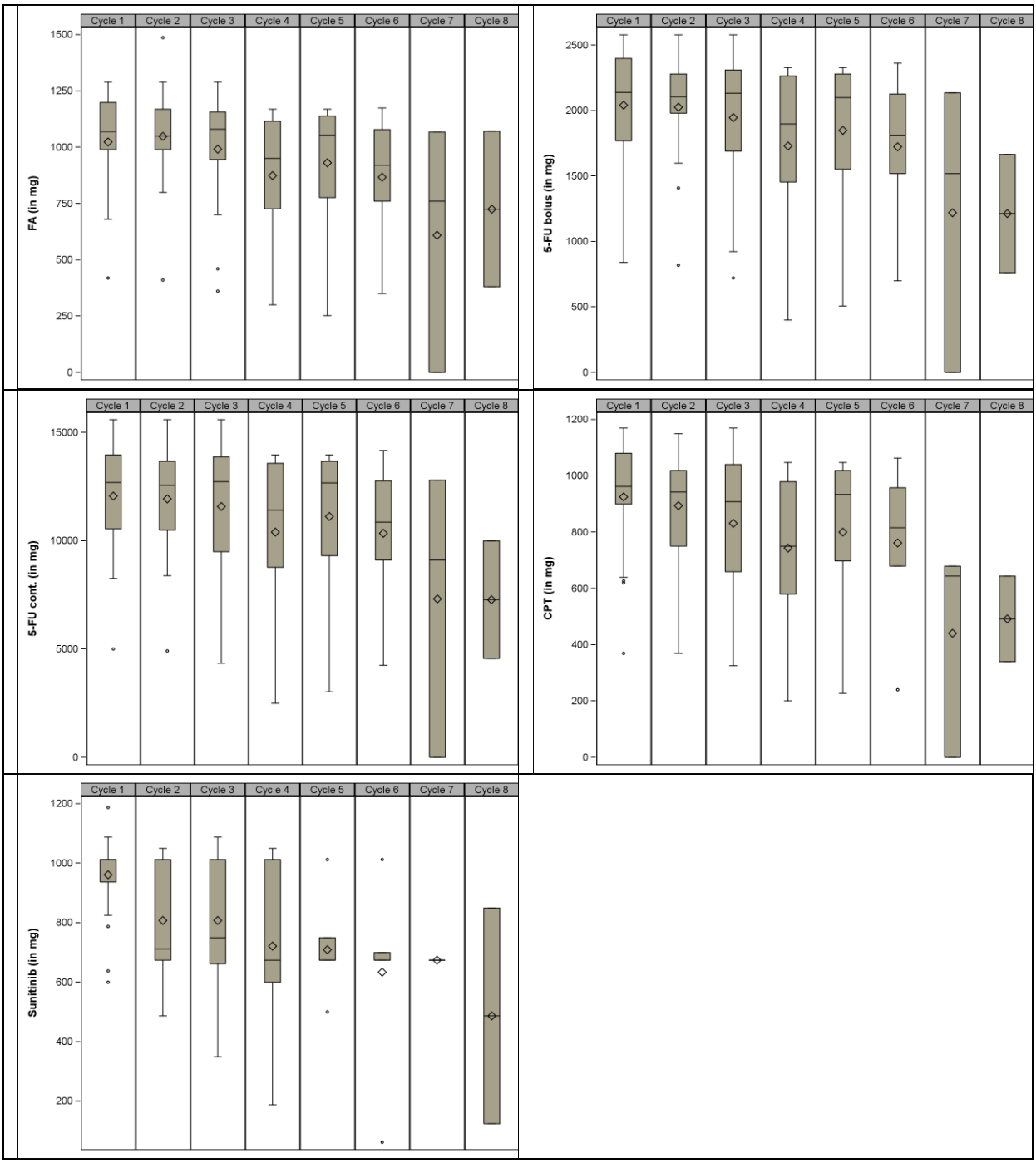
Table 28: Cumulative doses (SAS)

		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	3642.6	7163.4	42568	3134.0	2913.0
	SD	2358.04	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
Source: Table 3.1.

Additionally, the cumulative dose per cycle and medication was calculated and summarized in Appendix Table 3.2. Boxplots of cumulative dose per cycle is presented in Figure 9.

Figure 9: Boxplot of cumulative dose per cycle (SAS)



Further, the ratio between the administered and the planned dose over all cycle was calculated and summarized in Table 29.

Table 29: Ratio between administered and planned dose (SAS)

		FA (in mg)	*5-FU bolus (in mg)*	*5-FU cont. (in mg)*	*CPT (in mg)*	*Sunitinib (in mg)*
Ratio between administered and planned dose over all cycles	n	23	23	23	23	23
	Mean	1.0	1.0	1.0	1.0	0.8
	SD	0.12	0.14	0.12	0.09	0.14
	Median	1.0	1.0	1.0	1.0	0.8
	Min	0.7	0.7	0.7	0.7	0.6
	Max	1.3	1.3	1.3	1.1	1.0

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 3.3.

Additionally, the ratio between administered and planned dose was calculated per cycle and medication and is summarized in Appendix Table 3.4.

At least one dose modification for FA occurred in 3 patients (13%) due to hematological toxicity (Patientrandom 0105, 0406 and 0407). At least on dose modification for 5-FU bolus was recorded in 4 patients (17%) due to hematological toxicity (Patientrandom 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.

Individual data on study medication are provided separately for each substance in Appendix Listing 3.1.1-3.1.5.

An individual listing of all 50 documented AEs leading to the adjustment or temporarily interruption of Sunitinib administration is given in Appendix Listing 3.1.6.1.

According to study protocol, the individual patients were treated until disease progression. Reasons to discontinue the treatment prior to disease progression are given in Chapter 6.6 of the study protocol.

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). Summary statistics of time under treatment are provided in Table 30.

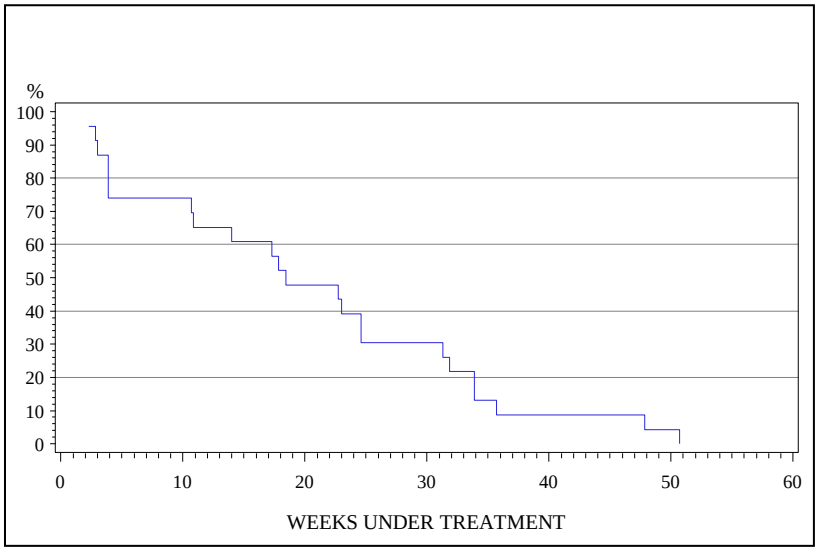
Table 30: Time under treatment (SAS)

		Total n(%)
Time under treatment (in weeks)	n	23
	Mean	20.4
	SD	14.42
	Median	18.4
	Min	2.3
	Max	50.7

Note: SD=Standard deviation, Min=minimum, Max=maximum
Source: Table 3.5.

Figure 10 shows the distribution function of time under treatment.

Figure 10: Time under treatment (SAS)



The reasons for end of treatment are summarized in Table 31. The most frequently documented reason for end of treatment was progression of disease in 10 patients (37%) followed by adverse events in 8 patients (30%).

Table 31: Reasons for end of treatment (SAS)

		Total n (%)
Reasons for end of treatment	Patient withdrew consent	1 (4%)
	Progression of disease	10 (43%)
	Adverse event(s)	8 (35%)
	lost to follow-up	1 (4%)
	other reason	3 (13%)

Note: Calculation of percentages based on number of patients in SAS (N=23)
Source: Table 3.6.

An individual listing of all 14 documented AEs leading to the discontinuation of Sunitinib administration is given in Appendix Listing 3.1.6.2.

Other reasons were tumor response, investigator's decision and explorative laparotmy with leftlateraler Liverresection.

Individual data on end of treatment together with explanation and comments are provided in Appendix Listing 3.2.

11.2 Concomitant Medications

Since concomitant medication was entered into the database without coding, it was only listed by patient identification number in Appendix Listing 3.3.

11.3 Adverse Events

Adverse events were coded using the terminology of MedDRA. The extent of AE was evaluated by determining the maximum CTC-grade over the complete study course (before and after start of

treatment). In total 412 AEs were recorded in the SAS. One AE was documented in a patient not belonging to the SAS (RandomNo. 0209: Pulmonary embolism). All recorded data in the SAS were used for analysis, even if the start of adverse event was documented before first intake of study medication. A total of 3 adverse events were reported before first intake of the study drug:

Patientrandom	Start Therapy	Begin AE	End AE	PT	CTC-grade	Relation
0208	03.03.2010	01.03.2010		Spinal osteoarthritis	1	Not related
0301	09.09.2008	07.09.2008		Back pain	2	Not related
0401	17.09.2008	16.09.2008	13.10.2008	Constipation	3	Unlikely

From the 412 AEs reported in the SAS, 152 were not related/unlikely to any of the study medications, whereas for 259 the relation to study drug was assessed as definite, probable or possible, which was summarized as suspected AE. The relation to study medication was not assessable in one patient (RandomNo. 0401 Pain).

All patients of the SAS had at least one AE during the study and 21 patients had at least one suspected AE.

The summary of the number of patients with one or more AEs during the course of study is presented by MedDRA System Organ Class (SOC) and Preferred Terms (PT) and are reflecting a count of patients experiencing at least one adverse event within a Preferred Term (see Table 32). Percentages were based on the number of patients in the SAS (N=23).

Table 32: Summary of patients with AE by MedDRA System Organ Class (SOC) and Preferred Terms (PT) in SAS

System Organ Class	***Preferred term***	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
Blood and lymphatic system disorders	**Anaemia**	3 (13 %)		1 (4 %)	1 (4 %)	1 (4 %)
	Bone marrow failure	1 (4 %)				1 (4 %)
	Leukopenia	12 (52 %)	1 (4 %)	4 (17 %)	5 (22 %)	2 (9 %)
	Lymphadenopathy	1 (4 %)	1 (4 %)			
	Neutropenia	11 (48 %)		1 (4 %)	5 (22 %)	5 (22 %)
	Thrombocytopenia	4 (17 %)		2 (9 %)	2 (9 %)	

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
Cardiac disorders	**Bradycardia**	1 (4 %)	1 (4 %)			
	Tricuspid valve incompetence	1 (4 %)	1 (4 %)			
Ear and labyrinth disorders	**Vertigo**	2 (9 %)	2 (9 %)			
Endocrine disorders	**Hyperaldosteronism**	1 (4 %)	1 (4 %)			
Eye disorders	**Conjunctival oedema**	1 (4 %)	1 (4 %)			
	Dry eye	1 (4 %)		1 (4 %)		
	Eyelid oedema	2 (9 %)	2 (9 %)			
	Vision blurred	3 (13 %)	3 (13 %)			
Gastrointestinal disorders	**Abdominal pain**	7 (30 %)	2 (9 %)	3 (13 %)	2 (9 %)	
	Abdominal pain upper	1 (4 %)	1 (4 %)			
	Anal pruritus	1 (4 %)		1 (4 %)		
	Anal ulcer	1 (4 %)		1 (4 %)		
	Anorectal discomfort	2 (9 %)	1 (4 %)	1 (4 %)		
	Ascites	1 (4 %)	1 (4 %)			
	Constipation	5 (22 %)	3 (13 %)	2 (9 %)		
	Diarrhoea	11 (48 %)	4 (17 %)	6 (26 %)	1 (4 %)	
	Dry mouth	1 (4 %)	1 (4 %)			
	Duodenal stenosis	1 (4 %)		1 (4 %)		
	Duodenal ulcer	1 (4 %)	1 (4 %)			
	Dyspepsia	4 (17 %)	3 (13 %)	1 (4 %)		
	Enterocolitis	1 (4 %)		1 (4 %)		
	Flatulence	5 (22 %)	5 (22 %)			
	Gastric ulcer	1 (4 %)		1 (4 %)		
	Gastritis	2 (9 %)	1 (4 %)		1 (4 %)	

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
	Gastrooesophageal reflux disease	1 (4 %)	1 (4 %)			
	Glossodynia	1 (4 %)	1 (4 %)			
	Haematemesis	1 (4 %)		1 (4 %)		
	Haematochezia	1 (4 %)	1 (4 %)			
	Haemorrhoids	1 (4 %)		1 (4 %)		
	Loose tooth	1 (4 %)		1 (4 %)		
	Lower gastrointestinal haemorrhage*	2 (9 %)	1 (4 %)			
	Melaena	2 (9 %)	1 (4 %)		1 (4 %)	
	Nausea	8 (35 %)	4 (17 %)	4 (17 %)		
	Oesophagitis	1 (4 %)		1 (4 %)		
	Oral discomfort	1 (4 %)	1 (4 %)			
	Painful defaecation	1 (4 %)		1 (4 %)		
	Rectal haemorrhage	1 (4 %)		1 (4 %)		
	Salivary hypersecretion	1 (4 %)	1 (4 %)			
	Stomatitis	6 (26 %)	1 (4 %)	2 (9 %)	3 (13 %)	
	Toothache	1 (4 %)		1 (4 %)		
	Vomiting	6 (26 %)	4 (17 %)	2 (9 %)		
General disorders and administration site conditions	**Asthenia**	3 (13 %)	2 (9 %)	1 (4 %)		
	Chills	2 (9 %)	2 (9 %)			
	Fatigue	8 (35 %)	4 (17 %)	4 (17 %)		
	General physical health deterioration	3 (13 %)		2 (9 %)	1 (4 %)	
	Infusion site haematoma	1 (4 %)	1 (4 %)			
	Infusion site mass	1 (4 %)	1 (4 %)			
	Mucosal inflammation	8 (35 %)	4 (17 %)	3 (13 %)	1 (4 %)	
	Mucosal ulceration	1 (4 %)	1 (4 %)			
	Oedema peripheral	3 (13 %)	3 (13 %)			
	Pain	1 (4 %)		1 (4 %)		

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
	Pyrexia	5 (22 %)	4 (17 %)	1 (4 %)		
	Ulcer	1 (4 %)			1 (4 %)	
	Unevaluable event	2 (9 %)	2 (9 %)			
Hepatobiliary disorders	**Hepatic pain**	1 (4 %)	1 (4 %)			
	Hyperbilirubinaemia	1 (4 %)				1 (4 %)
	Jaundice	1 (4 %)		1 (4 %)		
Infections and infestations	**Candidiasis**	1 (4 %)	1 (4 %)			
	Febrile infection	1 (4 %)		1 (4 %)		
	Gastroenteritis	1 (4 %)		1 (4 %)		
	Infected skin ulcer	1 (4 %)			1 (4 %)	
	Infection	1 (4 %)	1 (4 %)			
	Nasopharyngitis	2 (9 %)	2 (9 %)			
	Oral candidiasis	1 (4 %)		1 (4 %)		
	Oral herpes	1 (4 %)		1 (4 %)		
	Osteomyelitis	1 (4 %)	1 (4 %)			
	Pneumonia viral	1 (4 %)		1 (4 %)		
	Sinusitis	1 (4 %)	1 (4 %)			
	Staphylococcal infection	1 (4 %)		1 (4 %)		
	Subcutaneous abscess	1 (4 %)			1 (4 %)	
	Urinary tract infection	1 (4 %)		1 (4 %)		
Injury, poisoning and procedural complications	**Contusion**	1 (4 %)	1 (4 %)			
	Thermal burn	1 (4 %)	1 (4 %)			
	Wound complication	1 (4 %)	1 (4 %)			
Investigations	**Blood bilirubin increased**	1 (4 %)		1 (4 %)		

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
	C-reactive protein increased	1 (4 %)			1 (4 %)	
	Clostridium test positive	1 (4 %)	1 (4 %)			
	Haemoglobin decreased	2 (9 %)		2 (9 %)		
	Weight decreased	6 (26 %)	5 (22 %)	1 (4 %)		
	Weight increased	1 (4 %)	1 (4 %)			
Metabolism and nutrition disorders	**Decreased appetite**	6 (26 %)	4 (17 %)	2 (9 %)		
	Dehydration	1 (4 %)	1 (4 %)			
	Hyperglycaemia	1 (4 %)		1 (4 %)		
	Hypokalaemia	1 (4 %)	1 (4 %)			
	Iron deficiency	1 (4 %)	1 (4 %)			
Musculoskeletal and connective tissue disorders	**Back pain**	5 (22 %)	2 (9 %)	3 (13 %)		
	Bone pain	1 (4 %)		1 (4 %)		
	Musculoskeletal pain	1 (4 %)		1 (4 %)		
	Spinal osteoarthritis	1 (4 %)	1 (4 %)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Metastases to liver**	1 (4 %)		1 (4 %)		
	Tumour pain	1 (4 %)	1 (4 %)			
Nervous system disorders	**Ageusia**	1 (4 %)	1 (4 %)			
	Burning sensation	1 (4 %)	1 (4 %)			
	Dizziness	1 (4 %)		1 (4 %)		
	Dysgeusia	5 (22 %)	3 (13 %)	2 (9 %)		
	Headache	1 (4 %)		1 (4 %)		

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
	Loss of consciousness	1 (4 %)			1 (4 %)	
	Paraesthesia	2 (9 %)	1 (4 %)		1 (4 %)	
	Peripheral sensory neuropathy	3 (13 %)	1 (4 %)	2 (9 %)		
	Peroneal nerve palsy	1 (4 %)		1 (4 %)		
	Polyneuropathy	1 (4 %)		1 (4 %)		
	Presyncope	1 (4 %)			1 (4 %)	
	Spinal cord compression	1 (4 %)			1 (4 %)	
	Syncope	1 (4 %)			1 (4 %)	
	Transient ischaemic attack	1 (4 %)			1 (4 %)	
Reproductive system and breast disorders	**Pelvic pain**	1 (4 %)	1 (4 %)			
Respiratory, thoracic and mediastinal disorders	**Cough**	1 (4 %)	1 (4 %)			
	Dyspnoea	1 (4 %)	1 (4 %)			
	Dyspnoea exertional	1 (4 %)	1 (4 %)			
	Epistaxis	4 (17 %)	4 (17 %)			
	Hiccups	1 (4 %)	1 (4 %)			
	Pulmonary embolism	4 (17 %)		1 (4 %)	1 (4 %)	2 (9 %)
	Rhinitis allergic	1 (4 %)	1 (4 %)			
Skin and subcutaneous tissue disorders	**Acne**	1 (4 %)	1 (4 %)			
	Alopecia	6 (26 %)	6 (26 %)			
	Blister	2 (9 %)	2 (9 %)			
	Decubitus ulcer	1 (4 %)		1 (4 %)		
	Dry skin	2 (9 %)	1 (4 %)	1 (4 %)		
	Hyperhidrosis	1 (4 %)	1 (4 %)			
	Hyperkeratosis	1 (4 %)			1 (4 %)	
	Nail disorder	1 (4 %)	1 (4 %)			

System Organ Class	*Preferred term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
	Palmar-plantar erythrodysaesthesia syndrome	5 (22 %)	1 (4 %)	4 (17 %)		
	Rash	3 (13 %)	2 (9 %)	1 (4 %)		
	Skin burning sensation	1 (4 %)	1 (4 %)			
	Urticaria	1 (4 %)	1 (4 %)			
Vascular disorders	**Hypertension**	6 (26 %)	1 (4 %)	3 (13 %)	2 (9 %)	
	Hypotension	1 (4 %)	1 (4 %)			

* The remaining AEs were documented as CTC5.
Note: Calculation of percentages based on number of patients in SAS (N=23)
Note: A patient with more than one AE within a PT was counted once with maximum CTC grade
Source: Table 3.7

Additionally, adverse events were evaluated by determining the maximum CTC-grade per cycle in Appendix Table 3.8. The adverse events were analyzed by determining the strongest relation to study medication per patient and PT over the complete study time in Appendix Tables 3.9.1.

A total of 259 AEs were assessed as suspected AE. The cause of 10 possibly related AEs was recorded as “underlying diseases” an in two possibly related AEs “other cause” was documented. Since both causes were not compatible with the definition of a suspected AE, the relation of these 12 AEs was changed in “unrelated”.

Therefore a total of 247 suspected AEs were considered. Out of those 247 suspected AEs, the relation to study drug was assessed to be definite in 18 AEs, probable in 30 AEs and possible in 199 AEs. Out of the 18 definite AEs, 14 were assessed to be caused by the combination of Sunitinib and FOLFIRI, 2 AEs by the background therapy (FOLFIRI) and 2 by the study drug Suntinib. Out of the 30 probable AEs, 25 were assessed to be caused by the combination of Sunitinib and FOLFIRI and 5 by the study drug Suntinib. The cause of the 199 possible AEs were:

- Combination of Sunitinib and FOLFIRI (179)
- Background therapy (FOLFIRI) (6)
- Sunitinib (14).

The related adverse events were analyzed by determining the strongest relation to study medication per patient and PT over the complete study time in Appendix Tables 3.9.2.

Individual patient data on AEs are provided in Appendix 3.4.1.

Individual patient data on suspected AEs together with information on causality are presented in Appendix 3.4.2.

A total of 27 AEs in 13 patients were classified as Serious Adverse Events. The relation to the study medication was classified there as follows:

- definite: 1 patient (RandomNo. 0206: Gastrointestinal disorders-Melaena, CTC-grade 3)
- probable: 1 patient (RandomNo. 0104: Blood and lymphatic system disorders-Bone marrow failure, CTC-grade 4)
- possible: 14 patients
- unlikely: 2 patients
- not related: 9 patients.

Serious adverse events are summarized over the study time by SOC and PT and maximum CTC-grade in Table 33:

Table 33: Summary of patients with SAE by SOC and PT (SAS)

System Organ Class	*Preferred Term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
Blood and lymphatic system disorders	**Anaemia**	1 (4 %)				1 (4 %)
	Bone marrow failure	1 (4 %)				1 (4 %)
	Leukopenia	1 (4 %)				1 (4 %)
	Thrombocytopenia	1 (4 %)		1 (4 %)		
Gastrointestinal disorders	**Abdominal pain**	2 (9 %)			2 (9 %)	
	Diarrhoea	1 (4 %)		1 (4 %)		
	Lower gastrointestinal haemorrhage	1 (4 %)				
	Melaena	1 (4 %)			1 (4 %)	
	Stomatitis	2 (9 %)		1 (4 %)	1 (4 %)	

System Organ Class	*Preferred Term*	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
General disorders and administration site conditions	**General physical health deterioration**	2 (9 %)		1 (4 %)	1 (4 %)	
	Pyrexia	1 (4 %)		1 (4 %)		
	Ulcer	1 (4 %)			1 (4 %)	
Hepatobiliary disorders	**Hyperbilirubinaemia**	1 (4 %)				1 (4 %)
	Jaundice	1 (4 %)		1 (4 %)		
Infections and infestations	**Febrile infection**	1 (4 %)		1 (4 %)		
	Infected skin ulcer	1 (4 %)			1 (4 %)	
Nervous system disorders	**Presyncope**	1 (4 %)			1 (4 %)	
	Spinal cord compression	1 (4 %)			1 (4 %)	
	Transient ischaemic attack	1 (4 %)			1 (4 %)	
Respiratory, thoracic and mediastinal disorders	**Pulmonary embolism**	3 (13 %)		1 (4 %)		2 (9 %)
Skin and subcutaneous tissue disorders	**Palmar-plantar erythrodysaesthesia syndrome**	1 (4 %)		1 (4 %)		

Note: Calculation of percentages based on number of patients in SAS (N=23)
Note: A patient with more than one SAE within a PT was counted once with maximum CTC grade
Source: Table 3.10

An individual listing of all SAEs is provided in Appendix Listing 3.5.

11.4 Deaths

Under study conditions 5 deaths (22%) were documented. The reason for death was in 4 patients the underlying malignant disease and in one patient (RandomNo. 0302) toxicity (see Table 34). No further specifications were recorded. This patient with toxicity was treated after end of study treatment with FOLFORI and thereafter with FOLFOX. The death occurred approximately 4 months after end of study treatment and was not related to the study medication.

Table 34: Cause of death (SAS)

		Total n (%)
Cause of death	Underlying malignant disease	4 (80%)
	Toxicity	1 (20%)

Note: Calculation of percentages based on all dead patients
Source: Table 3.11.

Individual brief patient narratives are provided in Appendix Listing 3.6.

11.5 Clinical laboratory evaluation

Laboratory evaluations as well as conversion of laboratory parameters are described in Chapter 5.6.

The following laboratory values measured during the course of study were not compatible with the documented unit and were therefore corrected or deleted from the analysis:

RandomNo.	Parameter	Visit	Value	Conversion
0202	Total T4	Cycle 2 – Week 7	12.5 nmol/L	deleted
0202	Eosinophils	Cycle 3 – Week 17	4.2 /nL	deleted
0203	Total T4	Cycle 3 – Week 13	19 nmol/L	deleted
0204	Hematocrit	End of treatment	362 L/L	36.2%
0204	Monocytes	Cycle 4 – Week 21	47.0 /nL	deleted
0204	Neutrophils	End of treatment	46.0 /nL	deleted
0301	Bilirubin	End of treatment	11.85 U/L	deleted
0302	Total protein	Cycle 4 – Week 21	0.32 g/dL	deleted
0403	RBC	Cycle 7 – Week 37	33.7 $\cdot 10^6$/µL	deleted

A total of 7764 laboratory parameters were included in the analysis of the SAS (N=23). For each laboratory parameter the difference between the date of laboratory assessment and the date of first intake of study medication was calculated. Laboratory parameters were evaluated by setting up a grid of 2 weeks intervals around the planned laboratory evaluations. The following time grid was used for analysis:

Difference between laboratory date and first intake of study medication	Week label
<0	0
[0,1]	1
(1,3]	2
(3,5]	4

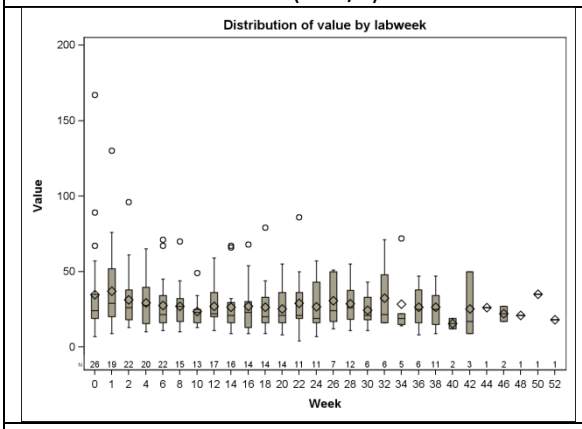
(5,7]	6
(7,9]	8
……	….
……	….
(51,53]	52

This time grid covers laboratory evaluations of all patients of the SAS. If more than one laboratory measurement was performed per interval, the first value in the respective interval was used for analysis. Therefore each patient contributes at most one measurement on summarizing statistics calculated for each time window. Summary statistics are provided in Appendix Table 3.12.

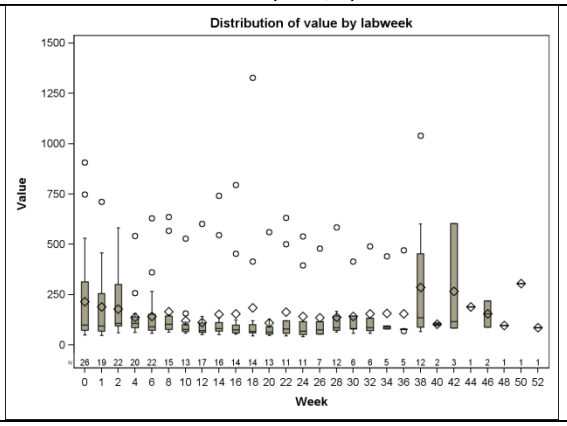
Additionally, the time course of laboratory parameters is visualized graphically by side-by side box- and whiskers plots. The upper and the lower edge of the box displayed the third and first quartile respectively. The line inside the box represented the median whereas the mean was marked by a diamond symbol. The whiskers were drawn from the upper or lower edges of the box to the largest or lowest observed value within 1.5 times the interquartile range (IQR) above the third quartile or below the first quartile respectively. Observations outside this range were marked with an open circle.

Figure 11: Boxplot of laboratory parameters (SAS)

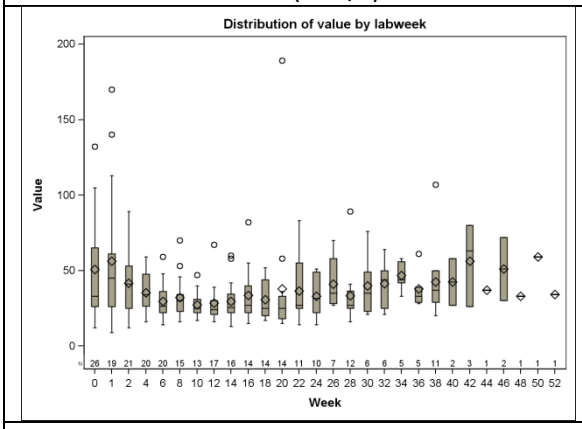
ALT (in U/L)



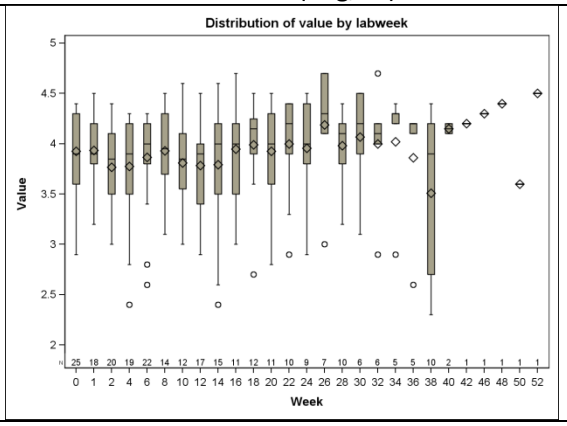
AP (in U/L)



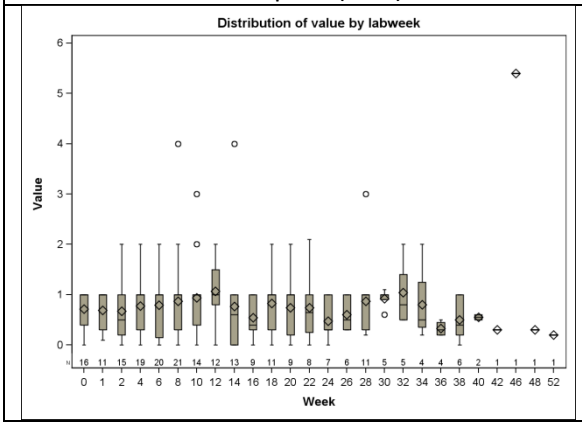
AST (in U/L)



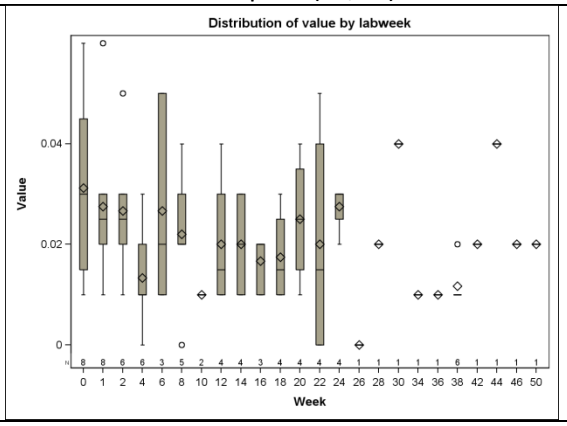
Albumin (in g/dL)

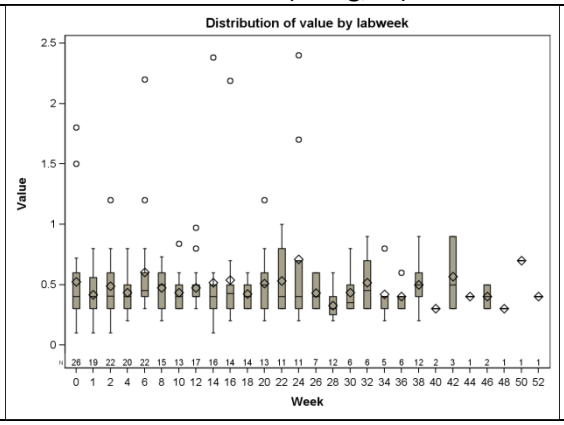
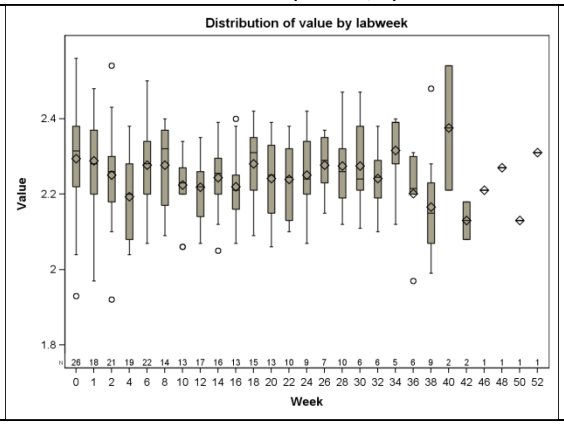
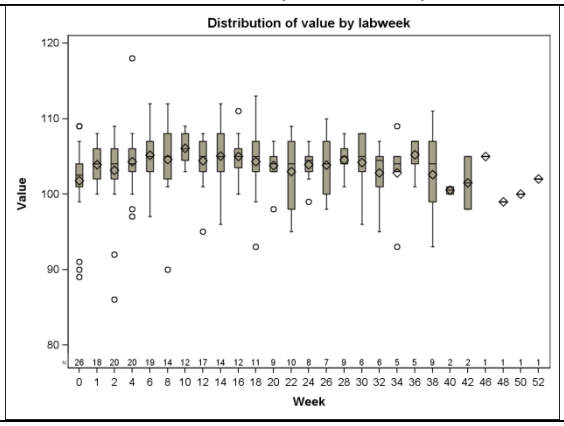
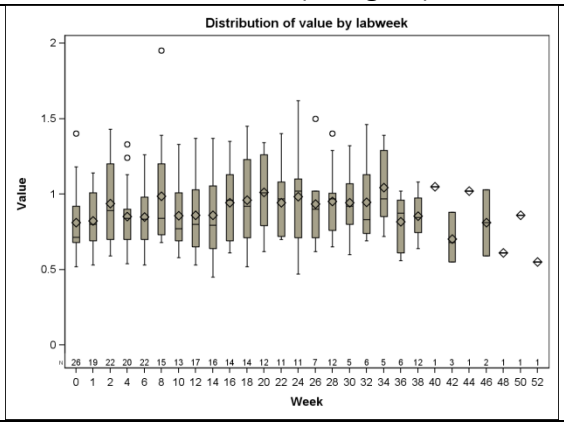
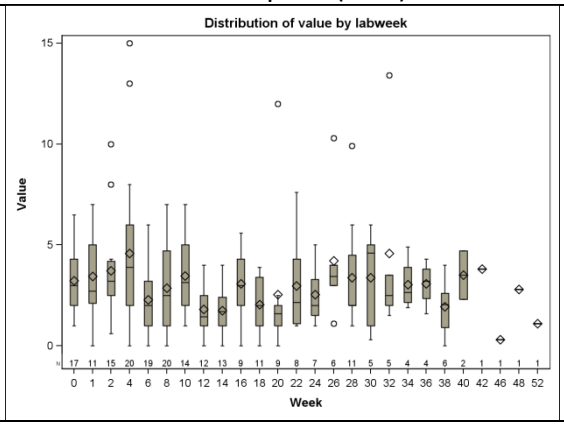
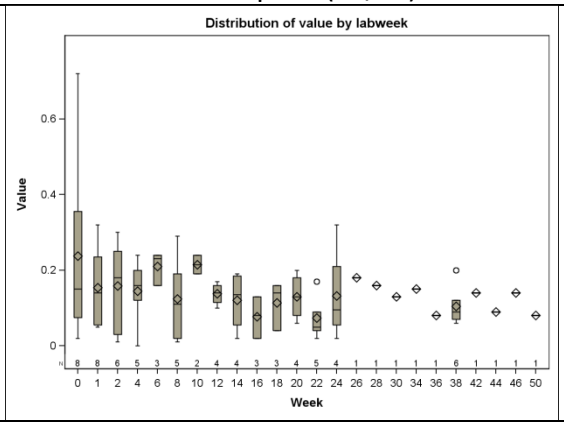


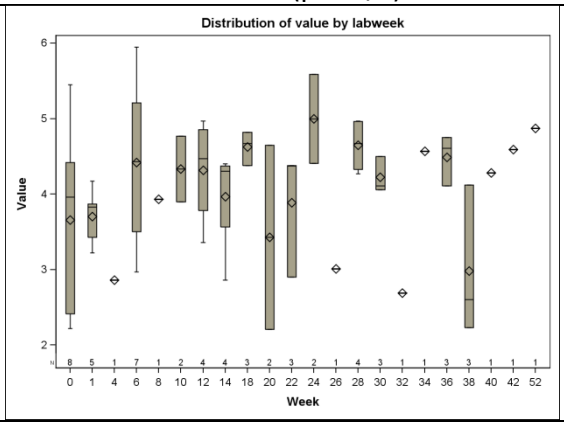
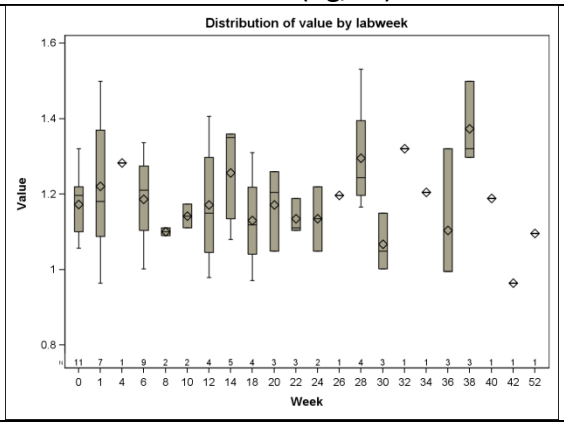
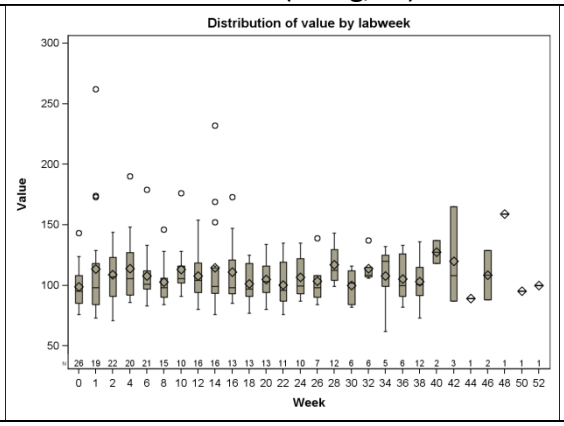
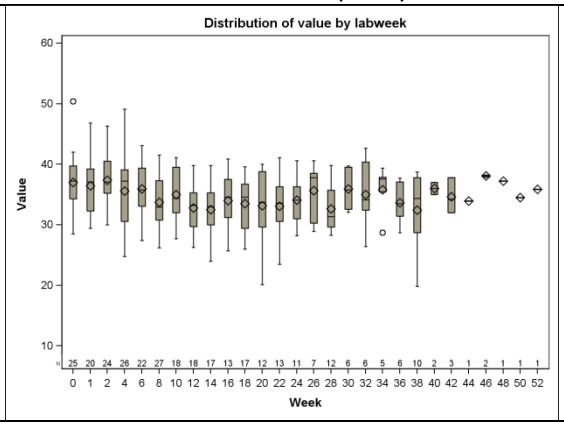
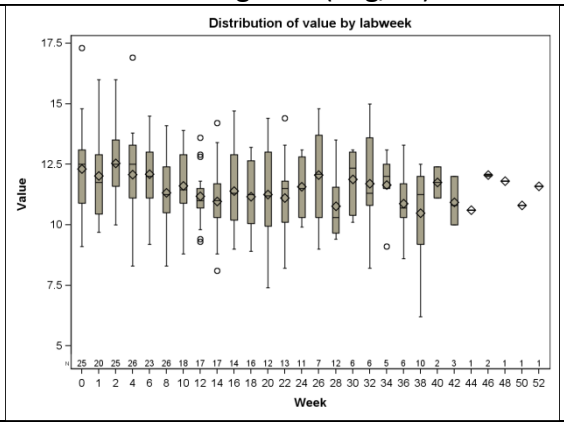
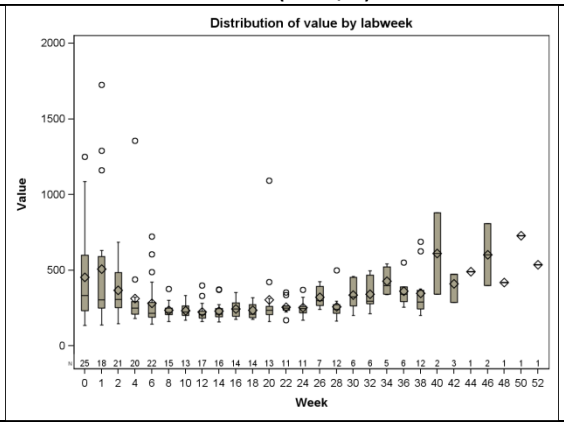
Basophils (in %)

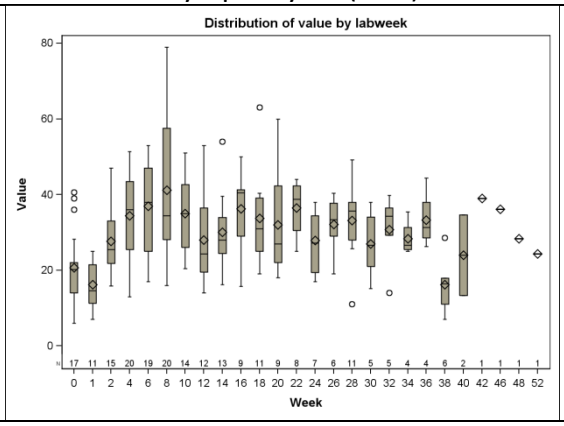
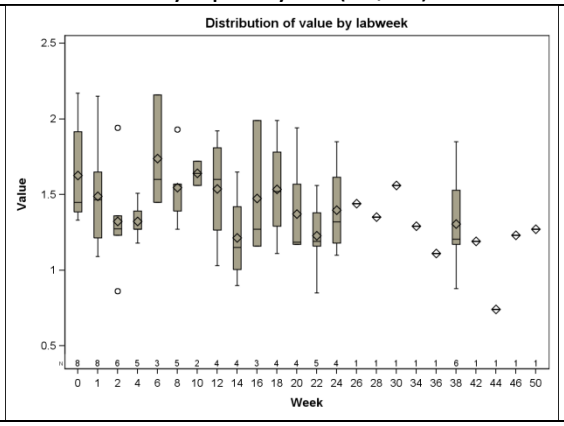
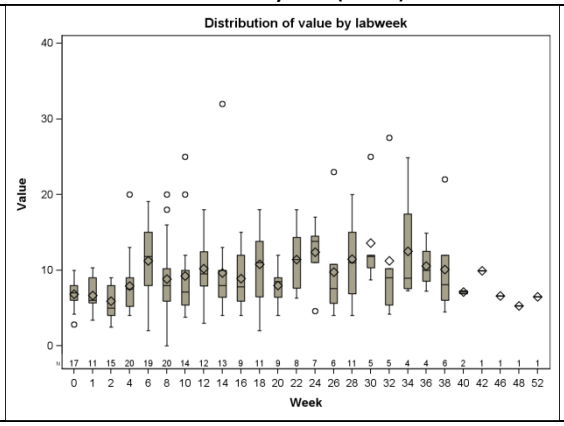
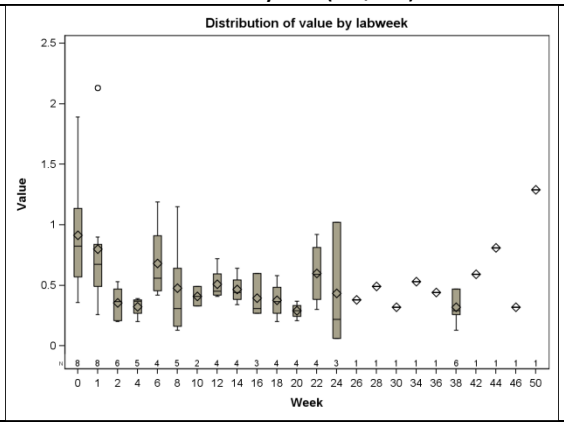
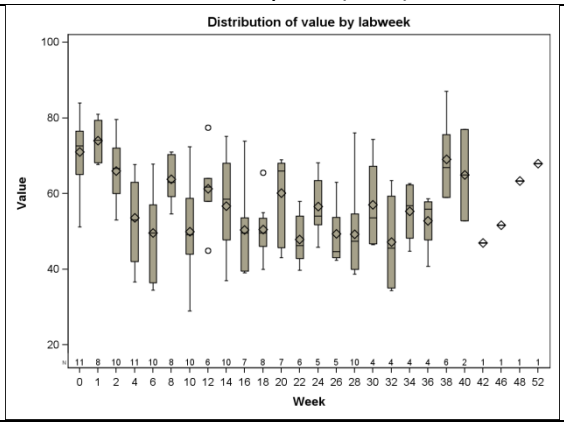
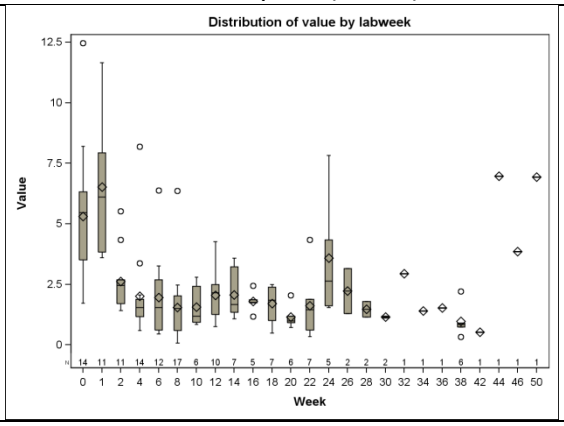


Basophils (in /nL)

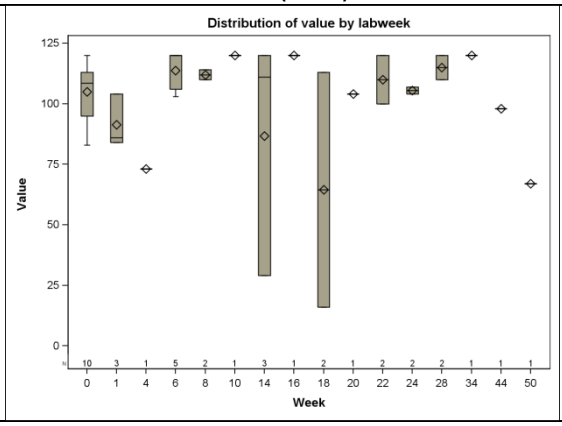


Bilirubin (in mg/dL)	Calcium (mmol/L)
	
Chloride (in mmol/L)	**Creatinine (in mg/dL)**
	
Eosinophils (in %)	**Eosinophils (in /nL)**
	

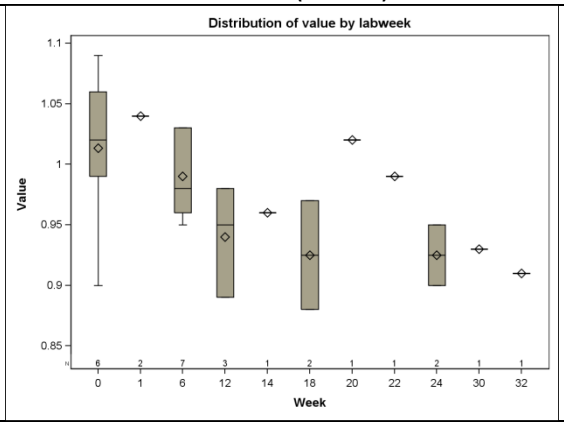
Free T3 (pmol/L)	Free T4 (ng/dL)
	
Glucose (in mg/dL)	**Hematocrit (in %)**
	
Hemoglobin (in g/dL)	**LDH (in U/L)**
	

Lymphocytes (in %)	Lymphocytes (in /nL)
	
Monocytes (in %)	**Monocytes (in /nL)**
	
Neutrophils (in %)	**Neutrophils (in /nL)**
	

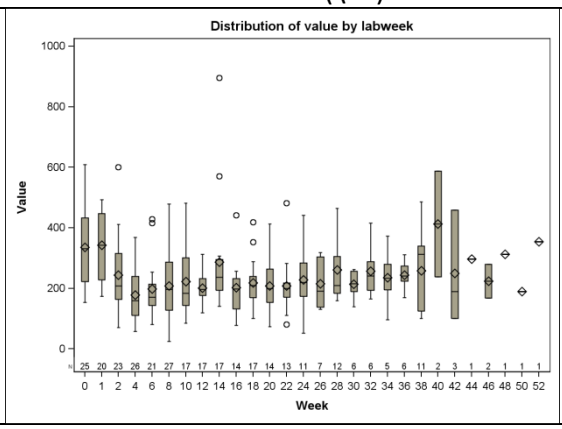
PT (in %)



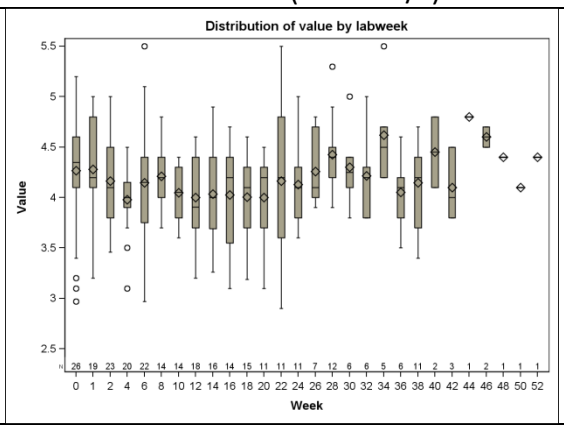
PT-INR (in INR)



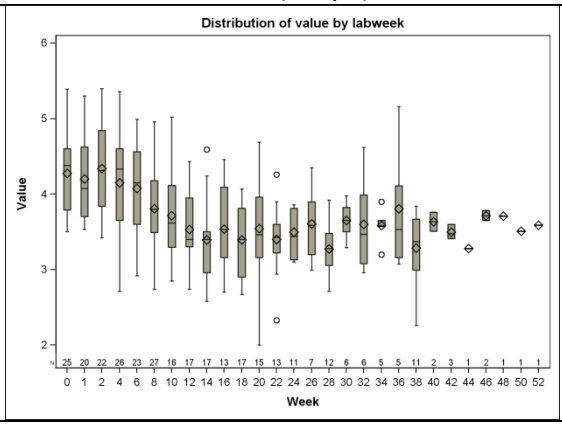
Platelets (\nL)



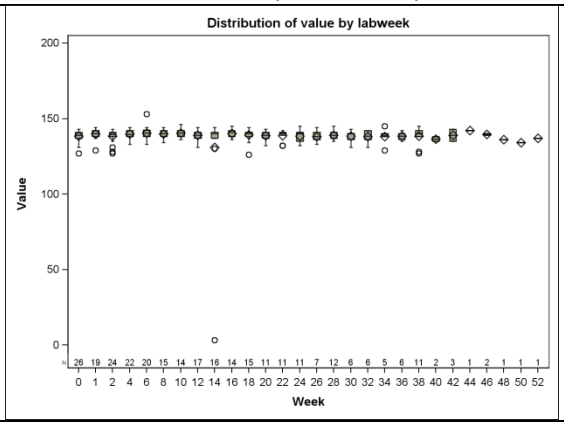
Potassium (in mmol/L)



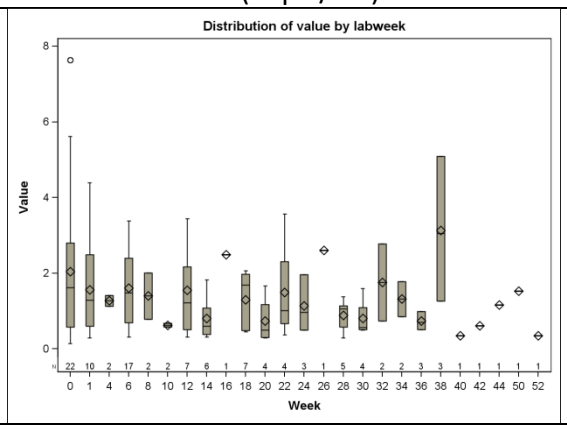
RBC (in \pL)



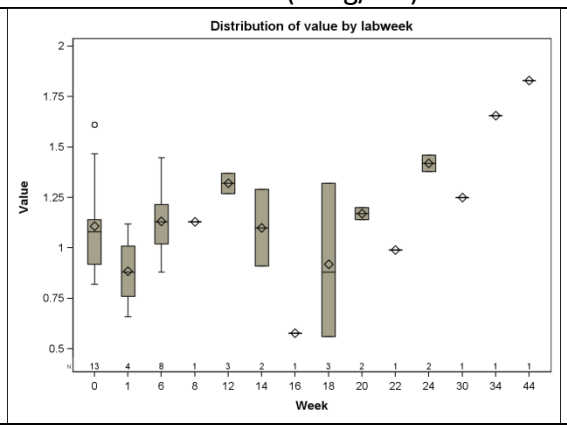
Sodium (in mmol/L)



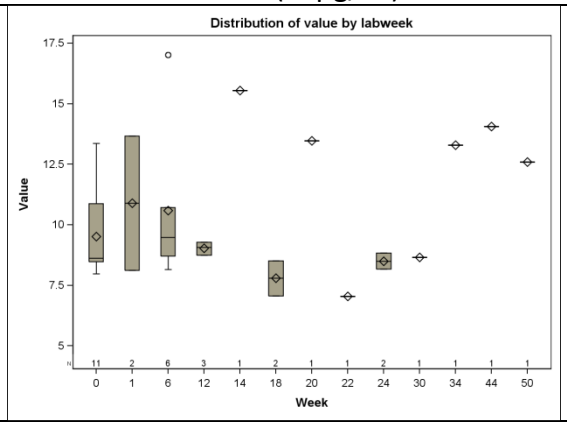
TSH (in µU/mL)



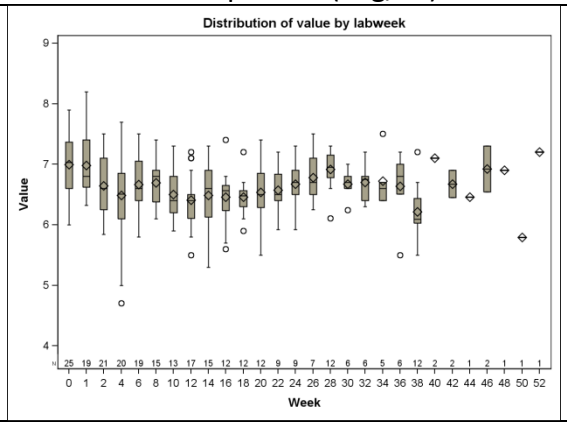
Total T3 (in ng/mL)



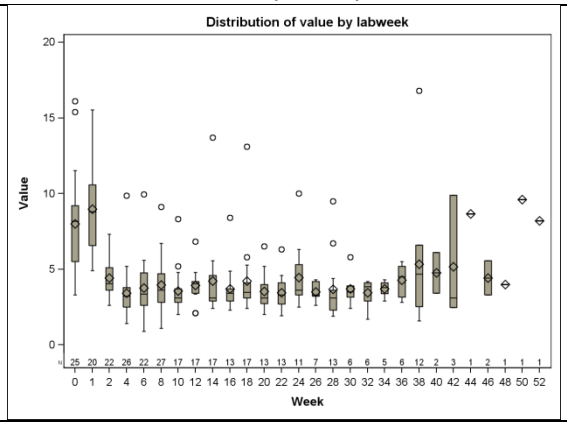
Total T4 (in µg/dL)



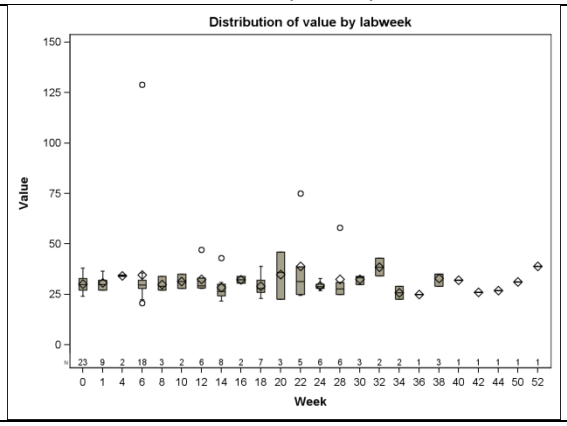
Total protein (in g/dL)

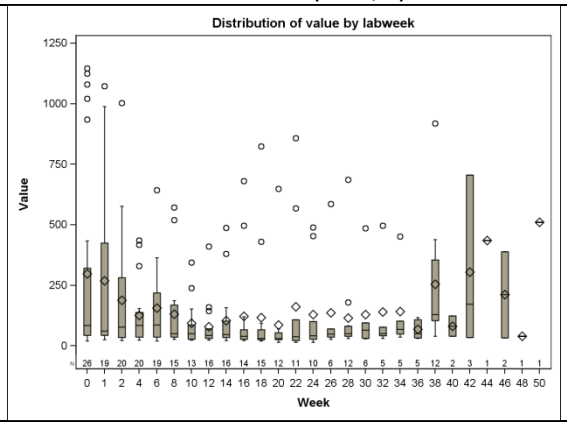


WBC (in /nL)



aPTT (in sec)



Gamma-GT (in U/L)	
	

It was noted that 2464 laboratory values of the total 7764 values were lower than the lower limit of normal or higher than the upper limit of normal. For safety analysis of laboratory parameters, CTC-grades were determined according to the NCI-CTC guidelines Version 3.0. The NCI-CTC guidelines contain no CTC-grading for the following parameters ALT (low), AST (low), Bilirubin (low), Chloride, Creatinine (low), Esosinophils, Free T3, Hematocrit, LDH, Monocytes, PT, PT_INR, RBC, Total T3, Total T4, Total Protein, aPTT, gamma-GT (low),TSH, Basophils (high), Lymphocytes (high), Neutrophils (high), Platelets (high), WBC (high), Lymphocytes (with unit %) and Neutrophils (with unit %). Therefore, these parameters without CTC-grading were classified as:

- Below LLN: if laboratory parameter was below LLN at least once during study
- Above ULN: if laboratory parameter was above ULN at least once.

Table 35 shows the incidences based on the 23 patients of the SAS of maximum CTC-grades per patient and laboratory parameter.

Table 35: Maximum CTC-grade per patient and laboratory parameter (SAS)

Laboratory parameter	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
ALT	14 (61 %)	12 (52 %)	2 (9 %)		
AP	11 (48 %)	4 (17 %)	3 (13 %)	4 (17 %)	
AST	17 (74 %)	12 (52 %)	5 (22 %)		
Albumin	8 (35 %)	5 (22 %)	3 (13 %)		
Bilirubin	5 (22 %)	1 (4 %)	4 (17 %)		

Laboratory parameter	*Total n(%)*	*CTC 1 n(%)*	*CTC 2 n(%)*	*CTC 3 n(%)*	*CTC 4 n(%)*
Calcium	12 (52 %)	9 (39 %)	3 (13 %)		
Creatinine	9 (39 %)	8 (35 %)	1 (4 %)		
Glucose	20 (87 %)	14 (61 %)	5 (22 %)	1 (4 %)	
Hemoglobin	20 (87 %)	13 (57 %)	5 (22 %)	1 (4 %)	1 (4 %)
Lymphocytes	2 (9 %)	1 (4 %)	1 (4 %)	4 (17 %)	4 (17 %)
Platelets	14 (61 %)	10 (43 %)	3 (13 %)		1 (4 %)
Potassium	11 (48 %)	9 (39 %)		2 (9 %)	
Sodium	8 (35 %)	3 (13 %)	1 (4 %)	3 (13 %)	1 (4 %)
WBC	19 (83 %)	2 (9 %)	10 (43 %)	6 (26 %)	1 (4 %)
gamma-GT	20 (87 %)	7 (30 %)	4 (17 %)	6 (26 %)	3 (13 %)

Note: Calculation of percentages based on number of patients in SAS (N=23)
Source: Table 3.13.

Non classifiable according to the NCI-CTC version 3.0. laboratory parameters are summarized in Table 36.

Table 36: Non classifiable according NCT-CTC v3.0 laboratory parameter (SAS)

Laboratory parameter	*Total n(%)*	*Below LLN n(%)*	*Above ULN n(%)*
ALT	2 (9 %)	2 (9 %)	
Basophils	8 (35 %)		8 (35 %)

Laboratory parameter	*Total n(%)*	*Below LLN n(%)*	*Above ULN n(%)*
Bilirubin	1 (4 %)	1 (4 %)	
Chloride	10 (43 %)	4 (17 %)	6 (26 %)
Creatinine	4 (17 %)	4 (17 %)	
Eosinophils	11 (48 %)	3 (13 %)	8 (35 %)
Free T3	5 (22 %)	5 (22 %)	
Hematocrit	21 (91 %)	21 (91 %)	
LDH	20 (87 %)		20 (87 %)
Lymphocytes	14 (61 %)	7 (30 %)	7 (30 %)
Monocytes	20 (87 %)	1 (4 %)	19 (83 %)
Neutrophils	15 (65 %)	2 (9 %)	13 (57 %)
PT	3 (13 %)	3 (13 %)	
PT-INR	2 (9 %)	2 (9 %)	
Platelets	12 (52 %)		12 (52 %)
RBC	23 (100 %)	23 (100 %)	
TSH	6 (26 %)	2 (9 %)	4 (17 %)
Total T3	4 (17 %)	3 (13 %)	1 (4 %)
Total T4	4 (17 %)		4 (17 %)

Laboratory parameter	*Total n(%)*	*Below LLN n(%)*	*Above ULN n(%)*
Total protein	18 (78 %)	18 (78 %)	
WBC	8 (35 %)		8 (35 %)
aPTT	13 (57 %)	3 (13 %)	10 (43 %)

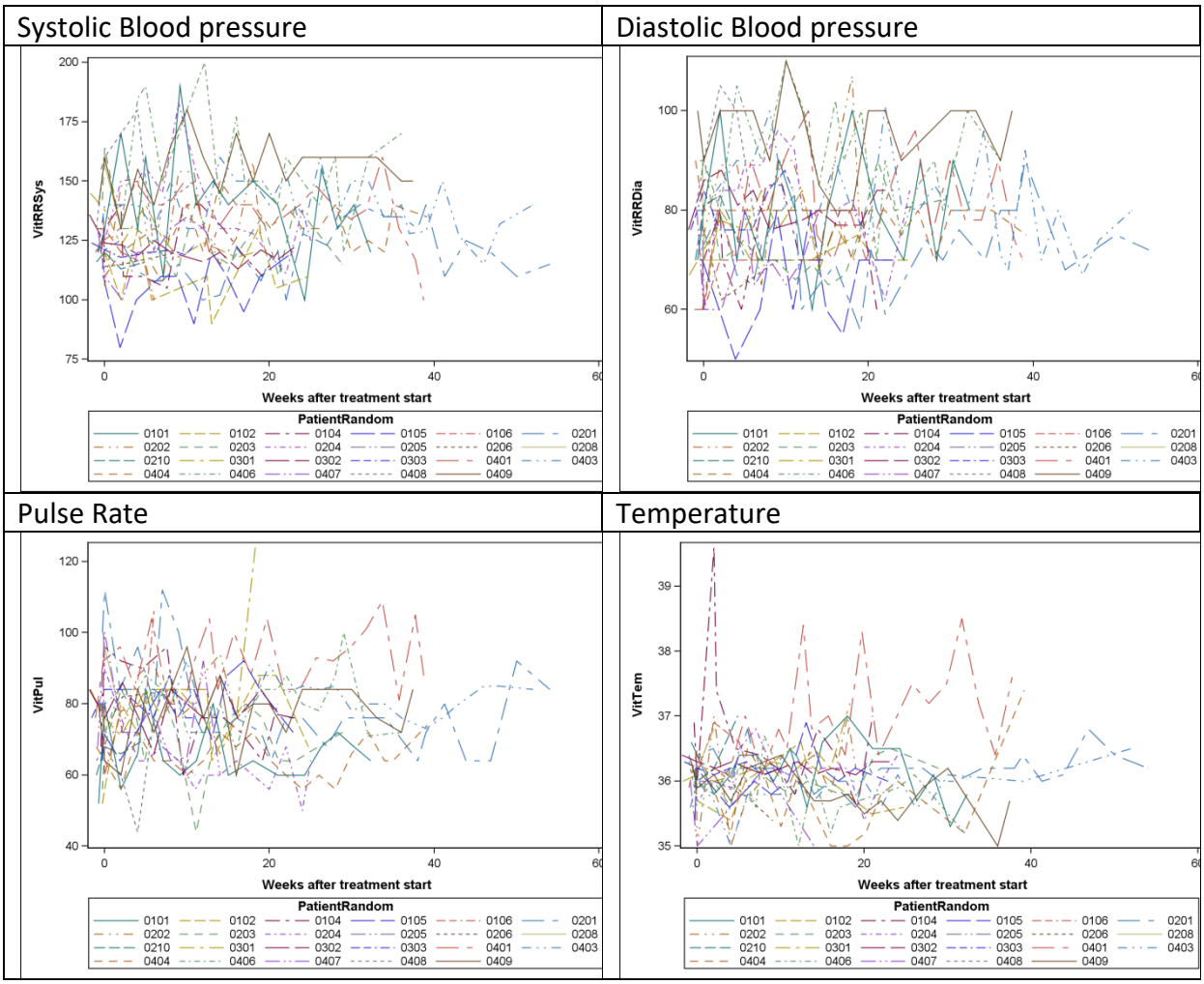
Note: Calculation of percentages based on number of patients in SAS (N=23)
Source: Table 3.14.

Individual data on laboratory evaluations together with CTC classification is provided in Appendix Listing 3.7.

11.6 Vital Signs

Vital Signs and physical examinations were done every 2 weeks when the patient comes to the site to receive FOLFIRI. The time course of the vital parameters blood pressure (systolic and diastolic), pulse and temperature are visualized in Figure 12.

Figure 12: Vital Signs over time (SAS)



Individual data on vital signs are given in Appendix Listing 3.8.