Report Synopsis of Study SUN-CASE

EudraCT-Nr.: 2009-014336-38

Vorlage-Nr.: 4035616

1) **Name of Sponsor/Company:** Faculty of Medicine Delegated to I. Medizinische Klinik und Poliklinik Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1 55131 Mainz, Germany	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** *Sutent®*		
3) **Name of Active Substance:** *Sunitinib*		

5) **Title of Study[2]:** A randomized, placebo-controlled phase II trial investigating Sunitinib versus placebo in patients with chemo-refractory advanced adenocarcinoma of the stomach or lower esophagus treated with chemotherapy FOLFIRI.

(Protocol Version 1.1/01.09.2009; Amendment 1 resulting in protocol version 2.0/20.08.2010, Amendment 2 resulting in final protocol version 3.0/16.02.2011)

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[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

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8) **Publication (reference):** Moehler M, Ruessel J, Hegewisch-Becker S, Wilke H, Al-Batran SE, Rafiyan R, Weißinger F, Schmoll HJ, Kullmann F, Fischer von Weikersthal L, Siveke J, Weusmann J, Kanzler S, Schimanski C, Otte M, Schollenberger L, Koenig J, Galle PR, Thuss-Patience PC. FOLFIRI combined with Sunitinib versus placebo in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase II AIO trial. Eur J Cancer. 2014 (*submitted*).

9) **Studied period (years)**[3]**:**	10) **Phase of development:** II
Date of first enrolment: December 17th, 2009 *Date of last completed: July 1st, 2013*	

11) **Objectives:** The primary objective was to evaluate the progression-free survival (PFS) according to RECIST 1.1 in patients with chemorefractory advanced or metastatic adenocarcinoma of the stomach or lower esophagus and FOLFIRI-based chemotherapy. Secondary Objectives: Objective response rate (Complete Response, CR + Partial Response, PR); Tumor control rate; Duration of disease stabilization, 1-year overall survival; Overall survival (OS); Safety and tolerability of placebo-controlled combination therapy in comparison to standard second line therapy.

12) **Methodology:** This was a prospective, randomized, double-blind, multicenter phase II study to evaluate the efficacy, safety and tolerability of Sunitinib versus placebo in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus treated with chemotherapy FOLFIRI. A total of 91 patients were enrolled in this study. All patients who fulfilled the inclusion criteria and none of the exclusion criteria were randomized to receive either Sunitinib or placebo. Sunitinib or placebo capsules were administered orally at 25 mg once daily for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks in addition to their chemotherapeutic standard treatment FOLFIRI. In patients experiencing toxicities, requiring treatment rest or dose reduction, doses were reduced or stopped completely according to dose adjustment recommendations. Treatment continued until disease progression or intolerable adverse events occurred. Subsequently, the patients were followed-up for one year after end of treatment.

Tumor measurements were done at Screening (between day -28 and day -1) and after first and second cycle, then after every second cycle (i.e. after fourth, sixth, eighth cycle etc.) or if clinically indicated until progress of disease. At each imaging time point, an abdominal CT-scan, chest CT- scan or chest X-ray were required. The determination of antitumor efficacy during this trial was based on objective tumor assessments according to the RECIST 1.1 system of unidimensional evaluation.

13) **Number of patients (planned and analyzed):**

Planned:	n= 90
Enrolled:	n= 91
Analyzed:	n= 90

14) **Diagnosis and main criteria for inclusion:** Chemorefractory advanced adenocarcinoma of the stomach or lower esophagus.

Inclusion criteria:

- Signed and dated informed consent before the start of specific protocol procedures
- Histological proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction or lower esophagus
- Failure of any prior chemotherapy (docetaxel and/or platinum-based chemotherapy); but patient has not previously received FOLFIRI treatment
- Measurable metastatic disease according to the RECIST 1.1 criteria. If locally recurrent disease, it must be associated with at

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

least one measurable lymph node

• Age: ≥18 years

• Karnofsky index 100 – 70 %

• Life expectancy >12 weeks

• Adequate hematological, hepatic and renal functions

• At least 3 weeks from previous docetaxel– and/or platinum-based chemotherapy

• Recovery from hematological side effects (CTC grade <1) and non-hematological side effects (CTC grade ≤1) of any prior therapy (except oxaliplatine induced neuropathy CTC grade ≤2)

• Able to comply with scheduled assessments and with management of toxicity.

15) **Test product, dose and mode of administration, batch number:** Sunitinib capsules for oral administration, starting dose 25mg once daily for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks. Dose adaptations of Sunitinib and treatment interruptions were based on toxicity.

16) **Duration of treatment:** Treatment continued until disease progression or intolerable adverse events occurred.

17) **Reference therapy, dose and mode of administration, batch number:** Placebo capsules for oral administration once daily for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks.

18) **Criteria for evaluation:**

Efficacy: Progression-free survival (PFS) according to RECIST 1.1. Secondary endpoints were objective response rate (CR + PR) according to RECIST 1.1, 1-year survival, safety and tolerability of placebo-controlled combination therapy in comparison to standard second line therapy, progression-free survival rate.

Safety: Assessment of clinical toxicities and safety laboratory during scheduled visits at the study centres. In this trial, all Adverse Events (AEs) that occurred between the first and up to 28 days after the last dose of trial medication were documented. All events were reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 4.0). The incidences of treatment interruption and dose reduction were also recorded for all patients.

19) **Statistical methods:** The study was planned to detect with 80% power a 50 % improvement in median PFS time from 3 months in the control group to 4.5 months in the intervention group when testing for superiority of Sunitinib at a one sides type one error of alpha = 15%.

PFS and OS were evaluated by Kaplan-Meier estimates and hazard ratios (HRs) resulted from a Cox model including location of the primary tumor (involvement of esophageal junction), number of metastatic sites (≤1/>1) and Karnofsky performance status at baseline (>80/≤80). The analysis of secondary endpoints and all further data were interpreted descriptively.

The primary analysis set was the intention-to-treat (ITT) set comprising all subjects with at least one available post-baseline assessment of the primary analysis variable. The safety analysis was carried out considering all subjects who had received at least one dose of trial medication. One randomized patient who resigned from participation immediately after randomization was excluded from all analyses. All but one patients entered ITT and safety analysis (45 in each treatment group).

The final analysis was based on a statistical analysis plan (Nov. 11th, 2012) and based on all data generated until June 11th, 2012. Follow-up was complete then for the majority of patients. A statistical analysis report was finalized by Nov. 27th, 2012. Then, some patients were further followed up until July 1st, 2013 (last patient out) and data were collected and cleaned until May 2014. A revised final analysis was performed in June 2014. Results of the planned final analysis and the revised final analysis were compared and results in respect of completeness, efficacy and safety were very similar. Therefore, only results of the revised final analysis are reported.

20) **Summary – Conclusions:**

Efficacy results: Treatment groups were comparable with respect to baseline characteristics: 12/45 and 15/45 were females, in Sunitinib (SUN) and placebo (PL), respectively; mean age (standard deviation, SD) was 59 (11) and 57 (11), Karnofsky performance status was 90% or better in 27/45 and 26/45 patients, 22/45 and 24/45 had adenocarninoma of the stomach, 11/45 and 11/45 had more than one line of treatment before study entry. All had at least one line of treatment. In 23/45 and 21/45 patients the primary tumor location was esophagus or gastro-esophageal junction in the SUN and PL group, respectively.

Five patients of the SUN and one patient of the PL group did not comply with the inclusion criteria (prior toxicities not resolved: 3 and 0, no signs of metastatic disease: 1 and 0, prior treatment with inhibitors of VEGF, VEGFR or RTK: 1 and 1). Furthermore, 2 and 4 patients stopped treatment within 21 days. These 12 patients were excluded from the per protocol analysis which comprised 38 and 40 patients of the SUN and PL group, respectively.

Treatment was started in all patients of the ITT analysis set (n=45+45). The average number of treatment cycles started in each

patient was 3.7 and 3.4 in the SUN and PL group, respectively. Starting dose of 25 mg was never increased; it was reduced to 12.5 mg in 9 and 5 patients (SUN and PL) and re-increased to the starting dose in one SUN-patient. Treatment was continued until disease progression in 32/45 and 28/45 patients of the SUN and PL group, respectively. It was terminated due to prolonged treatment interruption in 4 and 2 patients, due to toxicities in 1 and 3 patients, due to withdrawal of patient consent in 1 and 2 patients and due to other reasons in 7 and 9 patients of the SUN and PL group, respectively.

Disease progression was observed in 37 and 33 patients (SUN/PL) on the basis of scheduled staging applying RECIST 1.1 criteria; it was observed during follow-up after end of treatment in 2 and 8 patients (SUN/PL) and coincidental with death in 2 and 3 patients (SUN/PL), 2 and 1 patients (SUN/PL) died without signs of progression, and 2 and none (SUN/PL) patient were followed until withdrawal of consent (time in study: 114 and 196 days, respectively) and then lost to follow-up without signs of progressive disease.

Median PFS time was 111 (95% CI 47 – 161) days in the SUN group and 119 (95% CI 43 – 170) days in the PL group (HR SUN vs. PL 1.02 (95% CI 0.66 – 1.59), p=0.92, see Fig.1). Median OS time was 315 (95% CI 220-360) days in the SUN group and 278 (95% CI 138 – 325) days in the PL group (HR in favor of SUN 0.81 (95% CI 0.51 – 1.30), p=0.39, see Fig.2). Objective response, defined as CR+PR according to RECIST 1.1 criteria at least once, was achieved in 9 and 13 of 41 and 41 patients of the SUN and PL group, respectively, that were evaluable for best response. Tumor control, defined as CR + PR + SD according to RECIST 1.1 criteria, was observed in 27 and 25 of 41 and 41 patients of the SUN and PL group, respectively (see Tab.1).

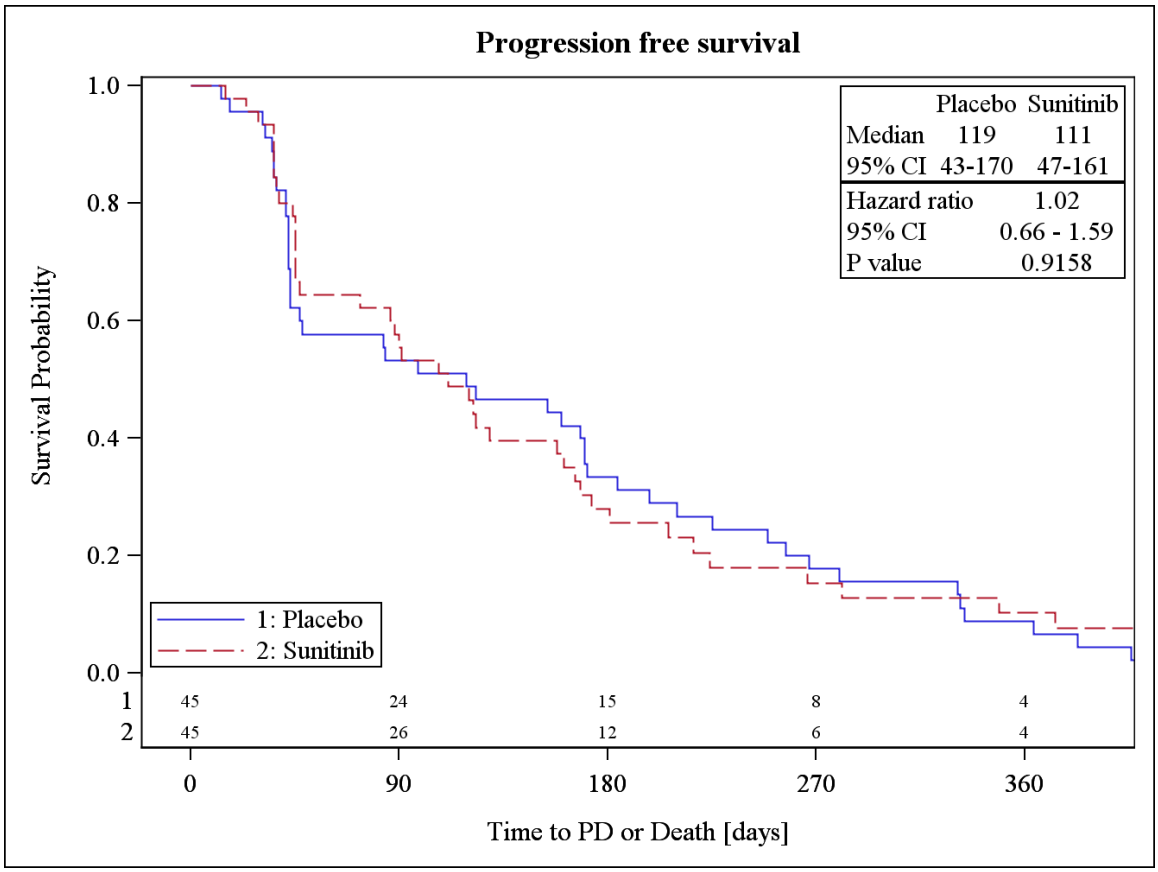

Figure 1: Kaplan-Meier estimates of progression-free survival. Analysis set ITT, N = 90

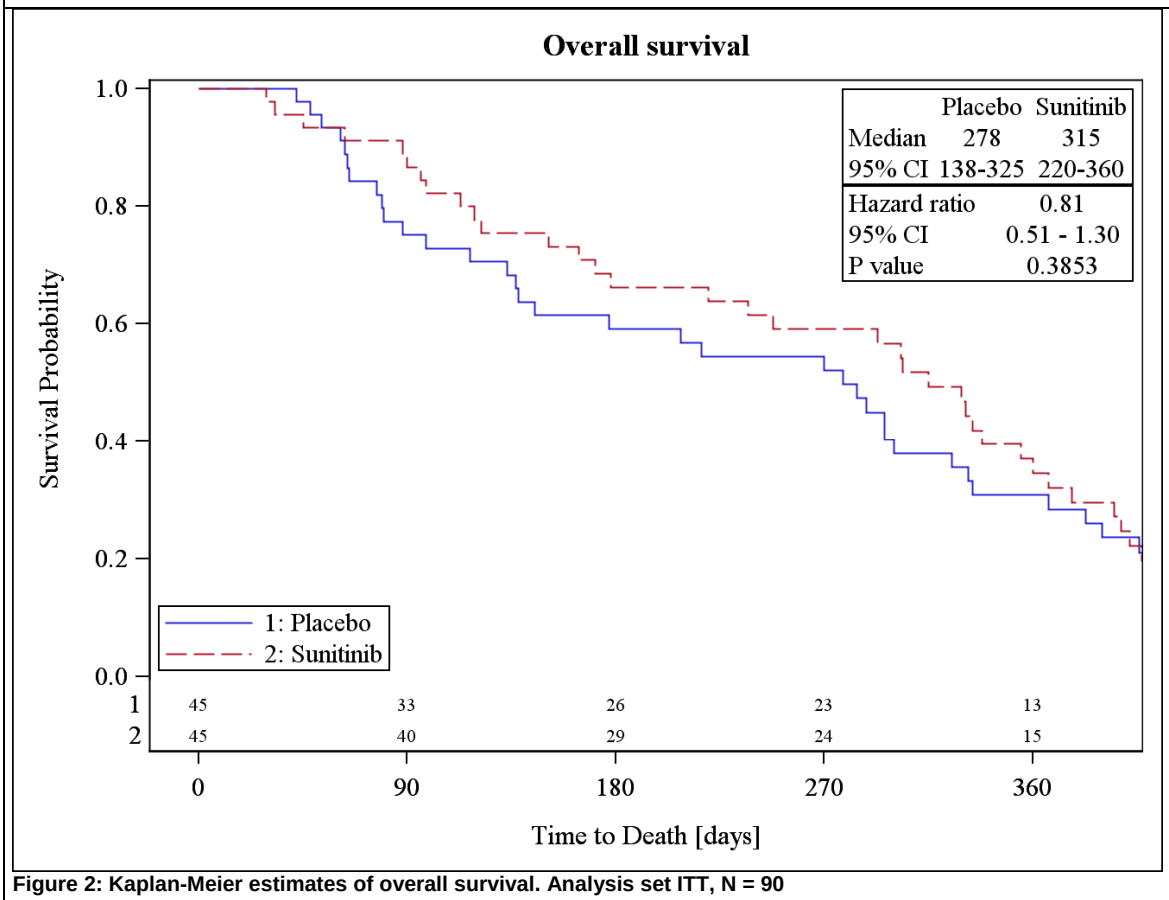

Figure 2: Kaplan-Meier estimates of overall survival. Analysis set ITT, N = 90

Table 1: Response and tumor control. ITT population (N=90)

	Sunitinib		Placebo	
	N=45	100%	N=45	100%
Best response				
Complete response (CR)	-	-	5	11
Partial response (PR)	9	20	8	18
Stable disease (SD)	18	38	12	27
Progressive disease (PD)	14	29	16	36
Not evaluable*	4	13	4	11
Objective response (CR + PR)	9	20	13	29
Tumor control rate (CR + PR + SD)	27	58	25	56

*Of 4+4 patients non evaluable for best response 2+3 the likely best response is PD, because progression or death occurred within 45 days, for 2+1 patients progression was seen not before day 114.

The per-protocol analysis did not show any differential efficacy, either: For PFS, the HR SUN vs. PL was 0.92 (95% CI 0.57 – 1.47) in favor of SUN and for OS, the HR SUN vs. PL 0.74 (95% CI 0.45 – 1.22) in favor of SUN.

Planned final ITT analysis performed in Nov. 2012 gave a HR SUN vs. PL of 1.11 (95% CI 0.70 – 1.74) for PFS and a HR SUN vs. PL of 0.82 (95% CI 0.50 – 1.34) for OS, based on follow-up until June 2012.

Safety results: All AEs were documented on the appropriate pages of the CRF, graded according to CTCAE Version 4.0 and coded with the Medical Dictionary for Regulatory Activites (MedDRA) Version 17.0. The relatedness between each event and the intake of study medication was judged by the investigators under blinded condition according to the modified WHO criteria. AEs assessed with "certain", "probable" or "possible" causal relationship to study treatment were graded as adverse reactions, causality assessed as "improbable" or "none" was considered as not related to study treatment.

Seriousness was defined according to the Seriousness Criteria of Good Clinical Practice Guideline (GCP). In addition, all hematologic laboratory values graded CTCAE grade 3 or higher were considered as serious, most of them with seriousness criterion "medically important". The following table shows an overview of the reported AEs:

Table 2: Overview of reported AEs

	Sunitinib		**Placebo**		**Total**	
	number of patients (N=45)	number of AEs (N=641)	number of patients (N=45)	number of AEs (N=572)	number of patients (N=90)	number of AEs (N=1213)
Any AEs	45 (100%)	641 (100%)	45 (100%)	572 (100%)	90 (100%)	1213 (100%)
SAE-Reports	35 (77.7%)	139 (21.7%)	36 (80%)	98 (17.1%)	71 (78.9%)	237 (19.5%)
SUSAR Reports	1 (2.2%)	1 (0.2%)	0 (0%)	0 (0%)	1 (1.1%)	1 (0.1%)
SAE-Terms	35 (77.7)	140 (21.8%)	36 (80%)	105 (18.3)	71 (78.9)	245 (20.2)
SAE-Reports hematological events*	33 (73.3%)	60 (9.4%)	12 (26.6%)	25 (4.3%)	45 (50%)	85 (7.0%)

* System Organ Class Blood and lymphatic system disorders CTCAE grade 3 or more

Adverse Events:

All patients reported at least one AE. A total of 1213 AEs were reported. Thereof, 641 (52.8%) AEs occurred in the SUN group, 572 (47.2%) in the PL group.

The following AEs occurred in at least 30 patients (MedDRA preferred terms): nausea (in 33 (73%) patients of the SUN vs. 32 patients (71%) of the PL group), diarrhea (in 24 patients (53%) of the SUN vs. 26 patients (58%) of the PL group), fatigue (in 22 patients (49%) of the SUN vs. 23 patients (51%) of the PL group), neutropenia (in 32 patients (71%) of the SUN vs. 12 patients (27%) of the PL group), vomiting (in 19 patients (42%) of the SUN vs. 20 patients (44%) of the PL group), alopecia (in 15 patients (33%) of the SUN vs. 17 patients (38%) of the PL group), and leucopenia (in 20 patients (44%) of the SUN vs. 10 patients (22%) of the PL group).

AEs that occurred in more than 5 patients (MedDRA preferred terms) with CTCAE grade 3 or more were: neutropenia in 28 (62%) patients of the SUN group vs. 10 patients (22%) of the PL group), leukopenia (in 13 patients (29%) of the SUN group vs. 7 patients (16%) of the PL group), diarrhea (in 1 patient (2%) of the SUN group vs. 2 patients (16%) of the PL group), vomiting (in 4 patients (9%) of the SUN group vs. 3 patients (7%) of the PL group), disease progression (in 4 patients (9%) of the SUN group vs. 3 patients (7%) of the PL group), nausea (in 3 patients (7%) of the SUN group vs. 3 patients (7%) of the PL group), general physical health deterioration (in 2 patients (4%) of the SUN group vs. 4 patients (9%) of the PL group), and gamma-glutamyltransferase increased (in 5 patients (11%) of the SUN group vs.1 patient (2%) of the PL group).

Adverse Events considered as related to study medication:

In 638 (52.6%) of all AEs a causal relation was assessed between the occurrence of the AE and the administration of study medication. 332 (52%) of these adverse reactions occurred in the SUN group and 306 (48%) in the PL group. The relationship was graded as possible (SUN: 215 AEs; PL: 192 AEs), probable (SUN: 78 AEs, PL: 80 AEs) or certain (SUN: 34 AEs, PL: 34 AEs). For 551 AEs (45%), thereof 290 in the SUN group and 261 AEs under PL, no causal relationship to study treatment was stated. They were assessed as "not related" (SUN: 197; PL: 173) or as "improbable" (SUN: 93, PL: 88). The remaining AEs (24, 2%) were judged as "not assessable".

Severity of Adverse Events:

The majority of the AEs (974; 80.3%) were judged as mild to moderate, i.e. CTCAE grade 1 or 2, respectively. A total number of 185 (15.2%) AEs were graded CTCAE grade 3 (severe), 30 (3.5%) AEs were graded CTCAE grade 4 (life-threatening; disabling), and 16 AEs (1.3%) were graded CTCAE grade 5 (death).

Seriousness of Adverse Events:

In summary, 245 AE terms were judged as serious according to the definition in the final study protocol version 3.0. These 245 SAE-terms were reported within 237 SAE-Reports. Thereof, 139 SAE-Reports occurred in the SUN group, and 98 in the PL group. The following table shows the number of SAE-Reports allocated to MedDRA system organ classes (SOC).

Table 3: SAE reports allocated to MedDRA system organ classes (SOC)

	SAEs graded as related		SAEs graded as not related		all SAEs	
	Sunitinib	Placebo	Sunitinib	Placebo	Sunitinib	Placebo
Blood and Lymphatic System Disorders	60	25	3	1	63	26
Cardiac Disorders	0	0	0	0	0	0
Congenital, Familial and Genetic Disorders	0	0	0	0	0	0
Ear and Labyrinth Disorders	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	0	0
Eye Disorders	0	0	0	0	0	0
Gastrointestinal Disorders	7	8	11	18	18	26
General Disorders and Administration Site Disorders	1	5	6	4	7	9
Hepatobiliary Disorders	0	0	2	2	2	2
Immune System Disorders	0	0	0	0	0	0
Infections and Infestations	0	4	13	3	13	7
Injury, Poisoning and Procedural Complications	0	0	0	0	0	0
Investigations	4	1	8	2	12	3
Metabolism and Nutrition Disorders	1	0	7	4	8	4
Musculoskeletal and Connective Tissue Disorders	0	0	0	3	0	3
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	0	0	4	2	4	2
Nervous System Disorders	0	2	0	1	0	3
Psychiatric Disorders	0	0	0	1	0	1
Pregnancy, Puerperium and Perinatal Conditions	0	0	0	0	0	0
Renal and Urinary Disorders	1	0	2	2	3	2
Reproductive System and Breast Disorders	0	0	0	1	0	1
Respiratory, Thoracic and Mediastinal Disorders	3	1	2	5	5	6
Skin and Subcutaneous Tissue Disorders	1	0	0	0	1	0
Social Circumstances	0	0	0	0	0	0
Surgical and Medical Procedures	0	0	0	0	0	0
Vascular Disorders	0	3	3	0	3	3

The SOCs with more than 15 SAE-Reports were Blood and Lymphatic System Disorders (89 SAE-Reports), followed by Gastrointestinal Disorders (44 SAE-Reports), General Disorders and Administration Site Conditions (16 SAE-Reports), and Infections and Infestations (20 SAE-Reports).

In the SOC Blood and Lymphatic System Disorders, neutropenia (70 events) and/or leucopenia (26 events) were most frequently documented. They were graded as serious adverse reactions (SUN: 60 SAE reports; 59 related SAE reports equates 98%; PL: 25 SAE reports; 24 related SAE reports equates 96%).

SAE terms that were reported in the SOC Gastrointestinal Disorders were, beside others, diarrhea (10), vomiting (9), ileus (5) and nausea (5). SAE terms in the SOC General Disorders and Administration Site Conditions were e.g. fatigue (6) or general physical health deterioration (4). In the SOC Infections and Infestations e.g. device related infection (3), infection (3), pneumonia (4) and urinary tract infection (2) were reported. One third (31.25%) of the SAE terms in these 3 SOCs were judged as “related to intake of study medication”. One patient died because of general physical health deterioration in combination with leucopenia, sepsis

(*Staphylococcus aureus*) and acute renal failure. The latter three adverse events are predescribed in the summary of product characteristics for Sutent®. However, since general physical health deterioration is unlisted for Sutent®, this serious adverse reaction (SAR) was judged as unexpected and therefore reported to the German competent authority (BfArM) and to the Ethics Committee.

Deaths:

Vital state was followed until death in 39 patients in each group. Disease progression was the cause of death in 35 patients of the SUN group and in 33 patients of the PL group (2/4 died due to other causes, 2/2 due to unknown cause). 6/6 patients (SUN group/PL group) were not followed until death, 2/0 of them had no signs of PD when withdrawing their consent in further participation.

Summary concerning Safety:

In summary it can be stated that the patients in the SUN-CASE trial experienced a relevant number of AEs. Possible explanations are reduced general health status due to severity of the underlying metastatic gastric adenocarcinoma, and acquired immune deficiency due to aggressive chemotherapy by itself. Investigators assessed without being aware of treatment allocation more than half of the AEs as related to study treatment.

Considering the SOC Blood and Lymphatic System Disorders, a notable difference in the number of adverse events between the two treatment groups was observed. In this system organ class, more serious adverse events occurred in the SUN treatment group than in the PL group [60 (9.4%) vs. 25 (4.3%)].

Conclusion:

Sunitinib added to FOLFIRI had a trend for better overall survival versus FOLFIRI alone and showed a reasonable tolerability. However, the addition of Sunitinib did not meet its primary end point, i.e. there was no significant improvement of PFS and response rates in chemorefractory-resistant gastric cancer patients. Further combinations with tyrosine kinase inhibitors (TKIs) are warranted.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** July 3rd, 2014

Print Name: Prof. Dr. med. Markus Möhler

Signature: