Clinical Study Report (Synopse ICH E3)

Study Title:	Phase II Trial in Platinum-Refractory Ovarian Cancer: A Randomized Multicenter Trial with SU11248 to evaluate Dosage, Tolerability, Toxicity and Effectiveness of a Multitargeted Receptor Tyrosine Kinase Inhibitor Monotherapy	
Study Acronym	**AGO-OVAR 2.11**	
Study Sponsor-ID	**AGO-OVAR 2.11**	
EudraCT No.	**2007-003089-16**	
CSR Version	V02F	
CSR Date	2013-08-16	
	Date	**Signature**
Coordinating Principal Investigator Prof. Dr. Uwe Wagner (Universitätsklinik Marburg)	19.08.2013	
Sponsor Stefanie Barth (AGO Research GmbH)		
Statistician Jörn Rau (KKS-Universität Marburg)	22.08.2013	Jörn Rau
Review Ursula Siegmund (KKS-Universität Marburg)	22.08.2013	U. Siegmund
Author Dr. Eckhard Bergmann (KKS-Universität Marburg)	22.08.2013	Bergmann

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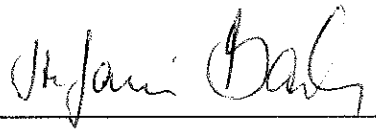
Sponsor Stefanie Barth (AGO Research GmbH)	19.08.2013	
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Index

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1 Name of Sponsor/Company

AGO Research GmbH, Kaiser-Friedrich-Ring 71, 65185 Wiesbaden

Vormals:
GYN Research GmbH, Kaiser-Friedrich-Ring 71, 65185 Wiesbaden

Vormals:
HSK Research GmbH, Ludwig-Erhard-Str. 100, 65199 Wiesbaden

2 Name of Finished Product

Sutent®

3 Name of Active Substance

Sunitinib (SU11248)

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N.A.

5 Title of Study

Phase II Trial in Platinum-Refractory Ovarian Cancer: A Randomized Multicenter Trial with SU11248 to evaluate Dosage, Tolerability, Toxicity and Effectiveness of a Multitargeted Receptor Tyrosine Kinase Inhibitor Monotherapy (Version 1.1, 13. August 2007)

Datum der BfArM Genehmigung (BfArM Vorlagen Nummer)	24.08.2007 4033137	
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V		
Non-Substantial Amendment N°1 (Adressänderung für AGO Studienzentrale, Adressänderung für Statistik)	genehmigt am	15.04.2009 (Bestätigung Kenntnisnahme)
Non - Substantial Amendment N°2 (Umfirmierung der HSK Research GmbH)	genehmigt am	20.05.2010
Abmeldung der klinischen Prüfung	erfolgte am	**09.07.2012**
Datum der zustimmenden Ethik Bewertung Aktenzeichen der EK Marburg		31.08.2007 113/07 (A)
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V		
Non-Substantial Amendment N°1 (Adressänderung für AGO Studienzentrale, Adressänderung für Statistik)	genehmigt am	28.01.2009
Non - Substantial Amendment N°2 (Umfirmierung der HSK Research GmbH)	genehmigt am	19.05.2010
Abmeldung der klinischen Prüfung	erfolgte am	**09.07.2012**

Beschreibung der Amendments:
Non-Substantial Amendment N°1 (15.01.2009) zu Protokollversion 1.1 vom 13. August 2007:
- Änderung der Anschrift und des Ansprechpartners der Biometrie
- Änderung der Anschrift des Studiensekretariates

Non-Substantial Amendment N°2 (04.05.2010) zu Protokollversion 1.1 vom 13. August 2007:

- Umfirmierung der HSK Research GmbH
  Die AGO Research GmbH hat per 6. November 2009 sämtliche Geschäftsanteile der HSK Research GmbH, die nunmehr unter GYN Research GmbH firmiert, erworben. Der Sitz der GmbH befindet sich im Kaiser-Friedrich-Ring 71 in 65185 Wiesbaden

6 Investigators

Wagner, Uwe15; Belau, Antje10; Bischoff, Joachim13; Canzler, Ulrich4; Dewitz, Thomas9; du Bois, Andreas[19]; Gropp, Martina[2]; Hanker, Lars[7]; Hasenburg, Annette[8]; Hilpert, Felix[12]; Hils, Rita[19]; Janni, Wolfgang[18]; Kreienberg, Rolf[18]; Kühnle, Henning[11]; Meier, Werner[5]; Park-Simon, Tjoung-Won[11]; Richter, Barbara[16]; Schröder, Willibald[3]; Sehouli, Jalid[1]; Solomayer, Erich[17]; Tomé, Oliver[14]; Wimberger, Pauline[6]

7 Study centres

Ort	Klinik	Abteilung
Berlin[1]	Charité, Campus Virchow Klinikum	Frauenklinik
Bonn[2]	Malteser Krankenhaus	Gynäkologie und Geburtshilfe
Bremen[3]	Klinikum Bremen-Mitte gGmbH	Frauenklinik
Dresden[4]	Universitätsklinikum Carl Gustav Carus	Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe
Düsseldorf[5]	Evangelisches Krankenhaus Düsseldorf	Frauenklinik
Essen[6]	Universitätsklinikum Essen	Frauenklinik
Frankfurt[7]	Klinikum der J. W. Goethe-Universität	Klinik für Gynäkologie und Geburtshilfe
Freiburg[8]	Universitätsklinikum	Universitätsfrauenklinik
Gifhorn[9]	Klinikum Gifhorn GmbH	Frauenklinik
Greifswald[10]	Klinikum der Ernst-Moritz-Arndt-Universität	Klinik u. Poliklinik für Gynäkologie u. Geburtshilfe
Hannover[11]	Med. Hochschule Hannover	Frauenklinik
Kiel[12]	Universitätsklinikum Schleswig-Holstein, Campus Kiel	Klinik für Gynäkologie u. Geburtshilfe
Magdeburg[13]	Otto-von-Guericke-Universität	Klinik für Frauenheilkunde u. Geburtshilfe
Mannheim[14]	Klinikum Mannheim GmbH, Universitätsklinikum	Frauenklinik
Marburg[15]	Universitätsklinikum Giessen und Marburg GmbH	Klinik für Gynäkologie, Gynäkologische Endokrinologie und Onkologie
Radebeul[16]	Elblandkliniken Meißen-Radebeul GmbH & Co KG	Gynäkologie
Tübingen[17]	Universitätsklinikum Tübingen	Frauenklinik
Ulm[18]	Universitätsklinikum Ulm	Universitätsfrauenklinik
Wiesbaden[19]	HSK, Dr. Horst Schmidt Klinik	Klinik für Gynäkologie und gynäkologische Onkologie

8 Publication (reference)

- *A phase II trial (AGO 2.11) in platinum-resistant ovarian cancer: a randomized multicenter trial with sunitinib (SU11248) to evaluate dosage, schedule, tolerability, toxicity and effectiveness of a multitargeted receptor tyrosine kinase inhibitor monotherapy*.
  Baumann KH, du Bois A, Meier W, Rau J, Wimberger P, Sehouli J, Kurzeder C, Hilpert F, Hasenburg A, Canzler U, Hanker LC, Hillemanns P, Richter B, Wollschlaeger K, Dewitz T, Bauerschlag D, Wagner U.
  Ann Oncol. 2012 Sep;23 (9):2265-71.

- *Evaluation of Potentially Predictive Markers for Anti-Angiogenic Therapy with Sunitinib in Recurrent Ovarian Cancer Patients.*
  Bauerschlag DO, Hilpert F, Meier W, Rau J, Meinhold-Heerlein I, Maass N, Dubois A, Sehouli J, Arnold N, Schem C, Oberg HH, Baumann K.
  Transl Oncol. 2013 Jun 1;6(3):305-10

9 Studied period (years): date of first enrolment, date of last completed

Date of first enrolment: 19.09.2007
Date of last completed: 05.06.2012

10 Phase of development

Phase II

11 Objectives

Primary objective:
Objective response (CR, PR) evaluated by RECIST criteria in case of measurable disease, and by tumor marker (CA°125) in case of non-measurable disease.

Secondary objectives:
• Tolerability, toxicity
• Time to progression
• Overall survival
• Duration of tumor response
• Stable disease

Additional objectives:
• Translational research (target expression in tumor tissues if available; IHC for VEGFR, PDGFR and c-kit)
• Cytokine profile in serum before and during therapy and proteomic analysis, if samples are available
• Circulating endothelial progenitor cells
• Proteomic analysis of serum samples
• Wound healing assay

12 Methodology

Prospective, randomized, open label, multi-center, 2-schedule and dose level

13 Number of patients (planned and analyzed)

Planned: 72 patients
Analyzed: 73 patients

14 Diagnosis and main criteria for inclusion

Diagnosis:
Histological confirmed epithelial ovarian cancer, primary cancer of the peritoneum or fallopian tube.

Main criteria for inclusion:

- Women, 18 years and older, written (signed and dated) informed consent
- Up to three prior chemotherapies, at least one platinum based chemotherapy
- Platinum refractory or resistant ovarian cancer (defined as stable (SD) or progressive disease (PD) during platinum containing chemotherapy, or treatment free interval < 6 months after stop of platinum based chemotherapy)
- Measurable or non-measurable disease
- Elevated CA°125 level (> 2 x ULN in case of normal CA°125 after prior chemotherapy; or ≥ 2 x nadir CA°125 value after prior chemotherapy, when CA°125 levels remained elevated above normal) in case of non-measurable disease
- ECOG performance status 0-2
- Negative pregnancy test within 5 days before randomization and adequate contraception in women with childbearing potential
- Adequate organ function as defined by the following criteria:
    - Serum aspartate aminotransferase (AST; serum glutamate-oxalate transferase [SGOT]) and serum alanine aminotransferase (ALT; serum glutamate-pyruvate transferase [SGPT]) ≤2.5 x upper limit of normal (ULN). If liver function abnormalities are due to underlying malignancy, then AST and ALT may be ≤5 x ULN
    - Total serum bilirubin ≤1.5 x ULN
    - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5 x ULN
    - Serum albumin ≥3.0 g/dL
    - Absolute neutrophil count (ANC) ≥1500/µL
    - Platelets ≥100,000/µL
    - Hemoglobin ≥9.0 g/dL
    - Serum creatinine ≤1.5 x ULN
    - TSH within normal range
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
- Resolution of all toxic effects of any prior chemotherapy, surgical procedures, radiotherapy, or other cancer related therapies to NCI CTCAE (Version 3.0) grade ≤1 and to the baseline laboratory values as defined in inclusion criterion (see before)

15 Test product, dose and mode of administration, batch number

Test product: SU 11248

Dose:
Arm 1 (**non-continuous treatment**): 50.0 mg, once daily for 28 days, followed by a two-week rest period.
Arm 2 (**continuous treatment**): 37.5 mg, once daily, continuously.

Mode of administration: orally

Batch number:
Sutent® 12.5 mg: 06-042994, F327A, F528U
Sutent® 25 mg: 05-033391, E955D, F559F
Sutent® 50 mg: 05-021479, F574C, F597C, F560E, G778A, H847B, K104A, K462A, K977A, L894C, L995A, M443N, N317H, N680A, P440A, P982A, R121B, R308L, R430A

16 Duration of treatment

Treatment was given for up to one year. Therapy can be continued in case of tumor response and benefit for the patient for more than one year.

17 Reference therapy, dose and mode of administration, batch number

N.A.

18 Criteria for evaluation: Efficacy, Safety

Efficacy criteria:

- Best overall response according to RECIST in patients with measurable disease and response according to GCIG (Gynecologic Cancer InterGroup) recommended “CA°125 Response Criteria" in patients with non- measurable disease. If applicable both criteria will be evaluated.
- Survival time
- Progression-free survival
- duration of best overall response
- number and proportion of patients with presently stable disease

Safety criteria:
-Adverse events (AEs) and serious adverse events (SAE)
-Incidence of and reason for SU11248 dosing delay and discontinuation
-Clinically significant laboratory values (hematology with differential blood count, clinical chemistry, coagulation, and urinalysis)
-Clinical history, physical examination, vital signs, ECG, blood pressure

19 Statistical methods

The statistical analysis of the primary end point was based on the intention-to-treat population.
The phase II selection design proposed by **Simon et al.** (Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1985; 69(12): 1375–1381) was employed to identify the better treatment arm. In order to achieve a 90% probability of correctly selecting the better treatment schedule, with at least an 11% better response rate than the other treatment schedule, 36 patients per arm were needed. Hence, a total sample size of 72 patients was required. OS and PFS were estimated using the Kaplan–Meier method and analyzed by log-rank tests with 95% confidence intervals (CIs).

20 Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

Efficacy results:

Six (16.7%) objective responses (CR or PR) were observed in the non-continuous group (exact 95% CI of 6.4%–32.8%), and two (5.4%) in the continuous treatment group (exact 95% CI 0.7%–18.1%). The same pattern was observed on the basis of the GCIG CA125 response criteria. Therefore, the absolute difference of response rates between both schedules was 11.3%.

In detail, the best reported response according to RECIST criteria in the non-continuous group was one patient with a complete remission (2,8%), five patients with a partial remission (13,9%) and 8 patients with a stable disease (22,2%). In the continuous group no patient achieved a complete remission (0,0%), two patients had a partial remission (5,4%) and seven patients (18,9%) had a stable disease.
The best reported response according to GCIG criteria in the group with non-continuous treatment was one patient (2,8%) with a complete remission, 4 patients (11,1%) with a partial remission and 6 patients (16,7%) with a stable disease. In the group with continuous treatment no patient achieved a complete remission (0,0%), 2 patients had a partial remission (5,4%), and 5 patients (13,5%) had a stable disease.

The absolute difference of response rates according to GCIG CA 125 criteria between both schedules was 8,9%.

Both treatment schedules resulted in similar median PFS and median OS. Median PFS in the non-continuous group was 4.8 months (range 2,9-8,1 months) and 2.9 months in the continuous treatment group (range 2,9-5,1 months).
Median OS in the non-continuous treatment group was 13.6 months (range 7,0-23,2 months and 13.7 months in the continuous treatment group (range 8,4-25,6 months).

Differential levels of VEGF, sVEGFR-3, and Ang-2 in sera of study participants were determined longitudinally.
From 43 patients, serum samples were collected, and in 29 cases, at least two serum samples were obtained in intervals as stated in the study protocol. First interval was 28 days, thereafter 21 days.

Using the baseline markers for VEGF, sVEGFR-3 and Ang-2 separately as a continuous covariate (Cox regression), no prognostic prediction in terms of PFS was found (please refer to Table 1).

Table 1: Results of the Cox Regression Model Evaluating the baseline Values of Biomarkers (n=29).

	Standard Error	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
VEGF	<0,001	0,2112	1,001	1,000	1,002
Ang-2	<0,001	0,8130	1,000	1,000	1,001
sVEGFR-3	<0,001	0,3889	1,000	1,000	1,000

Also the continuous differences between the baseline value and last available value of each patient were tested in a Cox regression model. Again, no significant results were observed (please refer to Table 2).
There were also no significant differences (P > 0,05) found after splitting the cohorts according to the treatment arm.

Table 2: Results of the Cox Regression Model Evaluating the Difference between Baseline and Last Available Value of Biomarkers (n = 29).

	Standard Error	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Diff-VEGF	0,003	0,4357	0.998	0,991	1,004
Diff-Ang-2	<0,001	0,1094	1,001	1,000	1,003
Diff-sVEGFR-3	<0,001	0,2960	1,000	0,999	1,000

Finally the increase respectively decrease of the three parameters VEGF, sVEGFR-3 and Ang-2 during Sunitinib therapy were analyzed as potential parameter for determining the progression free survival time.
Patients showing a decrease in VEGF concentration receiving sunitinib had a median PFS of 10.5 months [confidence interval (CI), 2.89–12.25] compared to 2.9 months (CI, 1.48–5.32) in case of an increase. In this post hoc analysis, the univariate log-rank test showed no significance [P = .17; hazard ratio (HR), 4.37; CI, 0.44–43.1] (please also refer to Table 3).

PFS was 8.4 months (CI, 2.89–12.26)in patients with a decrease of Ang-2 versus 2.7 months (CI, 1.05–5.32) in patients with an increase of Ang-2, respectively. The stratified log-rank test showed a trend for longer PFS if a decrease of Ang-2 was observed (P = .089; HR, 1.29; CI, 0.01–not estimable) (please also refer to table 3).

Patients with a reduction of the sVEGFR-3 concentration had a median PFS of 4.76 months (CI, 2.86–10.65) versus 8.61 months (CI, 1.05–not estimable) in patients with an increase of sVEGFR-3. This observation was statistically not significant in the log-rank test (P > .8; HR, 0.71; CI, 0.04–11.8

No significant differences using the univariate chi-squared test were observed (P = .68) when testing the three parameters VEGF, sVEGFR-3 and Ang-2 in the continuous or non-continuous treatment groups separately.

Table 3: Median PFS in Patients with an Increase or Decrease in VEGF, Ang-2, or sVEGFR-3 (n = 29).

	Median PFS (Months)		P Value	HR
	Increase (n)	Decrease (n)		
VEGF	2,9 (11)	10,5 (18)	0,17	4,37
Ang-2	2,7 (8)	8,4 (21)	0,089	1,29
sVEGFR-3	4,8 (4)	8,6 (25)	0,8	0,71

Due to a small number of samples no data could be collected for the following additional objectives of this study:
• Translational research (target expression in tumor tissues if available; IHC for VEGFR, PDGFR and c-kit)
• Circulating endothelial progenitor cells
• Proteomic analysis of serum samples
• Wound healing assay

Safety results:

In the continuous treatment arm, 46 adverse events grade 3 and 4 occurred in 22 patients, whereas in the non-continuous arm, 60 adverse events grade 3 and 4 were reported of 25 patients. Of all adverse events in the non-continuous group and in the continuous group, 88.8% and 88.4%, respectively, were classified as grade 1 and 2. There were no substantial differences between both treatment arms. There were no unexpected serious adverse events in both treatment groups.
In detail, according to NCI-CTC grade 3 and 4 hematological and biochemical toxic effects in the non-continuous group were hemoglobin 0,6%, platelets 1,6%, white blood cells 1,9%, neutrophils 3,9%, sodium 0,6%, potassium 0,6%, calcium 1,0%, gamma-GT 4,5%, ALT 1,0% and AST 0,3%. In the Continuous-group were hemoglobin 0,0%, platelets 4,3%, white blood cells 2,3%, neutrophils 3,3%, sodium 1,6%, potassium 0,8%, calcium 0,0%, gamma-GT 6,1%, ALT 1,2% and AST 0,8%.
NCI-CTC grade 3 and 4 non-hematological toxic effects in the group with non-continuous treatment encompassed gastrointestinal syndrome 3,0%, hematological aberrations 2,8%, hepatic laboratory findings 1,1%, abdominal symptoms 1,1%, infections 0,6%, pulmonary symptoms 0,4%, edema, 0,2%, fatigue and reduced general condition 0,6%, skin symptoms 0,0%, cardiovascular symptoms 0,9%, pain 0,2%, urological symptoms 0,4% and ear nose throat symptoms/mucositis 0,0%.
In the group of patients with continuous treatment grade 3 and 4 non-hematological toxic effects consisted of gastrointestinal syndrome 1,5%, hematological aberrations 2,3%, hepatic laboratory findings 2,0%, abdominal symptoms 2,0%, infections 0,3%, pulmonary symptoms 0,8%, edema, 0,3%, fatigue and reduced general condition 0,5%, skin symptoms 0,3%, cardiovascular symptoms 0,8%, pain 0,3%, urological symptoms 0,5% and ear nose throat symptoms/mucositis 0,3%.

Conclusion:
Sunitinib treatment is feasible and moderately active in relapsed platinum-resistant ovarian cancer. A non-continuous treatment schedule should be chosen for further studies in ovarian cancer. Ang-2 could potentially identify a patient population that might have a better PFS when under anti-angiogenic treatment, like the tyrosine kinase inhibitor sunitinib.

21 Date of report

2013-08-16