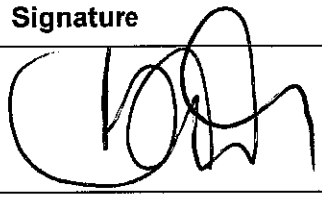
Clinical Study Report – CSR (Synopse ICH E3)

Study Title:	A prospective randomized Phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer.	
Study Acronym:	AGO-OVAR 17/BOOST; GINECO OV118; ENGOT Ov-15 Trial	
Study Sponsor-ID.:	AGO-OVAR 17	
EudraCT-No.:	2011-001015-32	
CSR Version	V01F	
CSR Date	09.11.2021	
	Date	**Signature**
Sponsor Stefanie Barth (AGO Research GmbH, Wiesbaden)	12.11.2021	
Principal Coordinating Investigator Prof. Dr. Jacobus Pfisterer (Zentrum für Gynäkologische Onkologie, Kiel)		
Statistician Jörn Rau (Koordinierungszentrum für Klinische Studien, Marburg)		

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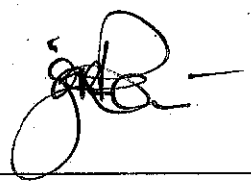
Statistician Jörn Rau (Koordinierungszentrum für Klinische Studien, Marburg)	10.11.2021	

Index

Clinical Study Report (Synopse ICH E3)

1 Name and address of Sponsor/Company

AGO Research GmbH
Kaiser-Friedrich-Ring 71
65185 Wiesbaden

2 Name of Finished Product

Avastin®

3 Name of Active Substance

Bevacizumab

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

NA

5 Title of Study

A prospective randomized Phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer [Amendment No. 1 (31/08/2020) to Protokoll V06 F]

Approval Date Competent Authority (Paul-Ehrlich-Institut, Germany)	28.09.2011	
CA Reference Number	1384/01	
Subsequent changes of the clinical trial according to § 10 Abs. 1 GCP-V		
Protocol Version 03 F incl. Substantial Amendment No. 1	approval date:	12.12.2011
SmPC Avastin 01/12	approval date:	24.01.2012
SmPC Avastin 09/12	approval date:	09.10.2012
Protocol Version 05 F incl. Substantial Amendment No. 2, Change of Location of Coordinating Investigator (LKP) in Germany	approval date:	11.04.2013
SmPC Avastin 05/13	approval date:	16.08.2013
SmPC Avastin 09/14, New Secondary Packager for IMP	approval date:	11.02.2015/11.12.2015
SmPC Avastin 02/15 and 03/15	approval date:	22.02.2016
Protocol Version 06 F incl. Substantial Amendment No. 3	approval date:	28.12.2016
Subproject Translational Research AGO BMB (only in Germany)	approval date:	06.06.2017
Change of Location of CRO	approval date:	19.08.2019
Substantial Amendment No. 1 (31/08/2020) to Protocol V06 F	approval date:	16.09.2020
Notification of End of Trial (§13 (8) GCP-V)	on:	02.02.2021

Approval Date Ethics Committee (Ärztekammer Nordrhein, Düsseldorf, Germany)	03.11.2011	
EC Reference Number	2011216	
Subsequent changes of the clinical trial according to § 10 Abs. 1 GCP-V		
Protocol Version 03 F incl. Substantial Amendment No. 1	approval date:	19.12.2011
SmPC Avastin 01/12	approval date:	06.02.2012
Protocol Version 05 F incl. Substantial Amendment No. 2, Change of Location of Coordinating Investigator (LKP) in Germany, SmPC Avastin 09/12	approval date:	27.03.2013
Patient Information and Informed Consent Form V07 F, SmPC Avastin 05/13	approval date:	19.07.2013
Additional Patient Information and Informed Consent Form V02 F, SmPC Avastin 09/14	approval date:	06.01.2015
SmPC Avastin 02/15 and 03/15	approval date:	27.05.2015
SmPC Avastin 07/15	approval date:	01.12.2015
Protocol Version 06 F incl. Substantial Amendment No. 3	approval date:	28.12.2016
Subproject Translational Research AGO BMB (only in Germany)	approval date:	07.08.2017
Change of Location of CRO	approval date:	18.07.2019
Substantial Amendment No. 1 (31/08/2020) to Protocol V06 F	approval date:	24.09.2020
Notification of End of Trial (§13 (8) GCP-V)	on:	02.02.2021

Description of Amendments (German language)

- *Protokoll V03 F inkl. Substantial Amendment Nr. 1:*

- Präzisierung des Ausschlusskriterium Nummer 22
- Ergänzungen bzgl. der Zweitbegutachtung für Patientinnen aus Frankreich
- Aktualisierung der Patientinneninformation und Einwilligungserklärung

- *Protokoll V05 F inkl. Substantial Amendment Nr. 2:*

- Aktualisierung der statistischen Überlegungen inkl. Aufstockung der Patientinnenzahl auf 900
- Aktualisierung der Patientinneninformation und Einwilligungserklärung

Protokoll V04 F und Patientinneninformation und Einwilligungserklärung V05 F ist nicht gültig, da auf Wunsch der Ethik-Kommission Änderungen an beiden Dokumenten vorgenommen werden mussten.

- *Patientinneninformation und Einwilligungserklärung V07 F:*

- Aktualisierung der Patientinneninformation und Einwilligungserklärung infolge Roter-Hand-Brief vom 15.05.2013

- *Zusatz-Patienteninformation und Einwilligungserklärung V02 F:*

- zusätzliche Patienteninformation und Einwilligungserklärung infolge Aktualisierung der Fachinformation Avastin 09/2014

Zusatz-Patienteninformation und Einwilligungserklärung V01 F ist nicht gültig, da auf Wunsch der Ethik-Kommission Änderungen am Dokument vorgenommen werden mussten.

- *Protokoll V06 F inkl. Substantial Amendment Nr. 3:*

- Formulierung zum Efficacy Follow-Up Zeitraum wurde korrigiert bzw. angepasst

- *Subprojekt Translational Research AGO BMB:*

- Subprojekt zur Speicherung und Sammlung von Daten und Proben in der Biomaterialbank der AGO Research GmbH und zu weiterführenden Untersuchungen anhand der gesammelten Daten und Proben

Patienteninformation und Einwilligungserklärung AGO BMB V01 F ist nicht gültig, da auf Wunsch der Ethik-Kommission Änderungen am Dokument vorgenommen werden mussten.

- *Substantial Amendment No. 1 (31/08/2020) to Protocol V06 F:*

- Aktualisierung der Bedingung für den Zeitpunkt des Daten-Cut-Offs für die primäre Analyse

6 Investigators

Please refer to section 7.
The Consent to Collection of Personal Data is not available for a Principal Investigator indicated with *.

7 Study center(s)

The AGO-OVAR 17 is a multi-centre, international trial. The trial was performed in Denmark, Finland, France, Germany, Norway and Sweden.

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8 Publication (reference)

<u>ASCO 2021/Abstract</u>

Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC) or peritoneal cancer (PPC): A multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890). Pfisterer J et al. DOI: 10.1200/JCO.2021.39.15_suppl.5501 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 5501-5501

<u>Publication</u>

In development.

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

Date of first enrolment: 11.11.2011 international
Date of last completed: 06.08.2013 international

10 Phase of development

Phase III

11 Objectives

The primary objective was to compare progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, clinical or symptomatic in patients randomized to front-line paclitaxel and carboplatin chemotherapy with bevacizumab treatment for either 15 or 30 months.

The secondary objectives were to compare:

- Objective response rate (ORR) by RECIST v1.1
- Overall survival (OS)
- Health related Quality of life (QoL)
  - QOL and symptom control will be assessed using EORTC QLQ-C30 and QLQ-OV28 questionnaires
- Safety and tolerability
- Further exploratory outcome measures on ancillary studies will include:
  - Translational Sub Studies
  - Complementary and Alternative Treatment Qestionnaires

12 Methodology

Prospective, Randomized, International, Intergroup, Multi-Centre, Open-Label

13 Number of patients (planned and analyzed)

Planned: 900 patients (450 in each treatment arm)
Analyzed: 927 patients (Arm I: 464 patients / Arm II: 463 patients)

14 Diagnosis and main criteria for inclusion

Diagnosis

Newly diagnosed, histologically confirmed, FIGO stage IIB - IV (all grades and all histological types) epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal cancer.

Main criteria for inclusion

- Written informed consent and patients awareness and willingness to comply with the study requirements
- Primary diagnosis is confirmed by specialized pathology review (Germany only)
- Age ≥ 18 years
- Histologically confirmed, newly diagnosed epithelial ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma and FIGO stage IIB - IV (all grades and all histological types)
- Patients should have already undergone surgical debulking and no planned surgical debulking prior to disease progression. Patients with stage III and IV disease in whom initial surgical debulking was not appropriate or possible are eligible providing other criteria are fulfilled
- Patients able to commence cytotoxic chemotherapy within 8 weeks of cytoreductive surgery
- ECOG performance status 0 - 2
- Life expectancy > 3 months
- Adequate bone marrow function, coagulation parameters, liver function, postoperative glomerulare filtration rate (based on the Cockroft-Gault or Jelliffe formula)

- Urine dipstick for proteinuria < 2+. If urine dipstick is ≥ 2+, 24 hour urine must demonstrate ≤ 1 g of protein in 24 hours

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

Test Product

Bevacizumab

Dose

Arm I (Standard Arm)

6 cycles Bevacizumab 15 mg/kg* + Paclitaxel 175mg/m² + Carboplatin AUC5 day 1 / every 3 weeks then 16 cycles Bevacizumab 15 mg/kg alone day 1 / every 3 weeks (for total of 15 months)

Arm II (Experimental Arm)

6 cycles Bevacizumab 15 mg/kg* + Paclitaxel 175mg/m² + Carboplatin AUC5 day 1 / every 3 weeks then 38 cycles Bevacizumab 15 mg/kg alone day 1 / every 3 weeks (for total of 30 months)

** Bevacizumab can be omitted in the first cycle of chemotherapy*

Mode of Administration

Intravenously

Batch Number (Germany):

Bevacizumab 100 mg: H0106B01, H0109B01, H0112B19, H0114B02, H0115B25, B7100B15, B7101B07, B7101B16, H0108B01, B7103B07, B7108B02, B7108B16, B7108B22

Bevacizumab 400 mg: H0117B01, H0019B01, H0127B02, H0140B05, H0146, H0148B15, H0151B01, B7102B10, B8005B01, H0124B01, B8007B02, B7009B01, B7038B02, B7032B01, B7200B01, 1148089, 1148090

16 Duration of treatment

Please refer to section 15.

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

NA

18 Criteria for evaluation: Efficacy, Safety

Efficacy Assessment

Progression free survival (PFS) is defined as the time from the date of randomization to investigator assessed disease progression. OS is defined as the time period from the date of randomization to the date of death.

Safety Assessment

Patients will undergo a complete physical examination (including observable tumor measurements). Measurement of vital signs (weight, blood pressure), and laboratory safety assessments and recording of all AEs grades 1 - 5 will be performed each visit until the follow-up visit.

A standard 12-lead ECG will be performed during the trial as clinically indicated.

AEs/SAEs resulting from the treatment will be reported and graded according to National Cancer Institute's Cancer Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0.

19 Statistical methods

Sample size calculation

Assuming a 30-month recruitment period and 10% dropout, it was calculated that 900 randomized patients (450 per arm) were required to detect a PFS hazard ratio (HR) of 0.66 for the time beyond 15 months favoring the experimental arm, with 80% power and a two-sided log-rank test at 5% alpha after 697 events. It was anticipated that 60% of patients in the trial would be able to complete 15 months of bevacizumab without progressive disease (based on observations in the ICON7 trial). Therefore for both groups, a constant hazard rate up to the completion of 15 months of $\lambda = -\ln 0.6/16 = 0.032$ was assumed. For the time beyond 15 months, based on the observation in ICON7 that approximately 50% of those patients who reached month 16 without disease progression were at risk at month 27, a constant hazard rate of $\lambda_{standard} = -\ln 0.5/11 = 0.063$ was assumed for the time beyond 15 months in the standard arm, and a constant hazard rate for the time >15 months of $\lambda_{experimental} = \lambda_{standard} * 0.66(HR) = 0.042$ was calculated for the experimental arm.

Analytic methods

The primary analysis of PFS was based on a non-stratified log-rank test for the difference between groups at a two-sided alpha level of 5%. Median PFS was estimated using Kaplan-Meier methodology, presented with corresponding 95% CIs. Similar methods were used to analyze OS. No interim analyses for efficacy/futility were planned. Efficacy was analyzed in all randomized patients. Safety was analyzed in the safety-evaluable population, defined as all randomized patients who received at least one dose of study drug and had at least one post-baseline follow-up. Due to the low event rate, the study was closed on November 30, 2020, after observing PFS events in 673 (97%) of the planned 697 events. At study closure, the conditional probability of reaching a significant result with the full event number was 7.5%. It was considered that the small chance of achieving the planned event numbers with a promising result within a reasonable time did not justify continuing follow-up.

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

Between November 11, 2011 and August 06, 2013 a total of 927 patients from 6 countries were enrolled. The patient were randomly assigned to treatment regimens (464 to standard arm and 463 to experimental arm), representing the intention-to-treat population (ITT). Of these, 890 patients received trial treatment (448 in the standard arm and 442 in the experimental arm), representing the safety population.

Baseline characteristics of the ITT population shows Table 1.

Table 1. Baseline Characteristics (ITT population)

Characteristic	CP plus Bevacizumab 15 months (n = 464)	CP plus Bevacizumab 30 months (n = 463)
Median age, years (range)	61 (25–86)	60 (21–89)
ECOG PS		
0	236 (51)	266 (57)
1	205 (44)	181 (39)
2	23 (5)	16 (3)
Residual tumor	187 (40)	204 (44)
Stratum		
FIGO IIB–IIIC and no residual tumor	236 (51)	230 (50)
FIGO IIB–IIIC with residual tumor or FIGO IV	228 (49)	233 (50)
Primary tumor type		
Ovary	388 (84)	388 (84)
Fallopian tube	35 (8)	39 (8)
Peritoneal	41 (9)	36 (8)
Histo-type/grading		
High-grade serous	362 (78)	368 (79)
Other	102 (22)	95 (21)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: CP, carboplatin plus paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat.

Efficacy results

The final analysis was performed after 673 PFS events (333 (72%) in the standard arm and 340 (73%) in the experimental arm). Median PFS was 24.2 months (95% CI, 22.2 to 26.5 months) with 15 months of bevacizumab versus 26.0 months (95% CI, 23.7 to 29.7 months) with 30 months of bevacizumab. The PFS HR was 0.99 (95% CI, 0.85 to 1.15, p=0.90). Given the non-proportional distribution of events, a restricted mean analysis was performed. This showed a difference mean PFS of 39.5 months in the standard arm (95% CI, 36.3 to 42.7 months) and 39.3 months in the experimental arm (95% CI, 36.2 to 42.2 months, p=0.92; Figure 1). In subgroup analyses within the two strata, there was no difference between treatment arms. Similarly, there was no difference between treatment arms in OS. The HR for OS was 1.04 (95% CI, 0.87 to 1.23, p=0.68). Median OS was 54.3 months in the standard arm (95% CI, 51.0 to 64.6 months) versus 60.0 months in the experimental arm (95% CI, 54.0 to 68.6 months). Restricted mean OS was 60.4 (95% CI, 57.2 to 63.6 months) vs 60.8 months (95% CI, 57.8 to 63.8 months), respectively.

Figure 1. Primary PFS analysis (Intention-to-treat population)

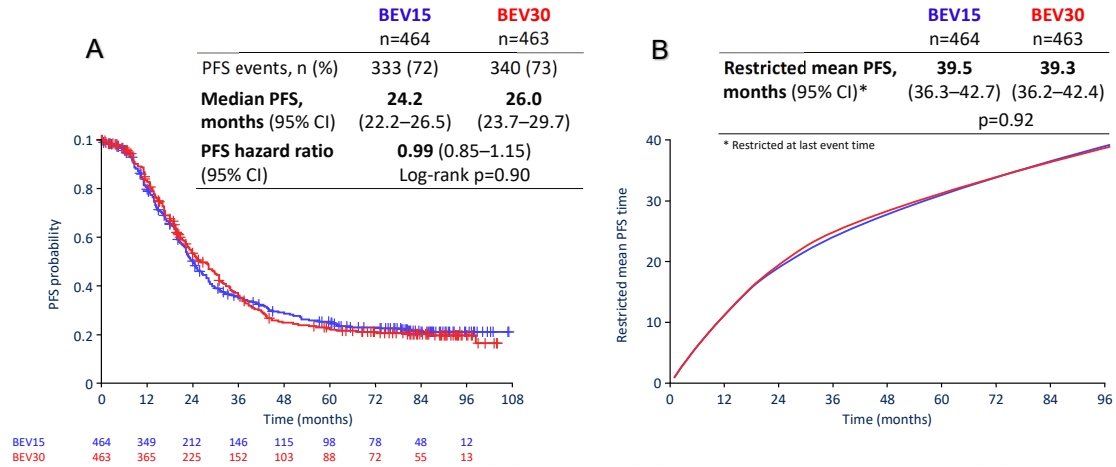

Figure 1: Kaplan Meier-estimtes of PFS (A). Restricted mean survival estimates of PFS (B).

Safety results

Almost all patients experienced AEs (445 (99%) of 448 in the standard arm vs 439 (99%) of 442 in the experimental arm). These were of grade ≥3 intensity in approximately two-thirds of patients in each arm (282 (63%) vs 300 (68%), respectively. Serious AEs occurred in 199 (44%) vs 204 (46%) of patients, respectively, and AEs or serious AEs of special interest occurred in 145 (32%) vs 168 (38%) of patients in the standard versus experimental arms, respectively. Overall, 10 patients had fatal AEs (8 (2%) in the standard arm and 2 (1%) in the experimental arm.

AEs of special interest are shown in Table 2. The extended duration of bevacizumab was associated with a slight increase in the incidence of grade ≥3 hypertension and grade ≥3 proteinuria, but there were no other relevant differences between treatment arms. Exploratory analyses indicated that in the experimental arm, the first appearance of grade ≥3 hypertension occurred in cycles 23–44 in 19 patients (4%), and the onset of grade ≥3 proteinuria occurred in cycles 23–44 in 10 patients (2%), accounting for the increased incidence across the entire treatment period in the extended bevacizumab arm. When comparing only those AEs occurring in cycles 1–22, there was no difference in incidence between patients receiving bevacizumab for 15 vs 30 months (grade ≥3 hypertension: 18% vs 18%, respectively; grade ≥3 proteinuria: 2% vs 2%, respectively).

Table 2. Overview of Adverse and Serious Adverse Events of Special Interest (Safety population)

Adverse Event	CP plus Bevacizumab 15 months (n = 448)	CP plus Bevacizumab 30 months (n = 442)
Hypertension, grade ≥3	88 (20)	109 (25)
Intestinal perforation/fistula, all grades	23 (5)	16 (4)
Thromboembolic events, grade ≥3	16 (4)	14 (3)
Proteinuria, grade ≥3	9 (2)	19 (4)
Myocardial infarction, grade ≥3	2 (0.4)	5 (1)
Wound dehiscence, grade ≥3	1 (0.2)	2 (0.5)
Posterior reversible encephalopathy syndrome, grade ≥3	2 (0.4)	0
Impaired wound healing, grade ≥3	1 (0.2)	1 (0.2)
Hemorrhage, grade ≥3	1 (0.2)	1 (0.2)
Stroke, grade ≥3	1 (0.2)	1 (0.2)
Acute coronary syndrome, grade ≥3	1 (0.2)	0

NOTE. Data are presented as No. (%). Abbreviations: CP, carboplatin plus paclitaxel.

Conclusion

Bevacizumab 15 mg/kg every 3 weeks for 15 months as part of the first-line treatment in advanced ovarian cancer remains standard-of-care.

21 Date of report

09.11.2021