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.

The BOOST (Bevacizumab Ovarian Optimal Standard Treatment) Trial

AGO-OVAR 17
GINECO OV118
ENGOT Ov-15 Trial

Amendment No. 1 / 31-08-2020

to

Protocol V06 F / 15-11-2016
EudraCT-Nr. 2011-001015-32

The contents of this Amendment No. 1 refer to changes to the Protocol V06 F dated 15.11.2016. The amended sections do not modify the scientific nor the medical basis of the protocol.

This Amendment No. 1 will be provided to each involved Ethics Committee and Competent Authority for approval.

Reason for this Amendment No. 1:

- Removes PFS events as a condition of the timing of the data cutoff for primary analysis

AMENDMENT AUTHORISATION

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. The BOOST (Bevacizumab Ovarian Optimal Standard Treatment) Trial:
Version	Amendment No. 1; 31-08-2020

Chief Investigator	Prof. Dr. med. Jacobus Pfisterer AGO Research GmbH Kaiser-Friedrich-Ring 71 65185 Wiesbaden Germany	01.09.20 Wiesbaden, date Signature
Biometrician	Jörn Rau Koordinierungszentrum für Klinische Studien (KKS) Philipps-Universität Marburg Karl-von-Frisch-Str. 4 35043 Marburg Germany	Marburg, date Joern Rau Digital unterschrieben von Joern Rau Datum: 2020.08.31 15:31:52 +02'00' Signature
Sponsor	Stefanie Barth AGO Research GmbH Kaiser-Friedrich-Ring 71 65185 Wiesbaden Germany	Wiesbaden, date Signature

Note: The current wording of the protocol is shown in comparison with the changed wording (new version); the new wording of the text is underlined; the part of the text that no longer applies is ~~crossed out~~.

AMENDMENT AUTHORISATION

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. The BOOST (Bevacizumab Ovarian Optimal Standard Treatment) Trial:
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DECLARATION OF INVESTIGATOR

I have read this Amendment No. 1 to the study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. In particular I agree to adhere to the moral, ethical and scientific principles governing clincal research as set out in the Declaration of Helsinki (Version 2008), the ICH Guideline on Good Clinical Practice and the appropriate national laws and regulations.

I agree to handle all information concerning the study confidentially.

Place / date

Signature

Principal Investigator

Name (in block letters)

DECLARATION OF INVESTIGATOR (Germany only)

I have read this Amendment No. 1 to the study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. In particular I agree to adhere to the moral, ethical and scientific principles governing clincal research as set out in the Declaration of Helsinki (Version 2008), the ICH Guideline on Good Clinical Practice and the appropriate national laws and regulations.

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Place / date	Signature Investigator	Name (in block letters)
Place / date	Signature Substitute of Investigator	Name (in block letters)
Place / date	Signature Physician	Name (in block letters)
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SYNOPSIS

Current wording:

Duration of study	… Follow-up period: at least 697 PFS events have been observed (appr. 4.5 years) Each patient will be followed for the primary endpoint PFS and for the secondary endpoint OS every six months at least for 5 years after study treatment start …

New wording:

Duration of study	… Follow-up period: at least 697 PFS events have been observed ~~(appr. 4.5 years)~~ or after data base closure on 30th of November 2020, which ever comes first. Each patient will be followed for the primary endpoint PFS and for the secondary endpoint OS every six months at least for 5 years after study treatment start …

SYNOPSIS

Current wording:

Statistical considerations Sample size calculation Analysis plan	With N = 900 patients randomized at a steady rate over a period of 30 months with an additional 24 months follow-up after the last patient randomized, the trial will have a power of 80.2% to detect a difference in PFS for the time >15 month of HR=0.66 between the treatment groups with a two-sided log rank test (significance level of 5%) including a drop-out rate of 10% under the assumption of exponentially distributed drop-out times. It is expected that 697 PFS events will have occurred at this point.

New wording:

Statistical considerations Sample size calculation Analysis plan	With N = 900 patients randomized at a steady rate over a period of 30 months with an additional 24 months follow-up after the last patient randomized, the trial will have a power of 80.2% to detect a difference in PFS for the time >15 month of HR=0.66 between the treatment groups with a two-sided log rank test (significance level of 5%) including a drop-out rate of

	10% under the assumption of exponentially distributed drop-out times. ~~It is expected that 697 PFS events will have occurred at this point.~~ The analysis of PFS will be either performed when 697 events have occurred or after data base closure on 30th of November 2020, which ever comes first.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample Size calculation

Current wording:

…

With N = 900 patients randomized at a steady rate over a period of 30 months with an additional 24 months follow-up after the last patient randomized, the trial will have a power of 80.2% to detect a difference in PFS for the time >15 months of HR=0.66 between the treatment groups with a two-sided log rank test (significance level of 5%) including a drop-out rate of 10% under the assumption of exponentially distributed drop-out times. It is expected that 697 PFS events will have occurred at this point.

…

New wording:

…

With N = 900 patients randomized at a steady rate over a period of 30 months with an additional 24 months follow-up after the last patient randomized, the trial will have a power of 80.2% to detect a difference in PFS for the time >15 months of HR=0.66 between the treatment groups with a two-sided log rank test (significance level of 5%) including a drop-out rate of 10% under the assumption of exponentially distributed drop-out times. ~~It is expected that 697 PFS events will have occurred at this point.~~

The analysis of PFS will be either performed when 697 events have occurred or after data base closure on 30th of November 2020, which ever comes first.

…

8.4 STATISTICAL ANALYSIS

8.4.1 Primary efficacy Analysis

Current wording:

The primary analysis of this trial will be a non-stratified log-rank test for the difference in the distribution of progression-free survival (PFS) between the groups with different bevacizumab schedules (two-sided at an alpha-level of 5%). Kaplan-Meier estimates for median PFS with the corresponding 95% confidence intervals will be presented. A stratified log-rank test (two-sided at an alpha-level of 5%, stratifying for the factors used for randomization) will also be performed to assess the robustness of the result. In addition, stratified and non-stratified Cox regression analyses will be performed to analyse the influence of baseline covariates. The analysis of PFS will be performed when 697 events have occurred. …

New wording

The primary analysis of this trial will be a non-stratified log-rank test for the difference in the distribution of progression-free survival (PFS) between the groups with different bevacizumab schedules (two-sided at an alpha-level of 5%). Kaplan-Meier estimates for median PFS with the corresponding 95% confidence intervals will be presented. A stratified log-rank test (two-sided at an alpha-level of 5%, stratifying for the factors used for randomization) will also be performed to assess the robustness of the result. In addition, stratified and non-stratified Cox regression analyses will be performed to analyse the influence of baseline covariates. The analysis of PFS will be either performed when 697 events have occurred or after data base closure on 30th of November 2020, which ever comes first. …

RATIONALE FOR THE CHANGE

Overall 927 patients were randomized into the study between 11th of November 2011 and 6th August 2013. Accordingly to the protocol, 697 PFS events were preplanned as a precondition for the final primary PFS analysis. Blinded data check at 17th of September 2019 revealed that 38 of the 697 PFS events were missing. Until 25th of May 2020 another blinded data check showed, that up to this time point only further 9 PFS events had been collected additionally, which means that further 29 PFS events for the predefined number are missing, representing a slow rate of PFS accumulation over the period of time.

Based on the data export of 25th of May 2020 and accordingly to the protocol (page 64, section 8.1), the CRP principle (conditional rejection error probability of a statistical test procedure) by Schäfer and Müller (2001) was used: The adaptive CRP-method allows by inspection potential adaptions of the design on the basis of the data collected at that time point of inspection in the case of unplanned interim looks without compromising the nominal alpha level and takes into account the actual observed treatment difference, when deciding about stopping or other design modifications of the trial. The CRP-calculations, based on information fraction of 95.8% of the number of preplanned events (cp. sample size calculation as laid out in the protocol 8.1, page 63), provided the conditional rejection error probability function to adapt for this unplanned interim look at final analysis - these results of the CRP-calculations are to be documented in detail in the trial master file acc. to Schäfer and Müller.

The conditional power for rejecting the null hypothesis - i.e. having a significant result of the primary analysis based on the preplanned 697 events - is < 7.5 % (under different assumptions regards the distribution of PFS times and scenarios in terms of expected duration of future follow-up) based on the same data export.

CONCLUSION

Taking the results of the data inspection together with the observed event rate and the fact that a small amount of 4.2% (29 PFS events) is missing until the preplanned number would be reached, it seems to be straightforward to not further adhere to the study's original sample size calculation, but to stop the follow-up based on the CRP-principle and to close finally the database (planned date: 30th of November 2020).

The small chance of achieving the planned event numbers with a promising result within a reasonable time does not provide sound justification to keep the follow-up furthermore ongoing.

Schäfer H, Müller HH, Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections. Stat Med 2001; 20(24): 3741-3751