Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, phase 3 trial

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Summary

Background State-of-the art therapy for recurrent ovarian cancer (ROC) suitable for platinum-based re-treatment includes bevacizumab-containing combinations (eg, carboplatin/paclitaxel, carboplatin/gemcitabine) or the most active non-bevacizumab regimen: carboplatin/pegylated liposomal doxorubicin (PLD). This head-to-head trial compared a standard bevacizumab-containing regimen versus carboplatin/PLD combined with bevacizumab.

Methods In this multicentre, open-label, randomised, phase 3 trial, eligible patients had histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube carcinoma with first disease recurrence >6 months after first-line platinum-based chemotherapy, and were aged ≥18 years with Eastern Cooperative Oncology Group performance status 0–2. Patients were stratified by platinum-free interval, residual tumour, prior anti-angiogenic therapy, and study group language, and centrally randomised 1:1 using randomly permuted blocks of size two, four, or six to six intravenous cycles of carboplatin (AUC 4, day 1) plus gemcitabine (1000 mg/m^2, days 1 and 8) every 3 weeks or six cycles of carboplatin (AUC 5, day 1) plus PLD (30 mg/m^2, day 1) every 4 weeks, both given with bevacizumab (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) until disease progression or toxicity. The primary endpoint was investigator-assessed progression-free survival (PFS). Efficacy data were analysed in the intention-to-treat population (all randomised patients). Safety was analysed in all patients who received at least one dose of study drug. This completed study is registered with ClinicalTrials.gov number NCT01837251.

Findings Between August 1, 2013, and July 31, 2015, 682 patients were randomised. Median follow-up for PFS at the data cut-off was 12·4 (IQR 8·3–21·7) months in the carboplatin/PLD/bevacizumab group and 11·3 (IQR 8·0–18·4) months in the carboplatin/gemcitabine/bevacizumab group. PFS was significantly longer with carboplatin/PLD/bevacizumab (experimental arm) than

carboplatin/gemcitabine/bevacizumab (hazard ratio 0·81, 95% confidence interval [CI] 0·68–0·96; p=0·012). Median PFS was 13·3 (95% CI 11·7–14·2) months versus 11·6 (95% CI 11·0–12·7) months, respectively. The most common grade 3/4 adverse events were hypertension (88 [27%] of 332 patients receiving carboplatin/PLD/bevacizumab *vs* 67 [20%] of 329 patients receiving carboplatin/gemcitabine/bevacizumab) and neutropenia (40/332 [12%] *vs* 73/329 [22%], respectively). Serious adverse events occurred in 33/332 patients (9·9%) receiving carboplatin/PLD/bevacizumab and 28/329 patients (8·5%) receiving carboplatin/gemcitabine/bevacizumab. Treatment-related deaths occurred in 1/332 patients receiving carboplatin/PLD/bevacizumab (0·3%; large intestine perforation) and 2/329 receiving carboplatin/gemcitabine/bevacizumab (0·6%; one case each of osmotic demyelination syndrome and intracranial haemorrhage).

Interpretation Carboplatin/PLD/bevacizumab is a new standard treatment option for platinum-eligible ROC.

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Introduction

Ovarian cancer is the eighth most common cancer in women globally, and the eighth most common cause of cancer death.[1] Almost 300,000 new cases were diagnosed worldwide in 2018, representing 3·4% of new cancers in women. In Europe, there were an estimated 65,500 cases of ovarian cancer in 2012 and 42,700 deaths.[2]

Management of newly diagnosed ovarian cancer typically involves cytoreductive surgery and platinum/taxane doublet chemotherapy. At relapse, patients may be candidates for platinum re-treatment, depending on several factors, including previous response and the interval since completing platinum-containing therapy. The ICON4/AGO-OVAR2·2 trial demonstrated superior efficacy with a platinum/paclitaxel doublet versus platinum alone,[3] establishing combination chemotherapy in this setting. Similarly, the AGO-OVAR2·5 trial demonstrated significantly superior progression-free survival (PFS) with a carboplatin/gemcitabine doublet versus carboplatin alone.[4] A meta-analysis of individual patient data from four randomised trials confirmed the role of platinum doublets in this setting, showing improved PFS and overall survival (OS) versus single-agent platinum across all subgroups.[5]

Subsequent randomised phase 3 trials have compared different chemotherapy doublets, including the CALYPSO/AGO-OVAR2·9 trial, which demonstrated significantly superior PFS with a carboplatin/pegylated liposomal doxorubicin (PLD) doublet versus carboplatin/paclitaxel,[6] without impairing quality of life.[7] This regimen has become widely used in recurrent ovarian cancer because of its more favourable therapeutic index (particularly the lower incidences of alopecia, hypersensitivity reactions, and sensory neuropathy) and schedule.

Anti-angiogenic strategies combined with chemotherapy represent an important development in systemic therapy for ovarian cancer. Several anti-angiogenic agents have demonstrated efficacy in platinum-sensitive recurrent ovarian cancer[8–13] but the only approved agent in ovarian cancer is bevacizumab, which is indicated in both newly

diagnosed and recurrent settings. In platinum-sensitive recurrent disease, the randomised phase 3 OCEANS trial demonstrated significantly superior PFS, objective response rate, and duration of response by adding bevacizumab to the 'AGO-OVAR2·5' gemcitabine/carboplatin chemotherapy backbone.[8] The subsequent GOG-0213 trial demonstrated significantly improved efficacy by adding bevacizumab to a carboplatin/paclitaxel doublet.[13] Until the present trial, the most active and widely used platinum combination – the 'CALYPSO' PLD/carboplatin regimen – had been evaluated in combination with bevacizumab only in a single-arm phase 2 study, indicating that bevacizumab/carboplatin/PLD was an active and well-tolerated regimen for platinum-sensitive ovarian cancer.[14] Therefore, we designed a trial to define the most appropriate platinum-based regimen to combine with bevacizumab by determining whether carboplatin/PLD was superior to carboplatin/gemcitabine with bevacizumab.

Methods

Study design and participants

This was a European Network for Gynaecological Oncological Trial groups (ENGOT)/Gynecologic Cancer InterGroup (GCIG) multicentre, open-label, randomised, phase 3 superiority trial, led by the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group and conducted in academic centres in Germany, France, Australia, Austria, and UK (Supplementary Appendix, page 1). The trial was conducted in accordance with the present version of the Declaration of Helsinki, the international Good Clinical Practice standards, and all local laws and regulations concerning clinical trials. The trial protocol, amendments, and other relevant study documentation were approved by each participating site's Independent Ethics Committee. There were four protocol amendments during the course of the study: 3 March, 2015; 3 May, 2016; 20 July, 2018; and 10 September, 2019. Those with a potential impact on study conduct are mentioned below. The final protocol is available in the Supplementary Appendix, page 12.

Eligible patients had histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube carcinoma (independent of International Federation of Gynecology and Obstetrics stage or histological grade or type) with first disease recurrence >6 months after first-line platinum-based chemotherapy. Patients were to have measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1·1, or CA-125-assessable disease according to GCIG criteria, or a histologically proven diagnosis of relapse. Additional inclusion criteria included age ≥18 years, Eastern Cooperative Oncology Group performance status 0–2, life expectancy >3 months, and adequate coagulation parameters and bone marrow, liver, and renal function. Cytoreductive surgery for recurrence and/or prior front-line anti-angiogenic therapy were allowed. Key exclusion criteria were: prior chemotherapy for recurrent disease; ovarian tumours of low malignant potential (borderline tumours); surgery within 4 weeks before the first bevacizumab dose; planned surgery during or within 4 weeks of study treatment; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess related to prior anti-vascular endothelial growth factor therapy; or a history of hypertensive crisis or hypertensive encephalopathy. All patients provided written informed consent before any trial-specific procedures or treatment.

Randomisation and masking

Eligible patients were enrolled by investigators and randomised using randomly permuted blocks of size two, four, or six stratified by: platinum-free interval (6–12 *vs* >12 months); residual tumour (yes [or no debulking surgery for recurrence] *vs* no); prior anti-angiogenic therapy (yes *vs* no); and study group language (initially participating study group, changed in the first protocol amendment in March 2015). Patients were randomised centrally by authorised personnel from KKS, Philipps-University of Marburg, Germany, in a 1:1 ratio. The assigned patient number of each patient was documented by using an enrolment log and subject ID list. There was no masking in this open-label trial.

Procedures

Eligible patients were randomised to receive either carboplatin/gemcitabine/bevacizumab (standard arm) or carboplatin/PLD/bevacizumab (experimental arm). Standard arm treatment comprised bevacizumab 15 mg/kg on day 1, gemcitabine 1000 mg/m^2 on days 1 and 8, and carboplatin area under the concentration curve (AUC) 4 on day 1, all administered intravenously and repeated every 3 weeks for six cycles (maximum), followed by intravenous single-agent maintenance bevacizumab at the same dose until disease progression or unacceptable toxicity. Treatment in the experimental arm comprised bevacizumab 10 mg/kg on days 1 and 15, carboplatin AUC 5 on day 1, and PLD 30 mg/m^2 on day 1, administered intravenously and repeated every 4 weeks for six cycles and followed by intravenous single-agent maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity. The first dose of bevacizumab could be omitted if chemotherapy was started within 4 weeks after debulking surgery for recurrent disease. No bevacizumab dose reductions for toxicity were permitted and the dose was to be modified only in the event of >10% weight change. Bevacizumab treatment was either temporarily or permanently interrupted in the event of hypertension, proteinuria, thrombosis/embolism, haemorrhage, congestive heart failure, wound-healing complications, or any other grade 3 or 4 bevacizumab-related toxicity. Bevacizumab was temporarily interrupted in the event of grade 4 febrile neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment). In addition, bevacizumab was to be permanently discontinued in any patient developing any of the following events: posterior reversible encephalopathy syndrome (PRES); grade 3/4 haemorrhagic/bleeding events; grade 3/4 left ventricular dysfunction (congestive heart failure); grade 4 venous thromboembolism including pulmonary embolism; grade 4 hypertension (hypertensive crisis) or hypertensive encephalopathy; grade 4 non-gastrointestinal fistula; grade 4 proteinuria (nephrotic syndrome); or any grade of CNS bleeding, arterial thromboembolism,

gastrointestinal perforation, tracheo-oesophageal fistula, or hypersensitivity/allergic reactions related to bevacizumab.

In the event of haematological toxicity, chemotherapy was to be delayed until haematological recovery. If neutrophil and/or platelet counts had not recovered within 7 days, the day 8 gemcitabine dose was to be reduced to 50% of the starting dose in case of absolute neutrophil count (ANC) 1·0–1·4 x 10^9/L and/or platelet count 75–99 x 10^9/L. Day 8 gemcitabine was to be omitted if the neutrophil count was <1·0 x 10^9/L and/or the platelet count was <75 x 10^9/L. Subsequent gemcitabine dose adjustment was based on toxicity observed during the preceding cycle. The day 1 and 8 gemcitabine dose was to be permanently reduced in the event of any of the following: ANC <0·5 x 10^9/L for more than 5 days; ANC <0·3 x 10^9/L for more than 3 days; febrile neutropenia; platelets <25 x 10^9/L; cycle delay of more than 1 week due to toxicity. If any of the above toxicities recurred after the initial dose reduction, gemcitabine was to be reduced to 800 mg/m^2 (no dose on day 8) and carboplatin to AUC 3. Granulocyte-colony stimulating factor (G-CSF) was required in case of delayed neutrophil recovery, administered according to American Society of Clinical Oncology guidelines or local practice guidelines. Hypersensitivity to carboplatin was to be managed according to local practice guidelines, with the option of substitution with cisplatin at the investigator's discretion. In the experimental arm, PLD was to be reduced to 25 mg/m^2 in the event of ANC <1·5 x 10^9/L and/or platelet count <100 x 10^9/L.

Any patient enrolled into the trial remained on study unless she withdrew consent (which was allowed at any time).

Tumours were assessed by the investigators at screening and then every 12 weeks for at least 30 months (or until disease progression if earlier). The method used at screening was used for each subsequent tumour assessment. CA-125 was assessed locally every 3 or 4 weeks during study treatment, and every 3 months thereafter until disease progression, unacceptable toxicity, or 30 months' follow-up. QoL was assessed using the European

Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module (QLQ-C30) and ovarian cancer-specific module (QLQ-OV28) at baseline, then every 12 weeks until disease progression, and at every visit thereafter for the 5-year follow-up.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4·03). Laboratory parameters and adverse events were assessed at each visit during treatment, at the safety follow-up visit, and at every 6-monthly visit thereafter. Left ventricular ejection fraction was assessed by echocardiogram or multigated acquisition scan in patients receiving PLD during the treatment period (and at the treating investigator's discretion at all other times).

Outcomes

The primary outcome measure was investigator-assessed PFS according to RECIST version 1·1, defined as the interval between randomisation and first documented disease progression or death, whichever occurred first. Secondary outcome measures included OS (defined as the interval between randomisation and death from any cause), biological PFS (assessed based on locally determined serum CA-125 levels according to GCIG criteria), quality of life (QoL), safety, and tolerability. Exploratory subgroup analyses of PFS according to randomisation stratification factors were prespecified.

Statistical analysis

The assumed median PFS with carboplatin/gemcitabine/bevacizumab was 12·4 months (based on the OCEANS trial[8]). Assuming randomisation of 654 patients recruited over 30 months with a further 30 months' follow-up, the trial would provide 80% power with a two-sided log-rank test at 5% significance to detect a 27% improvement in median PFS from 12·4 to 15·7 months (hazard ratio [HR] 0·79). Based on these assumptions, a total of 564 PFS events was anticipated at the time of the primary PFS analysis. Statistical results reported for OS and further secondary endpoints are exploratory (not corrected for multiple testing).

Efficacy data were analysed in the intention-to-treat population, defined as all randomised patients irrespective of whether they received treatment. PFS was compared between the two treatment arms using a stratified log-rank test at a two-sided 5% significance level, stratified by the factors used for randomisation. OS was analysed similarly. Median PFS and OS were estimated using Kaplan-Meier estimates with corresponding 95% confidence intervals (CIs). HRs were assessed using a stratified Cox regression analysis with corresponding 95% CIs for the HR ratio point estimate. Exploratory univariable subgroup analyses according to prognostically relevant predefined randomisation strata were analysed by Cox regression models. Exploratory multivariable Cox regression analyses were calculated to assess potential interactions between treatment arms and predefined randomisation strata. The assumption of proportional hazards for the Cox models was assessed according to the method described by Lin et al.[15] A post hoc exploratory sensitivity analysis excluding patients who received bevacizumab after progression (date of tumour assessment) was done to investigate potential impact on the outcome of the primary PFS analysis. Health-related quality of life was assessed using the QLQ-C30 and according to the scoring manual.[16] The summary score of the QLQ-C30 was calculated using the r-package QoLR.[17] The prespecified statistical analysis used a linear mixed-model analysis including study centre as a random effect, main effects for group and time, a group-by-group interaction term, and a generalised covariance matrix to account for serial dependency among observations to assess mean change over time from baseline every 3 months descriptively. Safety analyses were based on the safety population, comprising all patients who received at least one dose of study drug. There were no planned interim analyses. Statistical analyses were done using SAS version 9.4.

This trial is registered with ClinicalTrials.gov number NCT01837251.

Role of the funding source

The trial was performed according to ENGOT model A.[18] The sponsor (AGO Study Group, represented by the first author) was responsible for writing the report with the support of a medical writer. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JP and JR had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between August 1, 2013, and July 31, 2015, 682 patients were enrolled from 161 sites in Europe, Australia, and New Zealand; 682 were randomised (337 to standard therapy and 345 to the experimental arm), representing the intention-to-treat population, and 661 received study treatment, representing the safety population (figure 1). No patients were deemed ineligible. After completion of chemotherapy, 256 (78%) of 329 patients and 225 (68%) of 332 patients, respectively, continued bevacizumab as maintenance therapy. Baseline characteristics were generally well balanced with no relevant differences between treatment arms (table 1). Almost half of the patients (161 of 337 [48%] in the standard arm, 163 of 345 [48%] in the experimental arm had previously been treated with anti-angiogenic therapy, typically bevacizumab.

At the data cutoff for the final analysis (July 10, 2018), all but 20 patients (3%; 5 of 337 [1%] in the standard arm *vs* 15 of 345 [4%] in the experimental arm) had stopped all study treatments per protocol. Details of treatment exposure are presented in table 2.

In total, 84 of 661 treated patients (13%; 46 of 329 [14%] in the standard arm and 38 of 332 [11%] in the experimental arm) received bevacizumab after disease progression. The median duration of post-progression bevacizumab exposure was 20·5 days in both arms (IQR 7–424 with carboplatin/gemcitabine/bevacizumab and 5–385 with carboplatin/PLD/bevacizumab). A sensitivity analysis excluding these 84 patients did not

alter the conclusion for PFS (hazard ratio 0·81, 95% CI 0·67–0·97) or OS (hazard ratio 0·81; 95% CI, 0·66–0·99).

Median follow-up for PFS was 12·4 (IQR 8·3–21·7) months in the carboplatin/PLD/bevacizumab group and 11·3 (IQR 8·0–18·4) months in the carboplatin/gemcitabine/bevacizumab group. At the data cutoff, PFS events had been recorded in 571 patients (84%) (294 of 337 [87%] receiving carboplatin/gemcitabine/bevacizumab, 277 of 345 [80%] receiving carboplatin/PLD/bevacizumab). There was no indication that the proportional hazard assumption of the Cox regression models for PFS or OS had been violated (Supplementary Appendix, page 7). The HR for PFS was 0·81 (95% CI 0·68–0·96; stratified log-rank p=0·012) (figure 2A). Median PFS was 11·6 (95% CI 11·0–12·7) months with carboplatin/gemcitabine/bevacizumab and 13·3 (95% CI 11·7–14·2) months with carboplatin/PLD/bevacizumab.

Median follow-up for OS was 27·8 (IQR 15·6–36·8) months in the carboplatin/PLD/bevacizumab group and 25·5 (IQR 14·5–35·5) months in the carboplatin/gemcitabine/bevacizumab group. After 439 deaths (64%; 232 [69%] of 337 in the standard arm, 207 [60%] of 345 in the experimental arm), the OS HR was 0·81 (95% CI 0·67–0·98). Median OS was 27·8 (95% CI 25·5–30·2) months with standard therapy versus 31·9 (95% CI 28·5–34·8) months with experimental therapy (figure 2B). A similar effect to that observed for PFS was seen for biological PFS. After events in 583 patients (300 of 337 [89%] *vs* 283 of 345 [82%] in the standard *vs* experimental arms, respectively), median biological PFS was 10·0 (95% CI 9·0–10·7) months with standard therapy versus 11·5 (95% CI 10·6–12·5) months with experimental therapy (Supplementary Appendix, page 9). The HR was 0·76 (95% CI 0·64–0·90).

Univariable subgroup analyses of PFS favoured the experimental arm with respect to the HR point estimate in prognostically relevant predefined exploratory subgroups (figure 3A). In 470

patients with a platinum-free interval of >12 months, the HR was 0·81 (95% CI 0·66–0·99; median 14·0 [95% CI 11·8–15·9] months in the standard arm versus 14·9 [95% CI 13·6–17·1] months in the experimental arm). In 309 patients previously treated with anti-angiogenic therapy, the HR was 0·73 (95% CI 0·57–0·94); median 10·1 [95% CI 8·5–11·2] months with experimental therapy versus 11·3 [95% CI 10·1–13·8] months with standard therapy). Univariable subgroup analyses of the secondary endpoint OS are shown in figure 3B.

Compliance with QoL assessment was high at baseline (91% in the standard arm *vs* 86% in the experimental arm) and showed similar attrition over time in the two treatment arms. Mean global health status peaked at month 3 in the standard group and month 6 in the experimental group, showing a minor difference (not clinically relevant) favouring experimental therapy at month 6. Thereafter, mean score declined to below baseline levels in both treatment groups (Supplementary Appendix, page 10).

Almost all of the 661 treated patients experienced at least one adverse event during the study (319 of 329 [97·0%] of patients in the standard arm *vs* 327 of 332 [98·5%] in the experimental arm). Grade ≥3 adverse events were slightly more common with standard (267 of 329; 81·2%) than experimental (250 of 332; 75·3%) therapy. Ten patients had fatal adverse events: six (1·8%) in the standard arm (two cases of acute kidney injury, one case each of osmotic demyelination syndrome, intracranial haemorrhage, general physical health deterioration, and suicide) and four (1·2%) in the experimental arm (subileus, large intestine perforation, cardiac/renal failure, and disease-related general physical health deterioration), but of these, only three were considered treatment related (two [0·6%] of 329 patients receiving carboplatin/gemcitabine/bevacizumab [one case each of osmotic demyelination syndrome and intracranial haemorrhage] and one [0·3%] of 332 patients receiving carboplatin/PLD/bevacizumab [large intestine perforation]). Details of grade 3/4 adverse events and grade 1/2 adverse events in >10% of patients are provided in the Supplementary Appendix, page 4. Serious adverse events were reported in 28 (8·5%) of 329 patients in the

standard arm and 33 (9·9%) of 332 in the experimental arm. These serious adverse events were considered drug related in 24 (7·3%) of 329 and 32 (9·6%) of 332 patients, respectively. The most common treatment-related serious adverse events were pulmonary embolism (5/329 [2%] in the standard group *vs* 5/332 [2%] in the experimental group) and hypertensive crisis (3/329 [1%] vs 5/332 [2%], respectively). Adverse events led to treatment discontinuation in 78 (24%) of 329 patients in the standard group and 104 (31%) of 332 patients in the experimental group. Of these, adverse events were considered to be related to bevacizumab in 56 (17%) of 329 and 73 (22%) of 332 patients, respectively, most commonly hypertension (11/329 [3%] vs 22/332 [7%]), proteinuria (11/329 [3%] vs 18/332 [5%], and pulmonary embolism (2/329 [1%] vs 4/332 [1%], respectively). Incidences of grade ≥3 adverse events of special interest were similar in the two arms (149 of 329 [45·3%] *vs* 146 of 332 [44·0%] in the standard and experimental arms, respectively). Grade ≥3 thrombocytopenia was reported in more patients in the carboplatin/gemcitabine/bevacizumab group than the carboplatin/PLD/bevacizumab group. Blood transfusions were required in 52 of 329 (15·8%) and 38 of 332 (11·4%) of patients in the two groups, respectively. Only five patients (two [0·6%] in the control arm, three [0·9%] in the experimental arm) received G-CSF. Overall, 22 patients reported 47 episodes of hypersensitivity to carboplatin: 39 cases in 20 of 329 patients (6·1%) in the standard arm and 8 cases in 2 of 332 patients (<0·1%) in the experimental arm. Two isolated cases of hypersensitivity to gemcitabine were reported in two patients in the standard arm. There were no reports of hypersensitivity to PLD in the control arm.

Grade ≥3 neutropenia was more common with standard than experimental therapy but there was no difference in the incidence of febrile neutropenia (table 3). Grade ≥3 hypertension was less common in the standard arm. The incidences of grade ≥3 proteinuria and other typical bevacizumab adverse events were similar in the two treatment arms. Gastrointestinal perforation was rare.

Discussion

The trial met its primary objective, demonstrating significantly superior PFS with carboplatin/PLD/bevacizumab versus the carboplatin/gemcitabine/bevacizumab regimen established in the OCEANS trial.[8] To our knowledge, this is the first phase 3 trial comparing two bevacizumab-containing regimens in recurrent ovarian cancer. Furthermore, OS was significantly improved with PLD-containing therapy, with an increase in median OS of more than 4 months; while some may question the clinical meaningfulness of a 3-month median PFS advantage, improvement in OS represents the ultimate goal of treatment and a 4-month improvement in the recurrent setting is clinically meaningful. There was no clinically relevant difference in global health status between treatment arms.

Overall, the safety profile in both treatment arms was consistent with the known side effects of bevacizumab and the chemotherapy backbones. As expected, the gemcitabine-containing standard arm was associated with more grade ≥3 adverse events (81% *vs* 75% with PLD-containing therapy). However, grade 5 adverse events were infrequent in both arms (standard arm 1·8% *vs* experimental arm 1·2%). Qualitative differences included more frequent grade ≥3 neutropenia with carboplatin/gemcitabine/bevacizumab (22% *vs* 12% with carboplatin/PLD/bevacizumab) and more grade ≥3 thrombocytopenia (19% *vs* 10%) but less frequent grade ≥3 hypertension (21% *vs* 28%, respectively). Gastrointestinal perforations were rare in both arms and no new safety signals were observed.

Relative dose intensity and median treatment duration with bevacizumab for the standard arm are similar to those reported in the OCEANS[8] and AGO-OVAR2.5 trials.[4] The proportion of patients starting maintenance bevacizumab was higher in the standard arm (256 of 332 patients; 77%) than in the experimental arm (225 of 337 patients; 67%). A plausible explanation is the imbalance in cycle length, resulting in planned chemotherapy durations of 24 weeks for PLD/carboplatin versus 18 weeks for gemcitabine/carboplatin. Whether the duration of (perhaps more tolerable) induction chemotherapy contributes to the efficacy

benefit cannot be answered here; however, there was a clear PFS and OS benefit with the PLD-containing regimen. While we acknowledge the limitations of cross-trial comparisons, median PFS of 11·6 months in the standard arm is very similar to the assumptions used when designing the trial based on bevacizumab-containing therapy in OCEANS (12·4 months).[8]

Since AGO-OVAR2.21 was designed in 2012, polyADP ribose polymerase (PARP) inhibitors have become a standard of care in patients with recurrent ovarian cancer suitable for retreatment with platinum-based therapy. The PARP inhibitors olaparib, niraparib, and rucaparib are approved as maintenance therapy in patients with recurrent ovarian cancer after successful retreatment with platinum, and show the greatest effect in patients with *BRCA1/2*-mutated tumours.[19] Therefore the absence of a PARP inhibitor in either treatment arm in our trial is a limitation. In addition, the lack of information on *BRCA* mutation status in this trial is a weakness. Although *BRCA1/2* testing and PARP inhibition were not routinely available when this trial was designed, *BRCA1/2* testing is now recommended for all patients with non-mucinous ovarian cancer.[19] As well as guiding treatment decisions, knowledge of *BRCA* mutation status provides important prognostic information and may correlate with sensitivity to platinum and other chemotherapy agents.[20] Therefore any potential imbalance in *BRCA* mutation status between treatment arms in our trial could introduce unrecognised bias.

As the treatment landscape continues to evolve at a rapid pace and PARP inhibitors are used earlier in the treatment algorithm, the patient population enrolled in AGO-OVAR2.21 may become less representative of patients presenting in clinical practice in the future. Olaparib is already approved as monotherapy in the front-line maintenance setting based on results from the SOLO-1 trial,[21] and following positive results from the PAOLA-1[22] and PRIMA[23] trials, the use of PARP inhibitors in the front-line setting, alone or in combination with bevacizumab, is expected to increase further. Consequently, in the future, patients presenting with recurrent ovarian cancer, particularly those considered candidates for re-

exposure to platinum-based treatment, are likely to have received prior PARP inhibitor therapy.

The trial demonstrated a significant improvement in overall survival with the experimental regimen. However, the trial was not designed to estimate the impact of subsequent therapy after disease progression, and therefore potential imbalances in post-progression treatment, which may bias overall survival results, cannot be excluded. Moreover, although the trial has completed, a small number of patients (15 in the experimental arm, 5 in the control arm) remain on bevacizumab treatment and therefore the long-term effect of each regimen may not be fully captured in this final analysis.

AGO-OVAR 2.21 results support the design of the ongoing phase 3 ATALANTE/AGO-OVAR2.30 trial (NCT02891824) evaluating atezolizumab combined with bevacizumab-containing therapy in platinum-sensitive disease. The 'CALYPSO-bevacizumab' regimen evaluated here is one of the permitted backbone regimens in ATALANTE, alongside the OCEANS and GOG-0213 bevacizumab-containing regimens.

Overall, these results suggest that carboplatin/PLD/bevacizumab is a new standard regimen for patients with recurrent ovarian cancer suitable for platinum-based and anti-angiogenic treatment. This benefit is observed irrespective of prior anti-angiogenic therapy, expanding on findings from the randomised phase 3 MITO16b trial, which demonstrated significantly superior PFS with chemotherapy/bevacizumab re-treatment versus chemotherapy alone for platinum-sensitive recurrent ovarian cancer after front-line bevacizumab-containing therapy.[24]

Panel: Research in context

Evidence before this study

We searched PubMed for journal articles describing positive phase III trials in platinum-sensitive recurrent ovarian cancer published between 2001 and 2013 using the search terms

‘platinum-sensitive recurrent ovarian cancer’ and ‘phase III trial’. In addition to the ICON4/AGO-OVAR2.2 and AGO-OVAR2.5 phase III trials, which demonstrated superiority of a paclitaxel–platinum doublet and a gemcitabine–carboplatin doublet versus single-agent carboplatin, we identified two positive randomised phase III trials: the OCEANS placebo-controlled randomised phase III trial of bevacizumab in platinum-sensitive recurrent ovarian cancer, which demonstrated superior progression-free survival and objective response rate with the addition of bevacizumab to a gemcitabine/carboplatin chemotherapy doublet; and the CALYPSO randomised phase III trial, which demonstrated superior efficacy with a pegylated liposomal doxorubicin/carboplatin doublet compared with paclitaxel/carboplatin in platinum-sensitive recurrent ovarian cancer. We identified no additional positive phase III trials published when the AGO-OVAR2.21 trial was designed.

Added value of this study

In patients with recurrent ovarian cancer suitable for platinum-based retreatment, the approved chemotherapy regimens for use in combination with bevacizumab are gemcitabine/carboplatin (based on the OCEANS trial) and paclitaxel/carboplatin (based on the GOG-0213 trial). The present trial evaluates bevacizumab in combination with a more widely used, more active chemotherapy regimen, demonstrating superior efficacy and thus defining a new standard-of-care bevacizumab-containing regimen.

Implications of all the available evidence

These results suggest that carboplatin/PLD/bevacizumab is the new standard regimen for patients with recurrent ovarian cancer suitable for platinum-based and anti-angiogenic treatment. This regimen is a reasonable backbone for future immunotherapy-containing regimens in recurrent ovarian cancer.

Contributors

Trial conduct was performed by all authors, statistical analyses were performed by JR and were the responsibility of the Study Groups. JP wrote the manuscript supported by a medical writer funded by an unrestricted grant from F. Hoffmann-La Roche. All authors participated in manuscript development and finalisation, assume responsibility for the accuracy and completeness of the data, and vouch for the trial's fidelity to the protocol. All authors had full access to all study data; JP had final responsibility for the decision to submit for publication.

Declaration of interests

JP reports grants, personal fees, and non-financial support from F. Hoffmann-La Roche, during the conduct of the study; grants, personal fees and non-financial support from AstraZeneca and Tesaro outside the submitted work; personal fees and non-financial support from Amgen outside the submitted work; and personal fees from Clovis, MSD, and PharmaMar outside the submitted work. PH reports grants and personal fees from Roche during the conduct of the study; grants and personal fees from AstraZeneca, Tesaro, and Public funding bodies (ASCO, DKH, DFG) outside the submitted work; grants from GSK, Boehringer Ingelheim, Medac, and Genmab outside the submitted work; and personal fees from Sotio, Stryker, Zai Lab, MSD, Clovis, and Immunogen outside the submitted work. FJ reports personal fees and non-financial support from Roche; grants, personal fees, and non-financial support from AstraZeneca; personal fees and non-financial support from Tesaro; personal fees and non-financial support from BMS, MSD, Janssen, Ipsen, and Pfizer; and grants and personal fees from Astellas, all outside the submitted work. JS reports personal fees and other from Roche; grants and personal fees from Lilly; and personal fees from Johnson and Johnson, all outside the submitted work. UC reports personal fees from AstraZeneca, Roche, and Lilly, all outside the submitted work. FM reports personal fees and research funding from Roche during the conduct of the study; personal fees and research funding from AstraZeneca, Pfizer, Tesaro, and Novartis outside the submitted work; and

personal fees from Amgen, PharmaMar, Genomic Health, CureVac, Eisai, and Celgene outside the submitted work. AE-B reports personal fees from Roche, AstraZeneca, Tesaro, Clovis, PharmaMar, MSD, and Olympus outside the submitted work. RG reports personal fees and non-financial support from Roche, Clovis Oncology, Tesaro, and AstraZeneca outside the submitted work; personal fees from Immunogen, and Sotio outside the submitted work; grants from Boehringer Ingelheim and Lilly/Ignyta outside the submitted work; and site principal investigator roles for clinical trial run by Tesaro, AstraZeneca, Immunogen, and Lilly outside the submitted work. NdG reports personal fees and travel expenses for advisory boards from Tesaro, AstraZeneca, and Roche and personal fees for advisory boards from PharmaMar and Clovis, all outside the submitted work. SM reports grants and personal fees from AstraZeneca, Roche, and Tesaro and personal fees from Clovis during the conduct of the study; grants and personal fees from Medac, MSD, PharmaMar, and Teva outside the submitted work; and personal fees from Novartis, Olympus Europa, and Sensor Kinesis outside the submitted work. TMM reports a grant from Roche during the conduct of the study. T-WP-S reports reimbursement from AGO during the study conduct, and personal fees for lectures from Roche, AstraZeneca, and Tesaro outside the submitted work. AR reports research grants from Roche; speaker and advisory board honoraria from Amgen, AstraZeneca, MSD, PharmaMar, Roche, Tesaro, and Vifor Pharma; and travel expenses from Amgen, AstraZeneca, PharmaMar, Roche, and Tesaro outside the submitted work. JCG reports personal fees from AstraZeneca, MSD, Ipsen, Tesaro, MundiPharma; and sponsorship to attend international congresses from BMS, Astellas, and Roche, all outside the submitted work. SK reports personal fees from Roche, Tesaro, PharmaMar, Clovis, and AstraZeneca outside the submitted work. AdB reports personal fees for advisory boards from AstraZeneca, Tesaro, Clovis, Roche, Biocad, Pfizer, and Genmab outside the submitted work. J-EK reports personal fees and travel expenses for advisory boards from Tesaro and AstraZeneca, personal fees for advisory boards from PharmaMar and Clovis, and travel expenses from Roche outside the submitted work. CMS, KM, JR, BS, APD, AH, AGZ, LCH, TP, M-AM-R, CC, WM, TL'H, and SB-H have nothing to disclose.

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Data sharing statement

Currently no mechanism is in place to allow sharing of individual deidentified patient data. Requests sent to AGO Study Group, Kaiser-Friedrich-Ring 71, 65185 Wiesbaden, Germany, office-wiesbaden@ago-ovar.de, will be considered on a case-by-case basis.

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Table 1: **Baseline characteristics of the patients (all randomised patients)**

Characteristic		**Carboplatin/gemcitabine/bevacizumab (n=337)**	**Carboplatin/PLD/bevacizumab (n=345)**
Median age, years (range)		63 (23–85)	62 (25–80)
ECOG performance status	0	200 (59%)	225 (65%)
	1	130 (39%)	114 (33%)
	2	6 (2%)	5 (1%)
	Missing	1 (<1%)	1 (<1%)
Cytoreduction for recurrence		90 (27%)	92 (27%)
Residual tumour	Yes (no surgery for recurrence or surgery with residuals)	257 (76%)	260 (75%)

	No (surgery for recurrence with macroscopic complete resection)	80 (24%)	85 (25%)
Histological type/grade	High-grade serous	249 (74%)	258 (75%)
	Other	88 (26%)	87 (25%)
Platinum-free interval	6–12 months	105 (31%)	107 (31%)
	>12 months	232 (69%)	238 (69%)
Primary tumour type	Epithelial ovarian	298 (88%)	301 (87%)
	Primary peritoneal	25 (7%)	25 (7%)
	Fallopian tube	14 (4%)	19 (6%)
Previous anti-angiogenic treatment	Yes	161 (48%)	163 (48%)
	Bevacizumab	145 (43%)	138 (40%)
	Nintedanib	5 (1%)	15 (4%)
	Pazopanib	3 (1%)	2 (1%)
	Other (eg, trebananib)	8 (2%)	8 (2%)
	No	176 (52%)	182 (53%)

ECOG=denotes Eastern Cooperative Oncology Group, PLD=pegylated liposomal doxorubicin.

Table 2: **Summary of treatment exposure**

Exposure	**Carboplatin/gemcitabine/bevacizumab (n=332)**	**Carboplatin/PLD/bevacizumab (n=337)**
Bevacizumab mean relative dose intensity	(n=329)	(n=332)
Entire treatment period	93·8%	89·3%
Chemotherapy phase	92·2%	85·9%
Maintenance period	96·3%	96·6%
Bevacizumab treatment interruptions		
Entire treatment period	116 (35·3%)	230 (69·3%)
Chemotherapy phase	40 (12·2%)	195 (58·7%)
Maintenance phase	89 (27·1%)	86 (25·9%)
Median bevacizumab treatment duration, weeks	38	36

Bevacizumab administration for ≥12 months	101 (31%)	100 (30%)
Chemotherapy mean relative dose intensity	(n=332)	(n=337)
Carboplatin	91·1%	92·2%
Gemcitabine	77·5%	–
PLD	–	93·9%
Chemotherapy dose reductions		
Carboplatin	99 (30%)	73 (22%)
Gemcitabine	157 (48%)	–
PLD	–	61 (18%)

PLD=pegylated liposomal doxorubicin.

Table 3: **Summary of adverse events of special interest**

Adverse event of special interest	Carboplatin/gemcitabine/bevacizumab (n=329)	Carboplatin/PLD/bevacizumab (n=332)
Grade ≥3 neutropenia	73 (22%)	40 (12%)
Grade ≥3 febrile neutropenia	4 (1%)	3 (1%)
Grade ≥3 hypertension	68 (21%)	92 (28%)
Grade ≥3 proteinuria	22 (7%)	18 (5%)
Grade ≥3 venous thromboembolic event	9 (3%)	6 (2%)
Grade ≥3 congestive heart failure	5 (2%)	2 (1%)
Any-grade CNS bleeding	3 (1%)	4 (1%)
Any-grade fistula	3 (1%)	3 (1%)
Any-grade GI perforation	1 (<1%)	2 (1%)

Any-grade PRES	2 (1%)	1 (<1%)

CNS=denotes central nervous system, GI=gastrointestinal, PLD=pegylated liposomal doxorubicin, PRES=posterior reversible encephalopathy syndrome.

Figure legends

Figure 1: **Patient disposition**

Figure 2: **Kaplan-Meier estimates of (A) PFS and (B) OS in the intention-to-treat population**

CD-BEV=carboplatin/pegylated liposomal doxorubicin/bevacizumab, CG-BEV=carboplatin/gemcitabine/bevacizumab, CI=confidence interval, HR=hazard ratio, OS=overall survival, PFS=progression-free survival.

Figure 3: **Subgroup analyses of progression-free survival (intention-to-treat population)**

CD-BEV=carboplatin/pegylated liposomal doxorubicin/bevacizumab, CG-BEV=carboplatin/gemcitabine/bevacizumab, CI=confidence interval, HR=hazard ratio, PFI=platinum-free interval, PFS=progression-free survival.

Participating Investigators

The table below lists the lead investigator for each site that participated in this study.

Site	Country	Principal investigator	No. of patients randomised
Evang. Kliniken Essen-Mitte, Essen	Germany	Philipp Harter	34
Campus Virchow, Charité – Universitätsmedizin Berlin, Berlin	Germany	Jalid Sehouli	25
St. John of God Hospital, Subiaco	Australia	Andrew P Dean	18
Medical Faculty and University Hospital Carl Gustav Carus, Technical University Dresden, Dresden	Germany	Ulrich Canzler	16
Klinikum rechts der Isar, Technical University of Munich, Munich	Germany	Barbara Schmalfeldt	15
University Hospital Erlangen, Erlangen	Germany	Falk Thiel	12
Helios Dr Horst Schmidt Kliniken, Wiesbaden	Germany	Tanja Neunhöffer	12
University Women's Hospital Cologne	Germany	Peter Mallmann	11
University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck	Germany	Lars Hanker	11
Mater Cancer Care Centre, Brisbane	Australia	Catherine Shannon	9
Sir Charles Gairdner Hospital, Perth	Australia	Tarek Meniawy	9
Centre François Baclesse Caen, Caen	France	Florence Joly	9
Paul Strauss Cancer Center and Gynaecology Department, University of Strasbourg, Strasbourg	France	Thierry Petit	9
St. Vincenz-Krankenhaus, Paderborn	Germany	Wolfgang Meinerz	9
University of Frankfurt/Main, Frankfurt	Germany	Ahmed El-Balat	9
National Center for Tumor Disease, University of Heidelberg, Heidelberg	Germany	Frederik Marmé	9
Royal Brisbane & Women's Hospital, Brisbane	Australia	Jeffrey Goh	8
Klinikum der Stadt Ludwigshafen am Rhein, Ludwigshafen	Germany	Klaus Baumann	8
amO – Interdisziplinäres ambulantes Onkologiezentrum am Klieversberg, Wolfsburg	Germany	Clemens Liebrich	8
University Women's Hospital, Ulm	Germany	Wolfgang Janni	8
University Medical Center Hamburg-Eppendorf, Hamburg	Germany	Sven Mahner	8
Johannes Wesling Klinikum, Minden	Germany	Martin Griesshammer	8
Centre Jean Perrin, Clermont-Ferrand	France	Marie-Ange Mouret-Reynier	7
University Women's Hospital Tübingen, Tübingen	Germany	Eva-Maria Grischke	7
Medical University Hannover, Hannover	Germany	Tjoung-Won Park-Simon	7
Klinikum Mutterhaus, Trier	Germany	Rolf Mahlberg	7
Evangelisches Krankenhaus Düsseldorf, Düsseldorf	Germany	Werner Meier	7
Women's Health, Royal North Shore Hospital, Sydney	Australia	Sally Baron-Hay	6
Innsbruck Medical University, Innsbruck	Austria	Christian Marth	6
Department of Oncology, Hôpital Michallon, Grenoble	France	Cristina Costan	6
Centre Hospitalier Départemental les Oudairies, La Roche-sur-Yon	France	Tifenn L'Haridon	6
Marienhospital Stuttgart, Stuttgart	Germany	Manfred Hofmann	6
University Hospital Schleswig-Holstein, Campus Kiel, Kiel	Germany	Felix Hilpert	6
Gynäkologische Praxis Drs Uleer/Pourfard, Hildesheim	Germany	Christoph Uleer	6
Gynäkologisch-Onkologische Praxis Hannover, Hannover	Germany	Hans-Joachim Lück	6
Andrew Love Cancer Centre, Geelong	Australia	Inger Olesen	5
University Hospital for Gynaecology, Medical University Vienna, Vienna	Austria	Alexander Reinthaller	5
Centre Eugène Marquis, Rennes	France	Claudia Lafeuvre-Plesse	5
Hôpital Privé du Confluent, Nantes	France	Alain Lortholary	5
Medical Cancer, Hôpital Privé Villeneuve d'Ascq, Institut de Cancérologie, Villeneuve d'Ascq	France	Olivier Romano	5
ViDia Christliche Kliniken Karlsruhe, Karlsruhe)	Germany	Oliver Tomé	5
Ortenau-Klinikum Offenburg-Gengenbach, Offenburg	Germany	Matthias Frank	5
University Women's Hospital, Klinikum Südstadt, Rostock	Germany	Bernd Gerber	5
Agaplesion Markus Krankenhaus, Frankfurt	Germany	Marc Thill	5
DIAKO Ev. Diakonie-Krankenhaus, Bremen	Germany	Susanne Feidicker	5
Agaplesion Evangelisches Klinikum Schaumburg, Obernkirchen	Germany	Sabine Lemster	5
Klinikum Kulmbach, Kulmbach	Germany	Benno Lex	5
Praxis Dr Grafe, MVZ Nordhausen, Nordhausen	Germany	Andrea Grafe	5
University Hospital Essen, Essen	Germany	Martin Heubner	5
Gynäkologisch-Onkologische Gemeinschaftspraxis, Braunschweig	Germany	Ralf Lorenz	5
Gynaecology Department, Klinikum Darmstadt, Darmstadt	Germany	Sven Ackermann	5
Onkologie Ravensburg, Ravensburg	Germany	Martina Gropp-Meier	5
Beatson West of Scotland Cancer Centre, Glasgow	UK	Rosalind Glasspool	5
Ordensklinikum Linz, Barmherzige Schwester, Linz	Austria	Judith Lafleur	4
ICO Centre René Gauducheau, Saint Herblain	France	Dominique Berton-Rigaud	4
ORACLE – Centre d'Oncologie de Gentilly, Nancy	France	Célia Becuwe-Roemer	4
Centre Hospitalier Régional d'Orléans, Orleans	France	Jérôme Meunier	4
Centre Oscar Lambret, Lille	France	Anne Lesoin	4
University Hospital, Ludwig-Maximilian-University, Munich	Germany	Alexander Burges	4

Site	Country	Principal investigator	No. of patients randomised
Kreiskrankenhaus “Johann Kentmann”, Torgau	Germany	Simon Eike	4
Sana Klinikum Offenbach, Offenbach	Germany	Christian Jackisch	4
University Women’s Hospital, Medical University Graz, Graz	Austria	Edgar Petru	4
HELIOS Klinikum Berlin-Buch, Berlin	Germany	Antje Sperfeld	4
Klinikum Worms, Worms	Germany	Thomas Hitschold	4
Schwarzwald-Baar Klinikum Villingen-Schwenningen, Villingen	Germany	Wolfgang Bauer	4
University Hospital Mainz, Mainz	Germany	Marcus Schmidt	4
Florence-Nightingale-Krankenhaus, Kaiserswerther Diakonie, Düsseldorf	Germany	Björn Lampe	4
GYNAEKOLOGICUM Bremen, Bremen	Germany	Willibald Schröder	4
Klinikum Starnberg, Starnberg	Germany	Christoph Anthuber	4
Chris O’Brien Lifehouse, Camperdown	Australia	Philip Beale	3
St. George Hospital, Kogarah	Australia	Chee Lee	3
ICON Cancer Care Centre, Milton	Australia	Paul Vasey	3
North Coast Cancer Institute Port Macquarie, Port Macquarie	Australia	Stephen Begbie	3
Bankstown-Lidcombe Hospital, Bankstown	Australia	Sandra Harvey	3
CHRU de Strasbourg Hôpital Civil, Strasbourg	France	Jean-Emmanuel Kurtz	3
Hôpitaux Universitaires de Strasbourg, Strasbourg	France	Sophie Abadie-Lacourtoisie	3
Centre Hospitalier la Dracénie, Draguignan	France	Emmanuel Guardiola	3
Institute Daniel Holland, Groupe Hospitalier Mutualiste de Grenoble, Grenoble	France	C Garnier-Tixidré	3
Klinikum am Steinenberg, Reutlingen	Germany	Peter Krieger	3
Klinikum Hanau, Hanau	Germany	Thomas Müller	3
St. Elisabeth Krankenhaus Köln-Hohenlind, Cologne	Germany	Daniel Rein	3
Klinikum Frankfurt-Höchst, Frankfurt	Germany	Volker Möbus	3
Klinikum Chemnitz, Chemnitz	Germany	Petra Krabisch	3
Klinikum Kassel, Kassel	Germany	Gabriele Feisel-Schwickardi	3
Asklepios Klinik Lich, Lich	Germany	Alexandra Bender	3
Klinikum Bremen-Mitte, Bremen	Germany	Mustafa Aydogdu	3
Diakonie-Klinikum Schwäbisch Hall, Schwäbisch Hall	Germany	Andreas Rempen	3
Leopoldina-Krankenhaus, Schweinfurt	Germany	Michael Weigel	3
Städtisches Klinikum Dessau, Dessau	Germany	HermannVoß	3
Marienkrankenhaus, Hamburg	Germany	Gerhard Gebauer	3
Thüringen-Kliniken, Saalfeld	Germany	Dietrich Hager	3
Klinikum Konstanz, Konstanz	Germany	Andreas Zorr	3
Die Frauenarztpraxis in Grafin, Grafing	Germany	Isolde Gröll	3
Nambour General Hospital, Nambour	Australia	Mary Azer	2
Institut Paoli-Calmettes, Marseille	France	Maria Cappiello-Bataller	2
Clinique Armoricaine de Radiologie, St Brieuc	France	Anne-Claire Hardy-Bessard	2
Centre Hospitalier de Thonon-les-Bains, Thonon-les-Bains	France	Francesco Del Piano	2
Hôpital Antoine Béclère, Carmart	France	Sophie Barthier	2
Groupe Hospitalier Saint-Joseph, Paris	France	Gaël Deplanque	2
Polyclinique Bordeaux-Nord, Bordeaux	France	Nadine Dohollou	2
Hôpital de la Milétrie – Centre Hospitalier Universitaire de Poitiers – Pôle Régional de Cancérologie, Poitiers	France	Nadia Raban	2
Insitut d’Oncologie Hartmann, Levallois-Perret	France	Jean-Michel Vannetzel	2
CHR Metz-Thionville/Hôpital de Mercy, Metz	France	Raffaele Longo	2
Clinique Francheville, Périgueux	France	Charles-Briac Levache	2
Centre Catalan d’Oncologie, Perpignan	France	Stéphanie Catala	2
University Women’s Hospital Freiburg, Freiburg	Germany	Beate Rautenberg	2
Klinikum St. Marien, Amberg	Germany	Tanja Hauzenberger	2
Klinikum Esslingen, Esslingen	Germany	Thorsten Kühn	2
University Hospital Düsseldorf, Düsseldorf	Germany	Tanja Fehm	2
University Women’s Hospital Magdeburg, Magdeburg	Germany	Kerstin Wollschlaeger	2
Caritasklinikum St. Theresia, Saarbrücken	Germany	Mustafa Deryal	2
g.Sund Gynäkologisches Kompetenzzentrum, Stralsund	Germany	Carsten Hielscher	2
St. Vincenz-Krankenhaus, Limburg	Germany	Angelika Ober	2
University Hospital Mannheim, Mannheim	Germany	Axel Gerhardt	2
DIAKO Flensburg, Flensburg	Germany	Horst Ostertag†	2
University Hospital Jena, Jena	Germany	Ingo Runnebaum	2
Albertinen-Krankenhaus, Hamburg	Germany	Uwe Herwig	2
Lahn-Dill-Kliniken Wetzlar, Wetzlar	Germany	Ulrich Winkler	2
Praxisklinik Krebsheilkunde für Frauen, Berlin	Germany	Gülten Oskay-Özcelik	2
University Hospital Augsburg, Augsburg	Germany	Arthur Wischnik	2
Klinikum Kempten-Oberallgäu, Kempten)	Germany	Ricardo Felberbaum	2
University Hospital Greifswald, Greifswald	Germany	Antje Belau	2
Lukaskrankenhaus, Neuss	Germany	Hans-Joachim Koch	2

Site	Country	Principal investigator	No. of patients randomised
Klinikum Deggendorf, Donau-Isar-Kliniken, Deggendorf	Germany	Ronaldo Stuth	2
Heinrich-Braun-Klinikum Zwickau, Zwickau	Germany	Sabine Schnohr	2
Onkozentrum Dresden, Dresden	Germany	Steffen Dörfel	2
Auguste-Kranken-Anstalten, Bochum	Germany	Dirk Behringer	2
Klinikum Nürnberg, Nürnberg	Germany	Cosima Brucker	2
Praxis Dr med. WW Reiter, Viersen	Germany	Wilhelm Reiter	2
Schwerpunktpraxis Onkologie/Hämatologie, Bottrop	Germany	Carla Hannig	2
Hochtaunus-Kliniken, Bad Homburg	Germany	Dominik Denschlag	2
Kreisklinik Altötting-Burghausen, Altötting	Germany	Peer Hantschmann	2
Städtisches Klinikum Brandenburg, Brandenburg	Germany	Peter Ledwon	2
Onkologische Schwerpunktpraxis Lüneburg	Germany	Juliane Ebert	2
Velindre Cancer Centre, Cardiff	UK	Rachel Jones and Emma Hudson	2
NCCI – Coffs Harbour Health Campus, Coffs Harbour	Australia	Karen Briscoe	1
Gold Coast University Hospital, Southport	Australia	Marco Matos	1
Royal Hobart Hospital, Hobart	Australia	Allison Black	1
Peninsula Health – Frankston Hospital, Frankston	Australia	Yoland Antill	1
Centre Henri Becquerel, Rouen	France	Marianne Le Heurteur	1
Clinique Pasteur – ONCOSUD, Toulouse	France	Raymond Despax	1
Centre Hospitalier de Blois, Blois	France	Olivier Arsene	1
Centre Hospitalier de Cholet, Cholet	France	Alain Zannetti	1
Cancer Clinic, Institute Sainte-Catherine, Avignon	France	Julien Grenier	1
University Hospital Münster, Münster	Germany	Ludwig Kiesel	1
Marienhospital, Osnabrück	Germany	Götz Menke	1
Franziskus-Hospital Harderberg, Georgsmarienhütte	Germany	Trygve Daabach	1
Kliniken Südostbayern, Traunstein	Germany	Thomas Kubin	1
Rotkreuzklinikum Munich, Munich	Germany	Martin Pölcher	1
University Hospital Halle/Saale, Halle	Germany	Hans-Georg Strauß	1
HELIOS Kliniken Schwerin, Schwerin	Germany	Susanne Vogel	1
Klinikum Aschaffenburg-Alzenau, Aschaffenburg	Germany	Angelika Baldauf	1
Diakonie-Klinikum Jung-Stilling, Siegen	Germany	Volker Müller	1
Robert-Bosch-Krankenhaus, Stuttgart	Germany	Annette Steckkönig	1
Paracelsus-Klinik, Henstedt-Ulzburg	Germany	Tobias Zeiser	1
Johanniter-Krankenhaus, Evangelische Kliniken Bonn, Bonn	Germany	Yon-Dschun Ko	1
Kliniken des Landkreises Neumarkt, Neumarkt	Germany	Heinz Scholz	1
Klinikum Fürth, Fürth	Germany	Volker Hanf	1
Gynäkologische Praxis Dr med. Jürgen Terhaag Eggenfelden	Germany	Jürgen Terhaag	1

Supplementary Table S1: **Adverse events (grade 1–2 in >10% of patients, any grade ≥3).**

	Carboplatin/gemcitabine/bevacizumab (n=329)			Carboplatin/PLD/bevacizumab (n=332)		
Grade	**1–2**	**3**	**4**	**1–2**	**3**	**4**
Nausea	169 (51%)	8 (2%)	0	161 (48%)	12 (4%)	0
Fatigue	137 (42%)	11 (3%)	0	155 (47%)	10 (3%)	0
Hypertension	54 (16%)	66 (20%)	1 (<1%)	56 (17%)	88 (27%)	0
Anaemia	102 (31%)	32 (10%)	0	90 (27%)	32 (10%)	0
Constipation	110 (33%)	3 (1%)	0	111 (33%)	2 (1%)	0
Vomiting	73 (22%)	6 (2%)	0	84 (25%)	9 (3%)	0
Diarrhoea	64 (19%)	5 (2%)	0	78 (23%)	5 (2%)	0
Headache	70 (21%)	2 (1%)	0	79 (24%)	4 (1%)	0
Epistaxis	81 (25%)	2 (1%)	0	80 (24%)	2 (1%)	0
Proteinuria	48 (15%)	20 (6%)	2 (1%)	57 (17%)	18 (5%)	0
Dyspnoea	55 (17%)	8 (2%)	0	64 (19%)	10 (3%)	0
Palmar-plantar erythrodysaesthesia syndrome	5 (2%)	0	0	58 (17%)	7 (2%)	0
Thrombocytopenia	35 (11%)	30 (9%)	32 (10%)	29 (9%)	20 (6%)	13 (4%)
Neutropenia	30 (9%)	51 (16%)	22 (7%)	19 (6%)	33 (10%)	7 (2%)
Mucosal inflammation	38 (12%)	0	0	56 (17%)	3 (1%)	0
Alopecia	81 (25%)	0	1 (<1%)	59 (18%)	0	0
Stomatitis	41 (12%)	1 (<1%)	0	56 (17%)	0	0
Platelet count decreased	21 (6%)	15 (5%)	18 (5%)	27 (8%)	13 (4%)	13 (4%)
Abdominal pain	55 (17%)	7 (2%)	0	41 (12%)	10 (3%)	0
Urinary tract infection	50 (15%)	4 (1%)	0	43 (13%)	5 (2%)	0
Arthralgia	34 (10%)	3 (1%)	0	42 (13%)	0	0
Peripheral sensory neuropathy	32 (10%)	2 (1%)	0	34 (10%)	5 (2%)	0
Decreased appetite	24 (7%)	1 (<1%)	0	38 (11%)	1 (<1%)	0
Nasopharyngitis	30 (9%)	0	0	35 (11%)	0	0
Neutrophil count decreased	13 (4%)	26 (8%)	11 (3%)	12 (4%)	16 (5%)	6 (2%)
Leucopenia	23 (7%)	21 (6%)	1 (<1%)	21 (6%)	8 (2%)	0
Dizziness	19 (6%)	2 (1%)	0	27 (8%)	0	0
Pyrexia	25 (8%)	2 (1%)	0	24 (7%)	2 (1%)	0
Back pain	42 (13%)	1 (<1%)	0	24 (7%)	0	0
Asthenia	31 (9%)	1 (<1%)	0	20 (6%)	4 (1%)	0
Pain	12 (4%)	2 (1%)	0	19 (6%)	3 (1%)	0
White blood cell count decreased	22 (7%)	11 (3%)	1 (<1%)	14 (4%)	5 (2%)	0
Oedema	8 (2%)	3 (1%)	0	17 (5%)	1 (<1%)	0
General physical health deterioration	10 (3%)	6 (2%)	2 (1%)*	12 (4%)	4 (1%)	1 (<1%)*
Alanine aminotransferase increased	11 (3%)	5 (2%)	0	11 (3%)	2 (1%)	0
Aspartate aminotransferase increased	11 (3%)	1 (<1%)	0	9 (3%)	3 (1%)	0
Unevaluable event	8 (2%)	2 (1%)	0	12 (4%)	0	0
Pleural effusion	7 (2%)	2 (1%)	0	4 (1%)	7 (2%)	0
Ileus	2 (1%)	2 (1%)	0	6 (2%)	2 (1%)	2 (1%)
Subileus	6 (2%)	4 (1%)	0	5 (2%)	4 (1%)	1 (<1%)
Device-related infection	2 (1%)	4 (1%)	0	4 (1%)	6 (2%)	0
Sinusitis	8 (2%)	2 (1%)	0	8 (2%)	1 (<1%)	0

	Carboplatin/gemcitabine/bevacizumab (n=329)			Carboplatin/PLD/bevacizumab (n=332)		
Grade	**1–2**	**3**	**4**	**1–2**	**3**	**4**
Hyperkalaemia	4 (1%)	1 (<1%)	0	6 (2%)	1 (<1%)	1 (<1%)
Hypertonia	1 (<1%)	1 (<1%)	0	3 (1%)	5 (2%)	0
Gamma glutamyltransferase increased	3 (1%)	2 (1%)	1 (<1%)	5 (2%)	3 (1%)	0
Pulmonary embolism	3 (1%)	6 (2%)	0	3 (1%)	3 (1%)	1 (<1%)
Infection	4 (1%)	0	0	5 (2%)	2 (1%)	0
Pneumonia	1 (<1%)	3 (1%)	0	3 (1%)	3 (1%)	0
Ascites	1 (<1%)	2 (1%)	0	3 (1%)	3 (1%)	0
Lymphopenia	1 (<1%)	2 (1%)	0	6 (2%)	0	0
Renal impairment	0	1 (<1%)	0	0	3 (1%)	2 (1%)*
Hypertensive crisis	2 (1%)	1 (<1%)	0	1 (<1%)	2 (1%)	2 (1%)
Blood creatinine increased	0	1 (<1%)	0	1 (<1%)	4 (1%)	0
Embolism	2 (1%)	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Intestinal obstruction	0	0	0	1 (<1%)	3 (1%)	0
Hypoacusis	3 (1%)	0	0	2 (1%)	2 (1%)	0
Haematuria	3 (1%)	0	0	2 (1%)	2 (1%)	0
Chronic kidney disease	3 (1%)	0	0	2 (1%)	2 (1%)	0
Drug hypersensitivity	14 (4%)	5 (2%)	1 (<1%)	3 (1%)	1 (<1%)	0
Pelvic pain	3 (1%)	2 (1%)	0	4 (1%)	0	0
Acute kidney injury	1 (<1%)	0	2 (1%)†	4 (1%)	0	0
Nephrotic syndrome	0	0	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Febrile neutropenia	0	3 (1%)	1 (<1%)	0	3 (1%)	0
Hyperglycaemia	2 (1%)	1 (<1%)	0	0	3 (1%)	0
Large intestinal obstruction	0	0	0	1 (<1%)	2 (1%)	0
Haemoglobin decreased	6 (2%)	0	0	1 (<1%)	2 (1%)	0
Impaired healing	4 (1%)	2 (1%)	0	2 (1%)	1 (<1%)	0
Urinary tract obstruction	1 (<1%)	3 (1%)	0	3 (1%)	0	0
Large intestine perforation	0	0	0	0	0	2 (1%)*
Pancytopenia	3 (1%)	5 (2%)	0	0	0	2 (1%)
Device-related sepsis	0	0	0	0	0	2 (1%)
Cardiac failure	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)*
Hyponatraemia	1 (<1%)	4 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Anal abscess	0	0	0	0	2 (1%)	0
Infusion-related reaction	4 (1%)	2 (1%)	0	2 (1%)	0	0
Syncope	2 (1%)	2 (1%)	0	0	1 (<1%)	0
Sepsis	0	0	2 (1%)	0	1 (<1%)	0
Posterior reversible encephalopathy syndrome	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0
Confusional state	1 (<1%)	3 (1%)	0	1 (<1%)	0	0
Lymphocyte count decreased	2 (1%)	2 (1%)	0	1 (<1%)	0	0
Intervertebral disc protrusion	1 (<1%)	2 (1%)	0	1 (<1%)	0	0
Hepatic enzyme increased	1 (<1%)	2 (1%)	0	1 (<1%)	0	0
Neutrophil count	2 (1%)	2 (1%)	0	0	0	0
Dental caries	1 (<1%)	2 (1%)	0	0	0	0
Myocardial infarction	0	0	2 (1%)	0	0	0

PLD=pegylated liposomal doxorubicin.

*Includes one case at grade 5. †Includes two cases at grade 5.

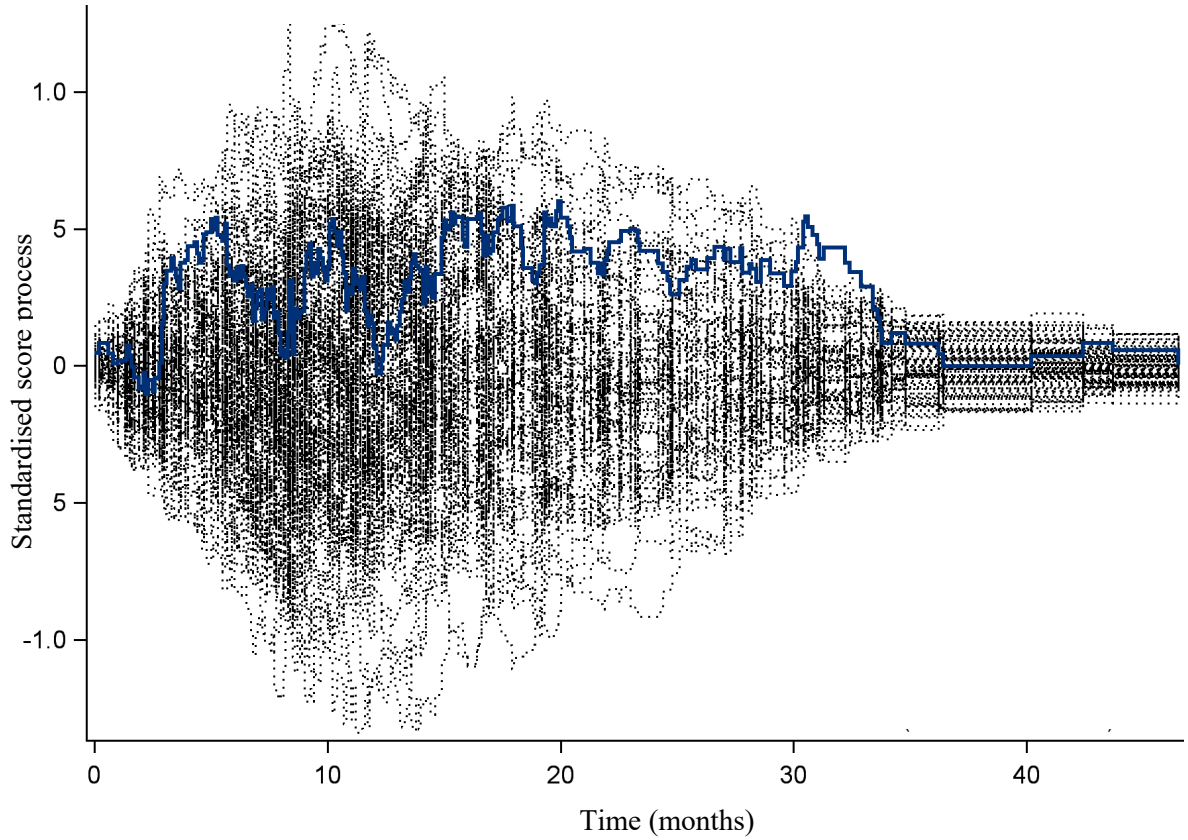
In addition, in the carboplatin/gemcitabine/bevacizumab arm there was: one grade 5 case each of suicide, osmotic demyelination syndrome neoplasm progression, and haemorrhage intracranial; one grade 4 case each of parainfluenzae virus infection, lung disorder, jaundice, haematotoxicity, brain oedema, and acute coronary syndrome; and one grade 3 case each of transaminases increased, tooth infection, spinal fracture, pyelonephritis, osteonecrosis of the jaw, malnutrition, hypoalbuminaemia, hypersensitivity, hydronephrosis, flank pain, cerebrovascular accident, vision blurred, urostomy complication, urinary fistula, tooth extraction, thyroid cancer, thrombophlebitis, tendon rupture, tachycardia, strangulated hernia, splenic infarction, small intestinal obstruction, skin ulcer, sinus node dysfunction, renal colic, presyncope, pain in extremity, neuropathy peripheral, migraine, lumbar vertebral fracture, kidney infection, intestinal perforation, infectious pleural effusion, incisional hernia, hypomagnesaemia, hyperbilirubinaemia, herpes zoster infection, hernia, hepatotoxicity, hepatic pain, haemorrhage, haematoma, gastrointestinal pain, gastrointestinal obstruction, gastrointestinal haemorrhage, gallbladder cancer, flushing, female genital tract fistula, fall, endocarditis, dysphonia, disease progression, diabetic ketoacidosis, depression, cystitis, computerised tomogram, coagulopathy, cellulitis, cell death, bone pain, blood disorder, bile duct stone, atrioventricular block, arterial occlusive disease, anxiety, angina unstable, allergic transfusion reaction, agitation, acute myocardial infarction, abdominal pain lower, and abdominal abscess.

In the carboplatin/PLD/bevacizumab arm there was: one grade 4 case each of cerebrovascular accident, staphylococcal bacteraemia, myelodysplastic syndrome, haemorrhagic stroke, gait disturbance, and fistula; and one grade 3 case each of transaminases increased, tooth infection, spinal fracture, pyelonephritis, osteonecrosis of the jaw, malnutrition, hypoalbuminaemia, hypersensitivity, hydronephrosis, flank pain, wound infection, vertigo, venous thrombosis, urinary tract stoma complication, urinary tract disorder, toothache, tooth development disorder, thrombotic microangiopathy, thoracic vertebral fracture, tension, surgery, subcutaneous abscess, small intestinal haemorrhage, seizure, retinal detachment, retinal artery embolism, renal artery stenosis, rectal haemorrhage, polyneuropathy, plantar fasciitis, pain in jaw, overdose, osteoarthritis, oesophagitis, myocardial strain, muscular weakness, mouth haemorrhage, metastases to meninges, libido decreased, lethargy, knee operation, insomnia, influenza-like illness, hypotension, hepatitis toxic, hemiparesis, hemianopia, haematochezia, groin abscess, granulocyte count decreased, gastrointestinal disorder, extravasation, enteritis infectious, embolism venous, dysphagia, dry skin, diaphragmatic hernia, diabetes mellitus, depressed mood, dehydration, cough, colostomy, circulatory collapse, cholelithiasis, chest pain, cerebral haemorrhage, central venous catheterisation, central venous catheter removal, campylobacter gastroenteritis, cachexia, C-reactive protein increased, bronchitis, breast abscess, brain stem haemorrhage, blood pressure increased, blood alkaline phosphatase increased, atrial fibrillation, anal fistula, acute abdomen, acidosis, abscess, abdominal wound dehiscence, and abdominal pain upper.

Supplementary Figure S1: **Proportional hazards**

Plots of the standardised score process against time for (A) the primary endpoint of PFS and (B) the secondary endpoint of OS for each of the observed and the first 100 simulated paths. Comparison of the observed and simulated paths of the martingale residual process did not indicate violations of the proportional hazard assumption of the stratified cox regression models according to the methods of Lin, Wei, and Ying.[1] The supremum tests for proportional hazard assumption were non-significant for both PFS (p=0.79, giving 0.6 for the maximum absolute value of the residuals) and OS (p=0.18, giving 1.05 for the maximum absolute value of the residuals). Overall, the observed processes of PFS/OS did not seem to be unusual compared with the simulated realisations. OS=overall survival. PFS=progression-free survival.

A



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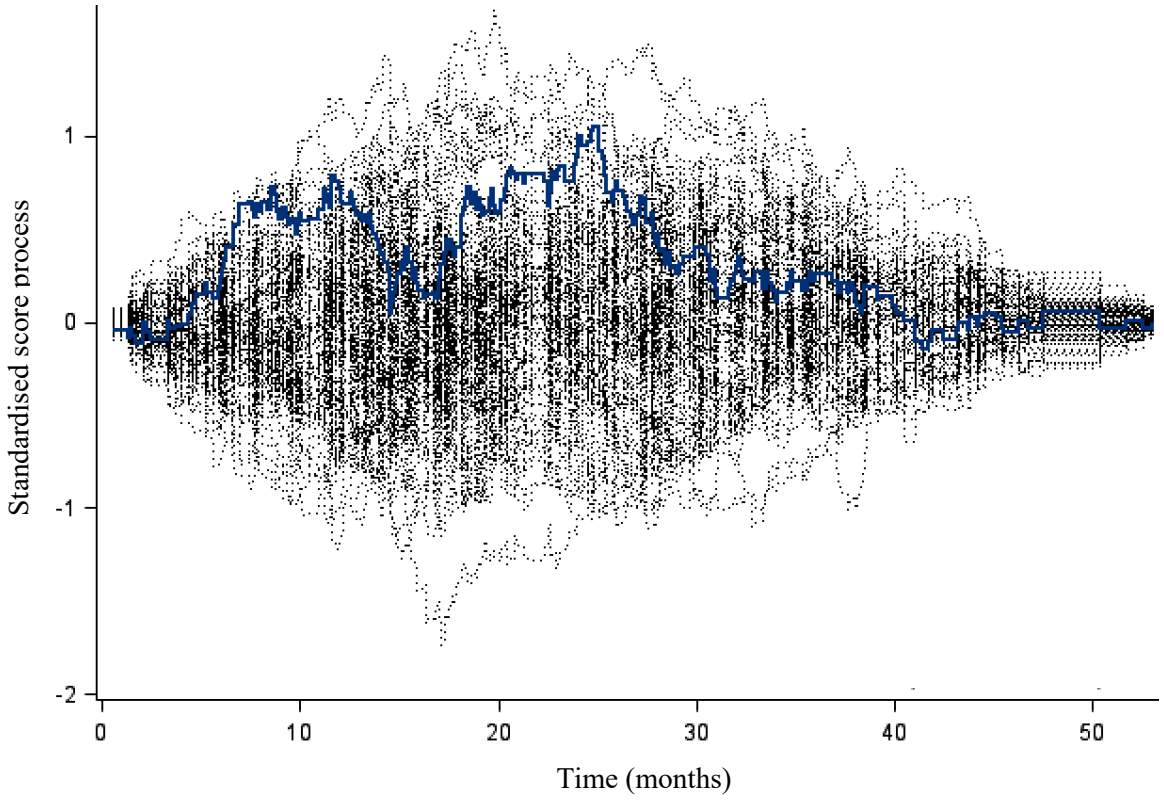
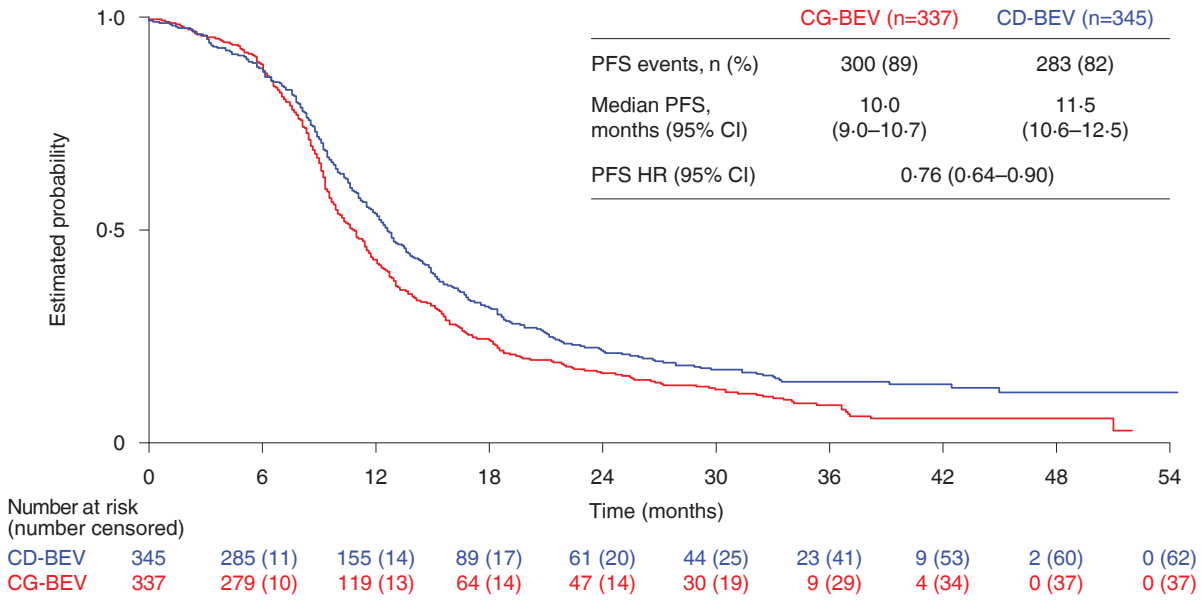


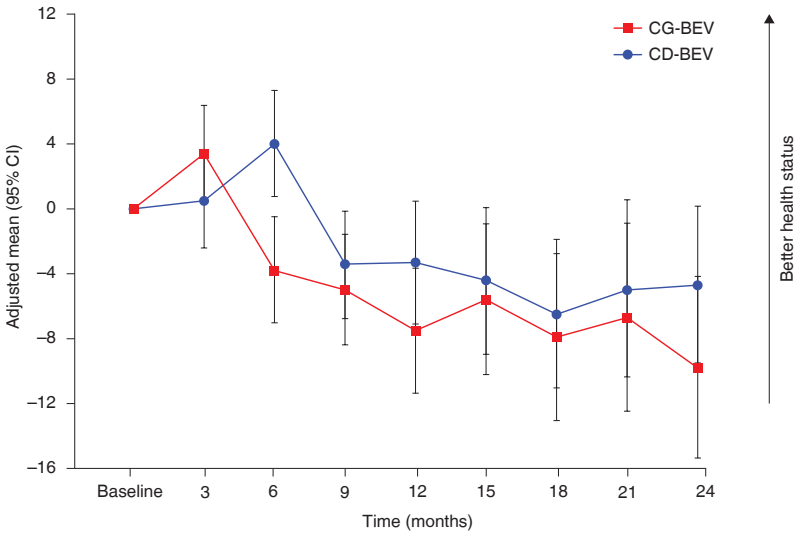
Supplementary Figure S2: **Biological PFS in the intention-to-treat population**

CD-BEV=carboplatin/pegylated liposomal doxorubicin/bevacizumab.
CG-BEV=carboplatin/gemcitabine/bevacizumab. CI=confidence interval. HR=hazard ratio. PFS=progression-free survival.



Supplementary Figure S3: **Quality of life (QLQ-C30 global health status)**

CD-BEV=carboplatin/pegylated liposomal doxorubicin/bevacizumab.
CG-BEV=carboplatin/gemcitabine/bevacizumab. CI=confidence interval. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module.



No. at risk, n (%)									
CD-BEV	298 (86)	252 (73)	200 (58)	152 (44)	113 (33)	75 (22)	59 (17)	36 (10)	32 (9)
CG-BEV	306 (91)	237 (70)	200 (59)	140 (42)	105 (31)	70 (21)	45 (13)	32 (10)	21 (6)

Reference

1. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; **80:** 557–72.

A prospective randomized Phase III trial of carboplatin/gemcitabine/bevacizumab vs. carboplatin/pegylated liposomal doxorubicin/bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. An ENGOT/GCIG Trial.

AGO-OVAR 2.21 / ENGOT-ov 18

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GLOSSARY OF ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AGO-OVAR	Arbeitsgemeinschaft Gynaekologische Onkologie-Studiengruppe Ovarialkarzinom
ALT (SGPT)	Alanine Aminotransferase
A()PTT	Activated ProThrombin Time
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase
ATE	Arterial Thromboembolic Event
AUC	Area Under the plasma Concentration-time curve
BC	Breast Cancer
BP	Blood Pressure
BR	Bilirubin
BSA	Body Surface Area
CA 125	Cancer Antigen 125
CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	maximum plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria: Adverse Events
CVA	Cerebrovascular Accident
CVAD	Central Venous Access Device
d	Day
dL	Decilitre
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENGOT	European Network of Gynaecological Oncological trial groups
EOC	Epithelial Ovarian Cancer
EORTC	European Organisation for Research and Treatment of Cancer
EPO	Erythropoetin
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FBC	Full Blood Count
FDA	U.S. Food and Drug Administration

GLOSSARY OF ABBREVIATIONS

FIGO	International Federation of Gynaecology and Obstetrics
FPI	First Patient In
FTC	Fallopian Tube Cancer
g	Gram
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GOG	Gynecologic Oncology Group
h/hrs	Hours
Hb	Hemoglobin
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICON	International Collaborative Ovarian Neoplasm
ID	Identification
IDMC	Independent Data Monitoring Committee
IgG	Immunglobuline G
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intent to Treat
i.v.	Intravenous
kg	Kilogram
KKS	Koordinierungszentrum für Klinische Studien
L	Liter
LD	Longest Diameter (RECIST)
LVEF	Left Ventricular Ejection Fraction
m^2	Square Metre
mBC	Metastatic Breast Cancer
mCRC	Metastatic Colorectal Cancer
mg	Milligram
min	Minute(s)
mL	Milliliter
mmHg	Millimeter of Mercury
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
muMAb	Murine Monoclonal Antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Inevaluable
NSCLC	Non Small Cell Lung Cancer
NYHA	New York Heart Association
OC	Ovarian Cancer
ORR / RR	Overall Response Rate
OS	Overall Survival

GLOSSARY OF ABBREVIATIONS

PET	Positron Emission Tomography
PD	Progressive Disease
PLD	Pegylated Liposomal Doxorubicin
PLT	Platelet
PFI	Platinum-free Interval
PFS	Progression-free Survival
PP	Per protocol
PPC	Primary Peritoneal Cancer
PPE	Palmar-plantar Erythrodysesthesia Syndrome
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Performance Status
PSC	Peritoneal Serous Cancer
QLQ / QoL	Quality of Life Questionnaire / Quality of Life
q4w	every 4 weeks
q3w	Three-weekly
q2w	Bi-weekly
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAH	Sub-arachnoid Hemorrhage
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SD	Stable Disease
SPC	Summary of Product Characteristics
SSL	Secure Sockets Layer
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water for Injection
TIA	Transient Ischemic Attack
TTP	Time To Disease Progression
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WNL	Within Normal Limits

TABLE OF CONTENTS

SYNOPSIS

TITLE	A prospective randomized Phase III trial of carboplatin/gemcitabine/bevacizumab vs. carboplatin/ pegylated liposomal doxorubicin/bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. An ENGOT/GCIG Trial.
SPONSOR	AGO Study Group AGO Research GmbH
INTERNATIONAL CHAIR	Prof. Dr. med. Jacobus Pfisterer, Wiesbaden, Germany
CLINICAL PHASE	III
INDICATION	Patients with first recurrence of epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinoma (PPC) and sensitive to platinum-based treatment regardless of FIGO stage, histological grades and types.
RATIONALE	Best standard of care treatment in patients with platinum-sensitive recurrence in ovarian cancer (OC) based on level I evidence are platinum-based combinations such as paclitaxel/carboplatin, gemcitabine/carboplatin and pegylated liposomal doxorubicin (PLD)/carboplatin and gemcitabine/carboplatin/bevacizumab. Bevacizumab has been shown single-agent activity in recurrent OC (single-arm studies), in upfront treatment in combination with carboplatin/paclitaxel and in platinum-sensitive recurrence. Today, more than 2600 patients with ovarian cancer were treated with bevacizumab in phase III trials [GOG 218, AGO-OVAR11/ICON7, AGO-OVAR2.15/AURELIA and OCEANS]. The treatment was well tolerated with a safety profile in line with that in other tumor types included in the Summary of Product Characteristics. It could be shown that chemotherapy in combination with bevacizumab was well tolerated. Especially, gastrointestinal perforations were not seen in the OCEANS trial. Chemotherapy with carboplatin/gemcitabine in combination with bevacizumab has a significant impact on PFS with a HR of 0.48. Additionally, there are phase II data of the combination of carboplatin/pegylated liposomal doxorubicin, showing that the combination is feasible. So far, carboplatin/pegylated liposomal doxorubicin was one of the options with the best therapeutic index for patients with platinum-sensitive recurrence and carboplatin/gemcitabine/bevacizumab has shown a dramatic improvement in PFS, the rationale of this clinical trial is to evaluate the best platinum-based regimen in combination with bevacizumab in platinum-sensitive recurrence. The question would be answered whether the addition of bevacizumab to pegylated liposomal doxorubi-

	cin/carboplatin is superior to bevacizumab combined with gemcitabine/carboplatin.
TRIAL DESIGN	Prospective, open-label, multinational, randomized, two-arm, superiority Phase III trial.
RANDOMIZATION	Random assignment in 1:1 ratio to the treatment arms. The stratification factors will be: ➢ platinum sensitive interval (6 -12 months vs. >12 months) ➢ in case of debulking surgery for recurrence: residual tumor (yes vs. no); (In case of no debulking surgery for recurrence all patients will be categorized as having residual tumor.) ➢ prior antiangiogenetic treatment (e.g. anti-VEGF; yes vs. no) ➢ group language
NUMBER OF PATIENTS	654 patients will be enrolled (327 per arm).
TARGET POPULATION	Adult female patients with epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC) with first platinum-sensitive recurrence, regardless of FIGO stage, histological grades and types.
OBJECTIVES	**Primary objective:** The primary efficacy outcome measure for this clinical trial is investigator-determined progression-free survival (PFS). **Secondary objectives:** • Overall Survival (OS) • Biological progression-free survival (PFS_{BIO}) by serum CA 125 assessed according to the GCIG criteria • Quality of Life (QoL) assessed by EORTC QLQ-C30 and QLQ-OV28 • Safety and Tolerability
INCLUSION CRITERIA	1. Signed written informed consent obtained prior to initiation of any trial-specific procedures and treatment as confirmation of the patients awareness and willingness to comply with the trial requirements. 2. Females aged ≥ 18 years. 3. Histologically confirmed diagnosis of • epithelial ovarian carcinoma (including mixed Mullerian tumors) or • fallopian tube carcinoma or

- primary peritoneal carcinoma.

All FIGO stages, histological grades and types are allowed.

4. First disease recurrence > 6 months after first-line platinum-based chemotherapy, no prior chemotherapy in the recurrent setting is allowed. Patients must have stopped any 1st line maintenance treatment with any type of anticancer treatment including bevacizumab at least 30 days prior randomization.
5. Patients with measurable or non-measurable disease (according to RECIST v1.1) or CA 125 assessable disease (according to GCIG criteria) or histological proven diagnosis of relapse.
6. In case of cytoreductive surgery for recurrence, patients must be able to commence cytotoxic chemotherapy within 8 weeks after cytoreductive surgery. The first dose of bevacizumab can be omitted in both arms if the investigator decides to start chemotherapy within 4 weeks after debulking surgery for recurrent disease.
7. ECOG performance status (PS) 0-2.
8. Life expectancy > 3 months.
9. Adequate bone marrow function (within 28 days prior to randomization)
    - Absolute Neutrophil Count (ANC) $\geq$ 1.5 x 10^9/L
    - Platelets (PLT) $\geq$ 100 x 10^9/L
    - Hemoglobin (Hb) $\geq$ 9.5 g/dL (Hemoglobin may be supported by transfusion or erythropoietin or other approved hematopoietic growth factors.)
10. Adequate coagulation parameters (within 28 days prior to randomization)
    - Patients not receiving anticoagulant medication who have an International Normalized Ratio (INR) $\leq$ 1.5 and an Activated ProThrombin Time (aPTT) $\leq$ 1.5 x ULN

      (The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to institution medical standard) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of randomization.)
11. Adequate liver function (within 28 days prior to randomization)
    - Serum bilirubin (BR) $\leq$ 2 x ULN

- Serum transaminases ≤ 2.5 x ULN (≤ 5 x ULN in the presence of liver metastasis)

12. Adequate renal function (within 28 days prior to randomization)

    - Serum creatinine < 1.6 mg/dL or creatinine clearance ≥ 40 mL/min
    - Glomerular filtration rate (GFR) > 40 ml/min (estimates based on the Cockroft-Gault or Jelliffe formula are sufficient)
    - Urine dipstick for proteinuria < 2+. If urine dipstick is ≥ 2+, 24 hour urine collection must demonstrate < 1 g of protein in 24 hours.

13. Normal blood pressure or adequately treated and controlled hypertension (neither systolic BP ≤ 140 mmHg and/nor diastolic BP ≤ 90 mmHg).

EXCLUSION CRITERIA

Disease-related

1. Non-epithelial origin of the ovary, the fallopian tube or the peritoneum (i.e. germ cell tumors).
2. Ovarian tumors of low malignant potential (i.e. borderline tumors)
3. Malignancies other than ovarian cancer within 5 years prior to randomization, except for adequately treated
    - carcinoma in situ of the cervix
    - and/or basal cell skin cancer
    - and/or non-melanomatous skin cancer
    - and/or carcinoma in situ of the breast
    - and/or endometrial carcinoma (FIGO stage ≤ IA).

    Patients may have received previous adjuvant chemotherapy for other malignancies e.g. breast or colorectal carcinoma if diagnosed over 5 years ago before randomization with no evidence of subsequent recurrence.

Prior, current or planned treatment

4. Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted as are steroidal antiemetics).
5. Any previous radiotherapy to the abdomen or pelvis.
6. Treatment with any other investigational agent, or participation in another clinical trial testing a drug within

the past 30 days before randomization.

7. Known hypersensitivity to used chemotherapeutic agents in this trial and bevacizumab and its excipients, chinese hamster ovary cell products or other recombinant human or humanised antibodies.
8. Current or recent (within 10 days prior to randomization) chronic use of aspirin > 325 mg/day.
9. Surgery (including open biopsy) within 4 weeks prior to anticipated first dose of bevacizumab (allowing for the fact that bevacizumab can be omitted for the first cycle of chemotherapy). It is strongly recommended that an interval of 7 days is left between the insertion of any central venous access devices (CVADs) and the onset of bevacizumab treatment.
10. Any planned surgery during the treatment period plus 4 additional weeks to allow for bevacizumab clearance.

Prior or concomitant conditions or procedures

11. History of VEGF therapy related abdominal fistula or gastrointestinal perforation.
12. Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease.
13. Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
14. Previous Cerebro-Vascular Accident (CVA), Transient Ischaemic Attack (TIA) or Sub-Arachnoid Haemorrhage (SAH) within 6 months prior to randomization.
15. Prior history of hypertensive crisis or hypertensive encephalopathy. Uncontrolled hypertension (sustained elevation of neither systolic blood pressure > 140 mmHg and / nor diastolic >90 mmHg despite antihypertensive therapy).
16. Clinically significant (i.e. active) cardiovascular disease, including:
    - myocardial infarction or unstable angina within ≤ 6 months of randomization
    - New York Heart Association (NYHA) ≥ grade 2 Congestive Heart Failure (CHF)
    - poorly controlled cardiac arrhythmia despite medication (patients with rate-controlled atrial fibrillation are eligible)
    - peripheral vascular disease grade ≥ 3 (i.e. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision).
17. Left ventricular ejection fraction (LVEF) defined by ECHO/MUGA below the institutional lower limit of normal.

18. Significant traumatic injury during 4 weeks prior to randomization.
19. Current brain metastases or spinal cord compression. CT/MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression.
20. History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy, e.g. uncontrolled seizures.
21. Non-healing wound, active ulcer or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require 3 weekly wound examinations.
22. History or evidence of thrombotic or hemorrhagic disorders within 6 months prior to randomization.
23. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic coagulation).
24. Fertile woman of childbearing potential not willing to use adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for the duration of the trial and at least 6 months afterwards.
25. Pregnant or lactating women.
26. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
27. Requirement of therapeutic anticoagulation using marcumar, warfarin or PTT-prolonging heparin.

INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ ROUTINE/ REGIMEN	This trial consists of 2 treatment arms with chemotherapy plus bevacizumab until protocol defined disease progression or further reason for treatment discontinuation (i.e. intolerable toxicity, withdrawal consent and others). Patients will be randomly assigned (1:1) to either arm. <u>Arm 1 (standard arm, q3w):</u> • Bevacizumab 15 mg/kg - d1 (until disease progression or unacceptable toxicity) • Gemcitabine 1000 mg/m^2 d1 + d8 for 6 cycles • Carboplatin AUC4 d1 for 6 cycles

	Arm 2 (experimental arm, q4w ⇒ q3w): • Bevacizumab 10 mg/kg. d1 +d15 q4w for 6 cycles • PLD 30 mg/m^2 d1 for 6 cycles • Carboplatin AUC5 d1 for 6 cycles In arm 2 bevacizumab (15mg/kg q3w) will be given as maintenance therapy until disease progression or unacceptable toxicity if chemotherapy treatment is finished. For arm 1 (standard arm (carboplatin/gemcitabine)) bevacizumab will be 'non-investigational drug' for those patients where it is standard of care in combination with gemcitabine and carboplatin and registered and reimbursed. Thus, bevacizumab will not be provided. For those patients in arm 1 where bevacizumab is not standard of care (e.g. prior anti-angiogenetic treatment) bevacizumab will be 'investigational drug'. Bevacizumab will be provided. Carboplatin in combination with gemcitabine is standard of care and will not be an 'investigational study drug' and will not be provided. For arm 2 (experimental arm (carboplatin/pegylated liposomal doxorubicin)) bevacizumab will be provided as 'investigational study drug'. Pegylated liposomal doxorubicin in combination with carboplatin is standard of care and will not be an 'investigational study drug' and will not be provided.
DURATION OF TRIAL	Recruitment: N=654 patients will be recruited into this clinical trial over a period of 30 months. Primary analysis will be done after 564 PFS events achieved. The analysis with respect to OS will be done after the last patient randomized has completed the 30 month follow-up.
ASSESSMENTS	***Efficacy*** Analysis of PFS: • Tumor assessments will include gynecological examination, including ultrasound scanning. Cross sectional imaging (by CT, or MRI in case of contrast allergy) of the pelvis and abdomen and (by X-ray or preferable by CT scan, evaluation based on RECIST v1.1) of the chest will be performed if clinically indicated. All subsequent follow-up scans should be the same modality. • Tumor assessments will be performed at screening

	and then every 12 weeks (starting before day 1 of cycle 1) until progressive disease or a minimum of 30 months, whatever occurs first. Patients will be classified as having measurable or non-measurable disease at screening and at each imaging visit (according to the local standard of care) conducted thereafter. Measurable tumors are to be assessed by RECIST v1.1 criteria. The same method should be used at screening and for all scans during conduct of this clinical trial if clinically indicated. Patients without any tumor residuals do not need CT scan or MRI, only in case of suspicion of disease progression. Overall survival (OS) is defined as the time period from the date of randomization to the date of death. Progressive serial elevation of serum CA 125 will be used to determine CA 125 response and PFS_{bio}. CA 125 will be analyzed locally and assessed according to GCIG criteria. ***Safety*** Clinical safety examinations are performed before administration of each treatment. All assessments will be scheduled as indicated in Table 1A. Additional assessments may be performed as clinically indicated. General physical examination, measurement of vital signs, laboratory safety assessments and recording of AEs (grades 1–5) will be completed at each visit. Clinical safety assessments will include prior and interval medical history, prior treatments for cancer and ECOG. Left ventricular ejection function (LVEF) by ECHO/MUGA need only to be performed on those patients receiving pegylated liposomal doxorubicin in the treatment period. Investigator discretion can be used at all other times. Treatment emergent AEs/SAEs will be reported and graded according to NCI-CTCAE version 4.03. ***Quality of Life*** Quality of Life questionnaires EORTC QLQ-C30 and QLQ-OV28 will be used in this trial. Questionnaires should be completed at baseline and then every 12 weeks until investigator determined progression-free survival and thereafter at every visit for the 5-year-follow-up or death, whichever occurs first.
SAMPLE SIZE CALCULATION / STATISTICAL ANALYSIS	The primary outcome measure of the trial is progression free survival (PFS). With 654 patients randomized at a steady rate over a period of 30 months with an additional 30 months follow-up after the last patient randomized, the trial will have 80% power (two-sided log-rank test, significance level of 5%, 15% exponential distributed drop-out

times) to show a 26.6% change in PFS from a median value of 12.4 months in the control arm to 15.7 months in the experimental arm, i.e. a Hazard Ratio (HR) of 0.79. It is expected that 564 PFS events will have occurred at the time point of primary analysis in the ITT population. The primary hypotheses are: H_0: HR=1 versus H_1: HR≤0.79.

Primary efficacy Analysis

The primary endpoint is progression-free survival defined as the time from the date of randomization to the first documented disease progression or death, whichever occurs first.

The primary analysis will be done by a stratified log-rank test (stratifying for the factors used for randomization) for the difference in the distribution of progression-free survival (PFS) between the groups (two-sided at an alpha-level of 5%). Kaplan-Meier estimates for median PFS with the corresponding 95% confidence intervals will be presented. To assess the hazard ratio a stratified cox regression analysis will be performed, the point estimate for the hazard ratio and corresponding 95%CI will be presented**.**

Secondary Analyses

Overall survival (OS) is defined as time from randomization to death from any cause. For OS the same analyses as for PFS will be performed.

To assess the secondary outcome biological progression-free survival PFS_{bio} according to GCIG criteria (see appendix) stratified log-rank test and a cox regression analyses will be performed, the point estimate for the hazard ratio and corresponding 95%CI will be presented**.** Kaplan-Meier estimates for median PFS_{bio} with the corresponding 95%CI will also be presented.

Further Cox regression models will be performed to analyze the impact of significant baseline covariates regarding PFS and OS; different subgroups (such as status of prior anti-angiogenetic treatment) will also be explored descriptively.

Quality of Life (QoL) with the scores EORTC QLQ-C30 and QLQ-OV28 will analysed descriptively.

Safety Summaries

The safety analyses will be based on the safety population. All safety parameters will be summarized and also listed by patient. Summary tables will be presented for incidence rates of all (serious) adverse events.

Analysis population

The Intent-to-treat (ITT) population will be defined as all patients randomized in the clinical trial, regardless of whether they actually received treatment. The Per Protocol (PP) population will be a subgroup of the ITT population containing all patients who will have a sufficient treatment exposition and will not have any major protocol violation.

Safety population will include all patients who received at least one dose of study drug.

Table 1A: FLOWCHART: Schedule of Assessments

Day	Screening	Baseline	Treatment Period						Mainte-nance Therapy	Follow-up	
	days prior to randomization[1]		(visits depending on randomization arm ± 3 days)						visits every 21 days ± 3 days	Safety Follow-Up[16]	Follow-up 6-monthly[17] (± 14 days)
			Cycle 1[2]	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6			
	-28 - -8	-7 - 0	1	1	1	1	1	1			
Bevacizumab[3,4]			X[5]	X	X	X	X	X	X		
Gemcitabine/Carboplatin[4]			X	X	X	X	X	X			
PLD/Carboplatin[4]			X	X	X	X	X	X			
Randomization		X[1]									
Informed Consent	X	X									
Demographics	X										
Medical History	X										
Physical Examination		X	X[6]	X	X	X	X	X	X	X	
Vital Signs/Blood Pressure		X	X	X	X	X	X	X	X	X	
ECOG		X	X[6]	X	X	X	X	X	X	X	
Laboratory Assessments[7]	X		X[6]	X	X	X	X	X	X	X	
Coagulation[7]	X										
Urinanalysis[8]	X		X[6]	X	X	X	X	X	X		
Pregnancy Test[9]	X										
CA 125[10]	X		X	X	X	X	X	X	X	X	X
Tumor Assessment	X[11]		every 12 weeks (± 7 days) until disease progression[12]								X
Chest X-ray	X[13]										
ECG	X		if clinically indicated								
LVEF[14]	X		every 12 weeks							X	
Concomitant Medication			X	X	X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
QoL[15]		X	every 12 weeks							X	X

1. Randomization is on day 0.
2. Day 1 of cycle 1 should be within 14 days after randomization.
3. Following completion of chemotherapy: Patients in both arms will have further administration of bevacizumab, scheduled every 3 weeks.
4. **Standard Arm (Arm 1):** Bevacizumab 15 mg/kg d1, q3w, Gemcitabine 1000 mg/m^2 d1+8, q3w 6 cycles; Carboplatin AUC4 d1, 30 min, q3w, 6 cycles
   Experimental Arm (Arm 2): Bevacizumab 10 mg/kg d1+15, q4w, in combination with PLD 30 mg/m^2 d1, q4w, 6 cycles; Carboplatin AUC5 d1, q4w 30 min, 6 cycles; in bevacizumab maintenance phase the schedule will switch to bevacizumab 15 mg/kg d1, q3w.
   Both arms: until protocol defined disease progression, and/or unacceptable toxicity (whichever occurs first)
5. Bevacizumab can be omitted for the first treatment cycle if treatment commences within 4 weeks of surgery, but cytotoxic chemotherapy must be started within 8 weeks of surgery.
6. Repeat assessments not required if already performed during previous 7 days for baseline purposes.
7. Laboratory assessments will be performed according to local standards (within 3 days prior to every treatment visit).
8. Dipstick result (and/or 24-h urine collection result) must be available before every bevacizumab administration.
9. A pregnancy test is only required for women of childbearing potential (within 28 days prior to randomization).
10. At baseline, every 3 or 4 weeks during study treatment; after that every 3 months until a minimum of 30 months.
11. The first tumor assessment for this clinical trial should be performed no more than 28 days prior to randomization.
12. Tumor assessments via gynecological examination including ultrasound scanning will be performed every 12 weeks starting before day 1 of cycle 1 until disease progression or up to 30 months (whatever comes first). Results of tumor assessments must be available before next scheduled cycle in order to exclude disease progression. CT scanning (or MRI in case of contrast allergy; evaluation based on RECIST v1.1) of the pelvis and abdomen and response assessment via RECIST v1.1 will be performed only if clinically indicated. All subsequent follow-up scans should be the same modality. Patients without any tumor residuals do not need CT scan or MRI, only in case of suspicion of disease progression.
13. If screening chest X-ray shows any suspicion of metastatic thoracic lesions then a chest CT scan should be performed and disease measured according to RECIST v1.1 criteria.
14. LVEF should be assessed via ECHO/MUGA within 28 days before randomization and afterwards every 12 weeks for patients randomized in PLD arm and for safety follow-up visit.
15. The QoL questionnaires (EORTC QLQ-C30 and QLQ-OV28) should be completed at baseline and then every 12 weeks until investigator-determined progression-free survival and thereafter at every visit for the 5-year-follow-up or death, whichever occurs first.
16. Regardless of reason of end of treatment, patients should have a safety follow-up visit prior to start of new anticancer-treatment, or if applicable 4 weeks (± 7 days) after last dose of bevacizumab, whichever occurs first.
17. Follow-up visits regardless of disease status should be performed every 6 months during 5 years after study treatment start to document survival and any ovarian cancer therapy.

STUDY DESIGN AND CONDUCT

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Epidemiology of ovarian cancer

Epithelial ovarian cancer and related malignancies (primary peritoneal carcinoma, fallopian tube carcinoma) represent the fifth most common cause of cancer-related death among women in Europe and the United States.[1,2] Ovarian cancer (OC) alone is the fourth most common cause of cancer-related death in women with an estimated 200,000 cases and 125,000 deaths annually worldwide. It is also the gynecological malignancy with the highest mortality rate.[3] According to statistics from the Robert-Koch-Institute, in Germany 2008, 7,790 patients were newly diagnosed and 5,529 died from this neoplasm.[3]

1.1.2 Natural history of ovarian cancer

Despite improvements in the treatment of ovarian cancer, increases in overall survival (OS) have been modest and as such, mortality remains high.[4,5] Ovarian cancer is often asymptomatic in early stages; consequently, patients typically have late stage disease at diagnosis, contributing to the high mortality rate.[6] The vast majority of patients diagnosed with OC respond to primary cytoreductive surgery followed by systemic chemotherapy.[7] However, disease recurs in most patients within five years of diagnosis and more than half of all patients die within 5 years of diagnosis.[8,9] Major trials published over the past 15 years reported that the median progression-free survival (PFS) for patients with advanced disease ranges between 16 and 23 months while the median OS is within 31 and 65 months.[10-16]

Since the introduction of platinum-based chemotherapy and the addition of paclitaxel further advances in treatment have been modest. Survival rates of patients with advanced, recurrent or relapsed ovarian cancer remain poor and there continues to be a significant unmet medical need for improved treatment regimens. In this regard, molecular targeted therapeutic agents herald a new era for cancer treatment. In the setting of epithelial ovarian cancer, a growing body of evidence supports the use of anti-angiogenic agents in combination with chemotherapies.[17] In particular, bevacizumab, a monoclonal antibody targeted against the pro-angiogenic vascular endothelial growth factor (VEGF), holds significant therapeutic potential. In combination with the chemotherapeutic agents paclitaxel and carboplatin bevacizumab is approved in the European Union (EU) and in some other countries outside Europe for the first-line treatment of advanced ovarian cancer (FIGO IIIB – IV).

1.1.3 Current treatment of recurrent ovarian cancer

Primary treatment for advanced-stage ovarian cancer usually consists of maximal cytoreductive surgery followed by chemotherapy using platinum- and taxane-based regimens, most often carboplatin and paclitaxel.[18,19] Addition of a third chemotherapeutic agent has failed to improve efficacy in numerous trials and this strategy has been largely abandoned. However, incorporation of bevacizumab into platinum- and taxane-containing front-line therapy, with continuation of single-agent bevacizumab, was considered acceptable by the Fourth International Gynecologic Cancer Intergroup (GCIG) Ovarian Cancer Consensus, based on the significantly improved progression-free survival (PFS) demonstrated in two randomized phase III trials.[20-22]

Patients with platinum-sensitive recurrent ovarian cancer (defined as recurrence of disease more than 6 months from the completion of a platinum-based chemotherapy regimen) have higher initial response rates to chemotherapy. Recently, the U.S. Food and Drug Administration (FDA) approved gemcitabine chemotherapy in combination with carboplatin for relapsed platinum-sensitive disease. Carboplatin and gemcitabine resulted in a statistically significant progression-free survival (PFS) compared with carboplatin alone in patients with platinum-sensitive disease.[8]

According to the NCCN and the German S3-guidelines the treatment options for patients with platinum sensitive recurrent ovarian cancer are the combinations carboplatin/gemcitabine/bevacizumab, carboplatin/pegylated liposomal doxorubicin, carboplatin/paclitaxel and carboplatin/gemcitabine.

Carboplatin / Gemcitabine

The combination of platinum and gemcitabine was established following the results of the randomized phase III AGO-OVAR 2.5 trial, which demonstrated significantly superior PFS with gemcitabine/carboplatin compared with carboplatin alone in this setting.[8] Overall response rate (RR) was also significantly improved with the addition of gemcitabine but there was no significant different in OS, since this trial was not powered for OS.

Recently, results of the OCEANS trial demonstrated significantly improved PFS and RR when bevacizumab was combined with gemcitabine/carboplatin chemotherapy for platinum-sensitive recurrent ovarian cancer and continued as a single agent until disease progression.[23] Details of the trial design and results are provided in section 1.1.4. This regimen is approved by the EMA in the EU and by other authorities in non-EU countries. According to the German S3 guidelines bevacizumab in combination with carboplatin and gemcitabine is a preferred treatment option for patients with recurrent platinum sensitive ovarian cancer.

Carboplatin / Pegylated Liposomal Doxorubicin

Based on the results of the CALYPSO trial, the combination of carboplatin and pegylated liposomal doxorubicin has become one of the options with the best therapeutic index in platinum sensitive recurrent ovarian cancer. The median PFS in this study was significantly better for patients receiving carboplatin/pegylated liposomal doxorubicin compared to those receiving carboplatin/paclitaxel. In addition, the safety profile showed a favorable toxicity profile for the combination of carboplatin/pegylated liposomal doxorubicin compared to carboplatin/paclitaxel.[24,25]

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) composed of human IgG1 framework regions and antigen-binding complementary determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) that blocks the binding of human VEGF to all VEGF-A receptors.[26]

Bevacizumab recognizes and neutralizes isoforms of VEGF with a K_d of around 8×10^{-10} M. It does not recognize other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor and nerve growth factor). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional antitumor activity may be obtained via the effects of bevacizumab on tumor vasculature, interstitial pressure and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells.[27] Furthermore, bevacizumab showed synergistic anti-angiogenic activity with docetaxel, as assessed by endothelial cell proliferation and tubule formation *in vitro*.[28]

Anti-VEGF antibodies have shown benefit when combined with chemotherapy in preclinical models of different tumor types. Bevacizumab can block the growth of a number of human cancer cell lines grown in nude mice, including metastatic colorectal cancer (mCRC), non-squamous non-small cell lung cancer (NSCLC), metastatic or locally recurrent breast cancer (BC), prostate cancer, head and neck cancer, metastatic renal cell carcinoma (mRCC) and ovarian cancer (OC).[29-32]

Bevacizumab has been evaluated in numerous phase I to IV trials in a variety of solid tumors as monotherapy and in combination with chemotherapy. The combination of bevacizumab with chemotherapy improves PFS and/or OS in mCRC[33-36], non-squamous NSCLC[37], metastatic BC (mBC)[38,39], mRCC[40,41] and OC[42,43]. As of mid 2009, bevacizumab has been approved in more than 100 countries worldwide (including the member states of the European

Union and the United States of America) for the treatment of some forms of colorectal, breast, renal, lung and brain cancer (MBC not in the United States of America). Over 800,000 patients have been exposed to bevacizumab in different indications.

The placebo-controlled, phase III OCEANS trial showed a clinically meaningful and statistically significant increase in PFS (the primary endpoint) with the use of 15mg/kg q3w bevacizumab in addition to carboplatin and gemcitabine in patients with platinum-sensitive recurrent ovarian, primary peritoneal or fallopian tube carcinoma (for more details please see section 1.1.4.).[23] The safety profile was consistent to earlier reports.

Bevacizumab, in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelian ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

1.1.2.1 *Safety of Bevacizumab*

The most common serious adverse events (SAEs) identified in clinical trials with bevacizumab were:

- Hypertension
- Proteinuria
- gastrointestinal perforation
- hemorrhage
- arterial thromboembolic events (ATE)
- fistula
- wound-healing complications
- venous thromboembolism
- congestive heart failure
- thrombocytopenia

The most frequently observed AEs across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhea and abdominal pain.

Increased rates of severe neutropenia, febrile neutropenia or infection with severe neutropenia have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES).

Gastrointestinal perforation – Bevacizumab has been associated with serious cases of gastrointestinal perforation or fistulae in 2.4% of patients (versus 0.3% in controls), with about one-third of cases being fatal (0.2%-1% of all bevacizumab treated patients). The typical presentation may include abdominal pain, nausea, emesis, constipation and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of therapy. In some cases underlying intra-abdominal inflammation was present (either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis). Caution should be exercised when treating such patients with bevacizumab.

In phase II trials in ovarian cancer, gastrointestinal perforation was most associated with refractory or resistant ovarian cancer and greater cumulative use of chemotherapy.[42,44,45]

In the phase III GOG 218 trial, gastrointestinal perforation, fistula, necrosis or leak ($\geq$ grade 2) occurred in 2.6% of those assigned to receive maintenance therapy (up to 22 cycles) of

bevacizumab following induction with 6 cycles of paclitaxel, carboplatin and bevacizumab and in 1.2% of those who received paclitaxel and carboplatin without bevacizumab.[42] In the phase III AGO-OVAR 11/ICON7 trial the incidence of gastrointestinal perforations (all grades) was even lower occurring in 1.3% of patients assigned to the treatment arm (6 cycles of paclitaxel, carboplatin and bevacizumab for 18 cycles) and in 0.4% of those in control arm (6 cycles of paclitaxel, carboplatin).[22]

Furthermore, no unexpected safety concerns or gastrointestinal perforations were noted from the Phase III trial of bevacizumab plus gemcitabine/carboplatin in platinum-sensitive patients (OCEANS)[23] but in resistant ovarian cancer patients (including AURELIA[46]) a few gastrointestinal perforations were observed.

Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

For information regarding other side effects associated with the use of bevacizumab (either alone or in combination with chemotherapy), please refer to the current version of the IB.

1.1.2.1 *Phase II trials of bevacizumab in platinum sensitive recurrent ovarian cancer in combination with carboplatin and pegylated liposomal doxorubicin*

A single-arm phase II trial of bevacizumab plus PLD/carboplatin in 54 patients with platinum-sensitive recurrent ovarian, fallopian tube or primary peritoneal cancer, ORR was 72.2% and median TTP was 13.9 months.[47] Four patients had have a grade 3 PPE, two patients had have a deep vein thrombosis, and one patient had a small intestinal perforation. Otherwise, the safety profile of this combination was similar to the known toxicities of the three agents.

1.1.2.1 *Phase III trials of bevacizumab in ovarian cancer*

Based on two phase III trials in the front-line setting for patients with ovarian cancer (GOG-0218, AGO-OVAR11/ICON7)[21,22] bevacizumab was approved in the EU and other countries.

The third most recently reported randomized phase III trial was OCEANS.[23] Unlike GOG-0218 and AGO-OVAR11/ICON7, patients in the OCEANS trial had platinum-sensitive recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer. A total of 484 patients received carboplatin AUC 4 plus gemcitabine 1000 mg/m², days 1 and 8, both given q3w for 6-10 cycles, plus either placebo or bevacizumab 15 mg/kg q3w given until disease progression. The stratification variables were platinum-free interval (6-12 vs. > 12 months) and cytoreductive surgery for recurrent disease (yes vs. no). The primary endpoint was PFS assessed by the investigator according to RECIST. Secondary endpoints included overall RR, duration of response, OS and safety.

Almost 60% of patients hat a PFI > 12 months. The median number of chemotherapy cycles delivered was 6 in both arms. Patients in the control arm received a median of 10 cycles of placebo (range 1-36); those on the investigational arm received a median of 12 cycles of bevacizumab (range 1-43).

The pre-specified primary analysis was performed after 317 PFS events. Results showed that the risk of progressive disease or death was halved (HR 0.484 [95% CI 0.388-0.605], p<0.0001). Median PFS was 12.4 months with bevacizumab/gemcitabine/carboplatin versus 8.4 months with placebo/gemcitabine/carboplatin. These findings were supported by the results of the PFS analysis according to Independent Review Committee assessment (HR 0.451 [95% CI 0.351-0.580], p<0.0001). The PFS benefit was seen consistently across all clinically relevant subgroups. Overall RR, a secondary endpoint, was also significantly superior in the bevacizumab-containing arm compared with chemotherapy alone (79% vs 58%, respectively, p<0.0001). The median duration of response was 10.4 months vs 7.4 months. At the time of primary analysis, 71% of patients were still alive and therefore the OS results were immature. Nevertheless, a trend favoring the bevacizumab-containing arm was seen. Bevacizumab or placebo was discontinued because of disease progression in more patients in the control arm than in bevacizumab arm; whereas discontinuation because of adverse events were more common in the bevacizumab arm than in the placebo arm. The safety pro-

file of bevacizumab-containing regimen was consistent with observations from clinical trials in other tumor types and the two front-line trials of bevacizumab-containing therapy for ovarian cancer. Based on these findings the combination of bevacizumab/carboplatin and gemcitabine has received the European Union (EU) marketing authorization in September 2012 for the treatment of patients with first recurrence of platinum-sensitive recurrent ovarian cancer and no prior anti-angiogenic treatment.

The randomized phase III CALYPSO trial compared pegylated liposomal doxorubicin/carboplatin with paclitaxel/carboplatin in patients with relapsed, platinum-sensitive ovarian cancer. PLD/carboplatin was not only non-inferior to paclitaxel/carboplatin, but was significantly superior: median PFS was 11.3 months with pegylated liposomal doxorubicin/carboplatin vs. 9.4 months with paclitaxel/carboplatin, with a more manageable adverse event profile.[24]

1.2 Rationale for Study Design

Despite standard treatment of initial debulking surgery followed by paclitaxel/carboplatin chemotherapy for patients with newly diagnosed ovarian cancer, most patients eventually relapse even after achieving a clinical response.[48] Patients who relapse after 6 months of initial platinum-based chemotherapy treatment have a better prognosis and are considered platinum-sensitive.[8,24,49] Retreatment with paclitaxel/carboplatin has been associated with improved PFS and OS,[50-54] but with significant cumulative toxicities such as peripheral neuropathy.

Bevacizumab in addition to chemotherapy followed by bevacizumab maintenance therapy has demonstrated an improvement for progression-free survival (PFS) in the most essential phase III trials in primary or recurrent ovarian cancer (OC). In the first-line setting both trials GOG-0218 and AGO-OVAR 11/ICON 7 the addition of bevacizumab to chemotherapy has shown a significant impact on PFS compared with chemotherapy alone. The clinical benefit was 3.8 and 1.7 months respectively in median PFS.[21,22]

This is important for the first-line therapy because in the last 12 years no clinical trial has shown an improvement of therapy by addition of further chemotherapeutical or immunotherapeutic agents to standard chemotherapy carboplatin/paclitaxel.

Therapeutic effects of bevacizumab in platinum-resistant recurrent ovarian cancer are also remarkable: median PFS was 5.6 months with bevacizumab and single-agent chemotherapy versus 2.5 months with single-agent chemotherapy alone. This effect could be demonstrated for several combinations and also for pegylated liposomal doxorubicin.

Gemcitabine/carboplatin combination in patients with platinum-sensitive recurrent ovarian cancer has demonstrated improved PFS compared with carboplatin alone in a phase III trial (median PFS 8.6 months; HR 0.72 [95% CI 0.58-0.90], p=0.0031).[8] Pegylated liposomal doxorubicin demonstrated a statistically significant benefit over topotecan in PFS in platinum-sensitive patients as well.[55] In addition, the combination of PLD and carboplatin has been shown to be safe and effective, with ORR of 63% and median PFS of 9.4 months.[24]

Bevacizumab has shown encouraging results in patients with recurrent ovarian cancer when administered in combination with standard chemotherapy. So, there is a positive effect in addition of bevacizumab to standard chemotherapy regarding median PFS as primary study endpoint in different therapeutic settings for ovarian cancer.

The phase III OCEANS trial evealed that the addition of bevacizumab to standard gemcitabine/carboplatin significantly improved PFS (8.4 months versus 12.4 months).[23,24]

Patients with platinum-sensitive recurrent ovarian cancer were evaluated in the phase III CALYPSO trial. In this trial carboplatin/pegylated liposomal doxorubicin was compared with standard chemotherapy carboplatin/paclitaxel. 12% of enrolled patients were pre-treated with another therapy for recurrent setting. The median PFS was 11.3 months for carboplatin/pegylated liposomal doxorubicin. So, the new combination of carboplatin/pegylated

liposomal doxorubicin could be established as a new standard of care therapy in this setting.[24]

Phase II data showed that the combination of carboplatin/PLD plus bevacizumab is safe and shows clinical activity (PFS 13.9 months).[47]

Because of expected favorable safety profile of PLD in the experimental treatment arm this trial is designed as a prospective, open-label, randomized, two-arm superiority Phase III trial of bevacizumab plus gemcitabine/carboplatin (standard arm) or bevacizumab plus PLD/carboplatin (experimental arm) in patients with first platinum-sensitive recurrent epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma. The superiority should be demonstrated in the median PFS: 12.4 months (standard arm) versus 15.7 months (experimental arm).

Patients in the present trial will receive bevacizumab 15 mg/kg on day 1 every 3 weeks with gemcitabine and carboplatin in the standard arm (arm 1) or bevacizumab on day 1 every 2 weeks with pegylated liposomal doxorubicin/carboplatin (q4w) in the experimental arm (arm 2) for 6 cycles.

After that, patients will treated with bevacizumab 15mg/kg on day 1 every 3 weeks until protocol defined disease progression and/or unacceptable toxicity (whichever occurs first).

1.2.1 Rationale for dose selection

The magnitude of benefit seen with bevacizumab plus gemcitabine/carboplatin was numerically greater than gemcitabine/carboplatin with a difference in ORR of 21%.[56] Therefore, the same regimen of bevacizumab 15 mg/kg on day 1 of each cycle prior to gemcitabine 1000 mg/m^2 on days 1 and 8 and carboplatin AUC4 on day 1 every 3 weeks will be used in this trial to maximize benefit. In a phase II trial of bevacizumab 10 mg/kg on days 1 and 15 of each cycle plus PLD 30 mg/m^2 and carboplatin AUC4 on day 1 every 4 weeks, the ORR was 72% and with median TTP of 13.9 months.[47] In this clinical trial, bevacizumab will be distributed on day 1 only with the PLD/carboplatin combination, then increased to 15 mg/kg on day 1 q3w when given alone as maintenance therapy.

1.2.2 Rationale for patient population

The phase III OCEANS trial patient population was including patients who had histological confirmed recurrent ovarian cancer and disease progression ≥ 6 months after completion of frontline platinum-based chemotherapy.[56] Patients with platinum-sensitive recurrent ovarian cancer were evaluated in the phase III CALYPSO trial comparing PLD/carboplatin with paclitaxel/carboplatin; PFS was statistically superior with the PLD/carboplatin combination.[49] Accordingly, for this AGO-OVAR 2.21 trial, patients with platinum-sensitive first recurrent ovarian cancer were selected with epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma, regardless of FIGO stage and histological grade or type.

2 OBJECTIVES OF THE TRIAL

2.1 Primary Objective

The primary efficacy outcome measure for this clinical trial is investigator-determined progression-free survival (PFS).

2.2 Secondary Objectives

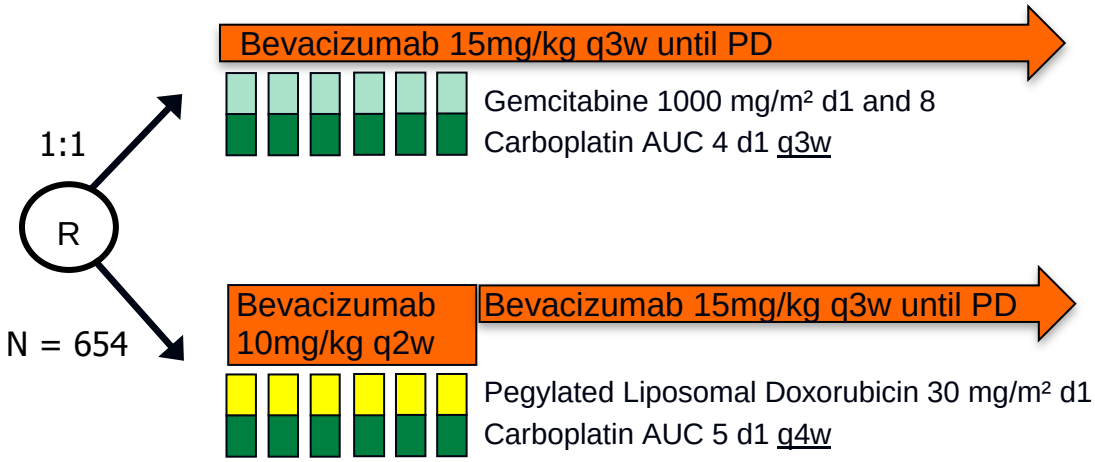
To compare

- Overall Survival (OS)
- Biological progression-free survival (PFS_{BIO}) by serum CA 125 assessed according to GCIG criteria
- Quality of Life (QoL)

- QoL will be assessed using EORTC QLQ-C30 and QLQ-OV28 questionnaires

- Safety and Tolerability

3 TRIAL DESIGN



- Tumor assessments every 12 weeks until disease progression or the occurrence of unacceptable toxicity (whichever occurs first) up to 30 months.
- For patients without disease progression: Safety follow-up visit 30 months after start of treatment (or if applicable 4 weeks after the last dose of Bevacizumab, whichever occurs later).
- Follow-up visits: regardless of disease status every 6 months for 5 years after study treatment start.

3.1 Overview of Trial Design and Dosing Regimen

This is a prospective, randomized (1:1 ratio) , two-arm, superiority, multi-national, open-label, phase III trial designed to evaluate optimal treatment combination of bevacizumab with chemotherapy consisting of gemcitabine/carboplatin or PLD/carboplatin.

Patients with epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinoma (PPC) sensitive to platinum-based treatment (regardless to all FIGO stages, histological grades and types) will be randomly assigned to one of the two treatment groups in a 1:1 ratio:

Arm 1 (Standard Arm): Patients will receive bevacizumab 15 mg/kg on day 1 q3w until disease progression or occurrence of bevacizumab-related toxicities, gemcitabine 1000 mg/m^2, days 1 and 8, q3w for 6 cycles and carboplatin AUC4 on day 1 q3w for 6 cycles.

Arm 2 (Experimental Arm): Patients will receive bevacizumab 10 mg/kg on day 1 and 15 q4w during combination phase with PLD and carboplatin. All patients in this arm will receive PLD 30 mg/m^2 on day 1 q4w for 6 cycles and carboplatin AUC5 on day 1 q4w for 6 cycles. Patients will then switch to bevacizumab 15 mg/kg on day 1 q3w when given as maintenance treatment until disease progression or the occurrence of unacceptable toxicity, whichever occurs first.

3.2 Number of Patients / Assignment to Treatment Groups

Patients will be randomly assigned to treatment groups. The randomization will be done by KKS, Philipps-University of Marburg, Germany. Stratification factors are described in section 6.4.

Enter the corresponding number for allocation to the treatment groups in the appropriate place on each patient's electronic Case Report Form (eCRF). The patient randomization numbers are to be allocated sequentially in the order in which the patients are enrolled.

The assigned patient number of each patient has to be documented by using an Enrolment Log and Subject ID-List.

3.3 Trial Duration

The clinical trial is planned to start in Q2 2013 with respect to first patient in (FPI) including a recruitment period of 30 months or until 654 patients are recruited in the trial. The treatment will last for a maximum of 6 cycles (18 weeks) for patients in the Standard Arm and in the Experimental Arm. If chemotherapy treatment is finished bevacizumab 15 mg/kg will be given every 3 weeks until disease progression or the occurrence of an unacceptable toxicity (whichever occurs first). Each patient will be followed until disease progression (primary endpoint PFS) and for the secondary endpoint OS at a minimum for 30 months.

3.4 End of Trial

The clinical trial will end when all patients have been followed for up at least 30 months after the last patient has started study treatment.

4 TRIAL POPULATION

4.1 Target Population

The target population comprises women who are ≥ 18 years old with histological confirmed epithelian ovarian, fallopian tube or primary peritoneal cancer, regardless of FIGO stage, histological grades and types, who have their first platinum-sensitive recurrence after first-line treatment.

4.2 Inclusion Criteria

To be eligible for this clinical trial, patients must have the following documented:

1. Signed written informed consent obtained prior to initiation of any trial-specific procedures and treatment as confirmation of the patients awareness and willingness to comply with the trial requirements.
2. Females aged ≥ 18 years.
3. Histological confirmed diagnosis of
   - epithelial ovarian carcinoma (including mixed Mullerian tumors) or
   - fallopian tube carcinoma or
   - primary peritoneal carcinoma.

   All FIGO stages, histological grades and types are allowed.
4. First disease recurrence > 6 months after first-line platinum-based chemotherapy, no prior chemotherapy in the recurrent setting is allowed. Patients must have stopped any first-line maintenance treatment with any type of anticancer treatment including bevacizumab at least 30 days prior to randomization.
5. Patients with measurable or non-measurable disease (according to RECIST v1.1) or CA 125 assessable disease (according to GCIG criteria) or histological proven diagnosis of relapse.
6. In case of cytoreductive surgery for recurrence, patients must be able to commence cytotoxic chemotherapy within 8 weeks after cytoreductive surgery. The first dose of bevacizumab can be omitted in both arms if the investigator decides to start chemotherapy within 4 weeks after debulking surgery for recurrent disease.

7. ECOG performance status (PS) 0-2.
8. Life expectancy > 3 months.
9. Adequate bone marrow function (within 28 days prior to randomization)
    - Absolute Neutrophil Count (ANC) $\geq$ 1.5 x 10^9/L
    - Platelets (PLT) $\geq$ 100 x 10^9/L
    - Hemoglobin (Hb) $\geq$ 9.5 g/dL

      (Hemoglobin may be supported by transfusion or erythropoietin or other approved hematopoetic growth factors.)
10. Adequate coagulation parameters (within 28 days prior to randomization)
    - Patients not receiving anticoagulant medication who have an International Normalised Ratio (INR) $\leq$ 1.5 and an Activated ProThrombin Time (aPTT) $\leq$ 1.5 x ULN.

      (The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to institution medical standard) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of randomization.)
11. Adequate liver function (within 28 days prior to randomization)
    - Serum bilirubin (BR) $\leq$ 2 x ULN
    - Serum transaminases $\leq$ 2.5 x ULN (≤ 5 x ULN in the presence of liver metastases)
12. Adequate renal function (within 28 days prior to randomization):
    - Serum creatinine < 1.6 mg/dL or creatinine clearance ≥ 40 ml/min
    - Glomerular filtration rate (GFR) > 40 ml/min (estimates based on the Cockroft-Gault or Jellife formular are sufficient)
    - Urine dipstick for proteinuria < 2+. If urine dipstick is $\geq$ 2+, 24-hour urine must demonstrate < 1 g of protein in 24 hours
13. Normal blood pressure or adequately treated and controlled hypertension (neither systolic BP ≤ 140 mmHg and/nor diastolic BP ≤ 90 mmHg)

4.3 Exclusion Criteria

1. Non-epithelial origin of the ovary, the fallopian tube or the peritoneum (i.e. germ cell tumors).
2. Ovarian tumors of low malignant potential (e.g. borderline tumors).
3. Malignancies other than ovarian cancer within 5 years prior to randomization, except for adequately treated
    - carcinoma in situ of the cervix
    - and/or basal cell skin cancer
    - and/or non-melanomatous skin cancer
    - and/or carcinoma in situ of the breast
    - and/or endometrial carcinoma (FIGO stage ≤ IA).

    Patients may have received previous adjuvant chemotherapy for other malignancies (e.g. breast or colorectal carcinoma) if diagnosed over 5 years ago before randomization with no evidence of subsequent recurrence.
4. Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted as are steroidal antiemetics).

5. Any previous radiotherapy to the abdomen or pelvis.
6. Treatment with any other investigational agent, or participation in another clinical trial testing a drug within the past 30 days before randomization.
7. Known hypersensitivity to used chemotherapeutic agents in this trial and bevacizumab and its excipients, chinese hamster ovary cell products or other recombinant human or humanised antibodies.
8. Current or recent (within 10 days prior to randomization) chronic use of aspirin > 325 mg/day.
9. Surgery (including open biopsy) within 4 weeks prior to anticipated first dose of bevacizumab (allowing for the fact that bevacizumab can be omitted from the first cycle of chemotherapy). It is strongly recommended that an interval of 7 days is left between the insertion of any central venous access devices (CVADs) and the onset of bevacizumab treatment.
10. Any planned surgery during the trial treatment period plus 4 additional weeks to allow for bevacizumab clearance.
11. History of VEGF therapy related abdominal fistula or gastrointestinal perforation.
12. Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease.
13. Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
14. Previous Cerebro-Vascular Accident (CVA), Transient Ischaemic Attack (TIA) or Sub-Arachnoid Hemorrhage (SAH) within 6 months prior to randomization.
15. Prior history of hypertensive crisis or hypertensive encephalopathy. Uncontrolled hypertension (sustained elevation of neither systolic blood pressure >140 mmHg and / nor diastolic >90 mmHg despite antihypertensive therapy).
16. Clinically significant (e.g. active) cardiovascular disease, including:
    - myocardial infarction or unstable angina within ≤ 6 months of randomization
    - New York Heart Association (NYHA) ≥ grade 2 congestive heart failure (CHF)
    - poorly controlled cardiac arrhythmia despite medication (patients with rate-controlled atrial fibrillation are eligible)
    - peripheral vascular disease grade ≥ 3 (e.g. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision)
17. Left ventricular ejection fraction (LVEF) defined by ECHO/MUGA below the institutional lower limit of normal.
18. Significant traumatic injury during 4 weeks prior to randomization.
19. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression.
20. History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures).
21. Non-healing wound, active ulcer or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require 3 weekly wound examinations.
22. History or evidence of thrombotic or hemorrhagic disorders within 6 months prior to randomization.

23. Evidence of bleeding diasthesis or significant coaugulopathy (in the absence of coagulation).
24. Fertile woman of childbearing potential not willing to use adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) for duration of the clinical trial and at least 6 months afterwards.
25. Pregnant or lactating women.
26. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
27. Requirement of therapeutic anticoagulation using marcumar, warfarin or PTT-prolonging heparin.

4.4 Concomitant Medication and Treatment

Only medications and therapies for treatment of cancer need to be recorded in the eCRF. These medications include all medications given as supportive therapy for chemotherapy, such as G-CSF and erythropoietin.

All non-cancer treatments that the responsible physician feels are appropriate are allowed in this trial. Only non-cancer medications for treating AEs should be recorded in the eCRF.

The gemcitabine/carboplatin and PLD/carboplatin chemotherapy regimens will be administered according to local standard of care.

Patients should receive full supportive care during and after the administration of bevacizumab with chemotherapy. This includes transfusion of blood and blood products and/or the use of erythropoietin as clinically indicated, antibiotics for infective complications and antihypertensives for the management of hypertension. Anaphylaxis precautions should be observed during administration of bevacizumab, gemcitabine, PLD and carboplatin as per local practice.

Treatment with experimental concomitant, systemic anti-tumor agents or other concurrent investigational agents of any type is not allowed in this trial before protocol defined termination of the clinical trial. The patient may only be entered into another therapeutic clinical trial after documented protocol defined disease progression or occurrence of unacceptable toxicities or withdrawal from this clinical trial.

The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of randomization.

Due to a possible risk of bleeding during treatment with bevacizumab patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily) at least until discontinuation of bevacizumab therapy.

In case of treatment with other inhibitors of platelet aggregation, such as prasugrel, ticlopidine, tirofibane or dipyridamol, patients taking these medications should not be included into the trial. As of today, no data on bevacizumab are available regarding the simultaneously taking of such compounds.

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

For details regarding the schedule of assessments and procedures please refer to table 1A.

5.1 Screening / Baseline Examination

After provision of written informed consent, potential participants will undergo the following screening procedures no more than 28 days prior to randomization:

- demographics, complete medical history including ovarian cancer history (to include all prior surgeries), concurrent illnesses.
- clinical laboratory testing according to local standards should include:
    - Hematology (including hemoglobin, hematocrit, platelet count, red blood cell count, and full white blood cell count including differential),
    - Coagulation tests (INR and aPTT),
    - Biochemistry: serum chemistry (including total protein [or albumin], alkaline phosphatase, AST/SGOT, ALT/SGPT, total bilirubin, creatinine, estimated creatinine clearance according to Cockroft-Gault or Jelliffe formula (estimated creatinine clearance has to be done only from cycle 1-6.)
    - Urinalysis by dipstick: In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1g per day). Alternatively, proteinuria testing can be performed according to local standards.
    - CA 125: The same method of assessment should be used for all CA 125 measurements during the trial.
- Pregnancy test: Women of childbearing potential will have a serum pregnancy test. Not required for women who have undergone and have documentation of a hysterectomy.
- Tumor evaluation: Measurable tumors are to be assessed by RECIST v1.1 criteria. The same method of assessment should be used at screening and for all scans during trial conduct. Patients will be classified as having measurable or non-measurable disease at screening and at each imaging assessment (according to the local standard of care) conducted thereafter.
- Chest X-Ray: A chest X-ray must be performed at screening to check for thoracic metastasis in all patients. If screening chest X-ray shows any suspicion of metastatic thoracic lesions then a chest CT scan should be performed and disease measured according to RECIST v1.1 criteria.
- Standard 12-lead electrocardiogram (ECG).
- LVEF should be assessed via ECHO/MUGA according to local standard.
- Adverse events (grades 1-5 according to NCI-CTCAE v 4.03).

Within 7 days prior to randomization the following assessments should be completed.

- Complete physical examination and measurement of vital signs (including height, weight, and blood pressure).
- ECOG PS assessment.
- QoL: Quality of life questionnaires EORTC QLQ-C30 and QLQ-OV28 will be used in this clinical trial. They will be assessed at baseline and every 12 weeks until investigator determined progression-free survival and thereafter at every visit for the 5-year follow-up or death, whichever occurs first.
- Adverse events (grades 1-5 according to NCI-CTCAE v 4.03).

All patients undergoing screening must be listed in the Enrolment Log and Subject ID-List.

5.2 Trial assessments during treatment period

All assessments will be scheduled as indicated in table 1A. Additional assessments may be performed as clinically indicated.

5.2.1 Tumor response criteria

Patients will be assessed for disease response or progressive disease throughout the clinical trial.

5.2.1.1 Response Criteria

A mandatory tumor assessment via gynecological examination including ultrasound scanning and only if clinically indicated, cross-sectional imaging (by CT, or MRI in case of contrast allergy; evaluation according to RECIST v. 1.1 criteria) of the pelvis and abdomen (by X-ray or preferably by CT scan) will be performed every 12 weeks (± 7 days of the scheduled visit) until progressive disease or up to 30 month, starting before day 1 of cycle 1, and during follow-up every 6 months (± 2 weeks) until disease progression. Patients without any tumor residuals do not need CT scan or MRI, only in case of suspicion of disease progression.

Results of tumor assessments must be available before next scheduled cycle in order to exclude disease progression.

Patients will be classified as having measurable or evaluable but non-measurable disease prior to day 1 of cycle 1 and at each imaging assessment (according to the local standard of care) conducted thereafter.

Tumor measurements should be made by the same investigator/radiologist for each patient during the trial to the extent that this is feasible. All follow-up scans should be the same modality.

5.2.1.2 Response Criteria according GCIG

Progressive serial elevation of serum CA 125 will be used to determine CA 125 and biological progression-free survival. CA 125 will be analyzed locally every 3 or 4 weeks during study treatment (starting on day 1 of cycle 1) and thereafter every 3 months until a minimum of 30 months or disease progression or occurrence of unacceptable toxicity. The same method of assessment should be used for all CA 125 measurements during this clinical trial. Values will be assessed according GCIG criteria.

5.2.2 Clinical efficacy assessments

Progression-free survival (PFS) and overall survival (OS) will be assessed according to table 1A. PFS is defined as the time from the date of randomization to investigator-determined disease progression. OS is defined as the time period from the date of randomization to the date of death.

5.2.3 Clinical safety assessments

Patients will undergo a complete physical examination. Measurement of vital signs (weight, blood pressure), and laboratory safety assessments according to local standards and recording of all AEs grades 1-5 in the source notes, will be performed by the investigator. These assessments will be recorded at each visit until the follow-up visit. Only concomitant cancer therapies, all cancer treatments prior to enrollment, chemotherapy given from cycle 1 through cycle 6, medication for AE treatment and medications for further treatment of cancer beyond disease progression need to be recorded in the concomitant medication eCRF at each corresponding visit.

The National Cancer Institute's Cancer Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to evaluate the clinical safety of the treatment in this clinical trial. Patients will be assessed for grades 1 to 5 adverse events, including SAEs, at each clinical visit and as necessary throughout the clinical trial. All AEs will be recorded in the eCRF.

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

LVEF should be assessed every 12 weeks until disease progression and during safety follow-up visit for patient randomized in PLD arm.

5.2.4 Performance Status

Performance status (PS) will be measured using the ECOG Performance Status Scale (see Appendix 20.4).

It is recommended, if possible, that a patient's PS will be assessed by the same person throughout the clinical trial.

PS will be assessed at each visit until and including the safety follow-up visit. At day 1 of cycle 1 a repeat assessment is not required if it was already performed during previous 7 days for baseline purposes.

5.2.5 Laboratory Assessments

Laboratory safety assessments will be performed within 3 days prior to every treatment visit before study drug is administered and at safety follow-up visit. All testing will be conducted locally. The total volume of blood taken will be approximately 15 ml per visit.

Regular safety assessments should be taken in accordance with local standard of care and may include:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential
- Coagulation tests (INR and aPTT) to be performed only if clinically indicated
- Biochemistry: serum chemistry (including total protein [or albumin only], alkaline phosphatase, AST/SGOT, ALT/SGPT, total bilirubin, creatinine, estimated creatinine clearance according to Cockroft-Gault or Jelliffe formula (estimated creatinine clearance has to be done only from cycle 1-6.)
- Urinalysis by dipstick: In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1g per day). Alternatively, proteinuria testing can be performed according to local standards.

5.2.6 Health-related Quality of Life Assessments (QoL)

Health related Quality of Life questionnaires EORTC QLQ-C30 and QLQ-OV28 will be used in this clinical trial. These will be assessed every 12 weeks starting on day 1 of cycle 1 until investigator determined progression-free survival and thereafter at every visit for the 5-year-follow-up or death, whichever occurs first.

QLQ-C30 incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, nausea and vomiting); and a global health and quality-of-life scale.

QLQ-OV28 is a specific ovarian cancer module consisting of 28 items that assess abdominal symptoms, peripheral neuropathy, other chemotherapy-related side effects, hormonal symptoms, body image, sexual functioning and attitudes towards disease and treatment.

5.3 Maintenance Therapy

After completion of chemotherapy and without disease progression or occurrence of unacceptable toxicity patients will be treated with bevacizumab only every 3 weeks. All assessments will be scheduled as indicated in table 1A. Additional assessments may be performed as clinically indicated.

- Complete physical examination and measurement of vital signs (including weight, and blood pressure).
- ECOG PS assessment.
- Clinical laboratory testing according to local standards:

- Hematology (including hemoglobin, hematocrit, platelet count, red blood cell count, and full white blood cell count including differential)
- Biochemistry: serum chemistry (including total protein [or albumin], alkaline phosphatase, AST/SGOT, ALT/SGPT, total bilirubin, creatinine)
- Urinalysis by dipstick: In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1g per day). Alternatively, proteinuria testing can be performed according to local standards.
- CA 125

- QoL: Quality of life questionnaires EORTC QLQ-C30 and QLQ-OV28 will be used every 12 weeks until investigator determined progression-free survival and thereafter at every visit for the 5-year-follow-up or death, whichever occurs first.
- Adverse events (grades 1-5 according to NCI-CTCAE v 4.03).

All assessments, except QoL, will be done until disease progression or occurrence of unacceptable bevacizumab-related toxicity, whichever occurs first.

5.4 Post-treatment follow-up

Safety follow-up visits: regardless of reason of end of treatment patients should have a safety follow-up visit prior to start of new anticancer-treatment, or if applicable 4 weeks (± 7 days) after last dose of bevacizumab, whichever occurs first. Patients will undergo a safety follow-up assessment, including general physical examination, measurement of vital signs, ECOG PS, laboratory assessments (hematology, biochemistry, urinanalysis, CA 125), QoL assessment and adverse event follow-up.

Follow-up: Follow-up visits regardless of disease status should be performed every 6 months during 5 years after study treatment start. Specific follow-up assessments are described in table 1A.

5.5 Treatment of the Patient after End of Trial

Upon clear evidence of disease progression, study treatment should be discontinued permanently and patients will receive standard of care treatment. The investigator takes responsibility for decision about the subsequent treatment.

6 STUDY TREATMENTS

(a) Investigational Medicinal Product (IMP)

According to Directive 2001/20 EC of the European Parliament an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication or when used to gain further information about the authorized form.

For arm 1 (standard arm (carboplatin/gemcitabine)) bevacizumab will be ‘non-investigational drug’ for those patients where it is standard of care in combination with gemcitabine and carboplatin and registered and reimbursed. Thus, bevacizumab will not be provided.

For those patients in arm 1 where bevacizumab is not standard of care (e.g. prior anti-angiogenetic treatment) bevacizumab will be ‘investigational drug’. Bevacizumab will be provided.

For those countries where bevacizumab is not registered and/or reimbursed for patients with platinum sensitive recurrent ovarian cancer Bevacizumab will be provided.

For arm 2 (experimental arm (carboplatin/PLD)) bevacizumab will be provided as 'investigational study drug'.

PLD in combination with carboplatin is standard of care and will not be an 'investigational study drug' and will not be provided.

(b) Standard of Care Chemotherapy

The chemotherapy consisting of gemcitabine/carboplatin and PLD/carboplatin are considered to be the standard of care chemotherapy.

The standard of care chemotherapy will not be supplied or reimbursed.

If bevacizumab associated to gemcitabine/carboplatin obtains market authorization and reimbursement according to national authorities, this will be also standard of care; then bevacizumab will not be supplied or reimbursed, too.

6.1 Dose and Schedule of Bevacizumab

For patients randomized in arm 1 bevacizumab will be administered intravenously with a dose of 15 mg/kg on day 1 every 3 weeks. The dose of 10mg/kg bevacizumab will be administered intravenously on day 1 and day 15 every 4 weeks for patients randomized in arm 2. Bevacizumab will be given until disease progression or the occurrence of an unacceptable toxicity. **Bevacizumab must be administered before gemcitabine followed by carboplatin or before PLD followed by carboplatin.**

Bevacizumab and chemotherapy will be administered at the same visit.

Bevacizumab will be calculated prior to every visit according to the actual weight.

If any or all chemotherapy is discontinued prior to disease progression, including for toxicity, bevacizumab will be continued as maintenance therapy with a dose of 15 mg/kg every 3 weeks until disease progression or the occurrence of an unacceptable toxicity related to bevacizumab.

6.2 Preparation and Administration of Bevacizumab

6.2.1 Formulation and Storage

Bevacizumab (Avastin®) is supplied as a clear to slightly opalescent, colorless to pale brown, sterile liquid for intravenous infusion in single-use vials which are preservative-free. Bevacizumab will be supplied in 5 mL glass vials with a 4 mL fill (100 mg, 25 mg/mL) and/or in 20 mL glass vials with a 16 mL fill (400 mg, 25 mg/mL). The formulation contains sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI) in addition to bevacizumab active ingredient.

Upon receipt of the study drug, vials are to be refrigerated at 2°C - 8°C and should remain refrigerated until just prior to use. **DO NOT FREEZE. DO NOT SHAKE.** Keep vial in the outer carton due to light sensitivity.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient. Vials should not be used after the re-test date shown on the pack.

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C - 30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.2.2 Packaging and Labeling

The labeling of bevacizumab will be in accordance with all local legal requirements and conducted according to Good Manufacturing Practice. Labels will include the following key information:

- Bevacizumab 400 mg or 100 mg
- FOR CLINICAL STUDY USE ONLY
- AGO Research GmbH
- AGO-OVAR 2.21
- Patient No.
- Store at 2°C - 8°C
- Expiry date

6.2.3 Route of Administration

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab for a dose of 15 mg/kg of body weight and dilute in a total volume of 100 mL of 0.9% sodium chloride injection. In case of administering a total dose exceeding 1000 mg, dilute the calculated dose of bevacizumab with a sufficient amount of 0.9% sodium chloride injection to keep final concentration between 2.3 mg/mL and 16.5 mg/mL. Keep 100 mL as the minimal volume to administer and limit the infusion volume as much as possible. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Diluted bevacizumab should be used within 8 hours.

Administration will be as a continuous intravenous (i.v.) infusion. Anaphylaxis precautions should be observed during study drug administration.

The first dose of bevacizumab will be administered over 90 minutes. If the first infusion is well tolerated without infusion-related reaction (e.g. fever and/or chills) the 2nd dose will be administered over 60 minutes. If the 2nd dose is also well tolerated without an infusion reaction all subsequent doses will be administered over 30 minutes.

- In case of an infusion-related reaction during the first cycle (during the 90-minute infusion or up to 24 hours later) the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated the next infusion and all subsequent infusions may be delivered over 120 minutes.
- If any infusion-related reactions occur during the second cycle (during the 60 minute infusion or up to 24 hours later) the next infusion must be administered over 90 minutes. If the 90 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 90 minutes.
- If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later all subsequent infusions may be delivered over 60 minutes or longer.

A rate-regulating device should be used for all study drug infusions. When the study drug bag is empty, 50 mL of 0.9% sodium chloride solution will be added to the bag or an additional bag will be hung, and the infusion will be continued for a volume equal to that of the tubing to ensure complete delivery of the study drug. If more saline is infused the extent of saline infusion does not factor into the study drug infusion time.

Should extravasation of the study drug infusion occur the following steps should be taken:

- Discontinue the infusion. Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent. If a significant volume of the study drug infusion remains restart the infusion at a more proximal site in the same limb or on the other side.

In the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb. Maintain an adequate airway. Administer antihistamines, corticosteroids, epinephrine, or other medications as required.
- Continue to observe the patient, document observations and administer further treatment as required.

The above events should be reported as AEs.

6.3 Dose and Schedule of Chemotherapy

Gemcitabine/carboplatin and PLD/carboplatin as standard of care chemotherapy will be administered as followed:

Arm 1:

Gemcitabine	1000 mg/m^2 d1 and 8, q3w; 6 cycles
Carboplatin	AUC4 d1, q3w; 6 cycles

Arm 2:

PLD	30 mg/m^2 d1, q4w; 6 cycles
Carboplatin	AUC5 d1, q4w; 6 cycles

6.3.1 Gemcitabine

Use normally available commercial stock in keeping with the normal practice of the institution and following the instruction of the SPC (summary of product characteristics).

There are no special accountability arrangements for gemcitabine.

Reconstitute gemcitabine 1000 mg/m^2 in 25 ml of normal saline according to the standard practice of the institution. Administer over 30 minutes on day 1 and day 8 of each cycle.

Monitor closely for allergic reactions and hematological events as per local institution guidelines.

If it becomes necessary to discontinue gemcitabine treatment due to toxicity patients can remain on carboplatin and bevacizumab.

6.3.2 Carboplatin

Use normally available commercial stock in keeping with the normal practice of the institution and following the instruction of the SPC (summary of product characteristics).

There are no special accountability arrangements for carboplatin.

Reconstitute carboplatin with 5% dextrose or according to the standard practice of the institution.

Administer over 15-60 minutes (depending on local institutional practice).

The carboplatin dose should be calculated according to the Calvert formula as follows:

- carboplatin dose = Target AUC (GFR + 25).

For the purpose of this protocol the GFR is considered equivalent to the creatinine clearance calculated according to the formula of Cockroft-Gault or Jelliffe. The exact dose of carboplatin therefore depends on the calculated GFR.

Dose capping of carboplatin may be carried out according to local institutional protocols.

If it becomes necessary to discontinue carboplatin treatment due to toxicity patients can remain on bevacizumab and gemcitabine or PLD.

6.3.3 Pegylated Liposomal Doxorubicin (PLD)

Use normally available commercial stock in keeping with the normal practice of the institution and following the instruction of the SPC (summary of product characteristics).

There are no special accountability arrangements for PLD.

Reconstitute PLD in 250 ml of 5% dextrose or according to the standard practice of the institution.

Administer over 60-90 minutes on day 1 of each cycle.

If it becomes necessary to discontinue PLD treatment due to toxicity, patients can remain on carboplatin and bevacizumab.

6.4 Method of randomization

Patients will be randomly assigned to one of the two treatment groups in a 1:1 ratio using permuted block sizes stratifying for the following prognostic factor:

Stratum I: platinum sensitive interval 6 -12 months vs. >12 months

Stratum II: residual tumor in case of debulking surgery for recurrence (In case of no debulking surgery for recurrence all patients will be categorized as having residual tumor.)

Stratum III: Previous vs. no anti-angiogenetic treatment (e.g. anti-VEGF)

Stratum IV: group language

Randomization will be performed through KKS, Philipps-University of Marburg, Germany.

Koordinierungszentrum für Klinische Studien Marburg (KKS)

Philipps University Marburg

Randomization FAX number +49 (0) 6421 28 66516

Monday - Thursday between 8 a.m. and 4 p.m.

Friday between 8 a.m. and 2 p.m.

At randomization, the patient number is checked for uniqueness by the randomization center and confirmed with the treatment assignment. If the uniqueness check is not successful, the randomization center has to clarify this before randomization.

Treatment assignment for each patient to one of the two groups will be given by FAX. Randomization will not be possible during official company closing days.

6.5 Compliance

Accountability and patient compliance will be assessed by maintaining adequate “drug dispensing”, “drug inventory”, and “drug destruction” records.

Accurate records must be kept for study drug vial provided by the sponsor. These records must contain the following information:

- documentation of drug shipments (date received, quantity and batch identity)
- disposition of unused study drug not administered to a patient

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the study drug was dispensed
- the date(s), quantity and batch identity of the study drug administered to the patient

This inventory must be available for inspection by the monitor. All supplies, including partially used containers and copies of the dispensing & inventory logs, must be returned to the sponsor before the end of the trial, unless alternate destruction has been authorized by the sponsor, or is required by local or institutional regulations. The destruction of partially used or empty vials should be documented in writing.

7 SAFETY ISSUES

The Investigator's Brochure of bevacizumab will be used as reference document for the study drug and will be provided.

Study drug means bevacizumab only for patients randomized in arm 2 or for patients randomized in arm 1 with e.g. prior anti-angiogenetic treatment (see also section 6).

All adverse events (either related to trial specific procedures or otherwise) experienced after the patient has signed the informed consent form but before they have received study drug should be recorded as adverse events or serious adverse events.

All adverse events occurring after signing the informed consent form up to 30 days after treatment discontinuation must be recorded on the AE form of the eCRF. Additionally, non-serious, new AEs considered related to study drug which occur up to 26 weeks after the last dose of study drug should also be reported. SAEs considered related to study drug are to be reported indefinitely.

7.1 Adverse Events

It is the responsibility of the investigator(s) to report all adverse events in the eCRF.

7.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions (except the underlying malignancy, see section 7.1.1.3) which worsen during the clinical trial are to be reported as adverse events. They can become serious adverse events if they fulfill one of the seriousness criteria described in section 20.2.

All clinical adverse events (AEs) encountered during the clinical trial will be reported on the AE page of the eCRF.

7.1.2.1 *Intensity*

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) on a five-point scale (grade 1 to 5) and reported in detail on the eCRF.

Table 2: Grading of adverse events not listed on the CTCAE:

CTC Grade	Equivalent To	Definition
Grade 1	Mild	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	severe or medical significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4	Life threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death	death related to AE

7.1.2.1 *Drug – adverse event relationship*

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No.

If there is a reasonable suspected causal relationship to the study drug, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

– Reasonable temporal association with drug administration

– It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– Known response pattern to suspected drug

– Disappears or decreases on cessation

– Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:

– It does not follow a reasonable temporal sequence from administration of the drug.

– It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– It does not follow a known pattern of response to the suspected drug.

– It does not reappear or worsen when the drug is readministered.

For more details please refer to section 20.1.

7.1.2.1 *Progression of underlying malignancy*

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST v1.1 criteria or GCIG criteria for CA 125. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of

disease progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under trial.

If there is any uncertainty about an adverse event being due only to the disease under the clinical trial it should be reported as an AE or SAE.

7.1.2 Adverse Events of Special Interest

Adverse Events of Special Interest for Bevacizumab which are listed in section 7.3 should be closely monitored as part of the study procedures.

7.1.3 Serious Adverse Events

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the clinical trial, irrespective of the treatment received by the patient, must be reported to the local Study Group within 24 hours of knowledge (expedited reporting).

The definition and reporting requirements according to national laws and ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting will be adhered (for details refer to section 20.2).

Specific exceptions to SAE reporting

The following events, in the context of this trial should not be considered as SAEs. No SAE form is required and they are exempt from expedited reporting. They must be reported on the appropriate eCRF section:

- disease progression or death as a result of disease progression
- elective hospitalization and surgery for treatment of advanced epithelial ovarian fallopian tube cancer or peritoneal cancer or its complications
- elective hospitalization to simplify treatment or procedures
- elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.

7.1.4 Laboratory Test Abnormalities

Any clinically significant laboratory result fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant (e.g. meeting one or more of the following conditions) should be recorded as a single diagnosis on the adverse event page in the eCRF:

– accompanied by clinical symptoms

– leading to a change in study drugs (e.g. dose modification, interruption or permanent discontinuation)

– requiring a change in concomitant therapy (e.g. addition of interruption of, discontinuation of or any other change in a concomitant medication, therapy or treatment)

7.2 Handling of Safety Parameters

7.2.1 Treatment and Follow-up of Adverse Events

Adverse events, especially those for which the relationship to study drug is not "unrelated", should be followed up until they have returned to baseline status or stabilized. If a clear explanation is established it should be recorded on the eCRF.

7.2.2 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an ade-

quate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.2.3 Pregnancy

Every patient must be instructed to immediately inform the investigator if she becomes pregnant during the clinical trial. Pregnancies occurring up to six months after the completion of the study drug must also be reported to the investigator. The investigator must report all pregnancies within 24 hours to the local Study Group. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

7.3 Dose Modifications of Bevacizumab for Toxicity

No dose reduction of bevacizumab is foreseen for an individual patient. Skipped doses or termination of treatment will be based on the observed toxicities. If any weight change of more than 10% is observed, the treatment dosage should be modified accordingly. Other than in cases of significant weight change, no other dose modifications are allowed for bevacizumab. **Missed doses will not be administered subsequently.**

In cases of toxicity, please refer to the current version of the bevacizumab Investigator's Brochure for guidance.

As described below, bevacizumab treatment may be either temporarily or permanently suspended in the case of hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF or wound healing complications in addition to any other serious bevacizumab-related toxicity (grade 3 or 4).

Bevacizumab should be temporarily withheld in the event of grade 4 febrile neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. In general, appropriate management for grade 3 or 4 bevacizumab-related events is described in sections 7.3.

In addition, bevacizumab treatment should be permanently discontinued in patients experiencing any of the following events:

- Posterior Reversible Encephalopathy Snydrome (PRES)
- grade 3/4 hemorrhagic/bleeding events
- grade 3/4 left ventricular dysfunction (CHF)
- grade 4 venous thromboembolism including pulmonary embolism
- grade 4 hypertension (hypertensive crisis) or hypertensive encephalopathy
- grade 4 non-gastrointestinal fistula
- grade 4 proteinuria (nephrotic syndrome)
- any grade of CNS bleeding
- any grade of arterial thromboembolism
- any grade of gastrointestinal perforation
- any grade of tracheo-esophageal fistula
- any grade of hypersensitivity/allergic reactions related to Bevacizumab

Table 3: Management of grade 3 or 4 bevacizumab-related adverse events

First occurrence	Hold bevacizumab until toxicity has improved to ≤ grade 1.
Second occurrence	Permanently discontinue bevacizumab treatment.

7.3.1 CNS bleeding

Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade. Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patients has not been prospectively evaluated.

7.3.2 Hypertension

Patients must be closely monitored on trial for the development or worsening of hypertension. Blood pressure measurements should occur after the patient has been in a resting position for ≥ 5 minutes. If the initial BP reading is neither ≥ 140 mmHg systolic and/nor≥ 90 mmHg diastolic pressures the result should be verified with a repeat measurement. If hypertension occurs bevacizumab treatment should be managed as described in table 4.

Table 4: Bevacizumab treatment management for hypertension

NCI CTCAE v4.03	Hypertension Pattern	Treatment Action
Grade 1	Prehypertension (Systolic BP 120 – 139 mmHg or diastolic BP 80 – 89 mmHg.)	Give bevacizumab.
Grade 2	Stage 1 hypertension (systolic BP 140 – 159 mmHg or diastolic BP 90 - 99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic increase by > 20 mmHg (diastolic) or to >140/90 mmHg if previously WNL; monotherapy indicated	Withhold bevacizumab. Start antihypertensive therapy. Once BP is < 140/90 mmHg, patients may continue bevacizumab therapy.
Grade 3	Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Hold bevacizumab for persistent or symptomatic hypertension and discontinue permanently if hypertension is not controlled according to investigator judgment.
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Permanently discontinue bevacizumab.

7.3.3 Proteinuria

Proteinuria will be assessed within 72 hours before each bevacizumab treatment by dipstick method unless assessed by 24-hour urine collection. Alternatively, proteinuria testing can be performed according to local standard. An algorithm for the appropriate management following a positive dipstick result with corresponding bevacizumab treatment management guidance is provided below (Table 5).

Nephrotic syndrome (grade 4 proteinuria): Bevacizumab must be permanently discontinued if nephrotic syndrome is detected at any time.

Table 5: Bevacizumab treatment management for proteinuria

NCI CTCAE v4.03	Urinalysis	Treatment Action
Grade 1	1+ proteinuria urinary protein < 1.0 g/24 hrs	No bevacizumab dose modification.
Grade 2	2+ proteinuria urinary protein 1.0 - 3.4 g/24 hrs	Suspend bevacizumab for urine protein level ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hrs. For 2+ dipstick: may administer bevacizumab; obtain 24-hour urine prior to next bevacizumab dose. For 3+ dipstick: obtain 24-hour urine prior to bevacizumab administration.
Grade 3	Urinary protein ≥ 3.5 g/24 hrs	Suspend bevacizumab. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection < 2.0 g.
Grade 4 (nephrotic syndrome)		Permanently discontinue bevacizumab.

7.3.4 Dose interruption due to infusion-associated reactions

For administration guidelines, see section 6.2.

• In case of an infusion-related reaction during the first cycle (during the 90-minute infusion or up to 24 hours later) the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated the next infusion and all subsequent infusions may be delivered over 120 minutes.

• If any infusion-related reaction occurs during the second cycle (during the 60 minute infusion or up to 24 hours later) the next infusion must be administered over 90 minutes. If the 90 minute infusion is well tolerated the next infusion and all subsequent infusions may be delivered over 90 minutes.

• If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later all subsequent infusions may be delivered over 60 minutes or longer.

7.3.5 Surgical procedures and wound healing complications

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported.

Bevacizumab therapy should be withheld for an interval of at least four weeks (28 days) before conducting elective surgery. In the case of unplanned surgical procedures bevacizumab should be stopped as soon as the indication for surgery is identified. Emergency surgery should be performed as appropriate without delay after a careful risk benefit assessment.

Necrotising fasciitis including fatal cases has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

It is strongly recommended that an interval of 7 days is left between the insertion of any central venous access devices (CVADs) and the onset of bevacizumab treatment.

Bevacizumab therapy should be restarted ≥ 28 days and ≤ 42 days following major surgery. In patients who experience wound healing complications during bevacizumab treatment

bevacizumab should be withheld until the wound is fully healed. If the wound is not fully healed within 42 days bevacizumab treatment should be discontinued.

Continuation of study treatment in patients who have had bevacizumab therapy delayed for more than 2 treatment cycles due to surgical procedures or wound healing must be discussed with the AGO Study Group.

7.3.6 Thromboembolism

Arterial thromboembolism: If a patient experiences any grade of arterial thromboembolism during the treatment period bevacizumab should be discontinued permanently.

Venous thromboembolism: Patients experiencing a grade 4 venous thromboembolism (including pulmonary embolism) must be discontinued from the clinical trial.

If a patient experiences a grade 3 venous thromboembolism bevacizumab must be withheld for 3 weeks. Bevacizumab may be resumed during the period of therapeutic-dose anticoagulant therapy.

Table 6: Bevacizumab treatment management for venous thromboembolism

NCI CTCAE v4.03	**Thromboembolic Event**	**Treatment Action**
Grade 1	Venous thrombosis (e.g. superficial thrombosis)	No bevacizumab dose modifications.
Grade 2	Venous thrombosis (e.g. uncomplicated deep vein thrombosis), medical intervention indicated	No bevacizumab dose modifications.
Grade 3	Thrombosis (e.g. uncomplicated pulmonary embolism), medical intervention indicated	Hold bevacizumab treatment for 3 weeks. If the planned duration of full-dose anticoagulation is < 2 weeks bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; heparin, coumadin or other anticoagulant dosing must be stable prior to restarting bevacizumab. • The patient must not have had a grade 3 or 4 hemorrhagic event while on anticoagulation.
Grade 4	Life-threatening (e.g. pulmonary embolism, cerebrovascular event); hemodynamic or neurologic instability; urgent intervention indicated	Permanently discontinue bevacizumab.

7.3.7 Hemorrhage

If grade 3 or 4 bleeding of any kind occurs during the study treatment period bevacizumab should be permanently discontinued.

If hemorrhagic complications occur in patients on full dose anticoagulation therapy permanently discontinue bevacizumab treatment and follow guidelines of the institution. Standard procedures such as antagonisation with protamine or vitamin K, infusion of vitamin K dependent factors or insertion of a vena cava filter, should be considered dependent on the severity of the bleeding event and the organ affected.

Dose modifications for the selected chemotherapy should be made according to local practice guidelines.

7.3.8 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of patients treated with bevacizumab that develop signs and symptoms consistent with Posterior Reversible Encephalopathy Syndrome (PRES), an occasional neurological disorder which can present with the following signs and symptoms among others and which can be permanent: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

7.3.9 Gastrointestinal Perforation

Patients with bevacizumab treatment have an increased risk of gastrointestinal perforation.

Any cases of gastrointestinal perforation and symptomatic fistulae should be managed aggressively with the involvement of the appropriate surgical team in the usual manner. Bevacizumab must be ceased indefinitely. The surgical team must be informed that the patient has been receiving bevacizumab and that this may potentially compromise wound healing.

Caution should be exercised when treating patients with intra-abdominal inflammatory processes, any clinical suspicion of frank or impending bowel obstruction or a history of any gastrointestinal perforation.

7.3.10 Fistula

An increased risk exists for the emergence of fistula. These are most often gastrointestinal in origin but may originate from other sites including the genitourinary system and rarely the trachea and/or esophagus (this specifically has not occurred in any patients with ovarian cancer).

Any patient who develops any of the following must cease bevacizumab permanently:

- a grade 4 fistula of any origin, irrespective of causality to bevacizumab

- any grade of fistula possibly, probably or definitely related to bevacizumab

- any grade of tracheosophageal fistula.

Any patient who develops any other fistula deemed by the treating physician to be unrelated to bevacizumab and to be related to surgery must have bevacizumab ceased at least until the fistula resolves completely (by either conservative management or surgery). At this point, if it is thought to be in the patient's best interest to continue with bevacizumab then this must be discussed with the AGO Study Group. Bevacizumab can not be restarted without formal approval.

Any patient who develops any other fistula deemed by the treating physician to be unrelated to bevacizumab and to be related to the disease process itself, including for example rapid disease regression, must also have bevacizumab ceased at least until the fistula resolves

completely. At this point, if it is thought to be in the patient's best interest to continue with bevacizumab, then this must be discussed on a case by case basis with the AGO Study Group. Bevacizumab cannot be restarted without formal approval. It is recognized that causality in these cases may be more difficult to assign with certainty, and in these cases bevacizumab will be ceased permanently.

7.3.4 Congestive Heart Failure (CHF)

No increased incidence of CHF has been seen in patients treated with bevacizumab in other clinical trials apart from metastatic breast cancer.

For patients with clinically important cardiovascular disease or preceding congestive heart failure caution is required.

If grade 3 or 4 of left ventricular dysfunction (CHF) occurs during the treatment period bevacizumab should be permanently discontinued.

7.4 Dose Modifications and Delays of Chemotherapy

7.4.1 Carboplatin and Gemcitabine

7.4.1.1 Hematologic toxicity

Treatment should be delayed if either of the following occurs within 24 hours prior to the administration of therapy:

- Absolute neutrophile count < 1.5 x 10^9/L (or < 1.0 x 10^9/L if the patient is planned to receive G-CSF)
- Platelet count < 100 x 10^9/L

Full blood count (FBC) should be repeated, at least weekly, until hematologic recovery has occurred (ANC ≥ 1.5 x 10^9/L or > 1.0 x 10^9/L if the patient is planned to receive G-CSF and PLT ≥ 100 x 10^9/L). If hematologic recovery occurs within 7 days, no dose modification is mandated and any dose modification is left to the discretion of the individual investigator. If hematologic recovery occurs beyond 7 days doses of gemcitabine/carboplatin should be modified according to the blood count. G-CSF may be used as stipulated by the ASCO guidelines or according to local practice guidelines.

Patients who fail to recover adequate counts after a delay of 2 weeks or more, or who have consecutive dose-limiting toxicities, are not likely to be able to tolerate standard chemotherapy treatment. If it is considered in the patient's best interest to remain within the clinical trial and to continue to receive treatment according to the protocol, then significant modifications to the chemotherapy dose may be required. Such extreme modifications are likely to be rare and should therefore be discussed on a case by case basis with the AGO Study Group. In this situation patients may continue to receive bevacizumab.

Dose modifications for gemcitabine on day 8 will be performed according to the guidelines in table 7.

Table 7: Guidelines for gemcitabine dose adjustments on day 8 for hematologic toxicities

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Level
≥ 1.5	and	≥ 100	100 %
≥ 1.0 to 1.4	and/or	75 – 99	50 %
< 1.0	and/or	< 75	omit dose

Patients may receive erythropoietin (EPO), iron supplements and/or blood transfusions as clinically indicated for the management of their anemia.

Dose adjustment for gemcitabine in combination with carboplatin for subsequent cycles is based on toxicity observed during the preceding cycle. The dose of gemcitabine should be permanently reduced on day 1 and day 8 in case of any of the following hematological toxicities:

- Absolute Neutrophil Count < 500 x 10^6/L for more than 5 days
- Absolute Neutrophile Count < 300 x 10^6/L for more than 3 days
- Febrile Neutropenia
- Platelets < 25 x 10^9/L
- cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction for the subsequent cycles, gemcitabine and carboplatin should be reduced according to table 8. Gemcitabine should be given only on day 1 (omit gemcitabine on day 8).

Table 8: Dose levels for gemcitabine and carboplatin

Drug	**Protocol Starting Dose**	**Protocol Dose Level -1**	**Protocol Dose Level -2**
Gemcitabine	1000 mg/m^2	800 mg/m²	-
Carboplatin	AUC4	AUC3	-

7.4.1.2 Non-hematologic toxicity

Renal toxicity

The combination of gemcitabine and carboplatin with bevacizumab is not directly expected to cause renal toxicity. Therefore, no specific dose modifications are recommended for renal toxicity. Any concerns should be discussed with the AGO Study Group.

However, the administered dose of carboplatin must be recalculated, based on a recalculated or remeasured GFR, for

- renal toxicity (CTC Grade 2, serum creatinine > 1.5 x ULN)
- changes in serum creatinine of ≥ 10%
- each dose modification of carboplatin
- cycle 2 if there has been significant doubt about the true GFR at cycle 1 (e.g. due to significant ascites).

Hepatic toxicity

If gemcitabine will be administered to patients with liver metastases or hepatitis in their history a deterioration of the existing liver insuffiency is possible. Transaminases should be checked on a regular basis.

Hypersensitivity to carboplatin

If there is a hypersensitivity reaction to carboplatin this should be managed as per local institutional protocols. Cisplatin can be substituted for carboplatin at the discretion of the treating physician. Cisplatin (75 mg/m^2) would be administered i.v. over 30 minutes every 3 weeks. For patients who experience dose-limiting toxicity with cisplatin, the dose can be reduced to 60 mg/m^2 and subsequently to 50 mg/m^2 if further dose-limiting toxicity occurs.

Other

There are no dose modifications planned for alopecia, nausea, diarrhea or constipation. These side effects should be treated with supportive medical measures. Non-steroidal anti-inflammatory agents can be used prophylactically or symptomatically, as per local practice.

Any CTC grade 4 non-hematologic AE (except nausea or vomiting) will require the patient to be taken off treatment. For any grade 3 non-hematologic toxicity (except nausea or vomiting) the drugs should be withheld until symptoms resolve to ≤ grade 1. If the grade 3 event persists for ≥ 3 weeks, or recurs, then discussion with the AGO Study Group is recommended.

7.4.2 Carboplatin and Pegylated Liposomal Doxorubicin

7.4.2.1 *Hematologic toxicity*

Treatment should be delayed if either of the following occurs within 24 hours prior to the administration of therapy:

- Absolute Neutrophil Count < 1.5 x 10^9/L (or < 1.0 x 10^9/L if the patient is planned to receive G-CSF)
- Platelet count < 100 x 10^9/L

FBC should be repeated, at least weekly, until hematologic recovery has occurred (ANC ≥ 1.5 x 10^9/L or > 1.0 x 10^9/L if the patient is planned to receive G-CSF and PLT ≥ 100 x 10^9/L). If hematologic recovery occurs within 7 days no dose modification is mandated and any dose modification is left to the discretion of the individual investigator. If hematologic recovery occurs beyond 7 days, doses of PLD/carboplatin should be modified according to the blood count (or subsequent FBC if lower; according to the criteria described in table 11). G-CSF may be used as stipulated by the ASCO guidelines or according to local practice guidelines.

Patients who fail to recover adequate counts after a delay of 2 weeks or more, or who have consecutive dose-limiting toxicities, are not likely to be able to tolerate standard chemotherapy treatment. If it is considered in the patient's best interest to remain within the clinical trial and to continue to receive treatment according to the protocol, then significant modifications to the chemotherapy dose may be required. Such extreme modifications are likely to be rare and should therefore be discussed on a case by case basis with the AGO Study Group. In this situation patients may continue to receive bevacizumab.

Hematologic dose-limiting toxicities and permitted dose modifications are defined in table 9 and table 10. Patients developing any other dose-limiting toxicity require dose modification independently of the ANC and platelets.

Patients may receive erythropoietin (EPO), iron supplements and/or blood transfusions as clinically indicated for the management of their anemia.

Table 9: Guidelines for PLD and carboplatin dose modification for delayed hematological recovery

	Delayed ANC recovery (> 7 days)	
Delayed PLT Recovery (> 7 days)	**ANC ≥ 1.5 x 10^9/l**	**ANC < 1.5 x 10^9/l**
PLT ≥ 100 x 10^9/l	**PLD:** No modification **Carboplatin:** No modification	**PLD:** Use G-CSF and continue current dose **Carboplatin:** No modification
PLT < 100 x 10^9/l	**PLD:** No modification **Carboplatin:** Reduce by 1 AUC unit	**PLD:** Either: Use G-CSF and continue current dose OR: Reduce by 1 dose level **Carboplatin:** Reduce by 1 AUC unit

Table 10: Guidelines for PLD and carboplatin dose modification for dose limiting toxicity

	Dose-Limiting Toxicity: ANC	
Dose-Limiting Toxicity: PLT	**No**	**Yes**
No	**PLD:** No modification **Carboplatin:** No modification	**PLD:** Use G-CSF and continue current dose **Carboplatin:** No modification
Yes	**PLD:** No modification **Carboplatin:** Reduce by 1 AUC unit	**PLD:** Either: Use G-CSF and continue current dose Or: Reduce by 1 dose level **Carboplatin:** Reduce by 1 AUC unit

Table 11: Dose levels for PLD and carboplatin

Drug	Protocol Starting Dose	Protocol Dose Level -1	Protocol Dose Level -2
PLD	30 mg/m^2	25 mg/m²	-
Carboplatin	AUC5	AUC4	-

7.4.2.2 Non-hematologic toxicity

Renal toxicity

The combination of PLD and carboplatin with bevacizumab is not directly expected to cause renal toxicity. Therefore, no specific dose modifications are recommended for renal toxicity. Any concerns should be discussed with the AGO Study Group.

However, the administered dose of carboplatin must be recalculated, based on a recalculated or remeasured GFR, for

- renal toxicity (CTC Grade 2, serum creatinine > 1.5 x ULN)
- changes in serum creatinine of ≥ 10%
- each dose modification of carboplatin
- cycle 2 if there has been significant doubt about the true GFR at Cycle 1 (e.g. due to significant ascites).

Cutaneous toxicity

The following table (table 12) shows the dose modification for PLD and the delays recommended as a function of the occurrence and severity of cutaneous toxicity (PPE).

Table 12: PLD treatment management for cutaneous toxicity

NCI CTCAE v4.03	Palmar-plantar erythrodysesthesia syndrome (PPE)	Situation at day 28	Situation at day 35	Situation at day 42
Grade 1	Minimal skin changes or dermatitis (e.g. erythema, edema or hyperkeratosis) without pain	Wait an additional week and redose at full dose unless patient had experienced a grade ≥ 2 toxicity in which case reduce dose by one level.	Wait an additional week and redose at full dose unless patient had experienced a grade ≥ 2 toxicity in which case reduce dose by one level.	Dose reduction by one dose level; back to 4-weekly interval.
Grade 2	Skin changes (e.g. peeling, blisters, bleeding, edema or hyperkeratosis) with pain; limiting instrumental ADL	Wait an additional week.	Wait an additional week.	Dose reduction by one dose level; back to 4-weekly interval.

NCI CTCAE v4.03	**Palmar-plantar erythrodysesthesia syndrome**	Situation at day 28	Situation at day 35	Situation at day 42
Grade 3	Severe skin changes (e.g. peeling, blisters, bleeding, edema or hyperkeratosis) with pain; limiting self-care ADL	Wait an additional week.	Wait an additional week.	Permanently discontinuation of PLD.
Grade 4	n/a	n/a	n/a	n/a

Gastrointestinal toxicity

Table 13 shows the dose modifications and delays for occurrence of mucositis during treatment with PLD.

Table 13: PLD treatment management for gastrointestinal toxicity

NCI CTCAE v4.03	**Mucositis**	Situation at day 28	Situation at day 35	Situation at day 42
Grade 1	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Wait an additional week and redose at full dose unless patient had experienced a grade ≥ 2 toxicity in which case reduce dose by one level.	Wait an additional week and redose at full dose unless patient had experienced a grade ≥ 2 toxicity in which case reduce dose by one level.	Dose reduction by one dose level; back to 4-weekly interval or permanently discontinuation of PLD in investigator's discretion.
Grade 2	Moderate pain not interfering with oral intake; modified diet indicated	Wait an additional week.	Wait an additional week.	Dose reduction by one dose level; back to 4-weekly interval or permanently discontinuation of PLD in investigator's discretion.
Grade 3	Severe pain interfering with oral intake	Wait an additional week.	Wait an additional week.	Permanently discontinuation of PLD.
Grade 4	Life-threatening consequences urgent intervention indicated	Wait an additional week.	Wait an additional week.	Permanently discontinuation of PLD.

Cardiac toxicity

Prior treatment with PLD an ECG assessment should be done routinely. More specific than an ECG assessment for evaluation and observation of the heart function will be the measurement of left ventricular ejection fraction (LVEF) by ECHO/MUGA. LVEF measurement has to be done for any patient treated with PLD during treatment period.

Hypersensitivity to carboplatin

If there is a hypersensitivity reaction to carboplatin this should be managed as per local institutional protocols. Cisplatin can be substituted for carboplatin at the discretion of the treating physician. Cisplatin (75 mg/m^2) would be administered i.v. over 30 minutes every 3 weeks. For patients who experience dose-limiting toxicity with cisplatin, the dose can be reduced to 60 mg/m^2 and subsequently to 50 mg/m^2 if further dose-limiting toxicity occurs.

Other

There are no dose modifications planned for alopecia, nausea, diarrhea or constipation. These side effects should be treated with supportive medical measures. Non-steroidal anti-inflammatory agents can be used prophylactically or symptomatically, as per local practice.

Any CTC grade 4 non-hematologic AE (except nausea or vomiting) will require the patient to be taken off treatment. For any grade 3 non-hematologic toxicity (except nausea or vomiting) the drugs should be withheld until symptoms resolve to ≤ grade 1. If the grade 3 event persists for ≥ 3 weeks, or recurs, then discussion with the AGO Study Group is recommended.

7.5 Criteria for Discontinuation or Termination of the Trial

7.5.1 Omission during maintenance treatment

It is permitted to omit a cycle (i.e. because of vacation) during maintenance treatment in case of patients wish. The omitted dose of bevacizumab will not be replaced at a later time point.

An interruption of two consecutive cycles or more must be discussed with the AGO Study Group.

7.5.1.1 *Criteria for Discontinuation of the Treatment or Premature Withdrawal of the Patient*

In addition to the common criteria described in section 13, the criteria described in section 7.3 concerning discontinuation of study treatment for toxicity lead to a discontinuation of the treatment or premature withdrawal of the patient.

In case of a premature withdrawal the patient must return for a safety follow-up assessment.

7.5.2 Criteria for Discontinuation or Termination of the Trial

Criteria which could lead to discontinuation or termination of the clinical trial are described in section 13.

7.6 Warnings and Precautions

No evidence available at the time of the approval of this protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure for bevacizumab.

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample Size calculation

The primary outcome measure is progression-free survival (PFS). The OCEANS trial reported a median PFS for the experimental arm with carboplatin/gemcitabine plus bevacizumab of 12.4 months with a 95% CI of 11.4 to 12.7 (HR=0.484; 95% CI: 0.388; 0.605) based on the investigator assessments (fig. 2, p. 2042), and a median PFS of 12.3 with a 95% CI of 10.7 to 14.6 (HR=0.451; 95% CI: 0.351; 0.580) based on the assessments of the independent re-

view committee (fig. 4, p. 2043).[23] A recently small “proof of concept” phase II trial reported as secondary outcome a median PFS of 13.9 months with a 95% CI of 11.2 to 16.0 for the combination therapy of carboplatin, PLD and bevacizumab indicating potentially effects of the combination therapy on PFS[47] which may point to the expectation of the benefit for the experimental therapy.[57]

Based on the in section 1.2 detail outlined rationale for the expected clinical effect sizes with bevacizumab, a minimal relevant clinical difference for PFS of Hazard Ratio (HR) 0.79 should be detectable with 80% power in favor of the experimental arm in this trial.

With N = 654 patients randomised at a steady rate over a period of 30 months with an additional 30 months follow-up after the last patient randomised, the trial will have 80% power (two-sided log-rank test, significance level of 5%) to show a 26.6% change in PFS from a median value of 12.4 months in the control arm to 15.7 months in the experimental arm, i. e. a Hazard Ratio (HR) of 0.79. It is expected that 564 PFS events will have occurred at the time point of primary analysis in the ITT population. With respect of a patient drop-out rate of 15% under the assumption of exponentially distributed drop-out times a total of N=654 patients has to be enrolled into the trial, 327 patients each arm.

The number of events can be recalculated during the trial to achieve a (conditional) power of 80% and to guarantee the experiment wise alpha error probability by means of the principle of Schäfer and Müller.[59] This method, based on the calculation of conditional error rejection probability, allows by inspection the adaption of the design (i.e., sample size adjustment, duration of the follow-up) on the basis of the data collected at that timepoint of inspection. A rejection of the nullhypothesis at timepoint of inspection is not possible for the trial. As the algorithmical definition for the conditional error rejection probability functions of $\varepsilon+ (\tau; \kappa)$ and $\varepsilon- (\tau; \kappa)$ (τ: value obtained by the logrank statistic; κ: total number of observed events up to the timepoint of inspection) the p-values defined version ($p=1-\Phi (\tau/\sqrt{\kappa 0})$ will be used according to Schäfer and Müller. The procedure will be described in more detail in the statistical analysis plan (SAP).

The formula of Schoenfeld (Biometrika, 1981, 316-19) was used for the calculation of the number of events to perform the sample size estimation with the software package ADDPLAN.

8.2 Definition of Population for Analysis

8.2.1 Intent-to-Treat Population

The Intent-to-treat (ITT) population is defined as all patients randomized in the trial, regardless of whether they actually received treatment. The treatment groups will be analyzed as randomized..

8.2.2 Per Protocol Population

The Per Protocol (PP) population is a subgroup of the ITT population containing all patients who do not have any major protocol violation and received both study treatments (chemotherapy and Bevacizumab) at least once. Major protocol violations will be defined in the Statistical Analysis Plan (SAP).

8.2.3 Safety Population

The safety population is defined to include all patients who received at least one dose of the study drug and a safety follow-up, whether withdrawn prematurely or not, will be included in the safety analysis.

8.3 Outcome measures

8.3.1 Primary outcome measure

- Progression-free survival (PFS)

8.3.2 Secondary outcome measure

- Overall Survival (OS)
- Biological progression-free survival (PFS_{BIO})
- Quality of Life (QoL)
    - QoL will be assessed using EORTC QLQ-C30 and QLQ-OV28 questionnaires
- Safety and Tolerability

8.4 Statistical Analysis

8.4.1 Primary Efficacy Analysis

The primary endpoint is progression-free survival defined as the time from the date of randomization to the first documented disease progression (according to RECIST v1.1/GCIG) or death, whichever occurs first.

The primary hypotheses are: H_0: H_0: HR=1 versus H_1: HR≤0.79.

The primary analysis will be done by a stratified log-rank test (stratifying for the factors used for randomization) for the difference in the distribution of progression-free survival (PFS) between the groups (two-sided at an alpha-level of 5%) when 564 events have occurred. Kaplan-Meier estimates for median PFS with the corresponding 95% confidence intervals will be presented. To assess the hazard ratio a stratified cox regression analysis will be performed, the point estimate for the hazard ratio and corresponding 95%CI will be presented**.** If necessary, design adaptations (i. e, recalculation of number of events) can be made according to Schäfer and Müller[59,60] (see section 8.1)

8.4.2 Secondary Analyses

Overall survival (OS) is defined as time from randomization to death from any cause. For OS the same analyses as for PFS will be performed.

To assess the secondary outcome biological progression-free survival PFS_{bio} according to GCIC criteria (see appendix 10) stratified log-rank test and cox regression analyses will be performed, the point estimate for the hazard ratio and corresponding 95% CI will be presented. Kaplan-Meier estimates for median PFS_{bio} with the corresponding 95% CI will also be presented.

Further cox regression models will be performed to analyze the impact of significant baseline covariates regarding PFS and OS; different subgroups (such as status of prior anti-angiogenetic treatment) will also be explored descriptively.

Quality of Life (QoL) with the scores EORTC QLQ-C30 and QLQ-OV28 will analysed descriptively.

8.4.3 Safety Data Analysis

The safety analyses will be based on the safety population. All safety parameters will be summarized and also listed by patient. Summary tables will be presented for incidence rates (number of patients with at least one incidence) of AEs, SAEs, AEs that led to premature withdrawal of trial treatment and interruptions/dose modifications, as well as summaries of severity (CTCAE v4.03 grades) and causal relationship. Tables of change from baseline will be presented for clinical laboratory assessments, vital signs, LVEF and ECOG performance status. Laboratory abnormalities will also be summarized in tables or figures showing shifts in grade.

8.4.4 Further methodological and statistical issues

8.4.4.1 *Interim Analysis*

No interim efficacy analysis and/or stopping rules are planned. The method of Schäfer and Müller allows by inspection necessary changes of the design (i.e., sample size adjustment, duration of the follow-up) on the basis of the data collected at that timepoint of inspection. A rejection of the the null hypothesis at the timepoint of inspection is not possible for the trial.

There will be regular safety review of data by IDMC (Section 10).

8.4.4.2 *Multiplicity*

All significance tests not included in the primary efficacy analysis for PFS are to be considered descriptive in nature since they are secondary or exploratory analyses and therefore will not be adjusted for multiplicity regards.

8.4.4.3 *Statistical analysis plan*

A statistical analysis plan (SAP) for the trial to include detailed information on the analysis of primary and secondary outcome measures and the definitions of major protocol deviations will be provided by the KKS, Philipps-University of Marburg, and the AGO Study Group.

9 DATA QUALITY ASSURANCE

Data for this trial will be recorded via an Electronic Data Capture (EDC) system MACRO using eCRF. It will be transcribed by the site from the paper source documents onto the eCRF.

Accurate and reliable data collection will be assured by verification and cross-checking of the eCRFs against the investigator's records by the monitoring (source document verification), and the maintenance of a drug-dispensing log.

Every investigator, study nurse, monitor or other person involved in the trial receives his or her personal login data (username and password). Access rights to the database will depend on the group affiliation. Users of the EDC-System MACRO will receive the training materials (EDC manual) by the data management of KKS, Philipps-University of Marburg. Every person who gets access to the system has to fill in a registration form (User-ID request) and has to confirm that they have been adequately trained.

Thus it is guaranteed that only authorised persons have access to the system to document patients in the trial. The data are transferred via high encryption (128-bit, SSL) across the internet

A comprehensive validation check program utilising front-end checks in the eCRF and back-end checks in the database will verify the data and discrepancies (queries) will be generated accordingly. These are transferred electronically to the eCRFs at the site for resolution by the investigator.

10 CLINICAL TRIAL COMMITTEES

An Independent Data Monitoring Committee (IDMC) will be established for the AGO-OVAR 2.21 trial. The IDMC will meet on a regular basis and will be responsible for independently evaluation of the safety for the patients participating in the clinical trial. The IDMC will also check the integrity and the validity of the data and the conduct of the clinical trial.

The IDMC will make recommendations concerning the conduct of the trial to the AGO Study Group.

The responsibilities of the IDMC will be documented in a separate Charter.

11 ETHICAL ASPECTS

Declaration of Helsinki / Good Clinical Practice

The Declaration of Helsinki in the present version is the accepted basis for clinical trial ethics and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol.

Additionally, it is the responsibility of all engaged in research on human beings to ensure that the clinical trial is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical trials.

12 CONDITIONS FOR MODIFYING THE PROTOCOL

All protocol modifications must be submitted to the appropriate Independent Ethics Committee for information and approval in accordance with local requirements, and to Regulatory Authorities if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (i.e. change of telephone number(s)).

13 DISCONTINUATION OR EARLY TERMINATION OF THE TRIAL

13.1 Withdrawal from trial treatment

A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

- disease progression whilst on therapy
- unacceptable toxicity
- intercurrent illness which prevents further treatment
- withdrawal of consent for treatment by patient
- any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion

Patients have the right to withdraw from the trial at any time for any reasons.

In case the patient decides to prematurely discontinue trial treatment ("refuses treatment"), she should be asked if she can still be contacted for further information. The outcome of that discussion should be documented in both, the patient clinical source documents and in the eCRF.

13.2 Termination of the trial

Both the AGO Study Group and the chief investigator, reserve the right to discontinue the trial at any time for the following reasons after consultating the IDMC:

- an accumulation of adverse events arises
- within the study period the planned number of patients cannot be achieved
- decision for termination by the competent authority
- the premature termination is decided by the principal investigators.

Should this be necessary both parties will arrange the procedures on an individual trial basis after review and consultation. In discontinuation of the clinical trial AGO Study Group and the investigator will ensure that adequate consideration is given to the protection of the patient's interests.

14 TRIAL DOCUMENTATION, ECRFS AND RECORD KEEPING

14.1 Trial Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the clinical trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into two different categories (A) Investigator's Site File and (B) patient clinical source documents.

The Investigator's Site File and patient clinical source documents (including CT/MRI scans) must be kept for at least 10 years or according to local laws after completion of discontinuation of the clinical trial.

14.2 Electronic Case Report Form(s)

For each patient enrolled, an eCRF must be completed and electronically signed (authorization of completed visits) by the principal investigator or authorized delegate from the staff. If a patients withdrawn from trial the reason must be noted on the eCRF. If a patient is withdrawn from the trial because of a treatment-limiting AE thorough efforts should be made to clearly document the outcome.

15 MONITORING THE CLINICAL TRIAL

A monitor dedicated to the study group (depending on country) will contact and visit all sites regularly. The monitor will verify the adherence to the protocol and the completeness, consistence and accuracy of the data being entered on eCRF.

The monitor will require access to all patient medical records including laboratory test results and surgery, pathology and radiology reports and supporting documents to verify the entries on the eCRF. The monitor should also have access to pharmacy records relating to trial medication (including receipt, dispensing and inventory documentation). The investigator (or his/her designee) should work with the monitor to ensure that any problems detected during these visits are resolved.

16 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this trial should be made available to authorized representatives of the sponsor and the regulatory agency(ies) after appropriate notification. The verification of the eCRF data must be done by direct inspection of source documents. This includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the clinical trial. The investigator is responsible for giving any requested support for any inspection or audit visit and has to be available during these visits.

In case of audits or inspections a direct access to the eCRF will be provided.

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must ensure that patient's anonymity will be maintained and that their identities are protected form unauthorized parties. On eCRFs or other documents patients should not be identified by their names but by an identification code. The investigator should keep a Patient Enrolment Log showing codes, names and addresses. The investigator should maintain documents not for submission to the sponsor (i.e. patients written consent form in strict confidence at the site).

18 PUBLICATION OF DATA

The data from the whole trial will be analyzed and reported together. Positive and inconclusive as well as negative results will be published or otherwise made publicly available.

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AGO Study Group prior submission.

The rights of the investigator and of the AGO Study Group with regard to publication of the results of this trial are described in the investigator contract. As general rule, no trial results should be published prior to finalization of the primary publication.

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20 APPENDICES

List of Appendices

Appendix 1	Adverse Events Categories for Determining Relationship to Study Drug
Appendix 2	Definitions according to national laws and ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting
Appendix 3	FIGO Staging
Appendix 4	ECOG Performance Status
Appendix 5	Estimation and Measurement of Glomerular Filtration Rate and Recommendations for Calculation of Carboplatin Dose
Appendix 6	NYHA Classification of Cardiac Disease
Appendix 7	Nomogram for the Determination of the Body Surface Area
Appendix 8	NCI Common Terminology Criteria for Adverse Events (v 4.0)
Appendix 9	Evaluation and Definitions of Response and Progression
Appendix 10	CA 125 Definitions agreed by GCIG November 2005
Appendix 11	Definitions of Responsibilities in Trial Sites

20.1 Appendix 1 - Adverse Events Categories for Determining Relationship to Study Drug

(a) Probable (must have first three)

This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the study drug. An adverse event may be considered probable, if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists: i.e. (1) bone marrow depression, (2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug.
5. It reappears upon rechallenge.

(b) Possible (must have first two)

This category applies to those adverse events in which the connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the suspected drug.

(c) Remote (must have first two)

In general, this category is applicable to an adverse event which meets the following criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

(d) Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under remote, possible, or probable.

	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	–	–	–	+
Reasonable temporal association with drug administration	+	+	–	–
May be produced by subject clinical state, etc.	–	+	+	+
Known response pattern to suspected drug	+	+	–	–
Disappears or decreases on cessation or reduction in dose	+	–	–	–
Reappears on rechallenge	+	–	–	–

20.2 Appendix 2 - Definitions according to national laws and ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose. This means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, (i.e. the relationship cannot be ruled out).

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction is any untoward medical occurrence or effect that at any dose:

- Results in death *(NOTE: death is an outcome, not an event)*
- Is life-threatening *(NOTE: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)*
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event (an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected Adverse Drug Reaction is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. With respect to report and documentation obligation (regulatory authorities, ethics committees and other investigators) for Serious Adverse Events, causality can be one of 2 possibilities:

- No (unrelated; equals not drug related).
- Yes (remotely, possibly, probably or definitely drug related).

All adverse events not assessed as definitive "not drug related" by either the investigator or the sponsor will be considered as adverse drug reaction.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

According to ICH Topic E2A Step 5 Clinical Safety DM, Definitions and Standards for Expedited Reporting the sponsor ensures that all relevant information about suspected unexpected serious adverse reactions, which are fatal of life threatening, is recorded and reported to the competent authority as soon as possible and no later than 7 days after the sponsor is informed of such a suspected adverse reaction. No later than 8 days after the reporting, the sponsor must inform the competent authority of relevant follow-up information on the sponsor’s and the investigator’s follow-up action to the reporting.

Any other suspected unexpected serious adverse reactions must be reported to the competent authority no later than 15 days from the time when the sponsor is informed about them.

It is important that the severity of an adverse event is not confounded with the seriousness of the event. For example, vomiting which persists for many hours may be severe, but is not necessarily a serious adverse event. On the other hand, stroke which results in only a limited degree of disability may be considered a mild stroke, but would be a serious adverse event.

All serious adverse events occurring during the clinical trial or within 30 days after treatment discontinuation whether considered treatment-related or not, must be reported. In addition, a serious adverse event occurring after this time should also be reported, if it is be considered related to study drug.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the eCRF: intensity, relationship to study drug, action taken, and outcome to date.

Document and report obligations have to be adhered according to the national and international laws and regulations.

Contact details and Fax No. for SAE and pregnancy reporting are:

For sites assigned to AGO Study Group:

AGO Study Group
Moltkeplatz 63
45138 Essen
Germany

Fax No.: +49 (0) 201 959812 21

For sites assigned to other participating Study Groups should report to their local Study Group (Fax No. is provided on the SAE form).

20.3 Appendix 3 - FIGO Staging

Appendix 3.1: Ovarian Cancer Stages

Stage I	Growth limited to the ovaries
Stage IA	Growth limited to one ovary; no ascites, no tumor on the external surface of the ovary, capsule intact
Stage IB	Growth limited to both ovaries: no ascites, no tumor on the external surface of the ovaries, capsule intact
Stage IC*	Tumor either stage IA or IB, but with tumor on surface or one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIA	Extension and/or metastases to the uterus and/or tubes
Stage IIB	Extensor to other pelvic tissues
Stage IIC	Tumor either Stage IIA or IIB, but with tumor on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
Stage III	Tumor involving one or both ovaries with histological confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor limited to the true pelvis, but with histological proven malignant extension to small bowel or omentum
Stage IIIA	Tumor grossly limited to the true pelvis, with negative nodes, but with histological conformed microscopic seeding of abdominal peritoneal surface, or histological proven extension to small bowel or mesentery
Stage IIIB	Tumor of one or both ovaries with histological confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter, nodes are negative
Stage IIIC	Peritoneal metastasis beyond the pelvis greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastases equals stage IV

*: in order to evaluate the impact on prognosis of the different criteria for allotting a case to Stage IC or IIC it would be of value to know if the source of malignant cells detected was 1) peritoneal washings or 2) ascites; if rupture of the capsule was a) spontaneous or b) caused by the surgeon

Petru E et al. Gynecologic Cancer Intergroup (GCIG) proposal for changes of the current FIGO staging system. EJOG 2009; 143:69-74.

Appendix 3.2: Fallopian Tube Cancer Stages

Stage I	Growth limited to the fallopian tubes
Stage IA	Growth is limited to one tube with extension into the submucosa and/or muscularis but not penetrating the serosal surface; no ascites
Stage IB	Growth is limited to both tubes with extension into the submucosa and/or muscularis but not penetrating the serosal surface; no ascites.
Stage IC*	Tumor either Stage IA or IB but with tumor extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both fallopian tubes with pelvic extension.
Stage IIA	Extension and/or metastasis to the uterus and/or ovaries.
Stage IIB	Extension to other pelvic tissues.
Stage IIC	Tumor either Stage IIA or IIB and with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involves one or both fallopian tubes with histological confirmed peritoneal implants outside of the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor appears limited to the true pelvis but with histological proven malignant extension to the small bowel or omentum.
Stage IIIA	Tumor is grossly limited to the true pelvis, with negative nodes, but with histological confirmed microscopic seeding of abdominal peritoneal surfaces, or histological proven extension to small bowel or mesentery.
Stage IIIB	Tumor of one or both tubes with histological confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter, nodes are negative.
Stage IIIC	Peritoneal metastasis beyond the pelvis greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to be stage IV. Parenchymal liver metastases equals stage IV.

*: in order to evaluate the impact on prognosis of the different criteria for allotting a case to Stage IC or IIC it would be of value to know if the source of malignant cells detected was 1) peritoneal washings or 2) ascites; if rupture of the capsule was a) spontaneous or b) caused by the surgeon

Petru Eet al. Gynecologic Cancer Intergroup (GCIG) proposal for changes of the current FIGO staging system. EJOG 2009; 143:69-74

Appendix 3.3: Primary Peritoneal Cancer

There is no recognised formal staging system for primary peritoneal carcinoma and the FIGO staging for epithelial ovarian carcinoma has been adopted. Surface involvement of the ovaries in the absence of more widespread peritoneal disease would be classified as FIGO stage IC. Patients with extension of disease beyond the ovaries would be classified as having stage IIC disease if confined to the pelvis, and stage III or IV disease for disease beyond the pelvis (defined according to the FIGO ovarian system).

20.4 Appendix 4 - ECOG Performance Status

Description	Scale
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	1
Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	4

Oken MM et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5):649-55.

20.5 Appendix 5 - Estimation and Measurement of Glomerular Filtration Rate and Recommendations for Calculation of Carboplatin Dose

Estimation and Measurement of Glomerular Filtration Rate (GFR)

For the purposes of this protocol, the GFR can be considered equivalent to the creatinine clearance (CrCl). The following methods are suggested; however it is advised that the centre calculates the GFR according to local guidelines:

- **Estimation of GFR using the Jelliffe formula**

$$GFR = \frac{0.9 \times [98-\{0.8(age-20)\}] \times [BSA/1.73]}{SCr \times 0.0113}$$

- **Estimation of GFR using the Cockcroft-Gault formula**

$$GFR = \frac{1.05 \times (140-age) \times Wt}{SCr}$$

Where
CrCl = Creatinine Clearance (ml/min)
GFR = Glomerular Filtration Rate (ml/min)
BSA = DuBois Body Surface Area (m^2)
SCr = Serum Creatinine (µmol/l)
Wt = Weight (kg)
Age = Age in years (20 to 80)

To convert serum creatinine in mg/dl to µmol/l use the following formula:

$$Cr\ (\mu mol/l) = Cr\ (mg/dl) \times 88.4$$

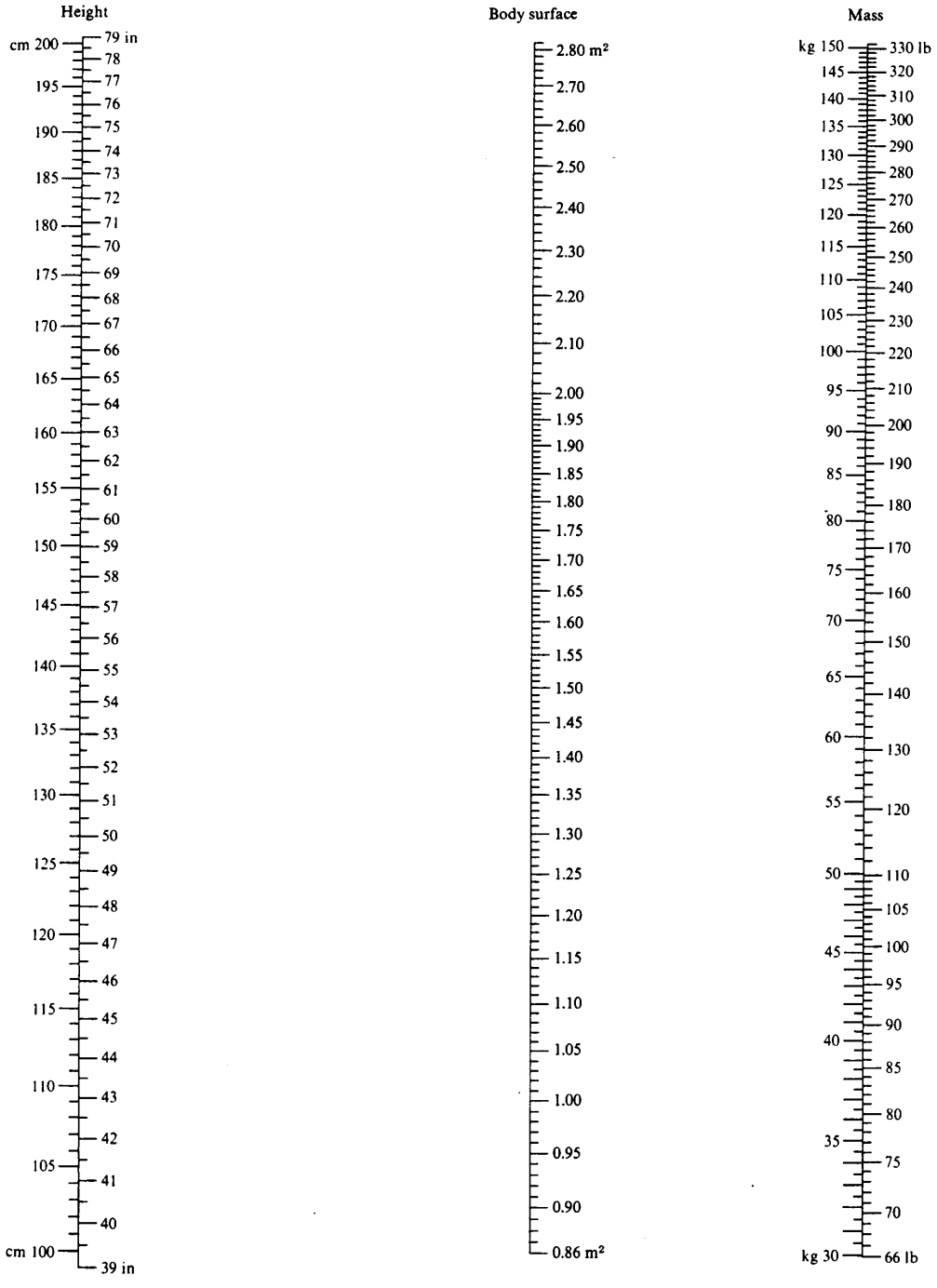
20.6 Appendix 6 - NYHA Classification of Cardiac Disease

Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pectoris.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Oxford Textbook of Internal Medicine: Vol 2; 1997

20.7 Appendix 7 - Nomogram for the Determination of the Body Surface Area

Nomogram for determination of body surface from height and mass[†]



[†]From the formula of Du Bois and Du Bois, *Arch. intern. Med.*, 17, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (S: body surface in cm², M: mass in kg, H: height in cm).

20.8 Appendix 8 - NCI Common Terminology Criteria for Adverse Events (v4.03)

The Common Terminology Criteria for Adverse Events v4.03, instituted June 14, 2010, is available at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

20.9 Appendix 9 - Evaluation and Definitions of Response and Progression

MEASURABLE DISEASE

Patients will be classified as having measurable or non-measurable disease at screening.

Method of assessment

Patients will be assessed for disease response or progression throughout the clinical trial according to RECIST v1.1 criteria. A mandatory tumor assessment via gynecological examination including ultrasound scanning and only if clinically indicated, CT scanning, or MRI in case of contrast allergy, will be performed every 12 weeks (± 7 days of the scheduled visit) until disease progression or up to 30 months, starting before day 1 of cycle 1 and during follow-up every 6 months (± 2 weeks) until disease progression. Patient without any tumor residuals do not need CT scan or MRI, only in case of suspicion of disease progression.

Definition of measurable disease lesions

Measurable disease is defined as accurately measured in at least one dimension (longest diameter [LD] in the plane of measurement is to be recorded with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At screening and in follow-up, only the short axis will be measured and followed. See also notes below on ‘Screening documentation of target and non-target lesions’ for information on lymph node measurement.

Definition of Non-measurable lesions

These are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Screening / Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as **target lesions** and will be recorded and measured at screening / baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

DEFINITION OF RESPONSE

Response Criteria based on RECIST v1.1 criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on trial
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
* Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Patients with measurable disease at screening / baseline

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = inevaluable			

Patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = Complete Response, PD = Progressive Disease, NE = inevaluable * Non-CR/Non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded on trial).

Duration of Stable Disease

SD is measured from the date of randomization until the criteria for disease progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD).

DEFINITION OF PROGRESSION

Determination of the time point of progression will be based first but not exclusively on imaging assessment of tumor manifestations according to modified RECIST v1.1 criteria. Due to the intrapelvic location of the primary tumor and the frequent occurrence of diffuse peritoneal disease at recurrence, both CT and MRI may not always be reliable for documentation of progressive disease. Therefore, criteria other than imaging may be applicable to define progressive disease.

For patients with measurable disease at randomization

Progression is defined as ANY of the following:

- At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on trial recorded since trial entry (this includes the baseline sum if that is the smallest on trail). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since trial entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

For patients with only non-measurable disease at randomization

Progression, for patients with non-measurable disease at randomization, is defined as increasing clinical, radiological or histological evidence of disease since trial entry.

Unequivocal progression of existing non-target lesions means an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an addition 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

Eisenhauer EA et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Schwartz LH et al. Evaluation of lymph nodes with RECIST 1.1. Eur J Cancer 2009; 45:261–67.

Ferrandina G et al.. Impact of pattern of reccurrence on clinical outcome ovarian cancer patients: clinical considerations. Eur J Cancer 2006; 42:2296-302.

20.10 Appendix 10 – CA 125 Definitions agreed by GCIG November 2005

The GCIG has agreed criteria for defining response and progression of ovarian carcinoma which use the serum marker CA 125, and the situations where these criteria should be used.

Evaluation of response according to CA 125

Definition of response: A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of normal within 2 weeks prior to starting treatment.

To calculate CA 125 responses accurately, the following rules apply.

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within normal range of CA 125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme.
- Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA 125 response results from both treatment modalities. CA 125 cannot distinguish between the effects of the two treatments.

The date when CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response rates, an intent-to-treat analysis should be used that includes all patients with an initial CA 125 level of at least twice upper limit of normal as eligible and evaluable. In addition, as a separate analysis, those patients who have both a CA 125 response and whose CA 125 level falls within the normal range, can be classified as CA 125 complete responders. Patients who have fall of CA 125 to within the normal range but whose initial CA 125 was less than twice the upper limit of normal, have not had a CA 125 response and cannot therefor be classified as a CA 125 complete responder.

Evaluation of response according to CA 125 in patients receiving maintenance or consolidation therapy

Patients whose CA 125 is greater than twice the upper limit of normal when they start maintenance or consolidation therapy can be evaluated according to the GCIG CA 125 response definition. It should be noted that there is no data to validate response evaluation in this situation. To prevent the prior therapy interfering with the response assessment the following requirement is recommended. Two pre-treatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA 125 there must be no more than a 10% fall in CA 125 between the two pre-treatment samples. The sample closest in time to the test therapy should be considered the pre-treatment sample.

Evaluation of response according to CA 125 in patients receiving first line therapy

The CA 125 response definition was produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities (e.g., surgery and chemotherapy), any CA 125 response is a result of both treatments, and it should be clearly stated that CA 125 cannot distinguish between the effects of the two treatments. It should be remembered that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA 125 must be within the normal range.

Evaluation of best overall response in patients without initial measurable disease and evaluable by CA 125

CA 125 may be used to evaluate response in patients without initial measurable disease, either because no measurable disease can be detected or because appropriate scans have not been performed.

CA 125	Non-Target Lesions[#]	New Lesions	**Overall serological Response**	**Best Response for this category also requires**
Response and Normalized	CR	No	**CR**	**Confirmed and maintained for at least 28 days.**
Response	Non PD	No	**PR**	
Normalized but not Response	Non CR / Non PD	No	**SD**	
Non PR / Non PD	Non PD	No	**SD**	
PD	Any	Yes or No	**PD**	
Any	PD*	Yes or No	**PD**	
Any	Any	Yes	**PD**	

[#]Non-Target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST

*Unequivocal progression in non-target lesions may be accepted as disease progression.

Evaluation of best overall response in patients with initial measurable disease and evaluable by CA 125

A report that combines both CA 125 and RECIST criteria, is likely to include patients that are measurable by one or both of the criteria, who may have events at different time points. In patients that are measurable by both criteria the date of response will be the date of the earlier of the two events. The following rules apply when determining the best overall response. If patients have PD according to RECIST within 28 days of CA 125 response they are classified as PD. If PD according to RECIST is > 28 days before or after the CA 125 response they are classified as PR. Patients whose best response according to RECIST is SD but who have a CA 125 response are classified as CA 125 responders.

Best overall response in patients with initial measurable disease and evaluable by CA 125, combining both criteria

Target Lesion[~]	Non Target[#]	New Lesion	CA 125	Overall Best Response	**Best RECIST response for this category**
CR	CR	No	Normal	CR	

CR	Non CR / Non PD	No	Not PD	PR	**also requires it to be confirmed and maintained for at least 28 days.**
CR	CR	No	PR not normal	PR	
PR	Non PD	No	Not PD	PR	
NE	Non PD	No	PR	PR	
PD or New > 28 days from CA 125 PR*			PR	PR	
SD	Non PD	No	PR	PR	
SD	Non PD	No	Not PR or PD	SD	
PD or New ≤ 28 days from CA 125 PR*			PR	PD	
PD	Any	Yes or No	Any	PD	
NE	PD	Yes or No	Any	PD	
NE	Any	Yes	Any	PD	
NE	Any	Yes or No	PD	PD	

˜target lesions include up to 10 measurable lesions as defined by RECIST

#non-target lesions includes ascites and peritoneal thickening which are not measurable according to RECIST

*patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA 125 response

Definition of progression on first line therapy and recurrence after first line therapy according to CA 125

Progression is defined according to RECIST but can also be based upon serum CA 125 (defined below) but tumor measurements should take precedence over CA 125. If measurable disease is shrinking during treatment, but the CA 125 indicates progression (as defined below) the patient should continue to receive protocol treatment. If measurable disease shows stable disease but CA 125 indicates progression after a minimum of 3 courses of chemotherapy, protocol treatment should be changed. If the GCIG definition based on CA 125 is used to define progression after relapse therapy it should be noted that it has not been validated.

Evaluation of progression according to CA 125

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125, according to the following criteria:

- A: Patients with elevated CA 125 pre-treatment and normalization of CA 125 must show evidence of CA 125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart **or**
- B: Patients with elevated CA 125 pre-treatment, which never normalizes must show evidence of CA 125 greater than, or equal to, two times the nadir value on two occasions at least one week apart **or**
- C: Patients with CA 125 in the normal range pre-treatment must show evidence of CA 125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received

mouse antibodies (unless the assay used has been showed not to be influenced by HAMA) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

A patient may be declared to have progressive disease on the basis of either the objective RECIST criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the two events if both are documented.

Definition of progression after first line therapy in ovarian cancer as proposed by the GCIG

GCIG subcategorized group	RECIST Measurable/non-measurable disease		CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or non-measurable) Date PD: date of documentation of increase or new lesions	**A N D** ***/*** **O R**	CA 125 ≥ 2 x ULN documented on two occasions[#] Date of PD: first date of the CA 125 elevation to ≥ 2 x ULN
B	As for A		CA 125 ≥ 2 x nadir value on two occasions[#] Date of PD: first date of the CA 125 elevation to ≥ 2 x nadir value
C	As for A		As for A

GCIG groups A, B & C defined above.

[#]Repeat CA 125 any time, but normally not less than 1 week after the first elevated CA 125 level. CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to influenced by HAMA) or if there has been medical and/or surgical interference with their peritoneum or pleura during previous 28 days, should not be taken into account.

http://www.gcig.igcs.org/CA-125.html (last access 21-Nov-2012)

20.11 Appendix 11 – Definition of Responsibilities in Trial Sites

Only valid for German sites.

Am 26. Oktober 2012 trat das Zweite Arzneimittelrechtsänderungsgesetz in Kraft. Infolge dessen gelten neue Anforderungen hinsichtlich Prüfer, Stellvertreter, Prüfstelle und Prüfgruppe.

§ 4 (25) AMG (*Prüfer*)

- **Prüfer ist** in der Regel ein für die Durchführung der klinischen Prüfung bei Menschen in einer Prüfstelle verantwortlicher Arzt oder in begründeten Ausnahmefällen eine andere Person, deren Beruf auf Grund seiner wissenschaftlichen Anforderungen und der seine Ausübung voraussetzenden Erfahrungen in der Patientenbetreuung für die Durchführung von Forschungen am Menschen qualifiziert.
- **Wird eine klinische Prüfung in einer Prüfstelle von einer Gruppe von Personen durchgeführt, so ist der Prüfer** der für die Durchführung **verantwortliche Leiter dieser Gruppe**.
- Wird eine Prüfung in mehreren Prüfstellen durchgeführt, wird **vom Sponsor ein Prüfer als Leiter der klinischen Prüfung benannt**.

§ 40 (1a) AMG (*Stellvertreter, Prüfgruppe*)

- Der **Prüfer bestimmt angemessen qualifizierte Mitglieder der Prüfgruppe**.
- Er hat sie **anzuleiten** und zu **überwachen sowie ihnen die für ihre Tätigkeit im Rahmen der Durchführung der klinischen Prüfung erforderlichen Informationen**, insbesondere den Prüfplan und die Prüferinformation, **zur Verfügung zu stellen**.
- Der Prüfer hat **mindestens einen Stellvertreter mit vergleichbarer Qualifikation zu benennen**.

§ 40(2) AMG (*Aufklärung der Patienten*)

- **Die betroffene Person ist durch einen Prüfer, der Arzt** oder bei zahnmedizinischer Prüfung Zahnarzt ist, **oder durch ein Mitglied der Prüfgruppe, das Arzt,** oder, bei zahnmedizinischer Prüfung, Zahnarzt **ist**, über Wesen, Bedeutung, Risiken und Tragweite der klinischen Prüfung sowie über ihr Recht aufzuklären, […]
- Der betroffenen Person ist ferner Gelegenheit zu einem **Beratungsgespräch mit Prüfer oder Mitglied der Prüfgruppe, das Arzt** oder Zahnarzt **ist**, über sonstige Bedingungen der klinische Prüfung […]

§ 67 (1) AMG (*Anzeigepflicht*)

- Ist […] eine klinische Prüfung bei Menschen anzuzeigen, so **sind der zuständigen Behörde** auch deren Sponsor, […] sowie **der Prüfer und sein Stellvertreter**, soweit erforderlich auch mit Angabe der Stellung Leiter der klinischen Prüfung, **namentlich zu benennen**.