ENGOT-ov-6/TRINOVA-2: Randomized, Double-Blind, Phase 3 Study of Pegylated Liposomal Doxorubicin Plus Trebananib or Placebo in Women With Recurrent Partially Platinum-Sensitive or Resistant Ovarian Cancer

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ABSTRACT

Aims: Trebananib, a peptide-Fc fusion protein, inhibits angiogenesis by inhibiting binding of angiopoietin-1/2 to the receptor tyrosine kinase Tie2. This randomized, double-blind, placebo-controlled phase 3 study evaluated whether trebananib plus pegylated liposomal doxorubicin (PLD) improved progression-free survival (PFS) in patients with recurrent epithelial ovarian cancer.

Methods: Women with recurrent ovarian cancer (platinum-free interval ≤12 months) were randomized to intravenous PLD 50 mg/m^2 once every 4 weeks plus weekly intravenous trebananib 15 mg/kg or placebo. PFS was the primary endpoint; key secondary endpoints were objective response rate (ORR) and duration of response (DOR). Owing to PLD shortages, enrollment was paused for 13 months; the study was subsequently truncated.

Results: Two hundred twenty-three patients were enrolled. Median PFS was 7.6 months (95%CI, 7.2–9.0) in the trebananib arm and 7.2 months (95%CI, 4.8–8.2) in the placebo arm, with a hazard ratio of 0.92 (95%CI, 0.68–1.24). However, because the proportional hazards assumption was not fulfilled, the standard Cox model did not provide a reliable estimate of the hazard ratio. ORR in the trebananib arm was 46% versus 21% in the placebo arm (odds ratio, 3.43; 95%CI, 1.78–6.64). Median DOR was improved (trebananib, 7.4 [95%CI, 5.7–7.6] months; placebo, 3.9 [95%CI, 2.3–6.5] months). Adverse events with a greater incidence in the trebananib arm included localized edema (61% versus 32%), ascites (29% versus 9%), and vomiting (45% versus 33%).

Conclusions: Trebananib demonstrated anticancer activity in this phase 3 study, indicated by improved ORR and DOR. Median PFS was not improved. No new safety signals were identified.

HIGHLIGHTS

- Trebananib + PLD did not meet the primary endpoint of improving PFS
- However, trebananib + PLD improved objective response rate and duration of response
- No new safety signals were identified in the ENGOT-ov-6/TRINOVA-2 study

Key Words: ENGOT-ov-6/TRINOVA-2, trebananib, pegylated liposomal doxorubicin, progression-free survival, objective response rate, duration of response

INTRODUCTION

First-line platinum/taxane therapy is effective in the treatment of ovarian cancer [1]. However, the risk of recurrence is high, and outcomes for these patients are poor [2,3]. For patients with recurrence following first-line platinum-based therapy, pegylated liposomal doxorubicin (PLD) represents an effective nonplatinum second-line therapy [4-8]. All patients will experience disease progression, underscoring the need to improve outcomes.

Angiogenesis is a multifactorial process that plays a key role in tumor growth, development, and metastasis [2]. Two distinct pathways are important regulators of angiogenesis: the VEGF pathway and the angiopoietin-Tie2 receptor axis [9-11]. Agents targeting the VEGF pathway have been shown to improve progression-free survival (PFS) in patients with ovarian cancer but have not been shown to prolong overall survival (OS) [12-20]. Preclinical studies support the angiopoietin pathway as an important target in ovarian cancer [11]. Angiopoietin-1 and angiopoietin-2 regulate angiogenesis and vascular remodeling both in normal ovarian physiology and in tumors [11].

Trebananib (AMG 386) is a peptide-Fc fusion protein that binds angiopoietin-1 and angiopoietin-2, preventing their interaction with the Tie2 receptor [21,22]. In a phase 1b study, trebananib plus either PLD or topotecan was tolerable in patients with recurrent ovarian cancer, with evidence of antitumor activity [23]. Trebananib combined with weekly paclitaxel has shown antitumor activity in women with recurrent ovarian cancer [24,25]. The primary objective of the phase 3 Trebananib in Ovarian Cancer-2 (TRINOVA-2) study was to evaluate PFS in patients with platinum-resistant or partially platinum-sensitive (platinum-free interval [PFI] ≤12 months) recurrent ovarian cancer receiving PLD in combination with trebananib or placebo.

METHODS

Patients

Eligible patients had epithelial ovarian, peritoneal, or fallopian tube cancer with radiographic evidence of disease progression on or following their last dose of prior chemotherapy (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 [26]), had received one prior platinum-based chemotherapeutic regimen for management of primary disease with a PFI ≤12 months, and could have received ≤2 additional cytotoxic regimens for recurrent/persistent disease. Patients were excluded if they had an ECOG performance status ≥2; previously received PLD or anthracycline/mitoxantrone-based chemotherapy; received trebananib or another inhibitor of angiopoietins/Tie2; received radiotherapy within 14 days; previous abdominal/pelvic radiotherapy; arterial/venous thromboembolism or clinically significant cardiovascular disease within 12 months; clinically significant bleeding within 6 months; CNS metastasis; nonhealing wound, ulcer, or fracture; higher-than-average risk of bowel perforation; or inadequate renal, hematologic, hepatic, or cardiovascular function. The protocol was approved by each center's independent ethics committee; patients provided written informed consent.

Study Procedures

This randomized, double-blind, phase 3 study was conducted at 69 sites in 16 countries, in collaboration with ENGOT (model C) [27]. Patients were randomized 1:1 to receive intravenous PLD 50 mg/m^2 once every 4 weeks plus intravenous trebananib 15 mg/kg once weekly or intravenous placebo once weekly. Randomization was stratified by PFI (≥0−≤6 versus >6−≤12 months), measurable disease (presence/absence), and geographic region (North America versus Western Europe/Australasia versus rest of world). Study treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. If toxicity

occurred, dose modifications for PLD were permitted (to 40 mg/m^2 and then 30 mg/m^2 for palmar-plantar erythrodysesthesia or stomatitis; to 37.5 mg/m^2 and then 25 mg/m^2 for other toxicities). Dose reductions for trebananib/placebo were not permitted.

The primary endpoint was PFS (time from randomization to radiographic disease progression per investigator by RECIST or death from any cause). Subjects not meeting these criteria at the analysis date were censored. Key secondary endpoints were OS (time from randomization to death), objective response rate (ORR), change in tumor burden, duration of response, and incidence of adverse events (AEs).

Enrollment began on April 18, 2011. Due to a global shortage of PLD, enrollment in the study was suspended from November 23, 2011, to January 10, 2013. On October 23, 2013, Amgen closed the study to patient screening, and the last patient was enrolled on November 12, 2013. In total, 223 patients were enrolled.

Assessments

Computed tomography or magnetic resonance imaging of at least the chest, abdomen, and pelvis was done before cycle 1 and every 8 weeks for the first 64 weeks after randomization, then every 16 weeks for 32 weeks, and every 24 weeks thereafter. Response was assessed by investigators per RECIST version 1.1. AEs occurring from start of treatment until the safety follow-up visit (30−37 days after last dose) were graded using the Common Terminology Criteria for Adverse Events, version 3.0 [28]. Health-related quality of life (HRQoL) was evaluated using Functional Assessment of Cancer Therapy–Ovary (FACT-O), FACT-O ovarian cancer subscale (OCS), EQ-5D or EQ-5D VAS [29,30].

Statistical Analysis

Enrollment was initially planned for 380 patients. At the time the study was closed to further enrollment, 223 patients had been enrolled. After this truncation, the statistical analysis

plan was adjusted so that the primary analysis of PFS occurred after 170 patients had PFS events; the original methods of statistical analysis were maintained. With 223 patients and assuming median PFS of 7.6 months for trebananib plus PLD and 5 months for placebo plus PLD (52% relative improvement; hazard ratio [HR], 0.66), the study had 80% statistical power to detect a reduction in the hazard of progression/death while limiting the overall one-sided type I error to 2.5%.

PFS and OS (contingent on positive PFS outcome) were evaluated on an intent-to-treat basis. ORR was evaluated for randomized patients with ≥1 measurable lesion. Duration of response was evaluated in patients who had an objective response. Safety analyses included patients who received ≥1 dose of trebananib/placebo or PLD and were summarized by treatment received.

PFS and OS were evaluated using log-rank tests stratified by randomization factors. A stratified Cox regression model was used to provide estimated HRs and two-sided 95% CIs. Nonproportionality of hazards between treatment groups was assessed by comparing the standardized Martingale residuals over time to normal distribution [31]; if this comparison was significant at the 5% level, a piecewise Cox model was used for analysis. An exact Cochran-Mantel-Haenszel test was used for analysis of ORR; the *P* value from this test was descriptive.

RESULTS

Patient Demographics and Clinical Characteristics

Two hundred twenty-three patients were randomized (trebananib, n=114; placebo, n=109; **Figure 1**). The baseline characteristics were generally balanced across treatment arms with only minor variations **(Table 1)**. Median number of cycles of trebananib was 6.0 (range, 1–19); median number of cycles of placebo was 5.0 (range, 1–38). Median number of cycles of PLD administered was 6.0 (interquartile range, 3–7; range, 1–19) in the trebananib arm and 4.0 (interquartile range, 2–6; range, 1–18) in the placebo arm. Median relative dose intensities for PLD were 87.7% and 90.3% in the trebananib and placebo treatment arms, respectively. At the time of this analysis (cutoff date, August 29, 2014), 16 patients continued on treatment (trebananib, n=8; placebo, n=8).

Progression-Free Survival

After a median follow-up time of 12.4 months (interquartile range, 8.2–15.5 months), 93 patients in the trebananib arm and 89 in the placebo arm had PFS events. Trebananib did not significantly prolong PFS: median PFS for the intent-to-treat population was 7.6 months (95%CI, 7.2–9.0) for trebananib and 7.2 months (95%CI, 4.8–8.2) for placebo **(Figure 2A)**. A Cox proportional hazards model yielded an HR of 0.92 (95%CI, 0.68–1.24, *P*=0.57), but because the proportional hazards assumption was not fulfilled this model did not provide a reliable estimate of treatment effect. Instead, a prespecified piecewise Cox model for PFS using 16-week intervals was used. This piecewise model provided further evidence of the non-proportionality of hazards: HRs ranged from 0.59 from 0–16 weeks to 2.38 at 64 weeks and later **(Table 2)**.

Secondary Endpoints

Trebananib plus PLD improved ORR compared with placebo plus PLD. Among patients with measurable disease, 46/99 (46%) in the trebananib arm had an objective response versus 20/94 (21%) in the placebo arm (odds ratio, 3.43; 95%CI, 1.78–6.64; stratified Cochran-Mantel-Haenszel test, *P*<0.001; **Table 3**). Odds ratios for trebananib versus placebo arms were generally similar across subgroups, including those defined by the stratification factors (**Figure 3B**). Notably, the odds ratio more strongly favored the trebananib arm among patients with ascites at baseline (10.55; 95%CI, 2.26–49.27) versus those without ascites at baseline (2.32; 95%CI, 1.09–4.94). Among patients with an objective response, the median durations of response (95%CI) in the trebananib and placebo arms were 7.4 (5.7–7.6) and 3.9 (2.3–6.5) months, respectively (**Figure 3A**). Overall, 78/99 patients in the trebananib arm and 63/94 patients in the placebo arm had a decrease from baseline in the sum of the longest diameters of target lesions (**Figure 3C**).

At the time of analysis, 104 patients (47%) had died. In a descriptive analysis, median OS was 19.4 months (95%CI, 14.9–22.6) in the trebananib arm and 17.0 months (95%CI, 12.9–24.4) in the placebo arm (HR, 0.94; 95%CI, 0.64–1.39, **Figure 2B**). Finally, trebananib treatment was not associated with a decrement in HRQoL when compared to placebo (**Supplemental Figure 1**).

Adverse Events

All patients who received ≥1 dose of study treatment (trebananib, n=113; placebo, n=108) experienced ≥1 treatment-emergent AE. The incidence of AEs of grade ≥3 was 77% versus 72% among those who received trebananib and placebo, respectively. The incidence of fatal AEs was 6% in the trebananib arm and 7% in the placebo arm. Two patients in each arm had fatal AEs considered possibly related to trebananib/placebo (trebananib: cerebral ischemia, right ventricular failure; placebo: pulmonary embolism, respiratory failure). AEs leading to

discontinuation of trebananib/placebo occurred in 27% of patients who received trebananib and 21% of patients who received placebo. AEs leading to discontinuation of PLD occurred in 18% of patients who received trebananib and 23% of patients who received placebo.

AEs with a greater incidence in the trebananib arm included localized edema (61% versus 32%), as well as ascites (29% versus 9%), vomiting (45% versus 33%), hypokalemia (21% versus 10%), fatigue (53% versus 44%), and cough (20% versus 15%) **(Table 4)**. Mucosal inflammation (18% versus 24%), abdominal pain (31% versus 38%), and neutropenia (13% versus 20%) occurred with greater incidence among patients who received placebo. Grade 3 edema events occurred in five patients who received trebananib and two patients who received placebo; there were no grade ≥4 edema events. Seven patients discontinued treatment due to edema (trebananib, n=5; placebo, n=2). Blurred vision occurred in 5% of patients who received trebananib and 3% of patients who received placebo. AEs previously associated with anti-VEGF antiangiogenic agents [32] did not occur with greater incidence among patients who received trebananib versus placebo; these included hypertension (trebananib, 11% versus placebo, 8%), arterial thrombotic events (1% in both patient groups), proteinuria (5% versus 4%), impaired wound healing (2% versus 7%), gastrointestinal perforations (1% versus 0%), and venous thromboembolic events (11% versus 8%).

DISCUSSION

Trebananib in combination with weekly paclitaxel has previously been shown to significantly improve PFS compared with placebo plus paclitaxel in women with recurrent ovarian cancer [25]. Consistent with this evidence, we found that trebananib plus PLD demonstrated anticancer activity, as shown by clinically meaningful improvements in ORR (46% versus 21%) and duration of response (7.4 months versus 3.9 months) for patients who received trebananib.

Despite this evidence of antitumor activity the planned statistical analysis did not reveal an improved PFS in the trebananib plus PLD arm versus the placebo plus PLD arm (the primary endpoint was not met). A requirement for the estimation of HRs using Cox models is that the risks of progression must remain proportional over time. However, this assumption was not met, and the planned method of analysis could not yield a reliable estimate of the treatment effect. Because the overall Cox model was thus not an appropriate method of analysis, we used a prespecified piecewise Cox model to evaluate PFS at 16-week intervals. Although there appeared to be a risk reduction in patients in the trebananib arm during the initial phase of the study, this treatment effect was not maintained after 16 weeks. Certain aspects of study conduct may have contributed to these results. Enrollment was temporarily halted for 14 months because of shortage of PLD. This enrollment hold resulted in two time-separated study cohorts, with different median actual follow-up times. Additionally, there were marked differences in exposure to PLD within treatment arms that were not anticipated before the study began. Continuation of PLD beyond six cycles of treatment (the minimum number of planned treatment cycles) was at the discretion of the investigator. Notably, a considerable proportion of patients received longer exposure to PLD (>6 cycles). This broad range of treatment intensity with PLD within each treatment arm made comparisons between the arms challenging. Together, these study-related factors may have affected the proportionality of risk of progression

over time and obscured any treatment effect on PFS. Notably, ORR—which is not a time-to-event endpoint and therefore may not have been confounded to the same extent as PFS—was 46% in the trebananib arm versus 21% in the placebo arm. Although the original enrollment target was not met, it appears unlikely that lack of statistical power was a primary driver for the failure to meet the primary endpoint.

The addition of trebananib to PLD did not result in an increase in the incidence of grade ≥3 AEs; no new safety signals associated with trebananib treatment were identified. As reported in other studies [25], edema events (in particular localized edema) occurred more frequently among patients who received trebananib; however, few patients (4%) had grade 3 edema and few discontinued owing to edema. The combination of trebananib and PLD did not result in exacerbation of toxicities associated with PLD (eg, palmar-plantar erythrodysesthesia).

Our results show that trebananib has incremental antitumor activity in combination with PLD, in terms of ORR and DOR, a finding that is consistent with previous studies that have demonstrated clinical activity of antiangiogenic agents in women with recurrent ovarian cancer. Combining anti-VEGF agents with chemotherapy has shown activity in this setting, although demonstrating robust improvements in outcomes has been challenging [12,13,19,33]. In the AURELIA trial, median PFS was significantly improved in the bevacizumab plus PLD group, whereas ORR and OS were not [34]. In the OCEANS study, addition of bevacizumab to chemotherapy improved PFS and ORR, but not OS [13,20]. In the ICON6 phase 3 trial, the combination of cediranib with platinum-based chemotherapy significantly improved PFS but OS was not significantly improved; notably there was evidence of nonproportional hazards [19]. Finally, in the MITO-11 phase 2 clinical trial pazopanib plus weekly paclitaxel improved PFS versus paclitaxel alone without significantly prolonging OS [33]. Our results are also consistent with those that have previously demonstrated activity of trebananib in ovarian cancer. Trebananib plus weekly paclitaxel has previously been shown to improve PFS and ORR (but not OS) compared with placebo plus paclitaxel in patients with recurrent ovarian cancer in the

TRINOVA-1 study [24,25]. Duration of response, an endpoint that is independent of the time of treatment initiation, was longer in the trebananib arm both in this study and in the TRINOVA-1 study (unpublished observation, 7.1 months [95%CI, 5.6–8.2] for trebananib versus 5.1 months [95%CI, 3.8–5.6] for placebo). Interestingly, we found that the odds ratio for response (trebananib:placebo) was higher among patients with ascites at baseline compared with those without ascites at baseline. This finding is consistent with subgroup analysis of the TRINOVA-1 study [35] and with analysis of studies evaluating bevacizumab in ovarian cancer [36-38]. Together, these results suggest that patients with ascites may have disease that is particularly susceptible to treatment with antiangiogenic agents [39,40].

In summary, although this study did not meet its primary endpoint of prolongation of PFS, trebananib added to PLD improved ORR and duration of response [25]. No new safety signals were identified with the combination of trebananib plus PLD.

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CONFLICT OF INTEREST STATMENT

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REFERENCES

[1] NCCN clinical practice guidelines in oncology: ovarian cancer v.2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

[2] Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. Nat Rev Clin Oncol 2013;10:211-24. doi: 10.1038/nrclinonc.2013.5.

[3] Ozols RF. Challenges for chemotherapy in ovarian cancer. Ann Oncol 2006;17 Suppl 5:v181-7. doi: 10.1093/annonc/mdj978.

[4] Rose PG, Maxson JH, Fusco N, Mossbruger K, Rodriguez M. Liposomal doxorubicin in ovarian, peritoneal, and tubal carcinoma: a retrospective comparative study of single-agent dosages. Gynecol Oncol 2001;82:323-8. doi: 10.1006/gyno.2001.6272.

[5] Campos SM, Penson RT, Mays AR, et al. The clinical utility of liposomal doxorubicin in recurrent ovarian cancer. Gynecol Oncol 2001;81:206-12. doi: 10.1006/gyno.2000.5980.

[6] Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. Phase 2 trial of liposomal doxorubicin (40 mg/m(2)) in platinum/paclitaxel-refractory ovarian and fallopian tube cancers and primary carcinoma of the peritoneum. Gynecol Oncol 2000;78:369-72. doi: 10.1006/gyno.2000.5921.

[7] Muggia FM, Hainsworth JD, Jeffers S, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol 1997;15:987-93.

[8] Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 2004;95:1-8. doi: 10.1016/j.ygyno.2004.07.011.

[9] Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol 2002;29:15-8. doi: 10.1016/S0093-7754(02)70065-1.

[10] Augustin HG, Koh GY, Thurston G, Alitalo K. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. Nat Rev Mol Cell Biol 2009;10:165-77. doi: 10.1038/nrm2639.

[11] Gavalas NG, Liontos M, Trachana SP, et al. Angiogenesis-related pathways in the pathogenesis of ovarian cancer. Int J Mol Sci 2013;14:15885-909. doi: 10.3390/ijms140815885.

[12] Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302-8. doi: 10.1200/JCO.2013.51.4489.

[13] Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45. doi: 10.1200/JCO.2012.42.0505.

[14] Coleman RL, Brady MF, Herzog TJ, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213) [abstract]. Gynecol Oncol 2015;137:3-4. doi: 10.1016/j.ygyno.2015.01.005.

[15] Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83. doi: 10.1056/NEJMoa1104390.

[16] Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96. doi: 10.1056/NEJMoa1103799.

[17] Du Bois A, Kristensen G, Ray-Coquard I, et al. AGO-OVAR 12: A randomized placebo-controlled GCIG/ENGOT-intergroup phase III trial of standard frontline chemotherapy +/- nintedanib for advanced ovarian cancer [abstract]. Int J Gyn Cancer 2013;23:PL01.

[18] du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol 2014;32:3374-82. doi: 10.1200/JCO.2014.55.7348.

[19] Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet;387:1066-74. doi: http://dx.doi.org/10.1016/S0140-6736(15)01167-8.

[20] Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol 2015;139:10-6. doi: 10.1016/j.ygyno.2015.08.004.

[21] Oliner J, Min H, Leal J, et al. Suppression of angiogenesis and tumor growth by selective inhibition of angiopoietin-2. Cancer Cell 2004;6:507-16. doi: 10.1016/j.ccr.2004.09.030.

[22] Coxon A, Bready J, Min H, et al. Context-dependent role of angiopoietin-1 inhibition in the suppression of angiogenesis and tumor growth: implications for AMG 386, an angiopoietin-1/2-neutralizing peptibody. Mol Cancer Ther 2010;9:2641-51. doi: 10.1158/1535-7163.MCT-10-0213.

[23] Vergote I, Schilder RJ, Pippitt Jr CH, et al. A phase 1b study of trebananib in combination with pegylated liposomal doxorubicin or topotecan in women with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer. Gynecol Oncol 2014;135:25-33. doi: 10.1016/j.ygyno.2014.07.003.

[24] Karlan BY, Oza AM, Richardson GE, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. J Clin Oncol 2012;30:362-71. doi: 10.1200/JCO.2010.34.3178.

[25] Monk BJ, Poveda A, Vergote I, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:799-808. doi: 10.1016/S1470-2045(14)70244-X.

[26] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47. doi: 10.1016/j.ejca.2008.10.026.

[27] Vergote I, Pujade-Lauraine E, Pignata S, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. Int J Gynecol Cancer 2010;20:476-8. doi: 10.1111/IGC.0b013e3181d3caa8.

[28] Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed December 2, 2015.

[29] Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.

[30] Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.

[31] Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 1993;80:557-72. doi: 10.1093/biomet/80.3.557.

[32] Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. Eur J Cancer 2006;42:3127-39.

[33] Pignata S, Lorusso D, Scambia G, et al. MITO-11: A randomized multicenter phase II trial testing the addition of pazopanib to weekly paclitaxel in platinum-resistant or -refractory advanced ovarian cancer (AOC). ASCO Meeting Abstracts 2014;32:5503.

[34] Poveda AM, Selle F, Hilpert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol 2015;33:3836-8. doi: 10.1200/JCO.2015.63.1408.

[35] Monk BJ, Poveda A, Vergote I, et al. Impact of trebananib plus weekly paclitaxel on overall survival (OS) in patients (pts) with recurrent ovarian cancer and ascites: Results from the phase III TRINOVA-1 study. ASCO Meeting Abstracts 2015;33:5503.

[36] Poveda AM, Selle F, Hilpert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol 2015;33:3836-8. doi: 10.1200/jco.2015.63.1408.

[37] Ferriss JS, Java JJ, Bookman MA, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: An NRG Oncology/GOG study. Gynecol Oncol 2015;139:17-22. doi: 10.1016/j.ygyno.2015.07.103.

[38] Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16:928-36. doi: 10.1016/s1470-2045(15)00086-8.

[39] Sangisetty SL, Miner TJ. Malignant ascites: a review of prognostic factors, pathophysiology and therapeutic measures. World J Gastrointest Surg 2012;4:87-95.

[40] Smolle E, Taucher V, Haybaeck J. Malignant ascites in ovarian cancer and the role of targeted therapeutics. Anticancer Res 2014;34:1553-61.

Table 1. Demographics and Baseline Clinical Characteristics

	Trebananib Plus PLD n=114	Placebo Plus PLD n=109
Median (range) age, y	61 (53–68)	60 (53–66)
Race/ethnicity, n (%)		
White	102 (89)	92 (84)
Asian	10 (9)	12 (11)
Black	1 (1)	2 (2)
Other	1 (1)	3 (3)
GOG performance status, n (%)		
0	75 (66)	67 (62)
1	39 (34)	41 (38)
2	0 (0)	1 (1)
Primary tumor type, n (%)		
Ovarian cancer	98 (86)	85 (87)
Peritoneal carcinoma	8 (7)	13 (12)
Fallopian tube cancer	8 (7)	1 (1)
Histologic type, n (%)		
Serous	89 (78)	82 (75)
Endometrioid	6 (5)	7 (6)
Undifferentiated	3 (3)	6 (6)
Mucinous	4 (4)	1 (1)
Other	12 (11)	13 (12)
Histologic grade, n (%)		
Well differentiated	3 (3)	5 (5)
Moderately differentiated	14 (12)	18 (16)
Poorly differentiated	77 (68)	70 (64)
Unknown	20 (18)	16 (15)
Prior lines of therapy, n (%)		
1	45 (40)	40 (37)
2	45 (40)	46 (42)
3	24 (21)	23 (21)
Platinum-free interval, n (%)		
≤6 months	64 (56)	67 (62)
>6 to ≤12 months	50 (44)	42 (39)
Prior antiangiogenic therapy, n (%)	20 (18)	16 (15)
Measurable disease at baseline, n (%)	99 (87)	94 (86)

Region, n (%)		
North America	18 (16)	14 (13)
Western Europe/Australasia	76 (67)	75 (69)
Rest of the world	20 (18)	20 (18)

GOG=Gynecologic Oncology Group; IQR=interquartile range; PLD=pegylated liposomal doxorubicin.

Table 2. Piecewise Cox Model for PFS Using 16-Week Intervals (Prespecified)

Time Interval, Week	HR*	95% CI	Weight†	*P* Value
0–16	0.59	0.34–1.01	0.31	0.05
16–32	1.07	0.60–1.92	0.27	0.81
32–48	1.00	0.58–1.72	0.31	0.99
48–64	1.55	0.56–4.29	0.09	0.40
≥64	2.38	0.41–13.95	0.03	0.34

HR=hazard ratio; PFS=progression-free survival.

*HRs within each time interval are presented as trebananib group: placebo group; an HR <1.0 indicates a lower average event rate and a longer time to event for the trebananib group relative to the placebo group.

†Weight is inversely proportional to the variance of each interval estimate. Values do not sum to 1.00 due to rounding.

Table 3. Objective Response Rates According to Treatment Arm

	Trebananib + PLD (n=99)	Placebo + PLD (n=94)
Objective response rate, % (95% CI)	46 (36–57)	21 (14–31)
Best response assessment, n (%)		
Complete response	1 (1)	2 (2)
Partial response	45 (46)	18 (19)
Stable disease	28 (28)	50 (53)
Progressive disease	14 (14)	16 (17)
Unevaluable*	1 (1)	1(1)
Not done†	10 (10)	7 (7)

PLD=pegylated liposomal doxorubicin.

*Patients for whom imaging was not performed at the scheduled assessment of response. †Patients with a response assessment of complete response, partial response, or stable disease before scheduled first assessment of response without an additional assessment of a response.

Table 4. Treatment-Emergent Adverse Events in 10% of Patients in Either Treatment Group

	Trebananib + PLD (n=113)				Placebo + PLD (n=108)			
	Any	**Grade ≥3**	**Grade ≥4**	**Fatal**	**Any**	**Grade ≥3**	**Grade ≥4**	**Fatal**
All treatment-emergent adverse events, n (%)	113 (100)	87 (77)	15 (13)	7 (6)	108 (100)	78 (72)	21 (19)	7 (6)
Treatment-emergent adverse events occurring in ≥10% of patients in either treatment arm, n (%)								
Palmar-plantar erythrodysesthesia*	69 (61)	22 (20)	0 (0)	0 (0)	61 (57)	13 (12)	0 (0)	0 (0)
Localized edema*	69 (61)	5 (4)	0 (0)	0 (0)	34 (32)	2(2)	0 (0)	0 (0)
Nausea	67 (59)	7 (6)	0 (0)	0 (0)	62 (57)	5 (5)	0 (0)	0 (0)
Fatigue*	60 (53)	8 (7)	0 (0)	0 (0)	48 (44)	5 (5)	1 (1)	0 (0)
Stomatitis	58 (51)	7 (6)	1 (1)	0 (0)	55 (51)	6 (6)	0 (0)	0 (0)
Vomiting*	51 (45)	7 (6)	0 (0)	0 (0)	36 (33)	6 (6)	0 (0)	0 (0)
Abdominal pain*	35 (31)	7 (6)	0 (0)	0 (0)	41 (38)	5 (5)	0 (0)	0 (0)
Constipation	39 (34)	2 (2)	0 (0)	0 (0)	35 (32)	2 (2)	0 (0)	0 (0)
Diarrhea	33 (29)	3 (3)	1 (1)	1 (1)	28 (26)	5 (5)	0 (0)	0 (0)
Ascites*	33 (29)	24 (21)	0 (0)	0 (0)	10 (9)	7 (7)	0 (0)	0 (0)
Rash	31 (27)	2 (2)	0 (0)	0 (0)	28 (26)	2 (2)	0 (0)	0 (0)
Mucosal inflammation*	20 (18)	1 (1)	0 (0)	0 (0)	26 (24)	2 (2)	0 (0)	0 (0)
Decreased appetite	27 (24)	1 (1)	0 (0)	0 (0)	23 (21)	2 (2)	0 (0)	0 (0)
Dyspnea	24 (21)	5 (4)	0 (0)	0 (0)	18 (17)	3 (3)	2 (2)	1 (1)
Hypokalemia*	24 (21)	8 (7)	1(1)	0 (0)	11 (10)	2 (2)	1 (1)	0 (0)
Cough*	23 (20)	0 (0)	0 (0)	0 (0)	16 (15)	0 (0)	0 (0)	0 (0)
Neutropenia*	15 (13)	8 (7)	1 (1)	0 (0)	22 (20)	13 (12)	4 (4)	0 (0)
Dyspepsia	21 (21)	1 (1)	0 (0)	0 (0)	16 (15)	0 (0)	0 (0)	0 (0)
Alopecia*	21 (19)	0 (0)	0 (0)	0 (0)	12 (11)	0 (0)	0 (0)	0 (0)

	Trebananib + PLD (n=113)				Placebo + PLD (n=108)			
	Any	Grade ≥3	Grade ≥4	Fatal	Any	Grade ≥3	Grade ≥4	Fatal
Pyrexia	20 (18)	1 (1)	0 (0)	0 (0)	18 (17)	0 (0)	0 (0)	0 (0)
Back pain*	11 (10)	0 (0)	0 (0)	0 (0)	18 (17)	0 (0)	0 (0)	0 (0)
Abdominal pain, upper	17 (15)	0 (0)	0 (0)	0 (0)	17 (16)	2 (2)	0 (0)	0 (0)
Headache	15 (13)	3 (3)	0 (0)	0 (0)	16 (15)	1 (1)	0 (0)	0 (0)
Pleural effusion	16 (14)	6 (5)	0 (0)	0 (0)	11 (10)	4 (4)	1 (1)	1 (1)
Dizziness	12 (11)	0 (0)	0 (0)	0 (0)	15 (14)	1 (1)	0 (0)	0 (0)
Anemia	11 (10)	3 (3)	1 (1)	0 (0)	15 (14)	4 (4)	0 (0)	0 (0)
Oropharyngeal pain	15 (13)	0 (0)	0 (0)	0 (0)	10 (9)	0 (0)	0 (0)	0 (0)
Asthenia	9 (8)	0 (0)	0 (0)	0 (0)	13 (12)	3 (3)	0 (0)	0 (0)
Dry skin	9 (8)	0 (0)	0 (0)	0 (0)	13 (12)	0 (0)	0 (0)	0 (0)
Weight decreased*	4 (4)	0 (0)	0 (0)	0 (0)	12 (11)	2 (2)	0 (0)	0 (0)
Nasopharyngitis	12 (11)	0 (0)	0 (0)	0 (0)	11 (10)	0 (0)	0 (0)	0 (0)
Insomnia	11 (10)	0 (0)	0 (0)	0 (0)	11 (10)	1 (1)	0 (0)	0 (0)
Hypertension	12 (11)	3 (3)	0 (0)	0 (0)	9 (8)	0 (0)	0 (0)	0 (0)
Muscle spasms	9 (8)	0 (0)	0 (0)	0 (0)	11 (10)	0 (0)	0 (0)	0 (0)
Neuropathy, peripheral	8 (7)	0 (0)	0 (0)	0 (0)	11 (10)	0 (0)	0 (0)	0 (0)
Abdominal distension	7 (6)	0 (0)	0 (0)	0 (0)	11 (10)	2 (2)	0 (0)	0 (0)
Skin hyperpigmentation	7 (6)	0 (0)	0 (0)	0 (0)	11 (10)	0 (0)	0 (0)	0 (0)
Pain in extremity*	12 (11)	0 (0)	0 (0)	0 (0)	5 (5)	0 (0)	0 (0)	0 (0)
Pruritus	11 (10)	0 (0)	0 (0)	0 (0)	8 (7)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	11 (10)	1 (1)	0 (0)	0 (0)	6 (6)	0 (0)	0 (0)	0 (0)
Hypomagnesaemia*	11 (10)	4 (4)	0 (0)	0 (0)	3 (3)	1 (1)	0 (0)	0 (0)

PLD=pegylated liposomal doxorubicin.

*Indicates a ≥5% difference in incidence between the trebananib plus PLD arm and the placebo plus PLD arm.

FIGURES

Figure 1. Disposition of patients in the study. IV=intravenous; PLD=pegylated liposomal doxorubicin; QW=once weekly.

Figure 2. (A) Kaplan-Meier analysis of progression-free survival. (B) Kaplan-Meier analysis of overall survival. HR=hazard ratio; PFS=progression-free survival; OS=overall survival; PLD=pegylated liposomal doxorubicin.

Figure 3. (A) Kaplan-Meier analysis of duration of response. (B) Objective response in patient subgroups defined by baseline characteristics. (C) Maximum change in tumor size from baseline to postbaseline nadir (measurable disease at baseline) in individual patients receiving PLD plus trebananib or PLD plus placebo. PLD=pegylated liposomal doxorubicin; SLD=sum of longest diameter. CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluated. *Number of patients with an objective response (complete or partial response per modified RECIST version 1.1). †Arrows indicates an inestimable confidence interval for the upper or lower bounds for the plot.

Figure 1.

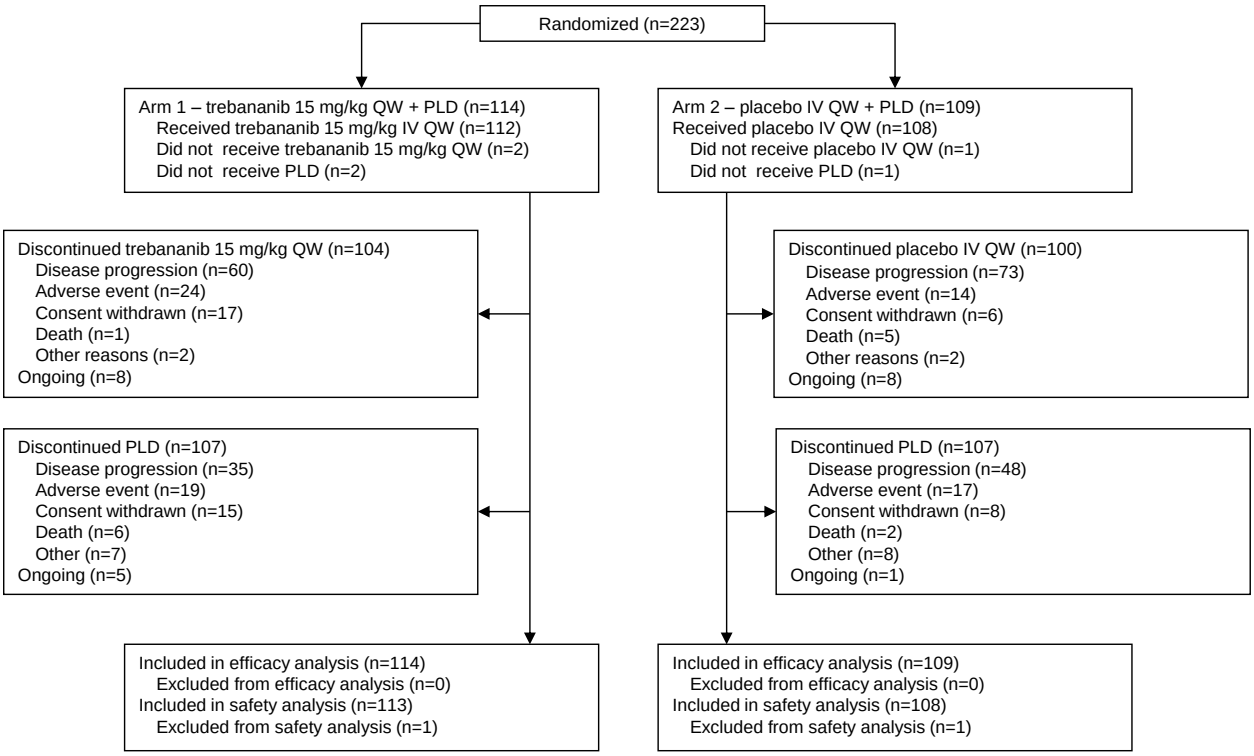
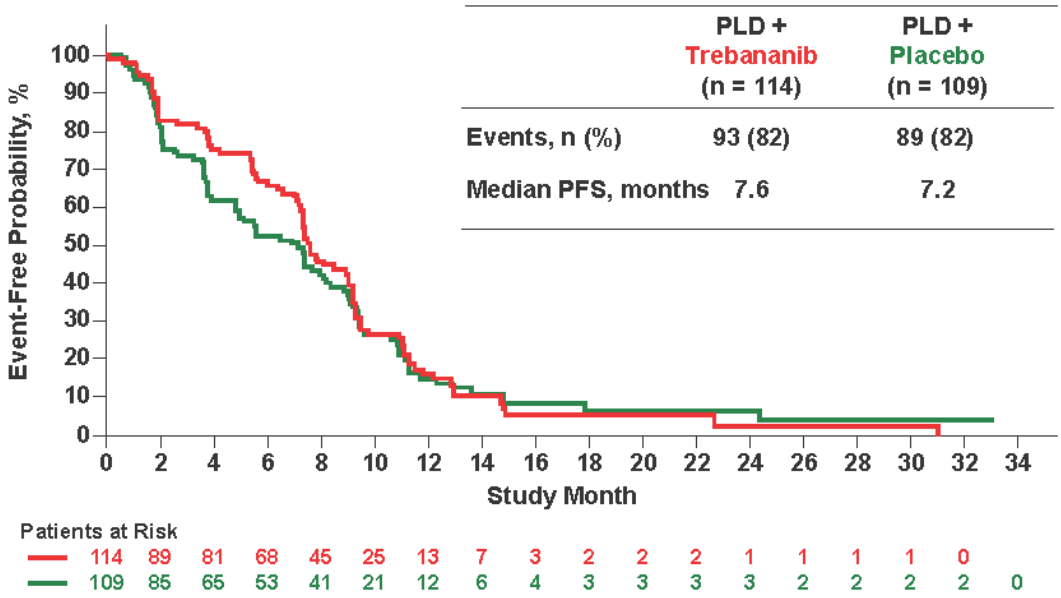

Randomized (n=223)
Arm 1 – trebananib 15 mg/kg QW + PLD (n=114)
Received trebananib 15 mg/kg IV QW (n=112)
Did not receive trebananib 15 mg/kg QW (n=2)
Did not receive PLD (n=2)
Arm 2 – placebo IV QW + PLD (n=109)
Received placebo IV QW (n=108)
Did not receive placebo IV QW (n=1)
Did not receive PLD (n=1)
Discontinued trebananib 15 mg/kg QW (n=104)
Disease progression (n=60)
Adverse event (n=24)
Consent withdrawn (n=17)
Death (n=1)
Other reasons (n=2)
Ongoing (n=8)
Discontinued placebo IV QW (n=100)
Disease progression (n=73)
Adverse event (n=14)
Consent withdrawn (n=6)
Death (n=5)
Other reasons (n=2)
Ongoing (n=8)
Discontinued PLD (n=107)
Disease progression (n=35)
Adverse event (n=19)
Consent withdrawn (n=15)
Death (n=6)
Other (n=7)
Ongoing (n=5)
Discontinued PLD (n=107)
Disease progression (n=48)
Adverse event (n=17)
Consent withdrawn (n=8)
Death (n=2)
Other (n=8)
Ongoing (n=1)
Included in efficacy analysis (n=114)
Excluded from efficacy analysis (n=0)
Included in safety analysis (n=113)
Excluded from safety analysis (n=1)
Included in efficacy analysis (n=109)
Excluded from efficacy analysis (n=0)
Included in safety analysis (n=108)
Excluded from safety analysis (n=1)

Figure 2

A Progression-Free Survival



B Overall Survival

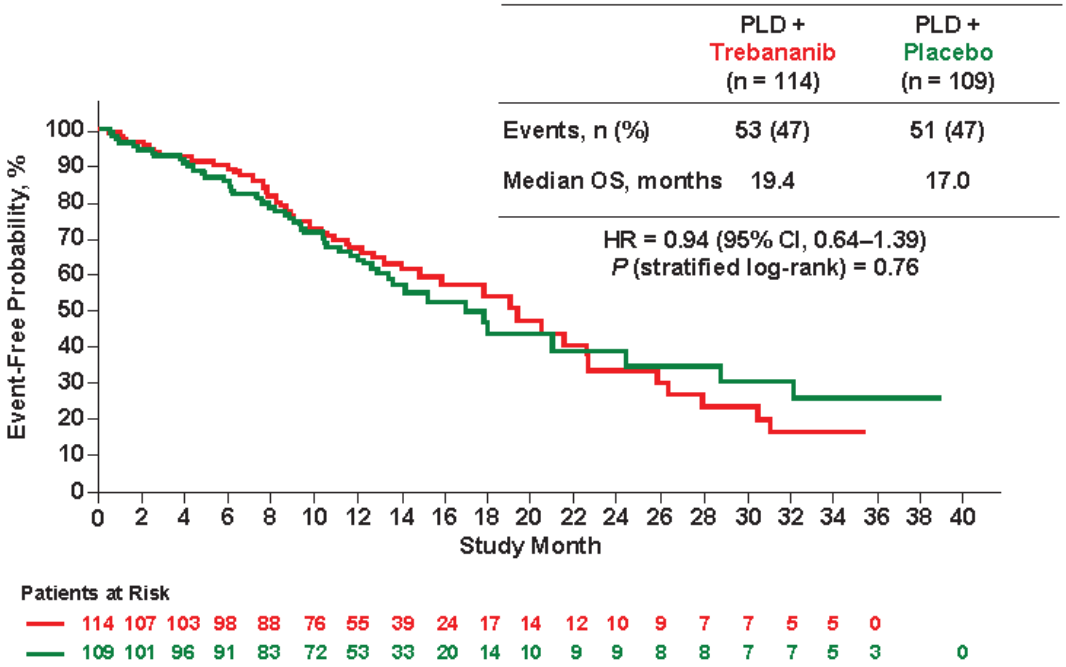


Figure 3A

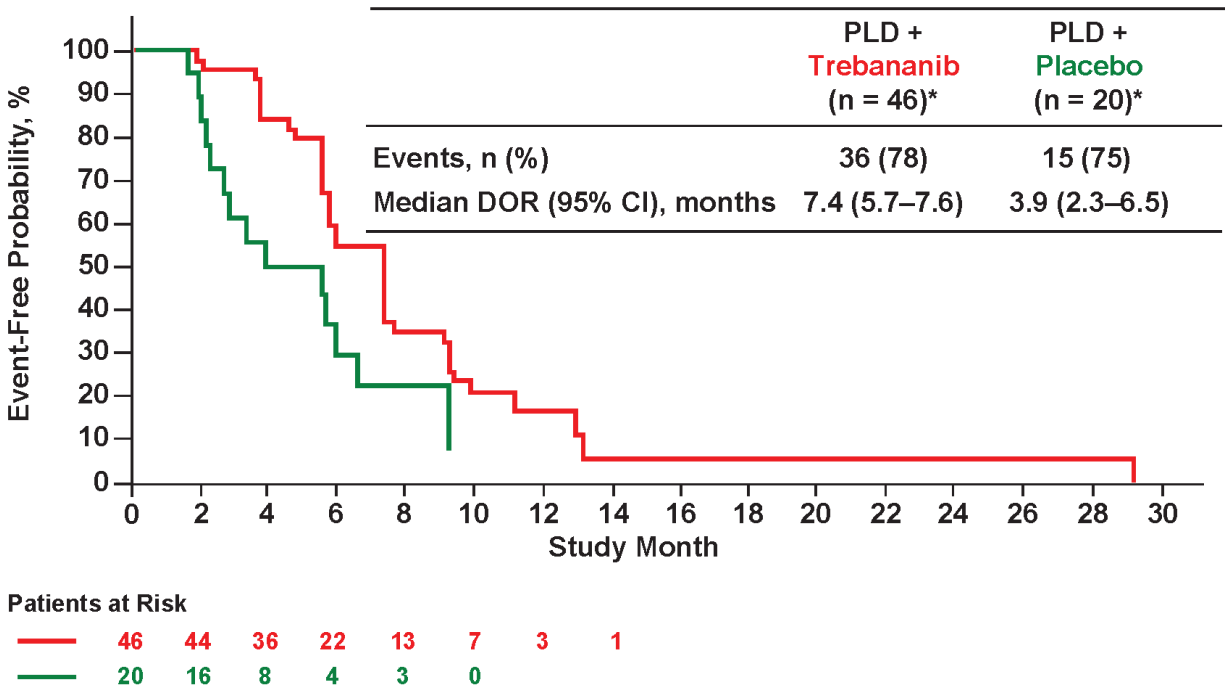

PLD + Trebananib (n = 46)*
PLD + Placebo (n = 20)*
Events, n (%) 36 (78) 15 (75)
Median DOR (95% CI), months 7.4 (5.7–7.6) 3.9 (2.3–6.5)
Event-Free Probability, %
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Study Month
Patients at Risk
46 44 36 22 13 7 3 1
20 16 8 4 3 0

Figure 3B

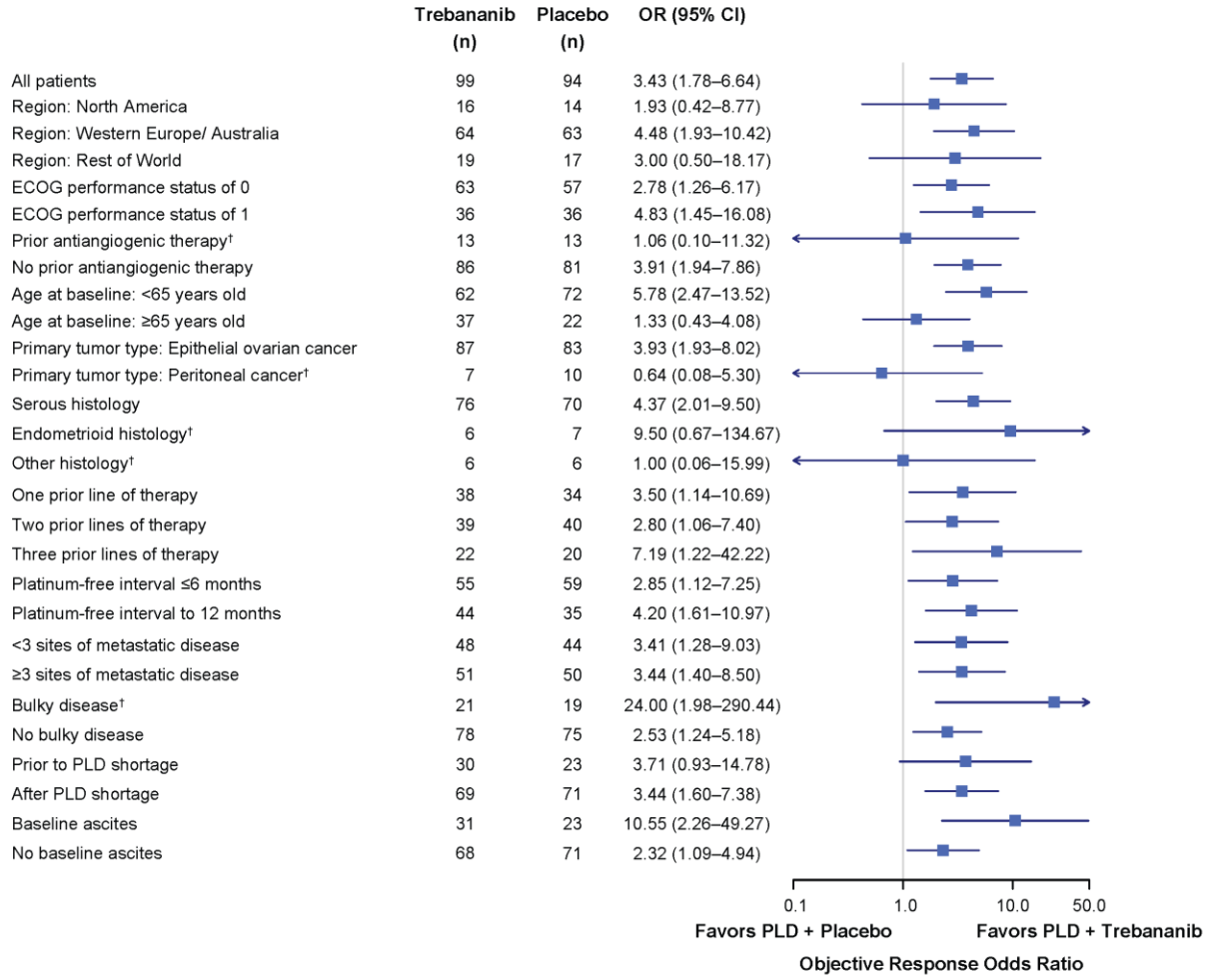
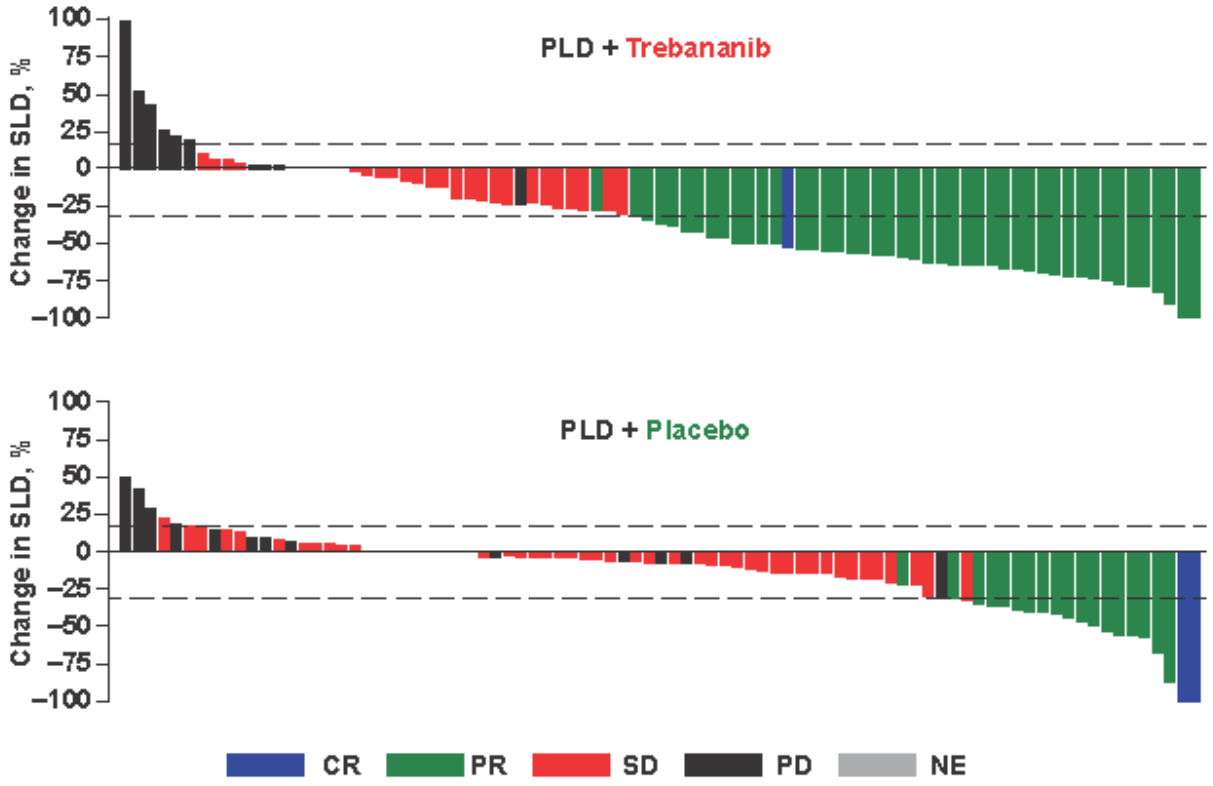

Trebananib (n)
Placebo (n)
OR (95% CI)
All patients 99 94 3.43 (1.78–6.64)
Region: North America 16 14 1.93 (0.42–8.77)
Region: Western Europe/ Australia 64 63 4.48 (1.93–10.42)
Region: Rest of World 19 17 3.00 (0.50–18.17)
ECOG performance status of 0 63 57 2.78 (1.26–6.17)
ECOG performance status of 1 36 36 4.83 (1.45–16.08)
Prior antiangiogenic therapy† 13 13 1.06 (0.10–11.32)
No prior antiangiogenic therapy 86 81 3.91 (1.94–7.86)
Age at baseline: <65 years old 62 72 5.78 (2.47–13.52)
Age at baseline: ≥65 years old 37 22 1.33 (0.43–4.08)
Primary tumor type: Epithelial ovarian cancer 87 83 3.93 (1.93–8.02)
Primary tumor type: Peritoneal cancer† 7 10 0.64 (0.08–5.30)
Serous histology 76 70 4.37 (2.01–9.50)
Endometrioid histology† 6 7 9.50 (0.67–134.67)
Other histology† 6 6 1.00 (0.06–15.99)
One prior line of therapy 38 34 3.50 (1.14–10.69)
Two prior lines of therapy 39 40 2.80 (1.06–7.40)
Three prior lines of therapy 22 20 7.19 (1.22–42.22)
Platinum-free interval ≤6 months 55 59 2.85 (1.12–7.25)
Platinum-free interval to 12 months 44 35 4.20 (1.61–10.97)
<3 sites of metastatic disease 48 44 3.41 (1.28–9.03)
≥3 sites of metastatic disease 51 50 3.44 (1.40–8.50)
Bulky disease† 21 19 24.00 (1.98–290.44)
No bulky disease 78 75 2.53 (1.24–5.18)
Prior to PLD shortage 30 23 3.71 (0.93–14.78)
After PLD shortage 69 71 3.44 (1.60–7.38)
Baseline ascites 31 23 10.55 (2.26–49.27)
No baseline ascites 68 71 2.32 (1.09–4.94)
0.1
1.0
10.0
50.0
Favors PLD + Placebo
Favors PLD + Trebananib
Objective Response Odds Ratio

Figure 3C


PLD + Trebananib
Change in SLD, %
100
75
50
25
0
–25
–50
–75
–100
PLD + Placebo
Change in SLD, %
100
75
50
25
0
–25
–50
–75
–100
CR
PR
SD
PD
NE

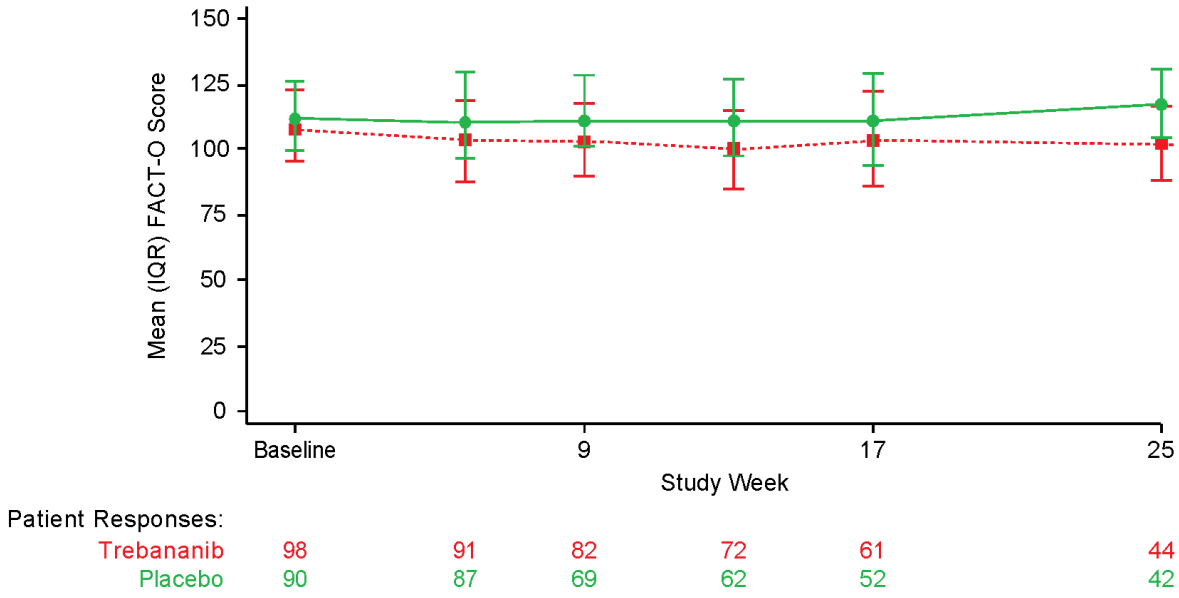
ENGOT-ov-6/TRINOVA-2: Randomized, Double-Blind, Phase 3 Study of Pegylated Liposomal Doxorubicin Plus Trebananib or Placebo in Women With Recurrent Partially Platinum-Sensitive or Resistant Ovarian Cancer

Christian Marth, Ignace Vergote, Giovanni Scambia, Willi Oberaigner, Andrew Clamp, Regina Berger, Christian Kurzeder, Nicoletta Colombo, Peter Vuylsteke, Domenica Lorusso, Marcia Hall, Vincent Renard, Sandro Pignata, Rebecca Kristeleit, Sevilay Altintas, Gordon Rustin, Robert M. Wenham, Mansoor Raza Mirza, Peter C. Fong, Amit Oza, Bradley J. Monk, Haijun Ma, Florian D. Vogl, Bruce A. Bach

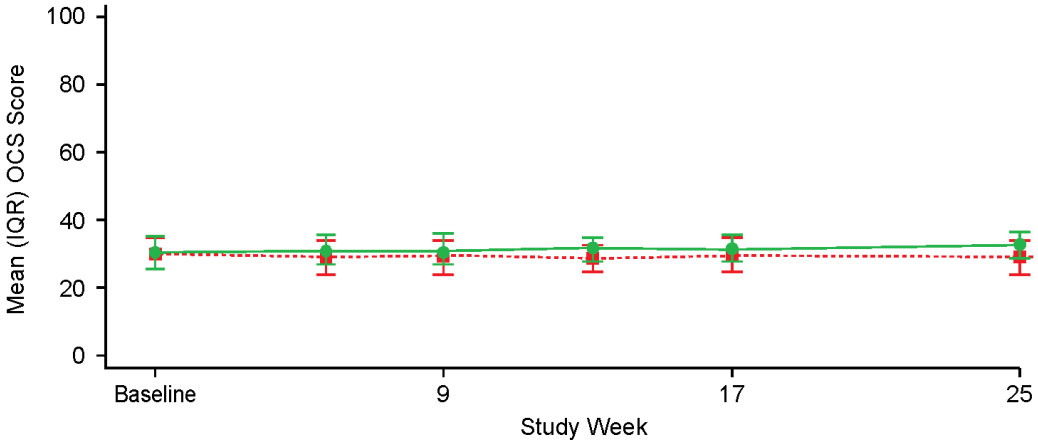
Supplemental Material

Supplemental Figure 1. Health-related quality of life among patients with ascites receiving paclitaxel plus placebo or trebananib plus placebo at week 1 (baseline) through week 25. Health-related quality of life was evaluated with (A) FACT-O, (B) OCS, (C) EQ-5D, and (D) EQ-5D VAS scores over time. FACT-O, Functional Assessment of Cancer Therapy–Ovary; OCS, ovarian cancer–specific subscale; VAS, visual analogue scale; IQR, interquartile range.

A. FACT-O

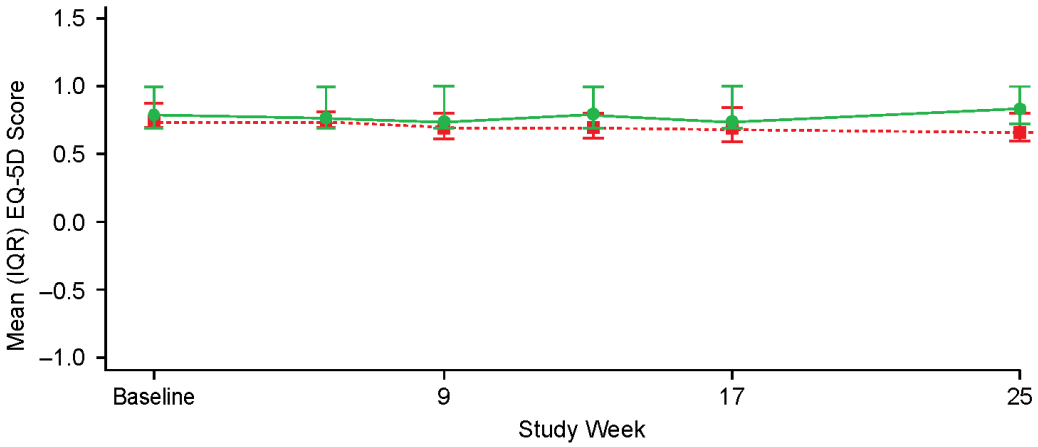


B. OCS



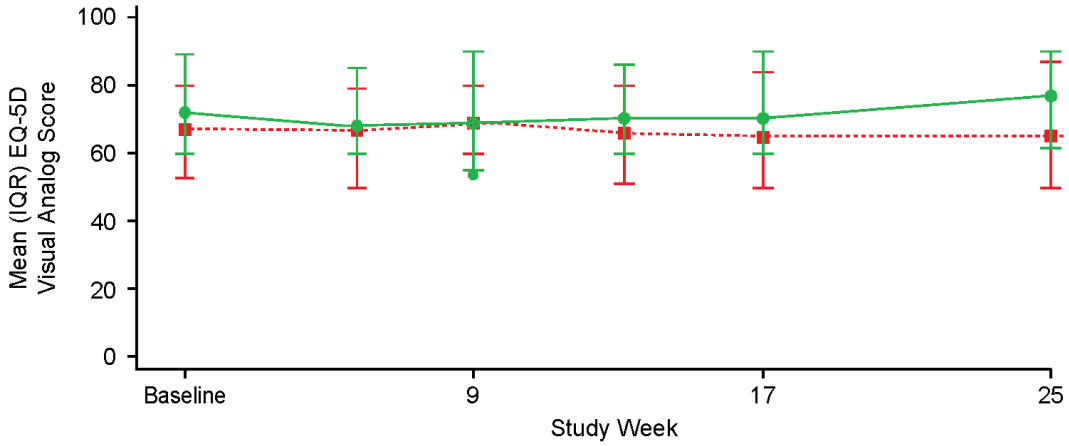
Patient Responses:						
Trebananib	98	91	83	73	62	45
Placebo	91	89	71	62	53	42

C. EQ-5D



Patient Responses:						
Trebananib	93	83	77	69	58	39
Placebo	86	82	66	55	45	38

D. EQ-5D VAS



Patient Responses:						
Trebananib	94	81	79	69	59	44
Placebo	90	86	69	60	51	40