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Original Research

ENGOT-ov-6/TRINOVA-2: Randomised, 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 [a,*], Ignace Vergote [b], Giovanni Scambia [c], Willi Oberaigner [d], Andrew Clamp [e], Regina Berger [a], Christian Kurzeder [f], Nicoletta Colombo [g], Peter Vuylsteke [h], Domenica Lorusso [i], Marcia Hall [j], Vincent Renard [k], Sandro Pignata [l], Rebecca Kristeleit [m], Sevilay Altintas [n], Gordon Rustin [j], Robert M. Wenham [o], Mansoor Raza Mirza [p], Peter C. Fong [q], Amit Oza [r], Bradley J. Monk [s], Haijun Ma [t], Florian D. Vogl [t], Bruce A. Bach [t]

[a] *AGO-Austria and Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria*
[b] *BGOG and Department of Obstetrics and Gynecology, University Hospital Leuven, Leuven Cancer Institute, KU Leuven, Belgium*
[c] *MITO and Dipartimento per la Tutela della Salute della Donna e della Vita Nascente del Bambino e Adolescente, Policlinico Universitario Agostino Gemelli, Roma, Italy*
[d] *AGO-Austria and Department of Clinical Epidemiology of the Tirol Kliniken Ltd., Cancer Registry of Tyrol, Innsbruck, Austria*
[e] *Department of Medical Oncology, Institute of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK*
[f] *AGO-Study Group and Department of Gynecology and Gynecologic Oncology, Kliniken Essen Mitte/Evang. Huyssens Stiftung/Knappschaft GmbH, Essen, Germany*
[g] *MANGO and Istituto Europeo di Oncologia and Università Milano Bicocca, Milano, Italy*
[h] *BGOG and Department of Medical Oncology, CHU Université Catholique de Louvain, Site Sainte Elisabeth, Namur, Belgium*
[i] *MITO and Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*
[j] *Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK*
[k] *BGOG and Department of Oncology, AZ St. Lucas, Ghent, Belgium*
[l] *MITO and Department of Urology and Gynecology, Istituto Nazionale Tumori "Fondazione G. Pascale" IRCCS, Naples, Italy*
[m] *Department of Medical Oncology, University College London Cancer Institute, London, UK*
[n] *BGOG and Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium*

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* *Corresponding author*: Department of Obstetrics and Gynecology, Medical University of Innsbruck, Anichstrasse 35, 6020, Innsbruck, Austria.
E-mail address: Christian.MARTH@tirol-kliniken.at (C. Marth).

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[o] Department of Gynecologic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
[p] NSGO & Department of Oncology, Rigshospitalet, København, Denmark
[q] Medical Oncology Department, Auckland City Hospital, Auckland, New Zealand
[r] Department of Medicine, Princess Margaret Hospital, University of Toronto, ON, Canada
[s] Department of Obstetrics and Gynecology, University of Arizona Cancer Center at Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA
[t] Global Development Oncology, Amgen Inc., Thousand Oaks, CA, USA

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Objective response rate;
Duration of response

Abstract ***Aims:*** Trebananib, a peptide-Fc fusion protein, inhibits angiogenesis by inhibiting binding of angiopoietin-1/2 to the receptor tyrosine kinase Tie2. This randomised, 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 randomised to intravenous PLD 50 mg/m^2 once every 4 weeks plus weekly intravenous trebananib 15 mg/kg or placebo. PFS was the primary end-point; key secondary end-points were objective response rate (ORR) and duration of response (DOR). Owing to PLD shortages, enrolment 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 months [95% CI, 5.7–7.6]; placebo, 3.9 months [95% CI, 2.3–6.5]). Adverse events with a greater incidence in the trebananib arm included localised oedema (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.

Trial registration: ClinicalTrials.gov, NCT01281254

1. 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 non-platinum 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 tumour growth, development and metastasis [2]. Two distinct pathways are important regulators of angiogenesis: the vascular endothelial growth factor (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 remodelling both in normal ovarian physiology and in tumours [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 antitumour activity [23]. Trebananib combined with weekly paclitaxel has shown antitumour 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.

2. Methods

2.1. 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 Eastern Cooperative Oncology Group performance status ≥2; previously received PLD or anthracycline/mitoxantrone-based chemotherapy; received trebananib or another inhibitor of angiopoietins/Tie2; received radiotherapy within 14 d; previous abdominal/pelvic radiotherapy; arterial/venous thromboembolism or clinically significant cardiovascular disease within 12 months; clinically significant bleeding within 6 months; central nervous system metastasis; non-healing wound, ulcer or fracture; higher-than-average risk of bowel perforation; or inadequate renal, haematologic, hepatic or cardiovascular function. The protocol was approved by each centre's independent ethics committee; patients provided written informed consent.

2.2. Study procedures

This randomised, double-blind, phase 3 study was conducted at 69 sites in 16 countries, in collaboration with the European Network for Gynaecological Oncological Trial Groups (ENGOT) (model C) [27]. Patients were randomised 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. Randomisation 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 the 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 end-point was PFS (time from randomisation 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 end-points were OS (time from randomisation to death), objective response rate (ORR), change in tumour burden, duration of response (DOR) and incidence of adverse events (AEs).

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

2.3. Assessments

Computed tomography or magnetic resonance imaging of at least the chest, abdomen and pelvis was performed before cycle 1 and every 8 weeks for the first 64 weeks after randomisation, 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 the start of treatment until the safety follow-up visit (30–37 d after the 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), EuroQol 5 dimensions questionnaire (EQ-5D) or EQ-5D visual analogue scale (VAS) [29,30].

2.4. Statistical analysis

Enrolment was initially planned for 380 patients. At the time the study was closed to further enrolment, 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 randomised patients with ≥1 measurable lesion. DOR was evaluated in patients who had an objective response. Safety analyses included patients who received ≥1 dose of trebananib/placebo or PLD and were summarised by treatment received.

PFS and OS were evaluated using log-rank tests stratified by randomisation factors. A stratified Cox regression model was used to provide estimated HRs and two-sided 95% confidence intervals (CIs). Non-proportionality of hazards between treatment groups was assessed by comparing the standardised 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.

3. Results

3.1. Patient demographics and clinical characteristics

Two hundred twenty-three patients were randomised (trebananib, n = 114; placebo, n = 109; Fig. 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 [IQR], 3–7; range, 1–19) in the trebananib arm and 4.0 (IQR, 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 (cut-off date, 29th August 2014), 16 patients continued on treatment (trebananib, n = 8; placebo, n = 8).

3.2. Progression-free survival

After a median follow-up time of 12.4 months (IQR, 8.2–15.5), 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 (Fig. 2A). The 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 the treatment effect. Instead, a pre-specified 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 at 0–16 weeks to 2.38 at 64 weeks and later (Table 2).

3.3. Secondary end-points

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).

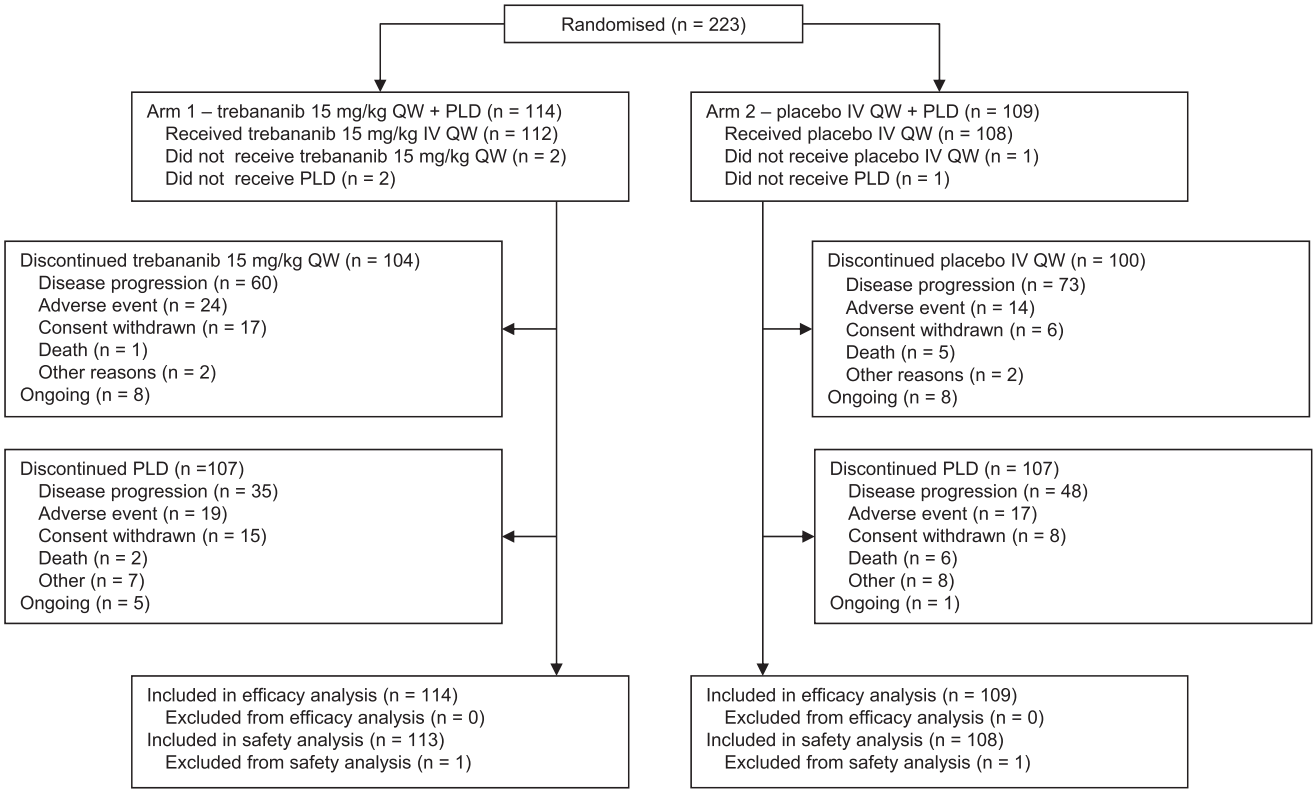

Fig. 1. Disposition of patients in the study. IV = intravenous; PLD = pegylated liposomal doxorubicin; QW = once weekly.

Table 1
Demographics and baseline clinical characteristics.

	PLD + Trebananib, n = 114	PLD + Placebo, n = 109
Median age, years (interquartile range)	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)
ECOG performance status, n (%)		
0	75 (66)	67 (62)
1	39 (34)	41 (38)
2	0 (0)	1 (1)
Primary tumour 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 anti-angiogenic 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)

ECOG = Eastern Cooperative Oncology Group; PLD = pegylated liposomal doxorubicin.

Odds ratios for trebananib versus placebo arms were generally similar across subgroups, including those defined by the stratification factors (Fig. 3B). Notably, the odds ratio more strongly favoured 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 DOR (95% CI) in the trebananib and placebo arms were 7.4 (5.7–7.6) and 3.9 (2.3–6.5) months, respectively (Fig. 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 (Fig. 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; Fig. 2B). Finally, trebananib treatment was not associated with a decrement in HRQoL when compared with placebo (Supplemental Fig. 1).

3.4. 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 localised oedema (61% versus 32%), as well as ascites (29% versus 9%), vomiting (45% versus 33%), hypokalaemia (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 oedema events occurred in 5 patients who received trebananib and 2 patients who received placebo; there were no grade ≥4 oedema events. Seven patients discontinued treatment due to oedema (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 anti-angiogenic 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%).

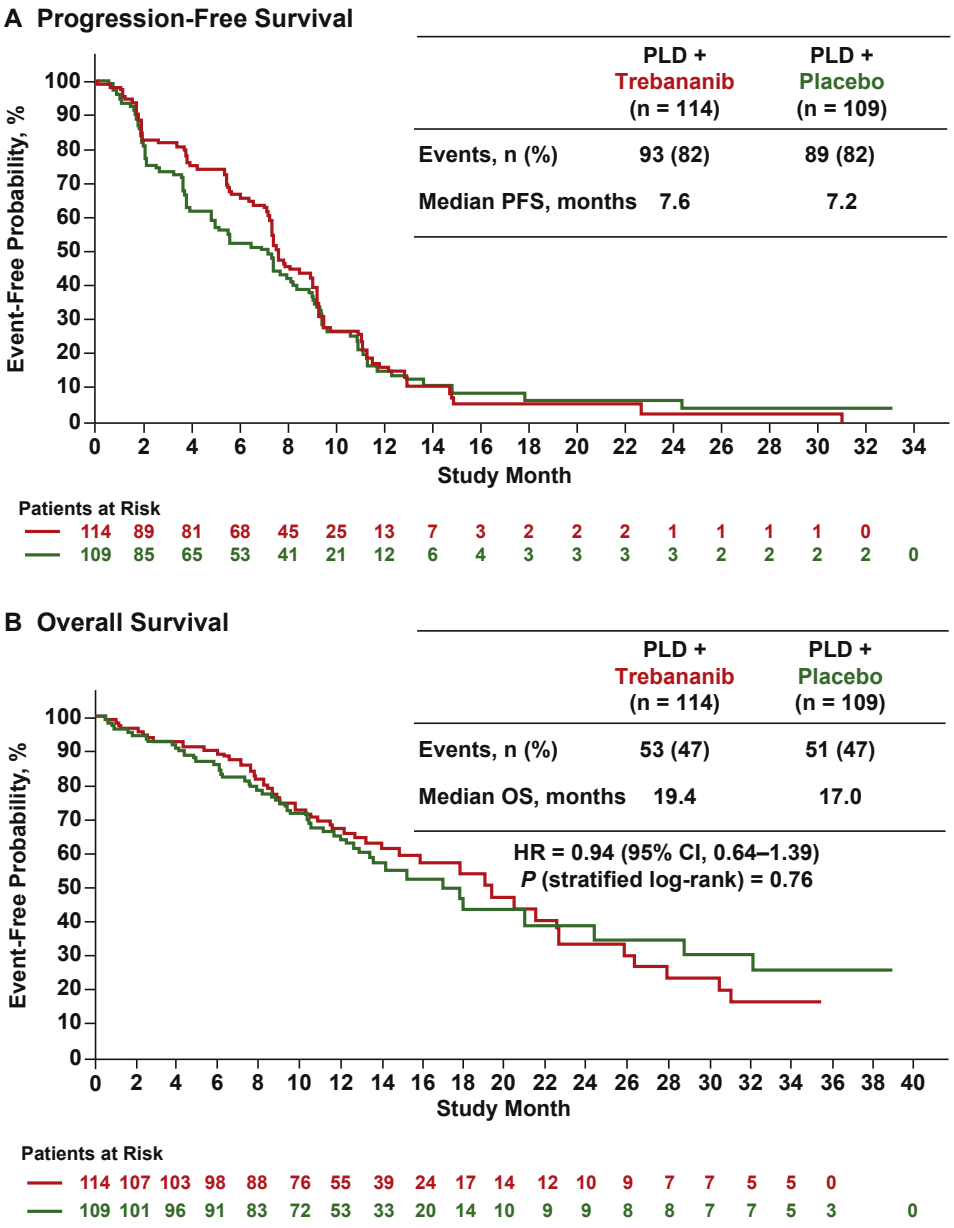

Fig. 2. Kaplan–Meier analysis of (A) PFS and (B) OS. CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; OS = overall survival; PLD = pegylated liposomal doxorubicin.

Table 2
Piecewise Cox model for PFS using 16-week intervals (pre-specified).

Time interval, week	HR[a]	95% CI	Weight[b]	*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

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

[a] 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.

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

4. 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 DOR (7.4 months versus 3.9 months) for patients who received trebananib.

Despite this evidence of antitumour activity, the planned statistical analysis did not reveal an improved

Table 3
Objective response rates according to treatment arm.

	PLD + Trebananib, n = 99	PLD + Placebo, 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[a]	1 (1)	1 (1)
Not done[b]	10 (10)	7 (7)

CI = confidence interval; PLD = pegylated liposomal doxorubicin.
[a] Patients for whom imaging was not performed at the scheduled assessment of a response.
[b] Patients with a response assessment of complete response, partial response or stable disease before the scheduled first assessment of a response without an additional assessment of a response.

PFS in the trebananib plus PLD arm versus the placebo plus PLD arm (the primary end-point 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 pre-specified 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. Enrolment was temporarily halted for 14 months because of a shortage of PLD. This enrolment hold resulted in two time-separated study cohorts, with different median actual follow-up times. In addition, 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 end-point 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 enrolment target was not met, it appears unlikely that lack of statistical power was a primary driver for the failure to meet the primary end-point.

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], oedema events (in particular localised oedema) occurred more frequently among patients who received trebananib; however, few patients (4%) had grade 3 oedema and few discontinued owing to oedema. The combination of trebananib and PLD did not result in exacerbation of toxicities associated with PLD (e.g. palmar–plantar erythrodysesthesia).

Our results show that trebananib has incremental antitumour 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 anti-angiogenic 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 non-proportional 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]. DOR, an end-point 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 [34,36,37]. Together, these results suggest that patients with ascites may have disease that is

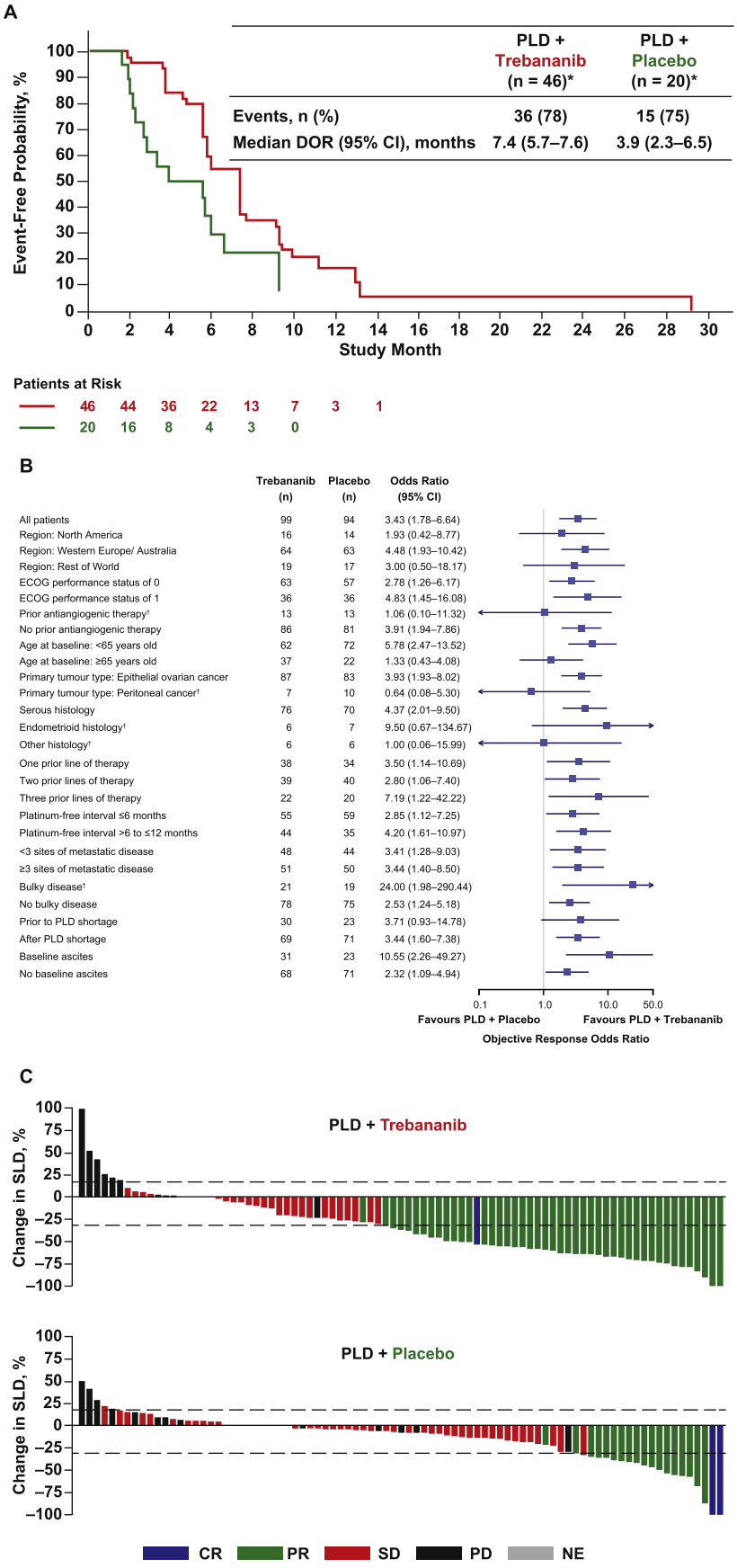

Fig. 3. (A) Kaplan–Meier analysis of DOR. (B) Objective response in patient subgroups defined by baseline characteristics. (C) Maximum change in tumour size from baseline to post-baseline nadir (measurable disease at baseline) in individual patients receiving PLD plus

Table 4
Treatment-emergent adverse events in ≥10% of patients in either treatment group.

	PLD + Trebananib, n = 113				PLD + Placebo, 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[a]	69 (61)	22 (20)	0 (0)	0 (0)	61 (57)	13 (12)	0 (0)	0 (0)
Localised oedema[a]	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[a]	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[a]	51 (45)	7 (6)	0 (0)	0 (0)	36 (33)	6 (6)	0 (0)	0 (0)
Abdominal pain[a]	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)
Diarrhoea	33 (29)	3 (3)	1 (1)	1 (1)	28 (26)	5 (5)	0 (0)	0 (0)
Ascites[a]	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[a]	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)
Dyspnoea	24 (21)	5 (4)	0 (0)	0 (0)	18 (17)	3 (3)	2 (2)	1 (1)
Hypokalaemia[a]	24 (21)	8 (7)	1 (1)	0 (0)	11 (10)	2 (2)	1 (1)	0 (0)
Cough[a]	23 (20)	0 (0)	0 (0)	0 (0)	16 (15)	0 (0)	0 (0)	0 (0)
Neutropenia[a]	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[a]	21 (19)	0 (0)	0 (0)	0 (0)	12 (11)	0 (0)	0 (0)	0 (0)
Pyrexia	20 (18)	1 (1)	0 (0)	0 (0)	18 (17)	0 (0)	0 (0)	0 (0)
Back pain[a]	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)
Anaemia	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[a]	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[a]	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[a]	11 (10)	4 (4)	0 (0)	0 (0)	3 (3)	1 (1)	0 (0)	0 (0)

PLD = pegylated liposomal doxorubicin.
[a] Indicates a ≥5% difference in incidence between the trebananib plus PLD arm and the placebo plus PLD arm.

particularly susceptible to treatment with anti-angiogenic agents [38,39].

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

Author contributions

Study concepts: C Marth, I Vergote, R Berger, C Kurzeder, D Lorusso, S Pignata, G Rustin and BJ Monk.

Study design: C Marth, I Vergote, R Berger, C Kurzeder, G Rustin, RM Wenham and BJ Monk.

trebananib or PLD plus placebo. CI = confidence interval; PLD = pegylated liposomal doxorubicin; ECOG = Eastern Cooperative Oncology Group; SLD = sum of the longest diameter; CR = complete response; DOR = duration of response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated. *Number of patients with an objective response (CR or PR per modified RECIST, version 1.1). †Arrows indicate an inestimable CI for the upper or lower bounds for the plot.

Data acquisition: C Marth, I Vergote, A Clamp, R Berger, C Kurzeder, D Lorusso, M Hall, S Pignata, R Kristeleit, G Rustin, RM Wenham, PC Fong, FD Vogl and BA Bach.

Quality control of data and algorithms: C Marth, R Berger, R Kristeleit, FD Vogl and BA Bach.

Data analysis and interpretation: all authors.

Statistical analysis: H Ma.

Article preparation, editing and review: all authors.

Conflict of interest statement

I Vergote: educational grant from Amgen (paid to institution) and honoraria for advisory boards from Amgen; A Clamp: honoraria from Roche and honoraria and research funding from AstraZeneca; C Kurzeder: personal fees from Amgen, Roche and AstraZeneca; N Colombo: advisory board participation for Amgen; P Vuylsteke: travel grants and advisory fees from Amgen; D Lorusso: participation in advisory boards for Roche, AstraZeneca and Pharmamar; G Rustin: participation on advisory boards for Amgen and OXiGENE; RM Wenham: steering committee honoraria and meeting travel expenses paid by Amgen; BJ Monk: grants and/or personal fees paid to his institution from Amgen, Novartis, Eli Lilly Genentech, Janssen/Johnson & Johnson, Array, TESARO and Morphotek; honoraria for speaker bureaus from AstraZeneca, Myriad, Janssen/Johnson & Johnson and Roche/Genentech; consultant for Roche/Genentech, Merck, TESARO, AstraZeneca, Gradalis, Cerulean, Amgen, Vermillion, ImmunoGen, Pfizer, Bayer, NuCana, Insys, GlaxoSmithKline, Verastem and Clovis; H Ma: employee of Amgen and owner of stock in Amgen; FD Vogl and BA Bach: employees of Amgen, ownership of stock in Amgen and inventors, with patent application pending; C Marth, G Scambia, W Oberaigner, R Berger, M Hall, V Renard, S Pignata, R Kristeleit, S Altintas, MR Raza Mirza, PC Fong and A Oza: none.

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Appendix A. Supplementary data

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