Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): a randomised, double-blind, phase 3 trial

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Summary

Background Angiopoietin 1 and 2 regulate angiogenesis and vascular remodelling by interacting with the tyrosine kinase receptor Tie2, and inhibition of angiogenesis has shown promise in the treatment of ovarian cancer. We aimed to assess whether trebananib, a peptibody that inhibits binding of angiopoietin 1 and 2 to Tie2, improved progression-free survival when added to carboplatin and paclitaxel as first-line therapy in advanced epithelial ovarian, primary fallopian tube, or peritoneal cancer in a phase 3 clinical trial.

Methods TRINOVA-3, a multicentre, multinational, phase 3, double-blind study, was done at 206 investigational sites (hospitals and cancer centres) in 14 countries. Eligible patients were aged 18 years or older with biopsy-confirmed International Federation of Gynecology and Obstetrics (FIGO) stage III to IV epithelial ovarian, primary peritoneal, or fallopian tube cancers, and an ECOG performance status of 0 or 1. Eligible patients were randomly assigned (2:1) using a permuted block method (block size of six patients) to receive six cycles of paclitaxel (175 mg/m²) and carboplatin (area under the serum concentration-time curve 5 or 6) every 3 weeks, plus weekly intravenous trebananib 15 mg/kg or placebo. Maintenance therapy with trebananib or placebo continued for up to 18 additional months. The primary endpoint was progression-free survival, as assessed by the investigators, in the intention-to-treat population. Safety analyses included patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT01493505, and is complete.

Findings Between Jan 30, 2012, and Feb 25, 2014, 1164 patients were screened and 1015 eligible patients were randomly allocated to treatment (678 to trebananib and 337 to placebo). After a median follow-up of 27·4 months (IQR 17·7–34·2), 626 patients had progression-free survival events (405 [60%] of 678 in the trebananib group and 221 [66%] of 337 in the placebo group). Median progression-free survival did not differ between the trebananib group (15·9 months [15·0–17·6]) and the placebo group (15·0 months [12·6–16·1]) groups (hazard ratio 0·93 [95% CI 0·79–1·09]; p=0·36). 512 (76%) of 675 patients in the trebananib group and 237 (71%) of 336 in the placebo group had grade 3 or worse treatment-emergent adverse events; of which the most common events were neutropenia (trebananib 238 [35%] *vs* placebo 126 [38%]) anaemia (76 [11%] *vs* 40 [12%]), and leucopenia (81 [12%] *vs* 35 [10%]). 269 (40%) patients in the trebananib group and 104 (31%) in the placebo group had serious adverse events. Two fatal adverse events in the trebananib group were considered related to trebananib, paclitaxel, and carboplatin (lung infection and neutropenic colitis); two were considered to be related to paclitaxel and carboplatin (general physical health deterioration and platelet count decreased). No treatment-related fatal adverse events occurred in the placebo group.

Interpretation Trebananib plus carboplatin and paclitaxel did not improve progression-free survival as first-line treatment for advanced ovarian cancer. The combination of trebananib plus carboplatin and paclitaxel did not produce new safety signals. These results show that trebananib in combination with carboplatin and paclitaxel is minimally effective in this patient population.

Funding Amgen.

Introduction

After cytoreductive primary debulking surgery, six cycles of carboplatin and paclitaxel every 3 weeks is the standard first-line treatment for patients with ovarian cancer, fallopian tube cancer, or primary peritoneal ovarian cancer.[1,2] Changes to the chemotherapy regimen, including the addition of targeted therapies, have had little success in improving overall survival;[3–5] therefore, there remains a substantial unmet need in first-line therapy for ovarian cancer.

Research in context

Evidence before this study

We searched PubMed for English language articles published between database inception and July 18, 2011, to identify articles that covered therapies for first-line, advanced, and refractory ovarian cancer (including surgery, chemotherapy, and agents targeting angiogenesis) and preclinical data on angiogenesis in cancer models. Results from this literature search included preliminary data from the ongoing phase 3 ICON7 and GOG-218 studies with bevacizumab as first-line therapy for ovarian cancer. The current published guidelines at the time of the search—from the National Comprehensive Cancer Network (NCCN) and the Gynaecologic Cancer Intergroup—were also included. The GOG-0218 and ICON7 clinical studies showed that bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor, had shown preliminary evidence in prolonging progression-free survival when combined with carboplatin and paclitaxel as a first-line therapy in advanced epithelial ovarian cancer. Positive findings from these studies suggested that angiogenesis plays an important role in the progression of ovarian cancer. Additionally, in a small phase 1b, open-label study, patients with epithelial ovarian cancer who had undergone primary debulking surgery or were to undergo interval debulking surgery received six cycles of the combination of trebananib with carboplatin plus paclitaxel followed by maintenance therapy with trebananib alone and showed antitumour activity and a favourable tolerability profile. We aimed to investigate whether trebananib improved progression-free survival when combined with carboplatin plus paclitaxel as first-line treatment in patients with advanced epithelial ovarian, primary fallopian tube, or peritoneal cancer.

Added value of this study

To our knowledge, this is the first phase 3 trial of trebananib given as a first-line treatment in combination with carboplatin plus paclitaxel in epithelial ovarian cancer. In TRINOVA-1 and TRINOVA-2, trebananib, when added to weekly paclitaxel or pegylated liposomal doxorubicin, showed anticancer activity in women with recurrent ovarian cancer. Median progression-free survival was also improved in TRINOVA-1, although no improvements in progression-free survival were seen in TRINOVA-2. In the current TRINOVA-3 study, the addition of trebananib to the standard first-line chemotherapy regimen of carboplatin plus paclitaxel did not improve progression-free survival compared with placebo. Patients who received trebananib had a greater incidence of adverse events, such as oedema, ascites, pleural effusion, and dyspnoea, but the drug did not show new safety signals and did not affect health-related quality of life compared with placebo.

Implications of all the available evidence

Although previous findings have shown that trebananib has anticancer activity in recurrent ovarian cancer when combined with either paclitaxel or pegylated liposomal doxorubicin, trebananib did not significantly improve progression-free survival when used in the first-line setting in combination with carboplatin plus paclitaxel in patients with epithelial, ovarian, fallopian tube, or primary peritoneal ovarian cancer.

Inhibition of angiogenesis has shown promise in treating ovarian cancer.[6] The vascular endothelial growth factor (VEGF) pathway and the angiopoietin axis are key regulators of angiogenesis, and both are potential targets in the treatment of ovarian cancer. In the ICON7 and GOG-0218 phase 3 studies,[7–9] first-line therapy with the anti-VEGF monoclonal antibody bevacizumab and carboplatin plus paclitaxel followed by maintenance therapy with bevacizumab improved progression-free survival compared with chemotherapy alone in ovarian cancer.

The angiopoietin pathway is distinct from the VEGF pathway; angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) regulate angiogenesis and vascular remodelling by interacting with the tyrosine kinase receptor Tie2.[10] Trebananib is a peptibody that neutralises the interaction between Ang1 and Ang2 and the Tie2 receptor.[10,11] Trebananib treatment showed anticancer activity among patients with recurrent ovarian cancer when given in combination with either paclitaxel or pegylated liposomal doxorubicin in the TRINOVA-1 and TRINOVA-2 phase 3 clinical trials.[12,13] A small phase 1b, open-label study[14] of primary debulking surgery and interval debulking surgery in patients with ovarian cancer receiving six cycles of trebananib plus carboplatin and paclitaxel followed by maintenance therapy with trebananib alone showed acceptable tolerability and encouraging anti-tumour activity.

We aimed to evaluate whether the combination of trebananib plus carboplatin and paclitaxel followed by trebananib maintenance therapy improved progression-free survival compared with placebo plus carboplatin and paclitaxel followed by placebo in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who had either primary debulking surgery or with planned interval debulking surgery.

Methods

Study design and participants

TRINOVA-3, a multicentre, multinational, phase 3, double-blind study, was done at 206 investigational sites (academic and community hospitals and cancer centres in 14 countries: the USA, Canada, Austria, Belgium, Denmark, Germany, Greece, Italy, the Netherlands, Spain, China, Japan, South Korea, and Russia (appendix pp 20, 58–63), according to European Network of Gynaecological Oncological Trial groups (ENGOT) model C.[15]

Eligible patients were aged 18 years or older and had biopsy-proven International Federation of Gynecology and Obstetrics (FIGO) stage III to IV epithelial ovarian,

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See Online for appendix

peritoneal, or fallopian tube cancer, with an indication for first-line treatment with six cycles of carboplatin and paclitaxel.

Patients were excluded if they had an ECOG performance status score of 2 or greater; inadequate haematological, renal, hepatic, or cardiovascular function; previously received anticancer or experimental therapy, trebananib, or any other inhibitor of angiopoietins or Tie2; uncontrolled arterial or venous thromboembolism or clinically significant cardiovascular disease within 12 months before randomisation; bleeding within 6 months before randomisation; a nonhealing wound, ulcer, or fracture; a history of central nervous system metastasis; known active or ongoing infection within 14 days before randomisation; a history of malignancy (except adequately treated nonmelanomatous skin cancer or lentigo maligna, adequately treated cervical carcinoma, or a malignancy that was treated with curative intent, with no known active disease for ≥3 years before randomisation); or any uncontrolled concurrent illness or history of a condition that would have interfered with interpretation of the study results. Full inclusion and exclusion criteria are available in the appendix (pp 3–6).

The protocol was approved by each centre's independent ethics committee, and all patients provided written informed consent before enrolment in the trial. The protocol is available in the appendix (pp 70–218).

Randomisation and masking

Investigators had to declare before randomisation whether or not they planned on performing interval debulking surgery. We enrolled patients using an interactive voice response system, which provided a unique personal identification number for dose dispensation. Patients were randomly assigned (2:1) to the trebananib or placebo group using a permuted block method with a block size of six patients. Patients were stratified on the basis of carboplatin dose (area under the serum concentration–time curve [AUC] 5 or 6) and by the following five clinical categories, based on FIGO disease stage and category of residual disease after primary debulking surgery or with planned interval debulking surgery: stage IIIA or IIIB, suboptimally debulked after primary debulking surgery; stage IIIA or IIIB, optimally debulked after primary debulking surgery; stage IIIC or IV, with planned interval debulking surgery and no primary debulking surgery; stage IIIC or IV, suboptimally debulked after primary debulking surgery; and stage IIIC or IV, optimally debulked after primary debulking surgery. When the study started, suboptimal debulking surgery was defined as the presence of residual macroscopic tumour (tumour >10 mm) after surgery. During the course of the trial, more detailed information about the actual size of residual tumours after primary debulking surgery was requested for additional post-hoc subgroup analysis.

This was a double-blind trial. The sponsor, investigator, site staff, patients, and study team personnel (including the study statisticians) were masked to treatment assignment. Meetings of an external independent data monitoring committee were scheduled at predefined times based on patient enrolment; the data monitoring committee reviewed unblinded data but did not have contact with study centre personnel or patients (appendix p 19). At the time of the primary analysis (data cutoff March 15, 2016), the statistical analysis was confirmed by an independent statistician from ENGOT.

Procedures

Patients in the primary debulking surgery strata had debulking surgery within 12 weeks of randomisation and received six cycles of intravenous trebananib 15 mg/kg or placebo weekly in combination with intravenous carboplatin (AUC 5 or 6) plus paclitaxel (175 mg/m²) every 3 weeks. Using the same doses, three cycles of weekly trebananib or placebo plus carboplatin and paclitaxel every 3 weeks were given to patients with planned interval debulking surgery. All treatments were withheld for 28 days before interval debulking surgery. Carboplatin and paclitaxel resumed 2 weeks after interval debulking surgery; trebananib or placebo resumed 28 days after interval debulking surgery. Patients with interval debulking surgery received an additional three cycles of combination therapy (six cycles in total).

After six treatment cycles for patients receiving interval debulking surgery and primary debulking surgery, a maintenance period of treatment with weekly trebananib (15 mg/kg) or placebo was started. Maintenance therapy continued for up to 18 months. Protocol-directed therapy continued until progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[16] toxicity, or withdrawal of consent.

Dose reductions for carboplatin and paclitaxel were based on haematological toxicities (neutropenia [any grade] for ≥7 days, febrile neutropenia [any grade], or thrombocytopenia [grade 4]) or hepatic toxicities of any grade for paclitaxel and included a dose reduction of 15 mg/m² for paclitaxel and a carboplatin dose of AUC 4 (appendix pp 8–12). Dose reductions, modifications, or interruptions for trebananib or placebo were not permitted.

We assessed disease severity via CT or MRI of at least the chest, abdomen, and pelvis at screening (for primary debulking surgery), within 28 days before randomisation (for interval debulking surgery and primary debulking surgery), at weeks 9 and 18 (±1 week), every 12 weeks (±1 week) for 18 months, every 24 weeks (±2 weeks) for the subsequent 18 months, and yearly (±1 month) thereafter for a maximum of 5 years. Imaging was assessed by the investigator for radiographic response and radiographic disease progression per RECIST version 1.1[16] with modifications (new onset or worsening ascites and pleural or pericardial effusions were not considered indicative of progressive disease if they occurred without tumour progression).[12,13,17]

Adverse events were recorded from the start of treatment until the safety follow-up visit (30–37 days after the last dose) and were graded using the Common Terminology Criteria for Adverse Events, version 3.0.[18] Fatal treatment-emergent adverse events were defined as fatal adverse events that occurred between study day 1 and safety follow-up or 30 days after the last dose of study drug, whichever occurred later. Serious adverse events were defined as an adverse event that meets at least one of the following serious criteria: fatal, life threatening (places the individual at immediate risk of death), requires in-patient hospital admission or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, congenital anomaly or birth defect, or other medically important serious event.

Blood samples were collected for all patients at baseline or postbaseline, or both, to analyse for binding and neutralising anti-trebananib antibodies using validated assays pre-infusion of AMG 386 or AMG 386 placebo on day 1 of weeks 1, 10, 19, and at safety follow-up. The assessment procedures were previously described.[17]

Blood samples were also collected for biomarker development before infusion of trebananib or placebo, paclitaxel, and carboplatin on day 1 of weeks 1 and 7. Correlations between serum biomarkers, including Ang1, Ang2, and Tie2, and measures of response were evaluated.

Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy–Ovary (FACT-O), the FACT-O ovarian cancer-specific subscale (OCS), the EuroQol-5 dimensions (EQ-5D), and the EQ-5D visual analogue scale questionnaires.[19–21] Patient-reported outcome questionnaires were done before trebananib, placebo, or paclitaxel infusion and at clinical assessments on day 1 of cycles 1, 3, and 5. During the maintenance phase, patient-reported outcome questionnaires were given before radiological assessments on the scheduled visit and at the safety follow-up visit.

Completion rates and summary statistics over time were generated for all instruments. We used a pattern-mixture model to estimate whether the change in the FACT-O or FACT-O OCS scores over time differed between treatment groups, adjusting for the dropout patterns seen.

Outcomes

The primary endpoint was progression-free survival in the intention-to-treat population, which was assessed by investigators and defined as the time from randomisation to radiographic disease progression per modified RECIST version 1.1[16] or death from any cause.[22] Secondary endpoints were overall survival (time from randomisation to death from any cause), incidence of adverse events and significant laboratory abnormalities, pharmacokinetics (maximum observed drug concentration [C_{max}] and minimum observed drug concentration [C_{min}]), frequency of anti-trebananib antibody formation, and patient-reported outcomes.[19–21]

Statistical analysis

The data cutoff date was March 15, 2016. In the initial design, the study was sized to achieve at least 90% power to detect a hazard ratio (HR) of 0·77 for progression-free survival at the significance level of 0·025 for a one-sided test. Conditional on a significant improvement in progression-free survival, the sample size of 2000 patients provided 80% power for an alternative overall survival HR of 0·82. However, owing primarily to slower than anticipated enrolment (other factors were the regulatory landscape, competitor drug development, and the preliminary results from the TRINOVA-1 and TRINOVA-2 studies[12,13]), the study protocol was amended on Jan 17, 2014 to enroll 1000 patients to enhance the feasibility of study completion while maintaining the integrity of the primary endpoint. The amendment occurred before the interim analysis for futility on Oct 13, 2014 and was not influenced by that analysis nor by previous safety reviews by the independent data monitoring committee. The boundary for futility was based on a beta spending function with a gamma parameter of –2, corresponding to a HR of 0·948 at the interim analysis.

With 1000 patients, and assuming a median progression-free survival of 20·8 months for the trebananib group and 16·0 months for the placebo group (30% relative improvement; HR 0·77), the study had 85% statistical power to detect a reduction in the hazard of progression or death, while limiting the overall one-sided type 1 error to 2·5%. The primary analysis of progression-free survival was planned to occur when 613 progression-free survival events (disease progression per RECIST or death) had occurred. An interim analysis was planned when 307 progression-free survival events occurred. Analysis of overall survival was contingent on positive progression-free survival outcomes and was evaluated on an intention-to-treat basis when 500 overall survival events had occurred. The sample size of 1000 gave 82% power for an alternative HR of 0·76.

Progression-free survival and overall survival were evaluated using log-rank tests stratified by randomisation factors. Stratification factors were collapsed if particular strata were sparse, in the order of collapsing carboplatin dose concentrations (ie, carboplatin AUC 5 and 6 were collapsed) then strata based on FIGO disease stage and category of residual disease (ie, FIGO stage IIIA–IIIB with optimal and suboptimal tumour resection were combined). We used a stratified Cox regression model to provide estimated HRs and two-sided 95% CIs. Non-proportionality of hazards between treatment groups was assessed by comparing the standardised martingale residuals over time to normal distribution;[23] if this comparison was significant at the 5% level, indicating non-proportionality of hazards, a piecewise Cox model was used for analysis. Efficacy endpoints were examined according to prespecified subgroups (geographic region, age, race,

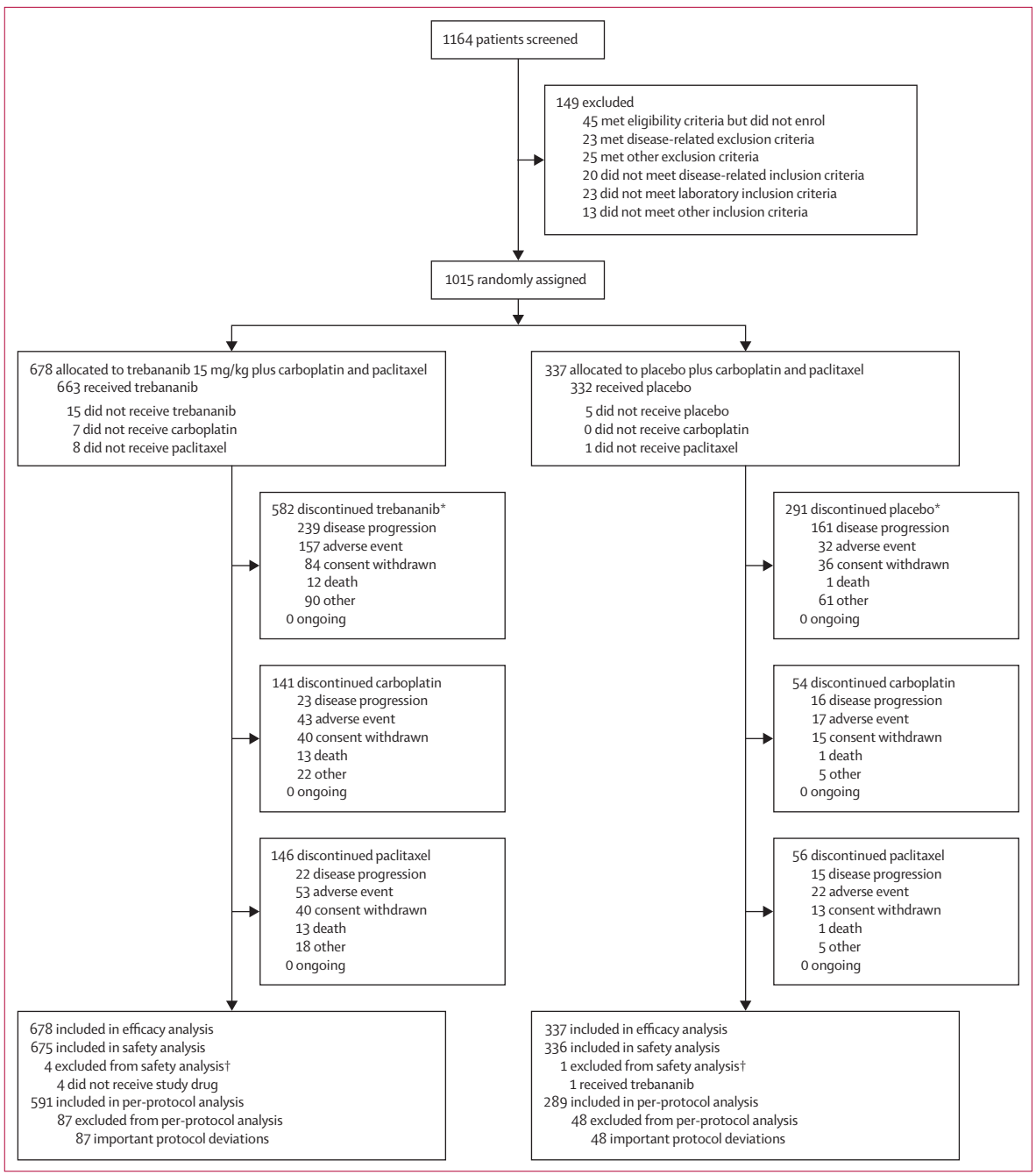


Figure 1: **Trial profile**
*98 patients (56 in the trebananib group and 42 in the placebo group) discontinued therapy in the maintenance phase owing to the decision of the study data monitoring committee to halt the trial. †One patient randomly assigned to the placebo group received trebananib and was included in the trebananib group for safety analyses.

baseline ECOG performance status, baseline carboplatin dose, primary tumour type, disease histology subtype, disease stage, primary debulking surgery, and category of residual tumor after primary debulking surgery) using baseline covariates. A sensitivity analysis of overall survival and progression-free survival was also done using the per-protocol analysis set, defined as patients in the full analysis set who did not have any important protocol deviations considered to affect efficacy outcomes.

A pattern-mixture model was used for quality of life analyses to provide an estimate and 95% CIs for whether the change in FACT-O, FACT-O OCS, or EQ-5D over time differed between treatment groups, adjusting for dropout patterns (appendix p 19). Completion rates and

	Trebananib and paclitaxel plus carboplatin group (n=678)	Placebo and paclitaxel plus carboplatin group (n=337)
Median age, years (IQR)	59 (51–66)	59 (51–66)
Ethnicity		
White	547 (81%)	279 (83%)
Asian	110 (16%)	51 (15%)
Black	13 (2%)	3 (1%)
Other	8 (1%)	4 (1%)
ECOG performance status		
0	375 (55%)	183 (54%)
1	298 (44%)	150 (45%)
2	4 (1%)	4 (1%)
Not available	1 (<1%)	0
Primary tumour type		
Ovarian cancer	583 (86%)	290 (86%)
Primary peritoneal carcinoma	65 (10%)	31 (9%)
Fallopian tube cancer	29 (4%)	16 (5%)
Not available	1 (<1%)	0
Histological subtype		
Serous	525 (77%)	262 (78%)
Undifferentiated	27 (4%)	9 (3%)
Endometriod	18 (3%)	9 (3%)
Other*	103 (15%)	54 (16%)
Not available	5 (1%)	3 (1%)
Histological grade		
Well differentiated	52 (8%)	27 (8%)
Moderately differentiated	58 (9%)	46 (14%)
Poorly differentiated	397 (59%)	170 (50%)
Unknown	170 (25%)	94 (28%)
Not available	1 (<1%)	0
FIGO stage at diagnosis		
Stage III	491 (72%)	257 (76%)
Stage IIIA	19 (3%)	9 (3%)
Stage IIIB	42 (6%)	19 (6%)
Stage IIIC	430 (63%)	229 (68%)
Stage IV	186 (27%)	80 (24%)
Not available	1 (<1%)	0
Primary debulking surgery	430 (63%)	213 (63%)
Residual tumour ≤10 mm†	244 (57%)	119 (56%)
Residual tumour >10 mm†	186 (43%)	94 (44%)
Interval debulking surgery	248 (37%)	124 (37%)
Carboplatin dose‡		
AUC 5	309 (46%)	153 (45%)
AUC 6	362 (53%)	183 (54%)
Not available§	7 (1%)	0
(Table 1 continues in next column)		
(Continued from previous column)		
Measurable disease at baseline	407 (60%)	213 (63%)
Ascites at baseline		
Patients who had primary debulking surgery	89 (26%)	190 (28%)
Patients who had interval debulking surgery	101 (30%)	182 (27%)
Pleural effusion at baseline	184 (27%)	91 (27%)
Oedema at baseline	55 (8%)	31 (9%)
Region		
Western Europe and Australia	303 (45%)	146 (43%)
North America	216 (32%)	108 (32%)
Rest of the world	159 (24%)	83 (25%)

Data are n (%), unless otherwise stated. AUC=area under the serum concentration–time curve. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. *Includes transitional, clear cell, and other. †Percentage based on the number of patients who had primary debulking surgery. ‡One patient in the placebo group received a carboplatin dose of AUC 4. §Seven patients in the trebananib group did not receive carboplatin.

Table 1: **Baseline characteristics**

summary statistics over time were generated for all health-related quality of life questionnaires. Analyses for safety, pharmacokinetics, biomarkers (Ang1, Ang2, and Tie2), and patient-reported outcomes (FACT-O and EQ-5D questionnaires to assess health-related quality of life and symptoms) were descriptive.

Safety analyses included patients who received at least one dose of study treatment and were summarised by treatment received.

We used SAS software (version 9.3) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01493505.

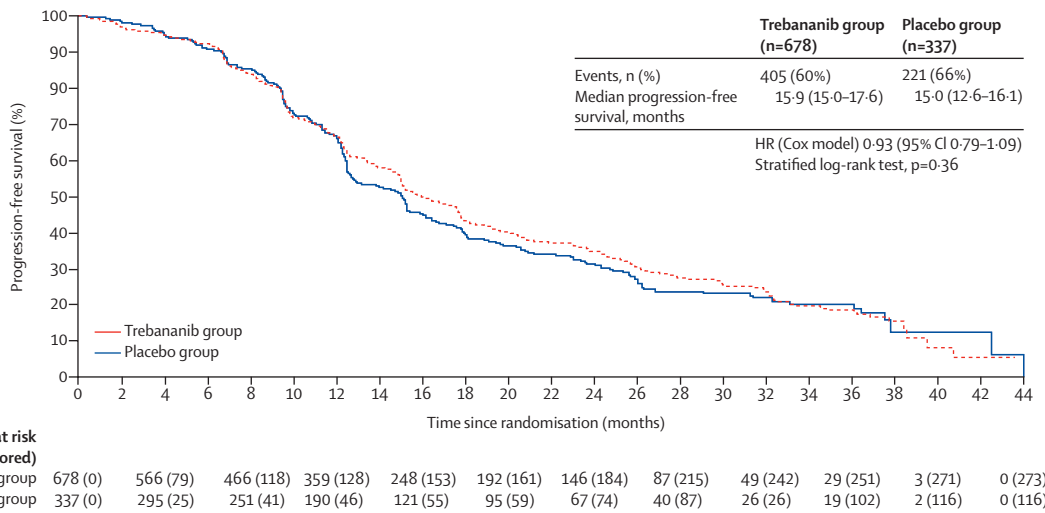
Role of the funding source

The study funder developed the protocol in collaboration with IV and ENGOT, provided project management support, and collected, analysed, and interpreted the data. Data analyses and interpretation were independently confirmed by the ENGOT biostatistician (BVC). HM and BVC did statistical analyses independently of one another. All authors had access to data outputs from the statistical analysis and interpreted the data. HM, BVC, and CAP had access to the raw data. The corresponding author had full access to all of the data and was responsible for the final decision to submit for publication.

Results

Between Jan 30, 2012, and Feb 25, 2014, 1164 patients were screened and 1015 patients from 206 study sites were enrolled and randomly allocated to treatment (figure 1), of whom 678 were assigned to trebananib and 337 to placebo. Baseline characteristics are shown in table 1. Median duration of combination therapy was 19·1 weeks (IQR 17·9–23·7) in the placebo group and 19·4 weeks (17·9–23·6) in the trebananib group; median duration of maintenance therapy was 39·9 weeks (22·9–57·3) in the placebo group and 37·0 weeks (16·9–61·7) in the

A



Number at risk (number censored)												
Trebananib group	678 (0)	566 (79)	466 (118)	359 (128)	248 (153)	192 (161)	146 (184)	87 (215)	49 (242)	29 (251)	3 (271)	0 (273)
Placebo group	337 (0)	295 (25)	251 (41)	190 (46)	121 (55)	95 (59)	67 (74)	40 (87)	26 (26)	19 (102)	2 (116)	0 (116)

B

	Trebananib group (n/N)	Placebo group (n/N)	HR (95% CI)
Age at baseline, years			
<65	276/471	151/231	0·92 (0·75–1·12)
≥65	129/207	70/106	1·00 (0·74–1·33)
<75	378/631	207/319	0·94 (0·79–1·11)
≥75	27/47	14/18	0·98 (0·51–1·87)
Region			
North America	121/216	75/108	0·82 (0·61–1·10)
West Europe and Australia	200/303	100/146	1·10 (0·86–1·39)
Rest of the world	84/159	46/83	0·84 (0·59–1·21)
Race			
White	332/547	188/279	0·94 (0·79–1·13)
Non-white	73/131	33/58	0·99 (0·65–1·50)
EGOG performance status			
0	217/375	112/183	0·95 (0·76–1·20)
1 or 2	188/302	109/154	0·94 (0·75–1·20)
Carboplatin dose at randomisation			
AUC 5	192/309	95/153	1·22 (0·95–1·56)
AUC 6	211/362	125/183	0·75 (0·60–0·94)
Primary tumour type			
Ovarian	348/583	192/290	0·97 (0·81–1·16)
Primary peritoneal	44/65	20/31	0·74 (0·43–1·27)
Fallopian tube	13/29	9/16	0·85 (0·36–2·00)
Histology subtype			
Serous	309/525	169/262	0·92 (0·76–1·11)
Non-serous	96/148	49/72	1·07 (0·76–1·52)
Disease stage			
IIIA–IIIB	24/61	14/28	0·76 (0·39–1·49)
IIIC–IV	381/616	207/309	0·96 (0·81–1·14)
Primary debulking surgery			
Yes	228/430	131/213	0·90 (0·72–1·12)
No	177/248	90/124	0·98 (0·76–1·27)
Residual tumour after primary debulking surgery			
0 mm	84/178	48/87	0·86 (0·60–1·22)
1–10 mm	39/58	18/25	0·84 (0·48–1·49)
>10 mm	39/66	23/33	1·04 (0·62–1·76)
Ascites at primary debulking surgery			
Yes	109/190	59/89	0·89 (0·65–1·23)
No	119/240	72/124	0·90 (0·67–1·20)
Ascites at enrolment for patients who had interval debulking surgery			
Yes	129/182	76/101	0·88 (0·66–1·17)
No	48/66	14/23	1·42 (0·78–2·59)
Overall	**405/678**	**221/337**	**0·93 (0·79–1·09)**

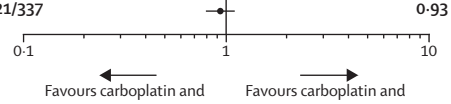


***Figure 2*: Progression-free survival**
By intention-to-treat (A) and prespecified subgroup analysis (B). AUC=area under the serum concentration–time curve. HR=hazard ratio.

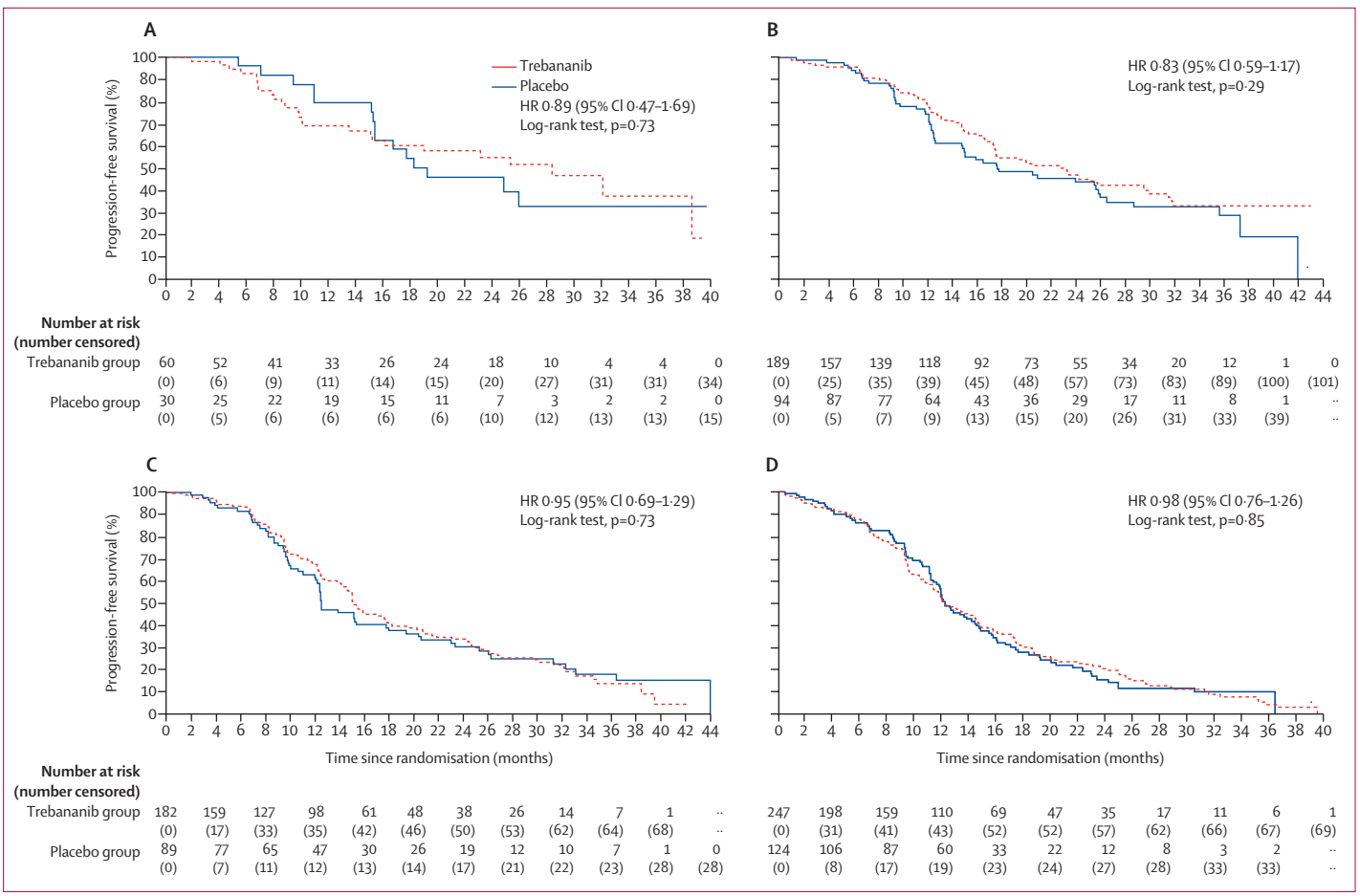


Figure 3: **Progression-free survival by disease stage and surgical procedure**

Data are for patients with FIGO disease stage IIIA or IIIB (A); FIGO disease stage IIIC or IV, with residual tumour ≤10 mm after primary debulking surgery (B); FIGO disease stage IIIC or IV, with residual tumour >10 mm after primary debulking surgery (C); and FIGO disease stage IIIC or IV, with planned interval debulking surgery (D). FIGO=International Federation of Gynecology and Obstetrics. HR=hazard ratio.

trebananib group (appendix p 21). Median relative dose intensity of trebananib in the trebananib group was 92% (IQR 81–98); median relative dose intensity for carboplatin was 81% (70–91) in the trebananib group and 80% (69–92) in the placebo group; and median relative dose intensity for paclitaxel was 92% (76–100) in the trebananib group and 92% (74–99) in the placebo group (appendix p 22). At the cutoff for the primary analysis, 81 (12%) of 678 patients in the trebananib group and 41 (12%) of 337 in the placebo group had completed the entire course of treatment. 87 patients (13%) in the trebananib group and 48 patients (14%) in the placebo group had at least one important protocol violation (appendix p 23). Disease progression was the most common reason for treatment discontinuation (trebananib 239 [35%]; placebo 161 [48%]). 56 (8%) patients in the trebananib group and 42 (12%) patients in the placebo group discontinued treatment during the maintenance phase of the study, owing to the data monitoring committee's recommendation to halt the study on April 13, 2015 after the sixth safety analysis; this decision was based on the low predictive power of the study and that its primary endpoint was unlikely to be met.

The prespecified interim progression-free survival analysis was done after 312 patients had progression-free survival events; the criteria for this were met during the fifth safety analysis by the data monitoring committee on Oct 13, 2014 (1015 patients were enrolled at this time). These data did not meet the definition for futility and the study continued.

The primary analysis was done after 626 patients had progression-free survival events. After a median follow-up of 27·4 months (IQR 17·7–34·2), 405 (60%) of 678 patients in the trebananib group and 221 (66%) of 337 patients in the placebo group had progression-free survival events. Trebananib did not improve progression-free survival compared with placebo; median progression-free survival was 15·9 months (95% CI 15·0–17·6) for trebananib and 15·0 months (12·6–16·1) for placebo (HR 0·93 [95% CI 0·79–1·09]; figure 2A). Subgroup analyses for progression-free survival are shown in figure 2B. A piecewise Cox model using 24-week intervals

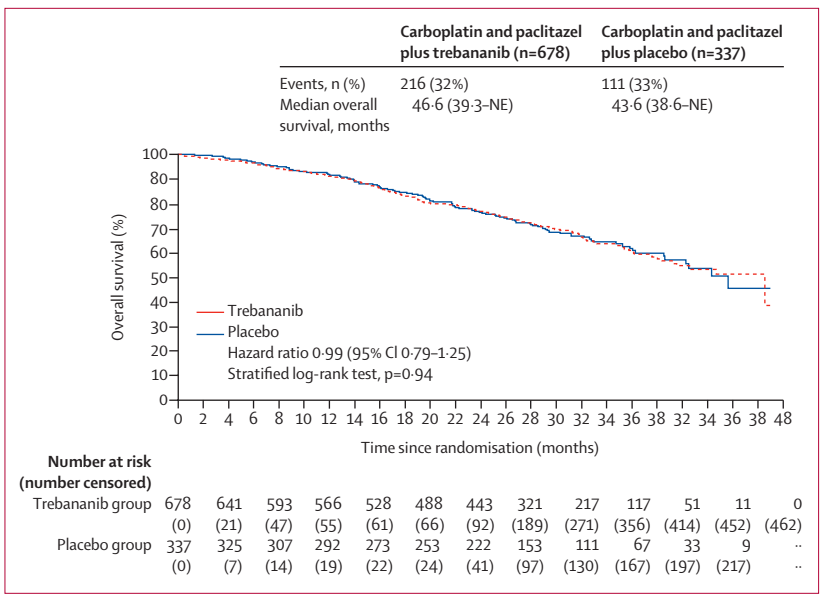


Figure 4: **Overall survival**
Intention-to-treat analysis. NE=not estimable.

to compare progression-free survival between the treatment groups gave an estimated HR for the 24-week intervals of 0·96 (0·59–1·56) for weeks 0–24, 1·05 (0·78–1·42) for weeks 24–48, 0·72 (0·54–0·97) for weeks 48–72, and 1·05 (0·76–1·44) for weeks 72 and above; and an overall inverse variance weighted HR of 0·92 (0·78–1·09). In the per-protocol analysis set, including 360 events in 591 patients in the trebananib group and 186 events in 289 patients in the placebo group, median progression-free survival was 15·6 months (95% CI 14·9–17·6) in the trebananib group and 15·0 months (12·5–16·1) in the placebo group (HR 0·95 [0·79–1·13], p=0·54; appendix p 24). The progression-free survival treatment effect was similar within clinically meaningful subsets defined by baseline covariates (including in patients with baseline ascites in both the primary debulking surgery and planned interval debulking surgery groups), except for carboplatin exposure. Patients receiving carboplatin at an AUC of 6 had an HR of 0·75 (0·60–0·94), compared with 1·22 (0·95–1·56) for those receiving AUC 5 (p=0·004 for interaction with treatment; figure 2B). In prespecified subgroup analyses, progression-free survival was not improved in the trebananib group compared with the placebo group in patient subsets defined by stratification factors (figure 3).

Overall survival in the intention-to-treat population was not mature at data cutoff and was estimated. 216 (32%) of 678 patients in the trebananib group and 111 (33%) of 337 patients in the trebananib and placebo group died. Median overall survival was 46·6 months (39·3–not estimable [NE]) in the trebananib group and 43·6 months (38·6–NE) in the placebo group (HR 0·99 [0·79–1·25]; figure 4). A piecewise Cox model using 24-week intervals to compare overall survival between the treatment groups gave an estimated HR of 1·31 (0·61–2·83) for weeks 0–24, 0·99 (0·53–1·85) for weeks 24–48, 1·06 (0·62–1·81) for weeks 48–72, and 0·93 (0·69–1·25) for weeks ≥72. The overall inverse variance weighted HR was 0·99 (0·79–1·25).

Among patients in the safety analysis set who received at least one dose of study medication, the incidence of any-grade adverse events was 666 (99%) of 675 in the trebananib group and 327 (97%) of 336 in the placebo group. Serious adverse events occurred in 269 (40%) patients in the trebananib group and 104 (31%) in the placebo group (appendix pp 25–28). The incidence of grade 3 or worse adverse events was 76% (512 patients) for trebananib and 71% (237 patients) for placebo (appendix pp 29–53); of which the most common events were neutropenia (trebananib 238 [35%] *vs* placebo 126 [38%]) anaemia (76 [11%] *vs* 40 [12%]), and leucopenia (81 [12%] *vs* 35 [10%]). Trebananib was associated with more adverse event-related treatment discontinuations than placebo (187 patients [28%] *vs* 44 [13%]). Trebananib was associated with more mandatory treatment discontinuations due to grade 3 or worse localised oedema (27 patients [4%] *vs* one [<1%]), grade 3 or worse generalised oedema (18 [3%] *vs* 0), and grade 3 or worse lymphoedema (12 [2%] *vs* 0). 20 (3%) patients in the trebananib group and one (<1%) patient in the placebo group had a fatal treatment-emergent adverse event. Fatal all-cause adverse events (including those that occurred after safety follow-up) occurred in 40 (6%) of 675 patients in the trebananib group and ten (3%) of 336 in the placebo group. Of the 20 fatal treatment-emergent adverse events reported in the trebananib group, six (1%) were associated with disease progression. Fatal events occurring in more than one patient in the trebananib group were general physical health deterioration (four patients; 1%) and cardiac arrest (two; <1%). Two of the fatal events in the trebananib group were considered related to trebananib, paclitaxel, and carboplatin (lung infection and neutropenic colitis); two events were considered related to paclitaxel and carboplatin (general physical health deterioration and platelet count decreased). 452 patients (67%) in the trebananib group and 99 (30%) in the placebo group developed oedema of any grade during treatment. Grade 3 or worse oedema was more prevalent in the trebananib group (67 patients [10%]) than in the placebo group (three (1%). Adverse events of grade 1–2 that presented with a 10% or higher frequency in either treatment group, and grades 3–5 occurring in at least 3% of patients in either group are shown in table 2.

Among 666 evaluable patients in the trebananib group, 72 (12%) developed anti-trebananib binding antibodies; none of whom had neutralising anti-trebananib antibodies at follow-up. At steady-state, the mean C_{max} (assessed by the end of infusion concentration) was 321 µg/ml (SD 232), which was similar to that observed after the first dose (appendix p 54). 38 (6%) of 666 patients had pre-existing anti-trebananib antibodies at baseline.

Patient-reported outcomes were analysed using the FACT-O (figure 5A) and FACT-O OCS (figure 5B) questionnaires; completion rates were about 90% for both groups throughout the combination phase and up to month 15 during the maintenance phase (appendix pp 55–56). Trebananib treatment did not result in an overall change in patient-reported outcome scores compared with placebo (appendix p 57). With the pattern-mixture model, the mean changes in the FACT-O and FACT-O OCS values over time were –3·86 (95% CI

	Trebananib and paclitaxel plus carboplatin group (n=675)				Placebo and paclitaxel plus carboplatin group (n=336)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	659 (98%)	490 (73%)	221 (33%)	20 (3%)	324 (96%)	222 (66%)	102 (30%)	1 (<1%)
Nausea	386 (57%)	21 (3%)	1 (<1%)	0	205 (61%)	6 (2%)	0	0
Localised oedema*	367 (54%)	34 (5%)	0	0	85 (25%)	3 (1%)	0	0
Alopecia	362 (54%)	1 (<1%)	0	0	179 (53%)	0	0	0
Fatigue	301 (45%)	22 (3%)	0	0	136 (41%)	9 (3%)	0	0
Constipation	267 (40%)	10 (2%)	0	0	142 (42%)	1 (<1%)	0	0
Diarrhoea	234 (35%)	21 (3%)	1 (<1%)	0	114 (34%)	7 (2%)	0	0
Vomiting	232 (34%)	15 (2%)	0	0	112 (33%)	7 (2%)	0	0
Abdominal pain	214 (32%)	27 (4%)	0	0	110 (33%)	11 (3%)	0	0
Peripheral neuropathy	212 (31%)	20 (3%)	1 (<1%)	0	102 (30%)	13 (4%)	0	0
Neutropenia	200 (30%)	180 (27%)	146 (22%)	0	111 (33%)	94 (28%)	77 (23%)	0
Arthralgia	188 (28%)	3 (<1%)	0	0	92 (27%)	0	0	0
Anaemia	182 (27%)	72 (11%)	7 (1%)	0	104 (31%)	40 (12%)	2 (1%)	0
Decreased appetite	172 (26%)	15 (2%)	0	0	87 (26%)	4 (1%)	0	0
Peripheral sensory neuropathy	139 (21%)	10 (2%)	0	0	63 (19%)	8 (2%)	0	0
Dizziness	130 (19%)	6 (1%)	0	0	48 (14%)	0	0	0
Myalgia	124 (18%)	1 (<1%)	0	0	64 (19%)	0	0	0
Thrombocytopenia	121 (18%)	42 (6%)	21 (3%)	0	54 (16%)	20 (6%)	7 (2%)	0
Headache	120 (18%)	5 (1%)	0	0	51 (15%)	1 (<1%)	0	0
Asthenia	118 (18%)	12 (2%)	0	0	70 (21%)	6 (2%)	0	0
Pain in extremity	118 (18%)	2 (<1%)	0	0	45 (13%)	1 (<1%)	0	0
Dyspnoea	111 (16%)	14 (2.1%)	0	0	36 (11%)	4 (1%)	0	0
Hypokalaemia	102 (15%)	40 (6%)	4 (1%)	0	39 (12%)	11 (3%)	2 (1%)	0
Insomnia	102 (15%)	0	0	0	55 (16%)	0	0	0
Cough	99 (15%)	0	0	0	49 (15%)	0	0	0
Back pain	89 (13%)	3 (<1%)	0	0	58 (17%)	2 (1%)	0	0
Hypomagnesaemia	85 (13%)	9 (1%)	3 (<1%)	0	39 (12%)	4 (1%)	1 (<1%)	0
Urinary tract infection	83 (12%)	6 (1%)	0	0	35 (10%)	1 (<1%)	0	0
Leucopenia	79 (12%)	76 (11%)	15 (2%)	0	39 (12%)	32 (10%)	6 (2%)	0
Dyspepsia	78 (12%)	0	0	0	32 (10%)	1 (<1%)	0	0
Lymphodema	78 (12%)	13 (2%)	0	0	11 (3%)	0	0	0
Ascites	77 (11%)	48 (7%)	1 (<1%)	1 (<1%)	11 (3%)	17 (5%)	0	0
Generalised oedema†	77 (11%)	20 (3%)	0	0	9 (3%)	0	0	0
Rash	76 (11%)	0	0	0	49 (15%)	0	0	0
Upper abdominal pain	73 (11%)	4 (1%)	0	0	35 (10%)	0	0	0
Paraesthesia	73 (11%)	4 (1%)	0	0	41 (12%)	1 (<1%)	0	0
Blurred vision	73 (11%)	1 (<1%)	0	0	24 (7%)	0	0	0
Platelet count decreased	72 (11%)	29 (4%)	10 (2%)	1 (<1%)	33 (10%)	7 (2%)	0	0
Pyrexia	72 (11%)	0	0	0	45 (13%)	2 (1%)	0	0
Dysgeusia	71 (11%)	0	0	0	37 (11%)	0	0	0
Abdominal distension	70 (10%)	3 (<1%)	0	0	26 (8%)	1 (<1%)	0	0
Pain	70 (10%)	2 (<1%)	0	0	32 (10%)	1 (<1%)	0	0
Pruritus	69 (10%)	1 (<1%)	0	0	29 (9%)	0	0	0
Pleural effusion	64 (10%)	21 (3%)	2 (<1%)	0	6 (2%)	4 (1%)	0	0
Musculoskeletal pain	38 (6%)	2 (<1%)	0	0	35 (10%)	2 (1%)	0	0

(Table 2 continues on next page)

	Trebananib and paclitaxel plus carboplatin group (n=675)				Placebo and paclitaxel plus carboplatin group (n=336)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Neutrophil count decreased	33 (5%)	22 (3%)	15 (2%)	0	16 (5%)	13 (4%)	8 (2%)	0
White blood cell count decreased	35 (5%)	28 (4%)	4 (1%)	0	16 (5%)	8 (2%)	1 (<1%)	0
Febrile neutropenia	1 (<1%)	15 (2%)	3 (<1%)	0	1 (<1%)	5 (2%)	0	0

Data are n (%). Shown are grade 1–2 adverse events that occurred in at least 10% of patients in either group, as well as grades 3–5 occurring in at least 3% of patients in either group. All grade 3 or worse adverse events are shown in the appendix (pp 29–53). Patients with multiple records of different grade level were counted multiple times. In addition to those listed in the table, fatal adverse events (grade 5) that occurred in the trebananib group were general physical health deterioration (n=4), cardiac arrest (n=2), pulmonary embolism (n=1), small intestine obstruction (n=1), disseminated intravascular coagulation (n=1), lung infection (n=1), respiratory failure (n=1), completed suicide (n=1), haemorrhagic disorder (n=1), multiorgan failure (n=1), neutropenic colitis (n=1), ovarian cancer (n=1), post-procedural infection (n=1), and sudden death (n=1). The only grade 5 adverse event that occurred in the placebo group was ovarian cancer (n=1). Two of the fatal events in the trebananib group were considered related to trebananib, paclitaxel, and carboplatin (lung infection and neutropenic colitis); two events were considered related to paclitaxel and carboplatin (general physical health deterioration and platelet count decreased). *Defined as oedema confined to a single body area. †Defined as oedema with contiguous extension to more than a single body area.

Table 2: **Adverse events**

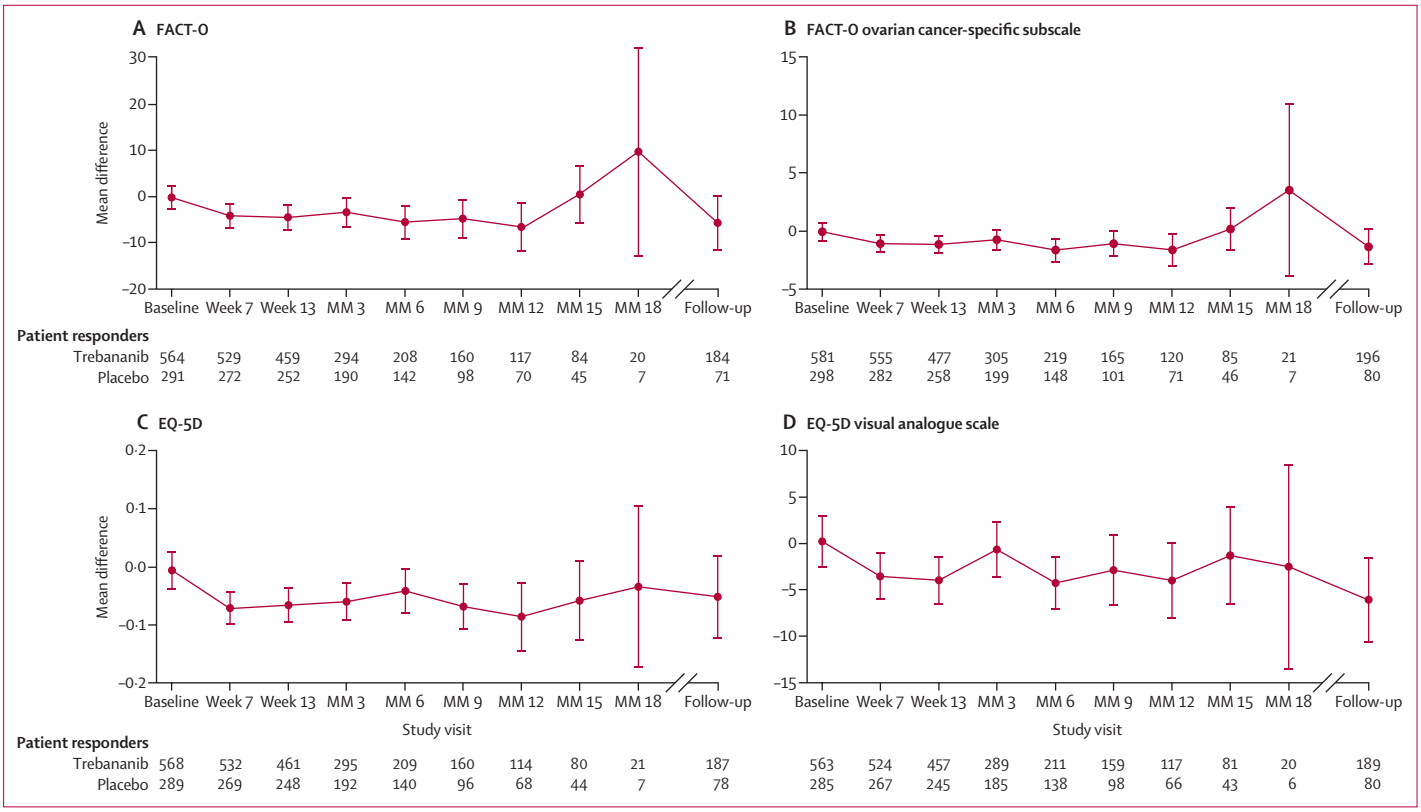


Figure 5: **Patient-reported outcomes**

Data are mean difference in outcome scores and error bars are 95% CIs. EQ-5D=EuroQoL-5 dimensions. FACT-O=Functional Assessment of Cancer Therapy–Ovary. MM=maintenance month.

–6·64 to –1·09) for FACT-O early dropout (last visit at or before 3 months), –4·35 (–6·87 to –1·83) for FACT-O late dropout (last visit after 3 months), –0·67 (–1·52 to 0·19) for FACT-O OCS early dropout, and –1·13 (–1·89 to –0·37) for FACT-O OCS late dropout (appendix p 57). Changes from baseline in the FACT-O questionnaire were slightly better for the placebo group than for the trebananib group; however, changes from baseline in the FACT-O OCS questionnaire did not differ between the trebananib and placebo groups (appendix p 53). Assessment of EQ-5D (figure 5C) and EQ-5D visual analogue scale (figure 5D) showed that health utility states were not affected by trebananib treatment compared with placebo.

In a prespecified exploratory analysis, Ang1, Ang2, and Tie2 were measured at baseline and compared with clinical response (ie, overall response, progression-free survival, and overall survival). Ang1 was neither predictive

nor prognostic of response (data not shown), yet Ang2 and Tie2 were prognostic of overall response, progression-free survival, and overall survival (appendix pp 64–67). Although some Ang2-defined patient subsets showed better treatment responses than were seen for the overall population, the trend was inconsistent, complicating a plausible hypothesis for a biological rationale for the predictive effect.

Discussion

In this phase 3 study, the Ang1 and Ang2 inhibitor trebananib administered in combination with standard carboplatin plus paclitaxel (six cycles) and then alone as maintenance treatment in the first-line setting for patients with advanced ovarian cancer did not improve progression-free survival compared with standard carboplatin plus paclitaxel treatment. By contrast, TRINOVA-1, a phase 3 study of trebananib in combination with paclitaxel in patients with recurrent ovarian cancer, showed a significant improvement of progression-free survival compared with paclitaxel alone.[17] TRINOVA-2/ENGOT-ov6, a phase 3 study of trebananib in combination with pegylated liposomal doxorubicin in patients with recurrent ovarian cancer, reported a higher number of patients who achieved an objective response and improved duration of response but did not show significant improvement in progression-free survival compared with pegylated liposomal doxorubicin alone.[13] The explanation for these differences in activity of trebananib in different ovarian cancer settings and lines of therapy is complex and highlights our scarce understanding of the mechanisms and interactions of angiogenic factors involved in ovarian cancer progression. Among the various considerations for differences in activity observed in ovarian cancer trials with the VEGF inhibitor, bevacizumab, multi-targeted angiogenic tyrosine kinase inhibitors (eg, nintedanib and pazopanib), and the Ang1 and Ang2 inhibitor, trebananib, are factors such as extent of residual or metastatic disease, the target of the antiangiogenic agent, the chosen chemotherapy combination or dosing of chemotherapy, duration of maintenance therapy (and size of the maintenance group), and patient differences in the susceptibility to a given antiangiogenic agent. Our previous phase 2 study[24] in ovarian cancer comparing paclitaxel plus trebananib versus paclitaxel plus placebo was exploratory in nature and, although a slight improvement in progression-free survival was seen in the trebananib group, the differences were not statistically significant.

Comparison of other phase 3 studies of ovarian cancer that evaluated antiangiogenic agents in the first-line setting suggests that there might be differences in response depending on the extent of residual disease and the specific antiangiogenic agent used. For example, in ICON7,[8] bevacizumab in combination with six cycles of carboplatin and paclitaxel followed by a 12-month maintenance phase with bevacizumab had a significant effect on progression-free survival versus therapy without bevacizumab during primary analysis (median progression-free survival 19·0 months *vs* 17·3 months, HR 0·81 [95% CI 0·70–0·94]; p=0·004), when 759 patients had disease progression or died. However, in the subsequent final analysis when 1080 patients had disease progression or died, this effect on progression-free survival for all enrolled patients was no longer significant (19·9 months [95% CI 19·1–22·0] *vs* 17·5 months [15·7–18·7], HR 0·93 [0·83–1·05]; p=0·25). Patients at high risk (stage IV, inoperable stage III, or suboptimally debulked) had a significant response that was greater than that seen in the lower-risk group (final analysis HR 0·73 [0·61–0·88]; p=0·001).[9] In the primary analysis of GOG-0218,[7] in which enrolled patients resembled the high-risk group in ICON7, bevacizumab improved progression-free survival versus standard therapy when given as a maintenance therapy after initial treatment with bevacizumab plus standard carboplatin and paclitaxel (median progression-free survival in the bevacizumab throughout group was 14·1 months *vs* 10·3 months in the standard therapy group; HR 0·72 [0·63–0·82]; p<0·001). Updated information from GOG-0218 suggests that this improved progression-free survival was sustained (HR 0·77 [0·68–0·87]; p<0·001).[25] By contrast, in AGO-OVAR 12,[26] a study of standard therapy with carboplatin plus paclitaxel with or without nintedanib (a small-molecule inhibitor of the VEGF receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor) with no maintenance nintedanib phase, median progression-free survival was improved in the overall population with nintedanib treatment (HR 0·84 [95% CI 0·72–0·98]; p=0·024), and a greater progression-free survival treatment effect was seen in non-high-risk patients than among high-risk patients (HR 0·74 *vs* 0·99). Finally, in AGO-OVAR 16,[27] a phase 3 study of pazopanib (a small-molecule inhibitor of the VEGF receptor, platelet-derived growth factor receptor, and c-Kit) given only as maintenance therapy after at least five cycles of platinum and taxane chemotherapy, in which patients with persistent bulky disease were excluded and 88% were free of disease at study entry (ie, a low-risk group), progression-free survival improved in the pazopanib group compared with those receiving no maintenance therapy (median 17·9 months [95% CI 15·9–21·8] *vs* 12·3 months [11·8–17·7], HR 0·77 [0·64–0·91]; p=0·0021).

Although the definition of high risk versus low risk varies among these studies (with TRINOVA-3 sharing greater similarity in its definition of high risk with that of ICON7[8] than with the other studies mentioned), no progression-free survival treatment effect was seen in the high-risk patient population in the present study. Notably, in our study, the HR for progression-free survival was higher in patients with FIGO disease stage IIIC or IV and suboptimal debulking (residual tumour >10 mm; ie, the higher risk group) than that for patients with stage IIIC to IV and optimal debulking (residual tumour

≤10 mm; ie, the lower risk group). Although neither comparison was statistically significant, these data suggest a possible greater effect of trebananib in the low-risk group as observed with AGO-OVAR 12 (nintedanib)[26] and possibly AGO-OVAR 16 (pazopanib; although this study lacks a high-risk group comparison).[27] In the present study, patients enrolled to the interval debulking surgery group (a higher risk group with extensive or poorly resectable disease at diagnosis) did not show any difference in progression-free survival compared with the primary debulking surgery population.

Although choice or dosing of chemotherapy might have contributed to differences in outcomes seen in trials of antiangiogenic agents in the recurrent setting, TRINOVA-3, like other studies in the first-line setting (ICON7, GOG-0218 and AGO-OVAR 12[7,8,26]) used standard carboplatin (AUC 5 or 6) and paclitaxel dosing (175 mg/m²) every 3 weeks for six cycles. In AGO-OVAR 16,[27] patients were not enrolled until after completion of the chemotherapy regimen and, therefore, less oversight of chemotherapy was possible. However, similar to other first-line trials, patients in this trial received platinum and taxane chemotherapy for at least five cycles. Therefore, differences in choice or dosing of chemotherapy do not explain the absence of progression-free survival benefit with trebananib. One interesting observation was that in our subgroup analysis of progression-free survival, patients enrolled at a carboplatin AUC 6 (rather than AUC 5) benefited more from trebananib than those who began at a lower dose. Clinical or biological reasons for this observation are unclear and the risk of a type 1 error is high.

Duration of dosing with angiogenic inhibitors in the combination phase and in maintenance monotherapy is likely to affect efficacy. There are no clear data regarding the optimal duration of maintenance angiogenic inhibitor treatment. Following the combination phase with chemotherapy in ICON7 and GOG-0218 (with bevacizumab), in AGO-OVAR 12 (with nintedanib), in AGO-OVAR 16 (with pazopanib), and in the present study (with trebananib), the allowed duration of maintenance monotherapy varied considerably (from 12 to 25 months).[7,8,26,27] In all five studies, more than 50% of patients did not complete the maintenance phase; as expected, the most common reason for discontinuing therapy in all trials was disease progression. However, variability existed in the size of the studies, the percentage of patients entering the maintenance phase, and the relative number of patients discontinuing maintenance for reasons other than disease progression—factors which could have contributed to the different progression-free survival effects.[7,8,26,27] It is difficult to compare all of these factors; however, in ICON7,[8] 62% of patients received bevacizumab up to cycle 18 (ie, about 9 months of maintenance therapy), whereas in GOG-0218,[7] only 19% of patients completed the planned treatment and neither the median or mean duration of maintenance therapy received in the bevacizumab throughout group (chemotherapy plus bevacizumab proceeding to bevacizumab maintenance) were reported. In AGO-OVAR 12,[26] only 135 (15%) of 902 patients completed the planned treatment with nintedanib; neither median nor mean duration of maintenance therapy were reported. In the AGO-OVAR 16 study,[27] the mean duration of monotherapy was 8·9 months; the percentage of patients completing treatment was not reported.[27] In the present study, only 12% of patients completed the entire 18 months of maintenance monotherapy; the median time spent on trebananib maintenance therapy was only 8 months (37 weeks). Various factors contributed to this relatively short trebananib maintenance phase, including disease progression, adverse events, consent withdrawal, and the decision by the data monitoring committee and Amgen to end treatment early (the latter truncating maintenance treatment in 56 (8%) patients in the trebananib group).

Finally, patient differences in susceptibility to targeting specific angiogenic drivers probably contribute substantially to the differences in efficacy across these trials. Even for the VEGF and VEGF receptor inhibitors, despite several decades of effort, no validated markers of tumour response or resistance have yet been identified. This situation is also true of angiopoietin/Tie 2-mediated tumour progression.

Not surprisingly, overall survival benefit with the addition of angiogenesis inhibitors to standard debulking surgery and chemotherapy in the first-line setting has been difficult to show. In phase 3 trials[9,25,27,28] in the first-line setting, only ICON7 (with bevacizumab) and GOG 0218 (bevacizumab throughout group) showed improved overall survival and only in the high-risk population. In the present study, estimated overall survival did not differ between groups.

Trebananib is distinct from other anti-angiogenesis agents not only because of its mechanism of action but also its toxicity profile; several adverse events typically associated with anti-VEGF and VEGF receptor inhibitors, such as hypertension, bleeding, and delayed wound healing are not increased with trebananib treatment.[7,8,26] The most common adverse event associated with trebananib is oedema, including ascites and pleural effusions.[29] The incidence and nature of these and other adverse events in the present trial were consistent with previous reports.[12,13,17] Likewise, as reported in TRINOVA-1 (with paclitaxel) and TRINOVA-2 (with pegylated liposomal doxorubicin), the combination of trebananib with carboplatin plus paclitaxel in the present trial was not associated with a decrease in patient-reported quality of life.[13,30]

Our study has some limitations. The planned study sample size was reduced about 2 years after enrolment began owing to enrolment difficulties, the regulatory landscape, competitor drug development, and the preliminary results from the TRINOVA-1 and TRINOVA-2

studies.[12,13] However, this reduction in sample size did not affect the determination of progression-free survival, the primary endpoint, and would have provided reasonable power if the effect size on overall survival was large. However, the reduction in size might have restricted the analyses of secondary endpoints and subgroup analyses of the trial.

In summary, the results from this study showed that trebananib in combination with carboplatin plus paclitaxel as first-line treatment following primary debulking surgery or interval debulking surgery did not improve progression-free survival compared with placebo plus carboplatin plus paclitaxel. Quality of life was maintained with the combination of trebananib plus carboplatin and paclitaxel compared with placebo plus carboplatin and paclitaxel.

Contributors

IV, GS, DMO'M, JMdC, AB, NC, RMW, AC, CM, MRM, JRK, and BJM conceived and designed the study, and collected, analysed and interpreted data. BVC and CAP conceived and designed the study and analysed and interpreted data. S-YP and WM collected, analysed and interpreted data. HM analysed and interpreted data. All authors approved the final version of the manuscript.

Declaration of interests

IV has acted as an advisory board consultant for GCI Health, Oncoinvent AS, Roche NV, Genmab, Advaxis, Morphotek, F Hoffmann-La Roche, Cerulean Pharma, Novocure, AstraZeneca, Mateon Therapeutics, ImmunoGen, Eli Lilly Benelux, Amgen, Theradex Europe, Pfizer, Debiopharm International, Vifor Pharma Belgie, Novartis Pharma, Merck Sharpe & Dohme, Oxigene, Janssen-Cilag, Nektar Therapeutics, and Bayer Pharma; has received accommodation and travel expenses from Tesaro, Theradex, and Elsevier; and has received research grants from Amgen and Roche. BJM has received honoraria from and served as a consultant for AbbVie, Advaxis, Amgen, AstraZeneca, Biodesix, Clovis, Genmab, Gradalis, ImmunoGen, Immunomedics, Incyte, Janssen–Johnson & Johnson, Mateon, Merck, Myriad, Perthera, Pfizer, Precision Oncology, Puma Biotechnology, Roche–Genentech, Samumed, Takeda, Tesaro, and VBL Therapeutics; and has served as a speaker for AstraZeneca, Clovis, Janssen–Johnson & Johnson, Roche–Genentech, and Tesaro. DMO'M has served on a steering committee for Amgen; has served as a consultant for Tesaro and AstraZeneca; and has served on advisory boards for Clovis, Tesaro, AstraZeneca, Novocure, Genentech–Roche, Janssen, and Eisai. BVC has received research grant support from Amgen. RMW has served on steering committees for Amgen, Tesaro, Ovation Diagnostics, and Tapimmune; advisory boards for Genentech, Tesaro, Clovis, Merck, Mersana, Ovation Diagnostics, and Oncomed; and speakers' bureaus for Genentech, Tesaro, Clovis, and Janssen. RMW has also received research grant support from Genentech and Merck. NC has received honoraria from Amgen, Roche, AstraZeneca, Tesaro, Clovis, PharmaMar, Pfizer, and Advaxis. CAP is an employee of and shareholder in Amgen. HM is employed by Amgen. All other authors declare no competing interests.

Data sharing

We plan to share these data. This plan might include deidentified individual patient data for variables necessary to address the specific research question in an approved data-sharing request, and also related data dictionaries, study protocol, statistical analysis plan, informed consent form, or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and this product and indication (or other new use) have been granted marketing authorisation in the USA and Europe, or clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers can submit a request containing the research objectives, the Amgen product(s) and Amgen study or studies in scope, endpoints or outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, requests may be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. Such information may include anonymised individual patient data or available supporting documents (or both), containing fragments of analysis code where provided in analysis specifications.

For further details on our **data sharing agreement** see https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

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