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A phase 1b study of trebananib in combination with pegylated liposomal doxorubicin or topotecan in women with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer☆,☆☆

Ignace Vergote [a], Russell J. Schilder [b], Charles H. Pippitt Jr. [c], Shirley Wong [d], Alan N. Gordon [e], Sidney Scudder [f], Frederic Kridelka [g], Luc Dirix [h], Joseph W. Leach [i], Sumitra Ananda [j], Nuwan Nanayakkara [k], Rebeca Melara [l], Michael B. Bass [l], Jason Litten [l], Henry Adewoye [l], Robert M. Wenham [m,*]

[a] University Hospitals Leuven and KU Leuven, Leuven, Belgium
[b] Thomas Jefferson University, Philadelphia, PA, USA
[c] Novant Health Oncology Specialists, Winston-Salem, NC, USA
[d] Western Hospital, Footscray, VIC, Australia
[e] Emory University, Atlanta, GA, USA
[f] UC Davis Comprehensive Cancer Center, Sacramento, CA, USA
[g] Centre Hospitalier Universitaire de Liége Sart Tilman, Liège, Belgium
[h] Sint Augustinus, Antwerpen, Belgium
[i] Virginia Piper Cancer Institute, Minneapolis, MN, USA
[j] Royal Women's Hospital, Melbourne, VIC, Australia
[k] Quintiles, San Diego, CA, USA
[l] Amgen Inc., Thousand Oaks, CA, USA
[m] H. Lee Moffitt Cancer Center, Tampa, FL, USA

HIGHLIGHTS

- Trebananib plus PLD or topotecan had acceptable toxicities in ovarian cancer.
- Antitumor activity was evident across all trebananib plus PLD or topotecan cohorts.
- No drug–drug interactions occurred between trebananib and PLD or topotecan.

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ABSTRACT

Objective. To examine the tolerability and antitumor activity of trebananib plus pegylated liposomal doxorubicin (PLD) or topotecan in recurrent platinum-resistant or partially platinum-sensitive ovarian cancer.

Methods. In this open-label phase 1b study, patients received trebananib 10 mg/kg or 15 mg/kg IV QW plus PLD 50 mg/m^2 (cohorts A1 and A3, respectively) or topotecan 4 mg/m^2 (cohorts B1 and B3, respectively). Endpoints were dose-limiting toxicity (DLT; primary); treatment-emergent adverse events (AEs), overall response rate, anti-trebananib antibodies, and pharmacokinetics (secondary).

Results. 103 patients were enrolled. One patient in A1 and B1 had DLTs. Across all cohorts, the most common AEs were nausea, fatigue, and peripheral edema. Across both trebananib plus PLD cohorts (A1/A3), grade 4 AEs were pulmonary embolism, disease progression, and anemia. Two patients had grade 5 intestinal perforation (n = 1) and sudden death (n = 1). Across both trebananib plus topotecan cohorts (B1/B3), grade 4 AEs were neutropenia, hypokalemia, decreased granulocyte count, chest pain, dyspnea, decreased neutrophil count, and pulmonary embolism. Two patients had grade 5 disease progression. One patient had grade 5 pleural effusion associated with progressive disease. Confirmed objective response rates were 36.0% (A1), 34.8% (A3), 16.7% (B1), and 0.0% (B3). Median progression-free survival duration (months) was 7.4 (A1), 7.1 (A3), 3.5 (B1), and 3.1 (B3), respectively. No drug–drug interactions were apparent.

☆ Previous presentation: The results of this study have not been previously published or submitted for publication elsewhere. The results were presented in part at the Clinical Oncology Society of Australia, Brisbane, Australia, November 13–15, 2012; Society of Gynecologic Oncologists, Orlando, FL, USA, March 6–9, 2011; European Society of Gynecological Oncology, Milan, Italy, September 11–14, 2011; and American Society of Clinical Oncology, Chicago, IL, USA, June 4–8, 2010.

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* Corresponding author at: H. Lee Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA. Fax: +1 813 745 7228.
E-mail address: Robert.Wenham@moffitt.org (R.M. Wenham).

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Conclusions. Trebananib 10 mg/kg and 15 mg/kg IV QW plus PLD or topotecan appear to have acceptable toxicity profiles in recurrent platinum-resistant or partially platinum-sensitive ovarian cancer. Antitumor activity was evident across all cohorts.

Introduction

Although patients with ovarian cancer generally respond to initial platinum-based chemotherapy, most patients will experience disease progression [1]. Patients whose disease recurs >12 months after completion of first-line platinum treatment tend to respond to reinduction platinum therapy (i.e., platinum-sensitive disease) and have a favorable prognosis [2]. In contrast, patients who relapse within one year after treatment with a platinum agent are generally less responsive to reinduction platinum therapy. Those patients are considered as having either platinum-resistant disease (i.e., disease recurrence <6 months after last platinum dose) or partially platinum-sensitive disease (i.e., disease recurrence 6 to 12 months after last platinum dose). For both groups of patients, standard second-line treatment can involve nonplatinum agents [3–5]. For patients with platinum-resistant disease, pegylated liposomal doxorubicin (PLD) and topotecan are currently FDA- and EMA-approved treatment agents. However, those treatments are not curative and largely considered as palliative. In patients with platinum-resistant disease who are treated with PLD and topotecan, 3-year survival rates have been found to be 13.8% and 9.5%, respectively [5]. For patients with partially platinum-sensitive disease, treatment with nonplatinum agents – such as PLD or topotecan – can be considered in order to extend the platinum-free interval and possibly increase the likelihood of a successful platinum retreatment at a later relapse [6].

To further extend the efficacy of second-line treatments in patients with suboptimal platinum-free intervals, clinical research has begun to examine the addition of targeted therapies to second-line chemotherapy regimens. Targeting angiogenesis, the process of new blood vessel formation that is required for solid tumor growth and metastatic spread, has been of particular interest [7]. To date, studies of angiogenic inhibitors have focused almost exclusively on treatments involving vascular endothelial growth factor (VEGF) pathway inhibitors combined with chemotherapy agents. Those combination treatments can provide clinical benefits in the platinum-resistant recurrent setting, although it is not clear yet whether those benefits translate into longer overall survival rates. In a phase 3 study of patients receiving bevacizumab combined with PLD, topotecan, or paclitaxel, the primary endpoint of improved progression-free survival (PFS) was met in patients receiving the combination compared with those receiving only PLD, topotecan, or paclitaxel [8]. However, a follow-up analysis did not detect a statistically significant difference in overall survival between the two patient groups [9]. In a phase 1/2 study of the VEGF receptor inhibitor vandetanib combined with PLD, the treatment was associated with antitumor activity, but was deemed intolerable because of the emergence of severe toxicities [10].

The angiopoietin axis is distinct from the VEGF pathway and critical to angiogenesis [7,11,12]. Angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) are endogenous ligands which bind to Tie2, a tyrosine kinase receptor expressed primarily on the vascular endothelium [13]. Ang1 contributes to vessel stabilization and maturation while Ang2 drives vessel destabilization and new vessel sprouting [13,14]. Trebananib is an investigational peptide–Fc fusion protein ("peptibody") that is administered intravenously (IV) and inhibits tumor angiogenesis by binding to Ang1 and Ang2, thereby blocking their interactions with the Tie2 receptor [14]. Preclinical xenograft models demonstrated that dual inhibition of Ang1 and Ang2, as achieved with trebananib, results in greater tumor suppression relative to inhibition of Ang1 or Ang2 in isolation [15]. In a first-in-human monotherapy study of patients with advanced solid tumors, trebananib exhibited a distinct toxicity profile and demonstrated antitumor activity [16]. One patient with refractory ovarian cancer in that study had a tumor reduction of 32.5% and a confirmed partial response (PR) at week 72; the patient withdrew from the study with a PR after 156 weeks of treatment. A phase 2 study suggested that patients with recurrent ovarian cancer receiving trebananib 3 mg/kg or 10 mg/kg once a week (QW) plus paclitaxel experienced longer PFS than patients receiving placebo QW plus paclitaxel [17]. In the randomized double-blind phase 3 TRINOVA-1 study, weekly trebananib 15 mg/kg combined with paclitaxel significantly improved PFS compared to weekly placebo combined with paclitaxel [18]. The combination of trebananib and PLD in patients with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer is currently under investigation in a phase 3 study (TRINOVA-2/ENGOT-ov6).

PLD and topotecan are FDA-approved chemotherapies for recurrent ovarian cancer [5,19]. Since trebananib blocks unique molecular targets, the addition of trebananib to PLD or topotecan was expected to improve efficacy without exacerbating known toxicities associated with PLD or topotecan monotherapy. Therefore, the objectives of the current study were to examine the tolerability and antitumor activity of trebananib plus PLD or topotecan in patients with recurrent ovarian cancer.

Methods

Patients

All women (≥18 years old) had radiographically documented progression of recurrent, invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer per Response Evaluation Criteria in Solid Tumors, version 1.0 (RECIST, v1.0) or CA-125 progression per Gynecologic Cancer Intergroup (GCIG) guidelines [20,21]. Other eligibility criteria included: patients had a Gynecologic Oncology Group (GOG) performance status ≤1, and a history of fewer than four anticancer therapies and at least one platinum-based regimen. Patients were excluded if they had a prior malignancy, unless the patient was treated with curative intent, did not exhibit the disease during the 3 years before enrolling in the study, and was considered to be at low risk for recurrence by the treating physician. Patients with nonmelanomatous skin cancer, lentigo maligna, or cervical carcinoma in situ who were adequately treated and did not show any evidence of disease were also eligible to enroll. Additional exclusion criteria included a higher-than-average risk of bowel perforation (i.e., symptoms or a recent history of fistula or bowel obstruction, or a need for parenteral nutrition or continuous hydration), a known history of central nervous system metastases, or arterial or deep venous thromboembolism during the year prior to enrollment. Patients were also excluded from study enrollment if they had prior treatment with abdominal or pelvic external beam radiotherapy, myeloablative high-dose chemotherapy with allogeneic or autologous stem cell transplant, or recent treatment with immune modulators. Patients previously treated with PLD or doxorubicin were excluded from the PLD cohorts; patients who previously received topotecan were excluded from the topotecan cohorts. All patients provided written informed consent. Study procedures were performed after approval by independent institutional review boards and in accordance with an assurance filed with and approved by the Department of Health and Human Services.

Study design and treatment

This 2-part open-label, dose-escalation/de-escalation phase 1b study was carried out across 13 international centers. The primary endpoint was the patient incidence of dose-limiting toxicities (DLTs). Secondary

Table 1
Baseline demographics and disease characteristics.[a]

	Cohort A1 Trebananib 10 mg/kg + PLD (N = 25)	Cohort A3 Trebananib 15 mg/kg + PLD (N = 27)	Cohort B1 Trebananib 10 mg/kg + topotecan (N = 25)	Cohort B3 Trebananib 15 mg/kg + topotecan (N = 26)
Race/ethnicity, n (%)				
White or Caucasian	21 (84)	25 (93)	24 (96)	24 (92)
Black or African American	3 (12)	2 (7)	0 (0)	1 (4)
Hispanic	0 (0)	0 (0)	1 (4)	1 (4)
Asian	1 (4)	0 (0)	0 (0)	0 (0)
Age, median (range), years	56 (36–73)	55 (34–81)	59 (46–78)	59 (28–75)
GOG performance score, n (%)				
0	17 (68)	17 (63)	18 (72)	13 (50)
1	8 (32)	10 (37)	7 (28)	13 (50)
Tumor histology, n (%)				
Serous	17 (68)	23 (85)	13 (52)	19 (73)
Endometrioid	0 (0)	3 (11)	4 (16)	3 (12)
Clear cell	0 (0)	0 (0)	1 (4)	3 (12)
Mucinous	0 (0)	0 (0)	2 (8)	0 (0)
Unclassified	5 (20)	1 (4)	5 (20)	1 (4)
Not available	3 (12)	0 (0)	0 (0)	0 (0)
FIGO disease stage at screening, n (%)				
I	0 (0)	1 (4)	0 (0)	0 (0)
II	0 (0)	0 (0)	1 (4)	1 (4)
III	14 (56)	13 (48)	10 (40)	9 (35)
IV	10 (40)	13 (48)	12 (48)	14 (54)
Unknown	1 (4)	0 (0)	2 (8)	2 (8)
Number of lines of prior anticancer therapy, n (%)				
1	10 (40)	11 (41)	10 (40)	7 (27)
2	9 (36)	12 (44)	6 (24)	12 (46)
3	6 (24)	4 (15)	9 (36)	7 (27)
Number of lines of prior platinum therapy, n (%)				
1	16 (64)	13 (48)	16 (64)	14 (54)
2	7 (28)	14 (52)	9 (36)	9 (35)
3	2 (8)	0 (0)	0 (0)	3 (12)
Prior PLD or doxorubicin therapy, n (%)	0 (0)	0 (0)	12 (48)	13 (50)
Prior topotecan therapy, n (%)	1 (4)	0 (0)	0 (0)	0 (0)
Platinum sensitivity status, n (%)[b]				
Primary platinum refractory (PFI <6 months)	0 (0)	1 (4)	2 (8)	2 (8)
Platinum-resistant (PFI <6 months)	21 (84)	18 (67)	17 (68)	14 (54)
Partially platinum-sensitive (PFI 6–12 months)	3 (12)	7 (26)	4 (16)	4 (15)
Platinum-sensitive (PFI >12 months)	1 (4)	0 (0)	1 (4)	3 (12)
Not available	0 (0)	1 (4)	1 (4)	3 (12)
Number of trebananib dosing cycles, median (range)	5.0 (1.0–18.0)	6.0 (2.0–15.0)	4.0 (1.0–35.0)	3.5 (1.0–17.0)
Relative trebananib dose intensity,[c] mean (SD)	0.810 (0.108)	0.808 (0.107)	0.773 (0.153)	0.811 (0.060)
Number of trebananib doses withheld, n (%)	69 (13)	54 (10)	37 (6)	44 (12)
Number of PLD dose changes, n (%)	64 (42)	60 (47)	NA	NA
Number of topotecan dose changes, n (%)	NA	NA	106 (28)	45 (16)
Follow-up time, median (range),[d] weeks	31 (4–78)	28 (0–61)	23 (9–144)	20 (0–74)

FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; PLD, pegylated liposomal doxorubicin; PFI, platinum-free interval; NA, not applicable; SD, standard deviation.

[a] The analyses were conducted with all enrolled patients in this study.

[b] The definition of platinum-refractory disease was based on the time to progression from the first dose of the first platinum regimen and was at most 182 days. This definition differs from the alternative definition of time to progression from the last dose of the last platinum regimen and is at most 28 days. The remaining platinum sensitivity categories were based on the time to progression from the last dose of the last platinum regimen.

[c] Relative dose intensity is the ratio of the actual cumulative trebananib dose relative to the protocol-specified cumulative trebananib dose up to study treatment discontinuation.

[d] Follow-up time is calculated from the date of enrollment to the date of the last study visit.

endpoints included the patient incidence of adverse events (AEs), objective response rate (ORR), PFS, CA-125 response, patient incidence of anti-trebananib antibody formation, and pharmacokinetic (PK) profiles. Changes in biomarkers were an exploratory endpoint. Patients received trebananib 10 mg/kg or 15 mg/kg IV QW plus PLD 50 mg/m^2 IV every 4 weeks (Q4W; cohorts A1 and A3, respectively), or trebananib 10 mg/kg or 15 mg/kg IV QW plus topotecan 4 mg/m^2 IV (cohorts B1 and B3, respectively). Topotecan in cohorts B1 and B3 was administered on days 1, 8, and 15 of a 28-day schedule. The original study design also included dose de-escalation cohorts of trebananib 3 mg/kg plus PLD or topotecan (cohorts A2 and B2, respectively) which were to be opened if trebananib 10 mg/kg were to be determined to be intolerable. Those cohorts were not initiated because of the low incidence of DLTs in cohorts receiving trebananib 10 mg/kg plus PLD or topotecan (cohorts A1 and B1, respectively). Instead, cohorts receiving trebananib 15 mg/kg plus PLD or topotecan (cohorts A3 and B3, respectively) were added. Trebananib was discontinued if dosing was withheld for >28 days. Trebananib dose levels were based on a first-in-human study that found trebananib monotherapy to be tolerable up to 30 mg/kg [16]. PLD dosing followed FDA-approved dosing guidelines. Weekly topotecan administration has been favored over FDA-approved daily dosing to attempt to minimize toxicities [22,23]. Dose modifications for PLD and topotecan are described in the Supplementary material section.

Patient enrollment is described in the Supplementary material section. All patients who received at least one dose of trebananib plus PLD or topotecan were included in all safety analyses, including DLT analyses

Table 2
Patient incidence of treatment-emergent adverse events by grade.[a]

	Cohort A1 Trebananib 10 mg/kg + PLD (N = 25)	Cohort A3 Trebananib 15 mg/kg + PLD (N = 25)	Cohort B1 Trebananib 10 mg/kg + topotecan (N = 25)	Cohort B3 Trebananib 15 mg/kg + topotecan (N = 24)
Patients with any adverse event, n (%)	25 (100)	25 (100)	25 (100)	24 (100)
Grade 1	1 (4)	0 (0)	1 (4)	1 (4)
Grade 2	3 (12)	4 (16)	7 (28)	6 (25)
Grade 3	19 (76)	17 (68)	13 (52)	12 (50)
Grade 4	1 (4)[b]	3 (12)[c]	4 (16)[d]	2 (8)[e]
Grade 5	1 (4)[f]	1 (4)[g]	0 (0)	3 (13)[h]

PLD, pegylated liposomal doxorubicin.

[a] All patients who received at least one dose of trebananib plus its cotherapy were evaluated for adverse events. Treatment-emergent adverse events included all adverse events that were recorded during study treatment and within 30 days of the last dose of any treatment agent.

[b] One patient had grade 4 disease progression.

[c] Three patients had grade 4 adverse events of pulmonary embolism (n = 2 [8%]) and anemia (n = 1 [4%]).

[d] Four patients with grade 4 adverse events had neutropenia (n = 2 [8%]), hypokalemia (n = 1 [4%]), decreased granulocyte count (n = 1 [4%]), chest pain (n = 1 [4%]), and dyspnea (n = 1 [4%]).

[e] Two patients with grade 4 adverse events had decreased neutrophil count (n = 1 [4%]) and pulmonary embolism (n = 1 [4%]).

[f] One patient had a grade 5 adverse event of intestinal perforation, which was not considered by the investigator to be related to trebananib or PLD treatment.

[g] This patient had a grade 5 adverse event of sudden death. No autopsy was performed, and the cause of death is unknown. The death was not considered by the investigator to be related to trebananib or PLD treatment.

[h] Three patients died of disease progression (n = 2 [8%]) and pleural effusion (n = 1 [4%]). Those deaths were not considered by the investigator to be related to trebananib or topotecan treatment.

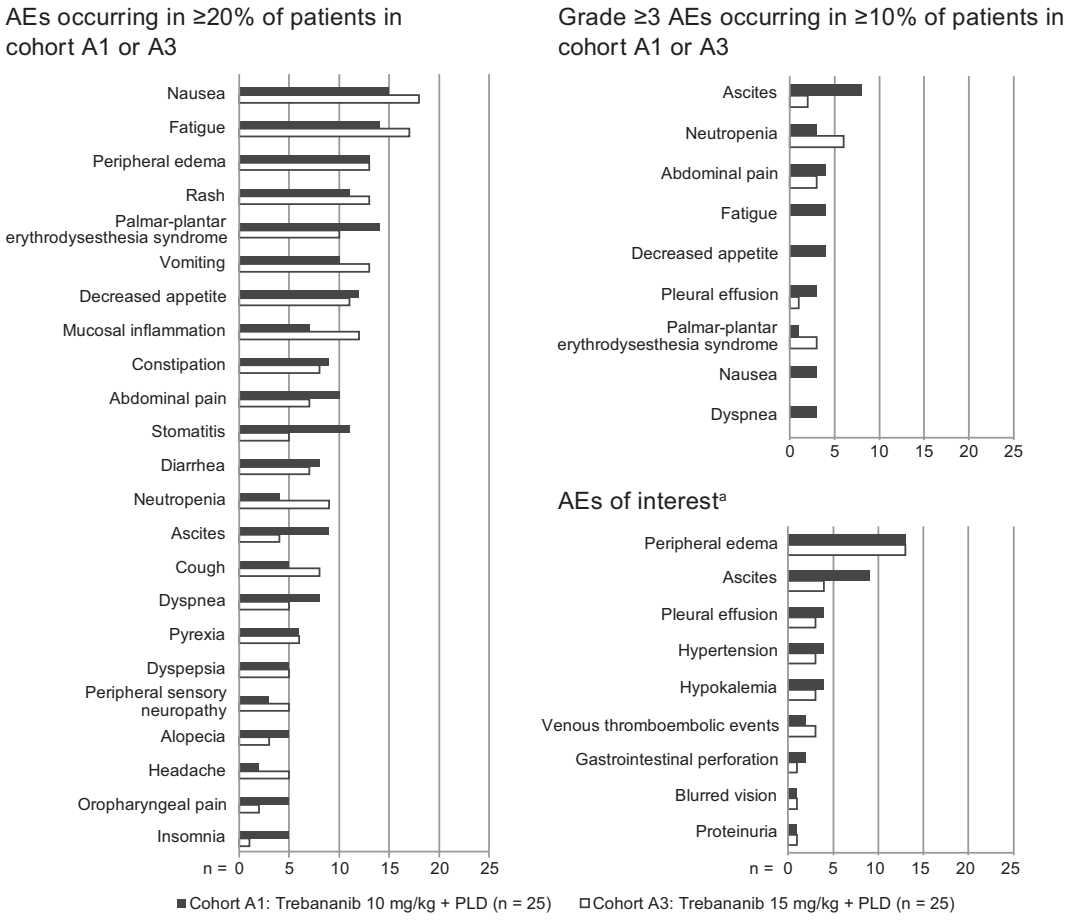

Fig. 1. Patient incidence of treatment-emergent adverse events (AEs) in the trebananib plus PLD cohorts. All patients who received at least one dose of trebananib plus its cotherapy were evaluated for AEs. Treatment-emergent adverse events AEs included all adverse events AEs that were recorded during study treatment and within 30 days of the last dose of any treatment agent.

Table 3
Summary of trebananib pharmacokinetic parameters.

Descriptive statistic	C_{max} (μg/mL)	AUC_{tau} (mg•h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	C_{min} (μg/mL)
Cohort A1: trebananib 10 mg/kg + PLD					
n	16	14	14	14	13
Mean	263	9.15	1.20	57.8	20.0
SD	59.2	2.93	0.370	16.9	12.1
Median	254	8.52	1.18	55.4	16.3
%CV	22.5	32.0	30.8	29.2	60.6
Cohort A3: trebananib 15 mg/kg + PLD					
n	19	18	18	18	17
Mean	352	11.9	1.41	67.6	26.0
SD	113	4.55	0.488	21.2	15.7
Median	330	9.69	1.56	67.9	21.2
%CV	32.1	38.2	34.7	31.4	60.6
Cohort B1: trebananib 10 mg/kg + topotecan					
n	17	16	16	16	15
Mean	242	9.06	1.20	61.9	20.8
SD	86.3	2.86	0.406	21.4	7.06
Median	213	8.59	1.14	60.0	19.8
%CV	35.7	31.6	33.8	34.5	33.9
Cohort B3: trebananib 15 mg/kg + topotecan					
n	20	16	16	16	14
Mean	352	12.7	1.33	60.0	29.2
SD	95.9	4.25	0.545	15.5	13.5
Median	336	12.7	1.14	61.9	27.1
%CV	27.2	33.4	41.0	25.8	46.2

C_{max}, maximum observed concentration after intravenous infusion of trebananib; AUC_{tau}, area under the concentration–time curve from time zero to 168 h; CL, serum clearance after intravenous infusion; V_{ss}, volume of distribution at steady state; C_{min}, minimum observed concentration (trough concentration); %CV, coefficient of variation, expressed as a percent; SD, standard deviation; PLD, pegylated liposomal doxorubicin.

(cohorts A1, A3, B1, B3; n = 25, 25, 25, 24). A DLT was defined as any grade ≥3 AE per Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE, v3.0) and related to trebananib treatment. The following AEs were not considered DLTs: grade 3 anemia, hypertension, or thrombocytopenia; grade 3 fatigue or grade 4 neutropenia lasting ≤7 days; grade 3 or 4 diarrhea, nausea, or vomiting lasting ≤72 h; grade 3 or 4 neutropenia with fever ≤38.5 °C; and aspartate or alanine aminotransferase less than 10 times the upper limit of normal.

Adverse events

Unless otherwise noted, this report presents treatment-emergent AEs occurring after study treatment initiation up to 30 days after the last dose of any study drug and recorded per CTCAE, v3.0.

Tumor response assessments

Computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.0 was conducted every 8 weeks during the first 2 years and every 6 ± 1 months thereafter or until progression. ORR was assessed in patients with at least one measurable lesion per modified RECIST v1.0. A complete response or PR required a confirmatory evaluation ≥28 days after the initial assessment. The analyses of progressive disease were based on modified RECIST v1.0, clinical or CA-125 progression, or death, and included all patients who received at least one dose of trebananib plus PLD or topotecan. For ORR and PFS analyses, RECIST was modified to include only radiographic imaging. Only imaging of the chest, pelvis, and abdomen was required. However, head lesions were followed up with CT or MRI assessments to confirm progression per RECIST. CA-125 responses were evaluated every 4 ± 1 weeks, with a confirmatory assessment ≥28 days after the initial assessment.

Clinical immunology

Immunogenicity of trebananib was evaluated via serum samples that were collected immediately before administration of trebananib, PLD, and topotecan at weeks 1, 5, 9, and every 16 weeks thereafter, and at the safety follow-up visit. The methodology for evaluating antibodies has been previously described [24].

Pharmacokinetics

Serum trebananib concentrations were measured using an enzyme-linked immunosorbent assay [16]. Plasma concentrations of PLD, doxorubicinol, topotecan, and topotecan lactone were evaluated with validated high-performance liquid chromatography (HPLC) methods. The schedule of PK assessments is detailed in the Supplementary material section. Noncompartmental analyses of PK parameters were conducted with WinNonlin Enterprise software, version 5.1.1 (Pharsight Corporation, Mountain View, CA, USA).

Pharmacodynamics

Angiogenic biomarkers from serum included soluble vascular cell adhesion molecule-1 (sVCAM-1), placental growth factor (PLGF), VEGF, soluble fms-like tyrosine kinase-1 (VEGFR-1), soluble KDR (VEGFR-2), soluble c-Kit (sKit), Ang1, Ang2, and soluble intercellular adhesion molecule-1 (sICAM-1). The methodology for assessing angiogenic biomarkers has been previously described [25]. The assays for Ang1 and Ang2 measured free and trebananib-bound angiopoietins and, therefore, were implemented only for predose samples. The schedule for collecting blood samples is described in the Supplementary material section.

Statistical analysis

Descriptive statistics were implemented to describe the tolerability, ORR, CA-125 response, and antibody formation. Kaplan–Meier estimates of median PFS were based on the definition of disease progression per modified RECIST v1.0, clinical, or CA-125 criteria. Statistical significance for pharmacodynamic responses was determined with an F-test comparing log-transformed analyte and baseline values. The study was not designed to compare endpoints between study cohorts. All protocol-defined statistical analyses were described in the statistical analysis plan, which was amended once. No formal statistical hypotheses were tested.

Results

Patients

Between January 2009 and October 2011, 103 patients were enrolled. Most patients had serous tumor histology and International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease. More than a third of patients had received at least two platinum-containing regimens. The majority of patients experienced disease progression ≤6 months after their last platinum-based therapy. Baseline demographic and disease characteristics are summarized in Table 1.

Toxicity

A total of 99 patients were included in the DLT analysis set (cohorts A1, A3, B1, B3; n = 25, 25, 25, 24). No DLTs occurred during the initial phase. During the expansion phase, one patient (4%) in cohort A1 developed DLTs of grade 3 appendiceal abscess and appendicitis. A DLT of grade 3 peripheral edema occurred in one patient (4%) in cohort B1.

Unless noted otherwise, this report summarizes treatment-emergent AEs occurring between study treatment initiation and 30 days after the last does of any study drug (Fig. 1 and 2). All patients had at

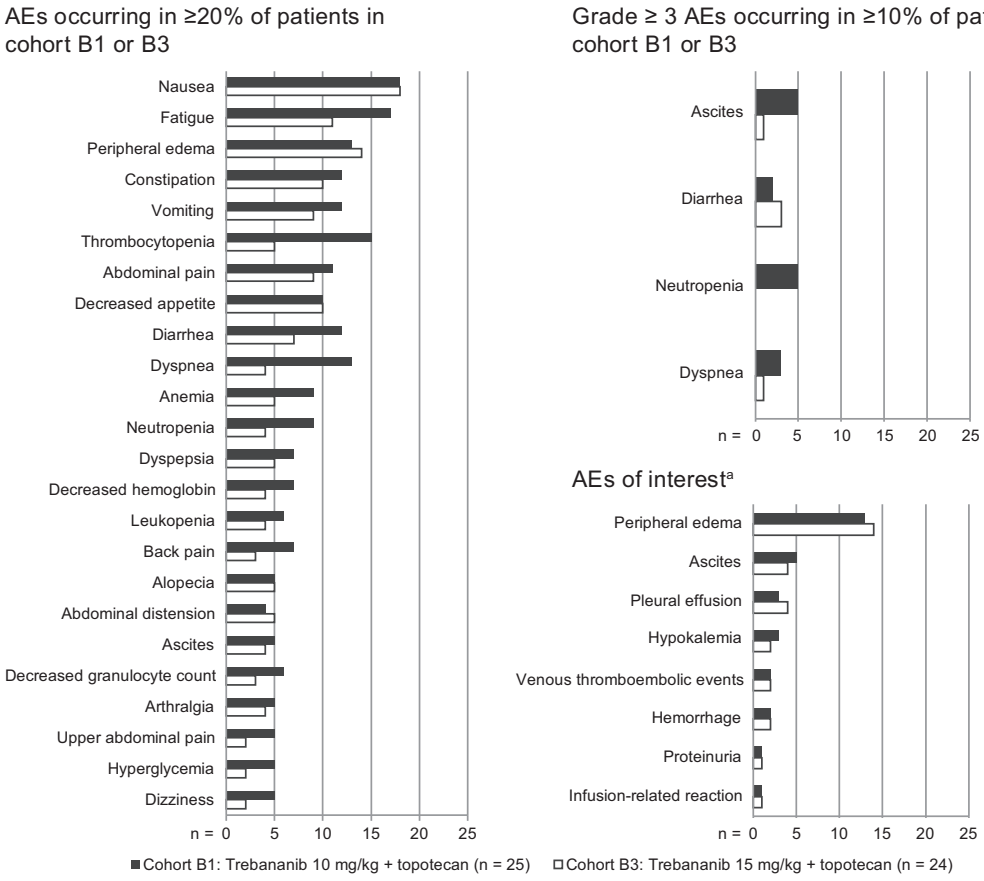

Fig. 2. Patient incidence of treatment-emergent adverse events (AEs) in the trebananib plus topotecan cohorts. All patients who received at least one dose of trebananib plus its cotherapy were evaluated for AEs. Treatment-emergent AEs included all AEs that were recorded during study treatment and within 30 days of the last dose of any treatment agent.

least one AE (Table 2). Across both trebananib plus PLD cohorts (A1 and A3), serious AEs occurred in 26 patients (52%). A grade 4 AE of pulmonary embolism in a patient (4%) in cohort A3 was considered by the investigator as possibly related to trebananib treatment. One patient (4%) in cohort A1 had a grade 5 intestinal perforation and died after developing bowel obstruction; this patient died 20 days after receiving the last dose of any study agent. The investigator rated the death as unrelated to trebananib or PLD and reported the cause of the perforation as growth of tumor in transversum, ischemic basis, or colon dilation. Treatment for the event included piperacillin and tazobactam sodium, sodium infusion, and morphine. Because of the patient's poor prognosis, she received conservative treatment. One patient (4%) in cohort A3 had a grade 5 AE of sudden death and died of unknown causes 2 days after the last dose of any study agent was administered. This death also was not considered by the investigator to be related to trebananib or PLD treatment. Across both trebananib plus topotecan cohorts (B1 and B3), 18 patients (37%) developed serious AEs. One patient (4%) in cohort B1 experienced a grade 4 decreased granulocyte count, which was considered by the investigator as possibly related to trebananib and topotecan treatments. Two patients (8%) in cohort B3 died of disease progression 24 and 30 days after receiving the last dose of any study drug. One patient (4%) in cohort B3 had a grade 5 pleural effusion associated with progressive disease 19 days after the last study drug administration. Those deaths were not considered by the investigator to be related to trebananib or topotecan treatment.

Grade ≥3 AEs of interest that were considered by the investigator as possibly related to trebananib treatment across cohorts A1 and A3 were peripheral edema (n = 4 [8%]), venous thromboembolic events (n = 3 [6%]), hemorrhages (n = 1 [2%]), ascites (n = 1 [2%]), gastrointestinal perforation (n = 2 [4%]), hypokalemia (n = 1 [2%]), and pleural effusion (n = 1 [2%]). Across cohorts B1 and B3, those criteria applied to peripheral edema (n = 3 [6%]) and hypokalemia (n = 1 [2%]). The AEs of gastrointestinal perforation related to trebananib administration in cohorts A1 and A3 occurred in a patient who developed gastric ulcer perforation 8 months after trebananib initiation; the other patient developed an appendiceal abscess one week after trebananib initiation, which resolved 11 days later. All AEs of hypertension occurred in cohorts A1 and A3 and were grade ≤2. Among those, no patient had the disease as a preexisting condition. For four patients (8%), hypertension was considered as possibly related to trebananib treatment.

Tumor response

Tumor response was evaluated in all patients with at least one measurable lesion per modified RECIST v1.0 (Table S1 in the Supplementary material section). Confirmed ORRs in cohorts A1, A3, B1, and B3 were 36.0%, 34.8%, 16.7%, and 0.0%, respectively. Tumor size decreased by a median of 18.9%, 28.2%, 2.4%, and 13.9% in cohorts A1, A3, B1, and B3, respectively. Median PFS (95% CI) in cohorts A1, A3, B1, and B3 was 7.4 months (2.5–7.8 months), 7.1 months (3.4–8.1 months), 3.5 months (1.7–5.1 months), and 3.1 months (1.8–5.3 months), respectively (Fig. S1A and B in the Supplementary material section). In CA-125 evaluable patients, 10 (47.6%) of 21 patients in cohort A1, 10 (55.6%) of 18 patients in cohort A3, 8 (34.8%) of 23 patients in cohort B1, and 7 (38.9%) of 18 patients in cohort B3 had a confirmed CA-125 response.

Clinical immunology

Evaluable postdose samples for testing of anti-trebananib antibodies were available for 49 patients across cohorts A1 and A3, and 47 patients across cohorts B1 and B3. One patient (4%) in cohort B1 had pre-existing anti-trebananib binding antibodies. Two patients (8%) in cohort A3, one patient (4%) in cohort B1, and one patient (4.5%) in cohort B3 developed anti-trebananib binding antibodies during study treatment. The patient in cohort B3 continued to test positive at treatment termination. The presence of anti-trebananib binding antibodies did not appear to affect trebananib PK (data not shown here). No neutralizing antibodies were detected.

Pharmacokinetics

The mean serum concentration–time profiles after four weekly infusions of trebananib 10 mg/kg when coadministered with PLD or topotecan were similar to those reported in the first-in-human monotherapy study (Table 3) [16]. No drug–drug interactions were apparent between trebananib 10 mg/kg or 15 mg/kg and PLD or topotecan and their metabolic byproducts (Fig. 3A–D).

Pharmacodynamics

Serum samples for pharmacodynamic analyses were available for 93 patients. Pharmacodynamic changes relative to baseline occurred in sVCAM-1, which peaked 24 to 48 h after trebananib administration across cohorts (Fig. S2 in the Supplementary material section). Baseline levels of VEGF correlated with PFS when the population was divided at the median VEGF level (595 ng/mL; HR = 2.09 [95% CI, 1.22–3.59; p = 0.007]); patients with lower baseline VEGF had longer PFS. Baseline levels of Ang2 correlated with PFS when the population was divided at the median Ang2 level (2440 pg/mL; HR = 2.04 [95% CI, 1.17–3.56; p = 0.011]); patients with lower Ang2 had longer PFS. The study design did not allow for an evaluation of the predictive or prognostic value of these markers.

Discussion

Single-agent treatment with PLD or topotecan is currently a treatment option for patients with platinum-resistant or partially platinum-sensitive recurrent ovarian cancer. While both treatments are considered to provide equal or improved efficacy relative to other chemotherapy agents, the clinical benefits of either treatment are modest. In patients with platinum-resistant disease, PLD monotherapy has been associated with response rates of 8.3% to 16% and PFS of 2.3 to 4.0 months [3,5,26,27]. In patients receiving weekly topotecan, results from a phase 2 study suggest a response rate of 22% and PFS of 4.2 months [22]. PLD or topotecan is often selected as the preferred treatment for platinum-resistant disease because treatment is focused on palliation of symptoms and the toxicities of both agents are considered relatively moderate. Although the efficacy of PLD or topotecan treatment is generally improved in patients with partially platinum-sensitive disease relative to those with platinum-resistant disease, the response rates for patients with partially platinum-sensitive disease are approximately 25%–30% [2,28,29]. The results of this study suggest that the addition of trebananib 10 mg/kg and 15 mg/kg to PLD or topotecan may provide an alternative treatment approach. The treatment combinations tested in this study were associated with acceptable toxicity profiles. Combining an antiangiogenic agent and chemotherapy has the potential risk of synergistic toxic effects [30,31]. In this study, toxicities were generally consistent with those that have been associated with monotherapy of trebananib, PLD, or topotecan [16,32,33]. Peripheral edema has been previously identified as a risk associated with trebananib treatment and generally manageable across studies [16,17,34,35]. Other AEs that have been associated with trebananib in combination with chemotherapy are ascites and pleural effusion [35]. More recently, blurred vision was identified as a risk associated with trebananib administration. The incidence of ascites and pleural effusion appeared largely consistent with results from the randomized phase 3 TRINOVA-1 study of patients with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer receiving trebananib 15 mg/kg plus paclitaxel [36]. All AEs of blurred vision were mild and manageable. Palmar–plantar erythrodysesthesia and stomatitis are toxicities that emerge typically with PLD treatment. The incidence rates of both AEs in the cohorts receiving trebananib plus PLD were consistent with results from an earlier phase 3 study investigating PLD monotherapy, although direct comparisons cannot be made given that the present investigation was a phase 1 study [26]. In the earlier study, hematological toxicities, including neutropenia, anemia, thrombocytopenia, and leukopenia, were identified as AEs associated with topotecan treatment. Those hematological AEs also emerged in the current study in the cohorts receiving trebananib plus topotecan. However, there was no evidence to suggest that the addition of trebananib to topotecan exacerbated the severity of such toxicities.

In this study, no patient developed arterial thromboembolic events or impaired wound healing. Hypertension occurred only in the trebananib plus PLD cohorts (A1 and A3); all were grade ≤2 and manageable. The incidence of hypertension was slightly higher compared to earlier studies of trebananib plus chemotherapy in ovarian, gastroesophageal, or metastatic colorectal cancer [17,35,37,38]. Two patients across cohorts A1 and A3 developed grade 3 gastrointestinal perforations that were considered by the investigator as possibly related to trebananib treatment. One patient in cohort A1 died of intestinal perforation, which was rated by investigators as unrelated to trebananib or PLD administration. No gastrointestinal perforations occurred in a phase 2 study of patients with recurrent ovarian cancer receiving trebananib plus paclitaxel [17]. The only AEs of gastrointestinal perforation were observed in one patient in a phase 2 study of trebananib plus FOLFIRI in patients with metastatic colorectal cancer and in one patient in a phase 2 study of trebananib plus cisplatin and capecitabine in patients with gastroesophageal cancer [35,38]. One patient in an ongoing phase 1b study of patients with ovarian cancer developed grade 2 female colovaginal fistula [39].

Trebananib at 10 mg/kg or 15 mg/kg plus PLD or topotecan showed evidence of antitumor activity. The ORRs in the trebananib plus topotecan cohorts (B1 and B3) appeared lower compared with those observed in cohorts A1 and A3. Patients in cohorts B1 and B3 relative to cohorts A1 and A3 tended to receive a higher number of prior anticancer therapies. Additionally, almost half of the patients across cohorts B1 and B3 received prior doxorubicin or PLD. Only one patient across cohorts A1 and A3 received prior topotecan. Any additional conjecture to explain the ORR differences between those cohorts would be speculative given that this phase 1b study was not designed to compare efficacy. There is some indication of a clinical benefit in an ongoing randomized phase 3 study of patients with platinum-resistant recurrent ovarian cancer receiving bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks plus PLD, topotecan, or paclitaxel [40]. Exploratory analyses from that study suggested median PFS duration of 5.4 months and 5.8 months in the PLD and topotecan cohorts, respectively; ORRs were 18.3% and 22.8%, respectively. The median PFS duration of 7.4 months and 7.1 months for cohorts A1 and A3, respectively, in the current study was consistent with results from the TRINOVA-1 study of trebananib plus paclitaxel in patients with recurrent ovarian cancer. Patients receiving trebananib 15 mg/kg IV QW plus paclitaxel had a median PFS of 7.2 months [36].

The PK of trebananib and PLD or topotecan did not appear to markedly affect the cotherapy agent. The PK parameters for trebananib at week 5 were similar to those reported in a monotherapy trial [16]. Furthermore, the concentration–time profiles of each chemotherapy agent did not change after coadministration of trebananib.

Most pharmacodynamic changes appeared time-dependent on trebananib administration, but were generally minor. Because of the

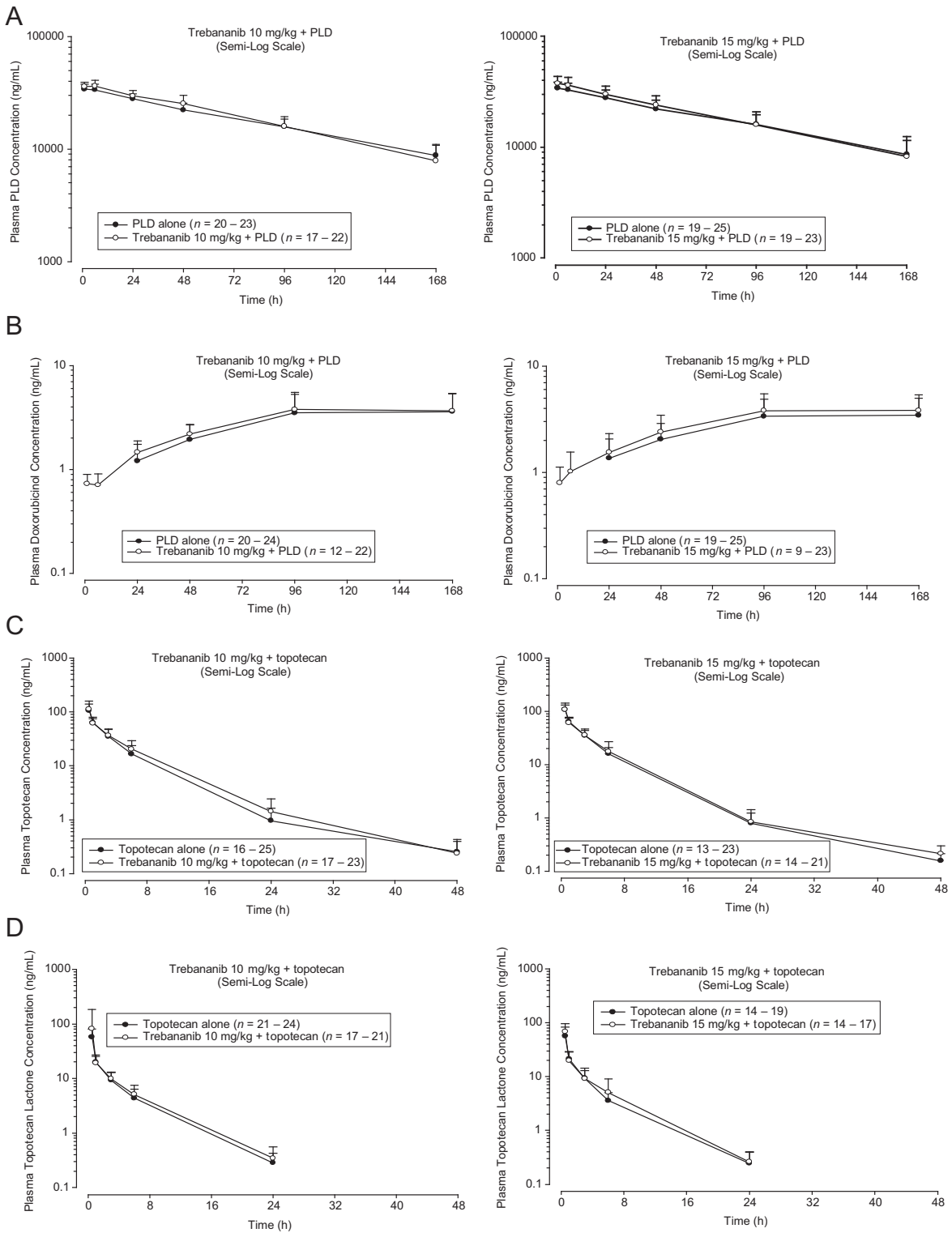

Fig. 3. Pharmacokinetic concentration–time profiles. Mean (+SD) plasma concentration–time profiles of pegylated liposomal doxorubicin (PLD; A), doxorubicinol (B), topotecan (C), and topotecan lactone (D) at week 1 prior to initiation of trebananib administration and at week 5 following weekly IV infusions of trebananib.

study design, it was not possible to distinguish between a predictive effect of trebananib and a prognostic effect of baseline VEGF or baseline Ang2 and PFS. This finding was an exploratory endpoint of the study and not corrected for multiplicity of testing. Future studies would benefit from a closer examination of such prognostic and predictive relationships by relying on larger samples and more appropriate study designs.

In conclusion, in patients with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer, the treatment combinations of the dual Ang1/Ang2 inhibitor trebananib 10 mg/kg or 15 mg/kg IV QW plus PLD 50 mg/m^2 Q4W or topotecan 4 mg/m^2 on days 1, 8, and 15 of a 28-day schedule appeared to have acceptable toxicity profiles. Results suggest antitumor activity across all cohorts. The combination of trebananib and PLD in patients with recurrent platinum-resistant or partially platinum-sensitive ovarian cancer is currently being studied in a phase 3 clinical trial (TRINOVA-2; ClinicalTrials.gov identifier: NCT01281254).

Conflict of interest statement

Ignace Vergote participated in advisory boards and received an educational grant (all Amgen Inc.). Rebeca Melara, Michael B. Bass, Jason Litten, and Henry Adewoye were or are current employees of Amgen Inc. and own stock in Amgen. Nuwan Nanayakkara is an employee of Quintiles, which is a paid consultant to Amgen. Robert M. Wenham participated in a steering committee and received honoraria and travel funding (all Amgen Inc.). Russell J. Schilder, Charles H. Pippitt, Shirley Wong, Alan N. Gordon, Sidney Scudder, Frederic Kridelka, Luc Dirix, Joseph Leach, and Sumitra Ananda have no relevant financial relationships to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2014.07.003.

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