1. EC-FV-06 Clinical Study Report

A RANDOMIZED DOUBLE-BLIND PHASE 3 TRIAL COMPARING VINTAFOLIDE (EC145) AND PEGYLATED LIPOSOMAL DOXORUBICIN (PLD/DOXIL®/CAELYX®) IN COMBINATION VERSUS PLD IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

Vintafolide (EC145): Targeted Therapeutic Agent
^{99m}Tc-etarfolatide: Companion Diagnostic Imaging Agent
Therapy for platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer

This was an international, multicenter, centrally-randomized, double-blind, Phase 3, two-arm study comparing EC145 + PLD and placebo + PLD, given until disease progression or unacceptable toxicity in patients platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer

Endocyte, Inc.
Protocol EC-FV-06 (PROCEED)
Phase 3
First patient enrolled (assigned to therapy): 22 April 2011
Date of early study termination: 20 May 2014
Data cutoff date: 17 March 2014
Approval Date: 15 February 2017

Responsible Medical Officer: Alison Armour MB.ChB., BSc., MSc., MD., MRCP., FRCR
Endocyte, Inc.
8910 Purdue Road, Suite 250
Indianapolis, IN 46268

2. Synopsis

Title of Study: A Randomized Double-Blind Phase 3 Trial Comparing Vintafolide (EC145) and Pegylated Liposomal Doxorubicin (PLD/DOXIL®/CAELYX®) in Combination Versus PLD in Patients with Platinum-Resistant Ovarian Cancer

Number of Investigator(s): This multicenter study included 194 principal investigators.

Study Center(s): This was a multicenter study at 194 study center(s) in 12 countries: United States, Canada, Belgium, Czech Republic, France, Hungary, Israel, Poland, Russia, South Korea, Spain, and United Kingdom.

Publication(s) Based on the Study:

R. Wendel Naumann, Lucy Gilbert, Anthonette M. Miller, Hong Ma, Sharad A. Ghamande and Ignace Vergote. A randomized double-blind phase III trial comparing vintafolide plus pegylated liposomal doxorubicin (PLD) versus PLD plus placebo in patients with platinum-resistant ovarian cancer (PROCEED). J Clin Oncol (Meeting Abstracts) May 2013 vol. 31no. 15_suppl TPS5613

R.W. Naumann , L. Gilbert , A. Habbe , H. Ma , S. Ghamande , I.B. Vergote. Trial in progress: A randomized double-blind phase 3 trial comparing vintafolide + pegylated liposomal doxorubicin (PLD) versus PLD + placebo in patients with platinum-resistant ovarian cancer (PROCEED). Gynecologic Oncology, Volume 133, Supplement 1, June 2014.

A.M. Oza , I.B. Vergote , L.G. Gilberta , Lucy , P. Ghatage , A. Lisyankaya , S. Ghamande , S.K. Chambers , J.A. Arranz , D.M. Provencher , P. Bessette , A. Amnon , J. Symanowski , R.T. Penson, R.W. Naumann , R. Clark. A randomized double-blind phase III trial comparing vintafolide (EC145) and pegylated liposomal doxorubicin (PLD/Doxil®/Caelyx®) in combination versus PLD in participants with platinum-resistant ovarian cancer (PROCEED) (NCT01170650). Gynecologic Oncology, Volume 137, Supplement 1, April 2015.

Length of Study:	**Phase of Development:** 3
Date of first patient enrolled: 22 April 2011 Data cutoff date: 17 March 2014	

Study Objectives:

The primary objective was to compare progression-free survival (PFS), based upon investigator assessment using RECIST v1.1 in patients with platinum-resistant ovarian cancer who received combination therapy with vintafolide and pegylated liposomal doxorubicin (PLD) (i.e., vintafolide + PLD) with that of patients with platinum-resistant ovarian cancer who received PLD and placebo. The primary analysis was conducted in FR(100%) patients as determined by ^{99m}Tc-etarfolatide scan.

Secondary objectives included a comparison of overall survival (OS) between treatment arms in the FR(100%) population, and comparison of PFS and OS between treatment arms in patient populations defined by the percentage of target lesions that are ^{99m}Tc-etarfolatide (FR) positive. A hierarchical stepdown analysis was to be conducted in a nested fashion to determine if there was a lower FR threshold that maintained statistical significance. Analyses of individual and mutually exclusive subgroups defined by FR levels was also to be conducted.

Exploratory objectives are listed in their entirety in Section 8.3 of this study report. They included, according to ^{99m}Tc-etarfolatide status, between treatment arm comparison of disease control rate (DCR) and duration of disease control, overall response rate (ORR) and duration of response, quality of life (QoL),CA-125 response rate, CA-125 PFS, pharmacokinetics, and archived tumor specimen biomarker analysis.

Study Design: This was an international, multicenter, centrally randomized, double-blind, phase 3 study of vintafolide + PLD combination therapy compared with placebo + PLD in patients with platinum-resistant ovarian cancer (PROC). Eligible patients were randomized in a 2:1 (randomized under protocol versions 1.0 or 3.0) or 1:1 (randomized under protocol version 6.0) ratio to either the vintafolide + PLD arm or to the placebo + PLD arm and received treatment for a minimum of 6 weeks until disease progression or unacceptable toxicity.

Number of Planned Patients: 350

	FR(0-100%)		FR(20-100%)		FR(100%)		FR(0%)	
	vintafolide +PLD	placebo +PLD	vintafolide +PLD	placebo +PLD	vintafolide +PLD	placebo +PLD	vintafolide +PLD	placebo +PLD
Randomized	199	122	186	118	143	87	13	4
Treated	189	120	176	117	136	86	13	3

Diagnosis and Main Criteria for Inclusion: Women, ≥18 years old, with a pathology-confirmed diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible for the study. Patients must have had prior debulking surgery and prior platinum-based chemotherapy; however, no more than 2 prior systemic cytotoxic regimens were allowed. Patients were required to have platinum-resistant ovarian cancer (based on the most recent exposure to a platinum-based regimen), defined as disease that responded (CR+PR+SD) to primary platinum therapy and then progressed within 6 months or disease that progressed during, or within 6 months of completing, secondary platinum therapy. Patients must have had radiographic evidence of measurable disease (i.e., at least 1 measurable target lesion according to RECIST criteria) and adequate bone marrow, hepatic, and renal function.

Study Drug, Dose, and Mode of Administration:
EC145 (vintafolide): 2.5 mg via bolus IV injection on Monday, Wednesday, and Friday of Weeks 1 and 3 of a 4-week cycle.
Placebo: 2.5 mg via bolus IV injection on Monday, Wednesday, and Friday of Weeks 1 and 3 of a 4-week cycle.

^{99m}Tc-etarfolatide, Dose, and Mode of Administration:
Prior to SPECT imaging, patients received 1 IV injection of 0.5 mg folic acid, 1 to 3 minutes before a 1 to 2 mL IV injection of 0.1 mg ^{99m}Tc-etarfolatide labeled with 20 mCi to 25 mCi of ^{99m}Tc.

Reference Treatment, Dose, and Mode of Administration: PLD was administered at a dose of 50 mg/m^2 IV once every 28 days (for a recommended minimum of 4 courses) until the maximum allowable cumulative dose of 550 mg/m^2 was attained, as long as the patient did not exhibit disease progression, did not show evidence of cardiotoxicity, and continued to tolerate treatment. For patients whose measured body weight was greater than their ideal body weight, the dose of PLD was to be calculated on the basis of ideal body weight. Commercial drug was used for PLD (Typically, Doxil® in the US and Canada and Caelyx® in Europe and Asia).

Duration of Treatment:

Vintafolide/Placebo: Patients who did not show disease progression could receive up to 20 cycles of vintafolide/placebo therapy. Patients who showed radiographic evidence of continuing tumor shrinkage at the end of the 20th cycle were allowed to continue to receive vintafolide/placebo until they showed SD on 2 sequential CT scans. Patients who had decreasing CA-125 levels and SD on imaging analysis at the end of the 20th cycle of therapy were allowed to receive additional cycles, as tolerated until stabilization of CA-125 levels was observed (i.e., decreases of < 10% maintained for 60 days). Patients who discontinued treatment with PLD (after >2 cycles) because of unacceptable toxicity were allowed to continue therapy with vintafolide/placebo as a single agent for the remainder of the 20 cycles and, if eligible, could continue to receive single-agent vintafolide beyond Cycle 20 until they showed SD on 2 sequential CT scans.

PLD (in combination with vintafolide or placebo): Patients could receive a maximum allowable cumulative dose of 550 mg/m^2 PLD, as long as the patient did not exhibit disease progression, did not show evidence of cardiotoxicity, and continued to tolerate treatment.

Criteria for Evaluation:
Efficacy: PFS (primary); OS (secondary); ORR, DOR, DCR, DDC, PFS2, CA-125 response, CA-125 PFS, (exploratory).
Safety: Adverse events (AEs), Serious AEs (SAEs), Deaths

Statistical Evaluation Methods:

Efficacy: The primary objective of this study was to compare PFS for the combination of vintafolide + PLD to Placebo + PLD in patients with previously treated recurrent ovarian cancer. PFS was based on investigator assessment using RECIST version 1.1 in PROC patients who had 100% of their target lesions FR positive [FR(100%)] as determined by ^{99m}Tc-etarfolatide scan. The final PFS analysis was to be conducted after 245 PFS events were observed in FR(100%) patients. This plan provided approximately 98% nominal power to detect a PFS hazard ratio equal to 0.60 based on a 1-sided $\alpha = 0.025$ significance level. An interim analysis (IA) for futility was planned after ~ 98 PFS events in FR(100%) patients. The trial would cross the futility bound if PFS HR>0.8.

Overall survival in the FR(100%) population was the secondary objective. The final OS analysis was planned after approximately 280 deaths had been observed. With a median of 12 months in the control group, a 0.7 hazard ratio would correspond to an increase to approximately 17 months. This would provide approximately 85% power to demonstrate a benefit for Vintafolide + PLD compared to PLD alone with 2.5% (1-sided) Type I error.

Safety: The assessment of safety was based on extent of exposure, AEs, and laboratory tests.

Summary:

Results presented in this clinical study report are based on the analysis of data collected up to and including 17 March 2014, the data cut-off date that was used for the first interim futility analysis.

Overview of Study EC-FV-06 Enrollment

The first patient was enrolled into Study EC-FV-06 in April 2011. Initial enrollment was somewhat slow. Fewer than 12 patients had enrolled into the study, when enrollment was suspended from August 2011 through April 2012 due to an interruption in the study's PLD supply (Figure 1). Once the PLD supply had been secured, enrollment steadily and rapidly increased such that approximately 57% of patients (i.e., approximately 182 of 321 patients) were enrolled within 12 months of the first planned PFS event-triggered interim analysis for futility.

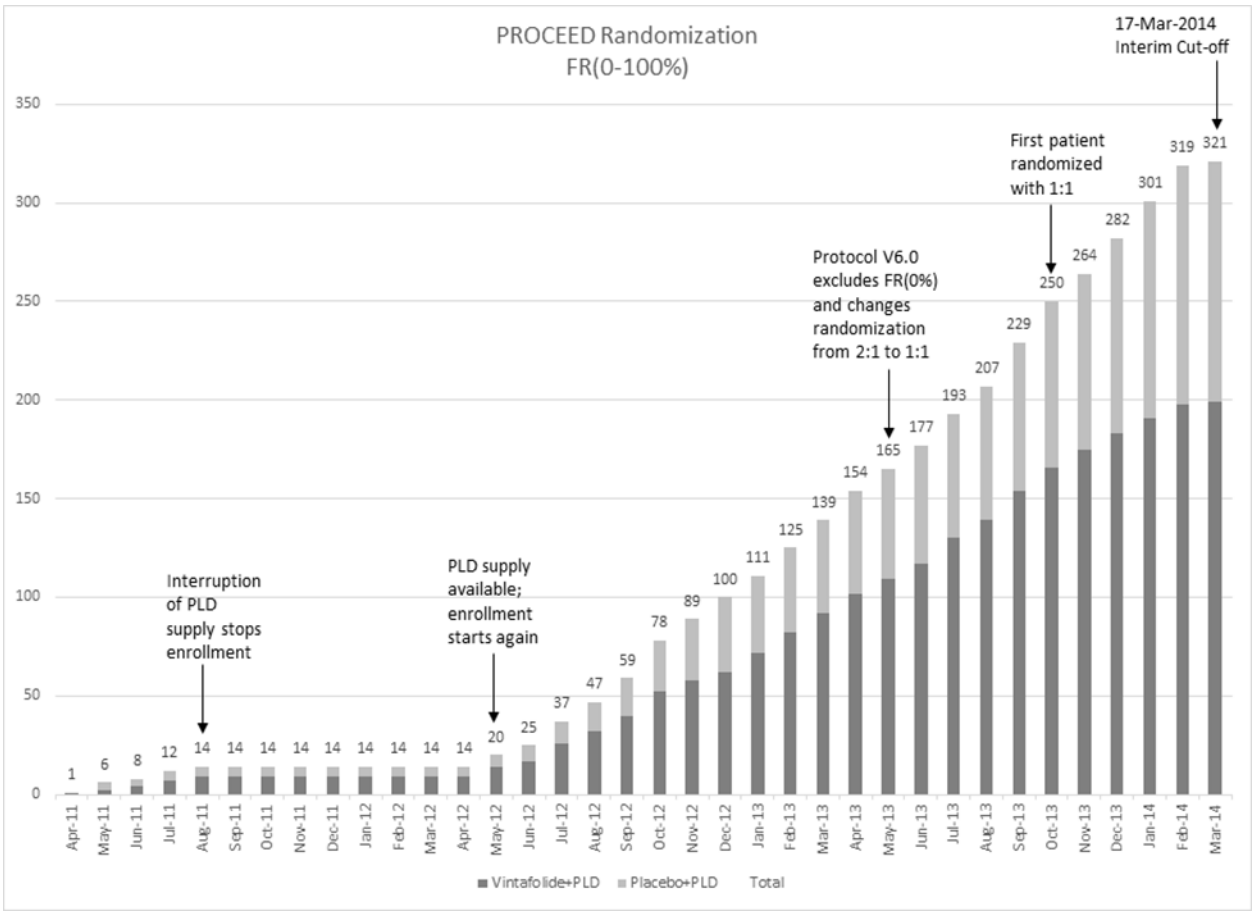

Figure 1. EC-FV-06 Study Enrollment Timeline

Overview of First Interim Futility Analysis

An extract of data to create static datasets for the first interim futility analysis occurred on 17 March 2014. The study DSMB met on 30 April 2014 to review efficacy and safety data as part of the first scheduled interim futility analysis for the trial. Among the 230 FR(100%) patients, 73 PFS events (51%) had occurred in the vintafolide + PLD arm and 32 events (36.8%) had occurred in the placebo + PLD arm; 54.3% of FR(100%) patients were censored for PFS (vintafolide +PLD arm: 49.0%; placebo + PLD arm: 63.2%). Censoring occurred at the date of the last radiologic assessment not indicating progression, prior post discontinuation of anticancer therapy, or for more than 2 missed scheduled assessments.

Median PFS was 5.3 months for the vintafolide + PLD treatment arm and 4.8 months placebo + PLD. There was not a statistically significant difference in PFS between treatment arms (HR: 0.976; 95% CI: 0.633, 1.505; 1-sided stratified log-rank test p-value: 0.4617). This point estimate of 0.976 for the PFS hazard ratio crossed the pre-specified PFS futility bound of 0.80. The DSMB did not identify any new safety issues in either treatment arm. Based on these interim data, the DSMB recommended that the trial be stopped because it did not meet the efficacy hurdle specified in the statistical analysis plan (SAP).

On 02 May 2014, this information was communicated to investigators who were told to temporarily halt screening and randomization procedures while the Sponsors reviewed the interim data and the DSMB recommendation. After

review of the interim data, the Sponsor accepted the DSMB recommendation. On 20 May 2014 investigators were notified that trial screening and enrollment were to be permanently stopped, effective immediately, and unblinding of treatment assignments occurred.

As data cleaning for the 17 Mar 2014 extract was focused mainly on the primary efficacy analysis, RECIST 1.1 data for PFS, additional data from existing and active patients still needed to be entered, source data verified, and cleaned since the study was halted early. Therefore, an extract of data to create static datasets for the CSR analyses occurred on 13-Nov-2014; from this extract, cut-off datasets that only included patients from the interim analysis and only data through 17 Mar 2014 were created to produce the tables, listings and figures for all analyses presented in this CSR. Although there are some differences in the PFS data the DSMB members reviewed at the first interim futility analysis meeting and the data presented in this CSR, the efficacy hurdles still were not met.

Overview of Patient and Disease-Related Characteristics in FR(100%) Patients

Of the 321 randomized patients, 230 had FR(100%) PROC. Patients ranged in age from 24 to 84. Overall, demographics and baseline disease characteristics were similar between the treatment arms. The majority of patients were Caucasian, middle-aged (median age, 62 years) with ECOG performance status 0-1. Following primary platinum therapy, 42.7% of patients had secondary platinum therapy and 17.1% had additional therapy. Residual tumor >2 cm post debulking surgery, higher median baseline sum of RECIST target lesion diameters, and higher baseline mean CA-125 levels occurred more commonly in the vintafolide +PLD arm than in the placebo + PLD arm. However, these imbalances in baseline factors did not impact the results on PFS, as determined by post-hoc, adjusted PFS analyses.

Table 1 Patient and Disease Characteristics – FR(100%) Efficacy Analysis Population

	Vintafolide + PLD N=143	Placebo + PLD N=87	All N=230
Age in years (n)			
Mean ± SD	60.8 ± 9.99	61.0 ± 10.64	60.9 ± 10.22
Median (range)	62.0 (27-84)	61.0 (24-80)	62.0 (24-84)
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	1 (1.2)	1 (0.4)
Asian	14 (9.8)	10 (11.6)	24 (10.5)
Black/African American	8 (5.6)	0 (0.0)	8 (3.5)
White	121 (84.6)	75 (87.2)	196 (85.6)
ECOG (n), n (%)			
0	71 (49.7)	51 (58.6)	122 (53.0)
1	72 (50.3)	36 (41.4)	108 (47.0)
Type of cancer n (%)			
Ovarian	123 (86.0)	73 (83.9)	196 (85.2)
Primary peritoneal	13 (9.1)	12 (13.8)	25 (10.9)
Fallopian tube	7 (4.9)	2 (2.3)	9 (3.9)
Regimen[1], n (%)			
Primary platinum therapy	143 (100)	87 (100)	230 (100)
Secondary platinum therapy	58 (40.6)	36 (41.4)	94 (40.9)
Additional therapy	21 (14.7)	15 (17.2)	36 (15.7)

	Vintafolide + PLD N=143	Placebo + PLD N=87	All N=230
Treatment-free interval[2], n (months)			
Mean ± SD	5.7 ± 4.71	5.7 ± 3.72	5.7 ± 4.36
Median (range)	5.1 (0-38)	5.3(1-24)	5.1 (0-38)
Platinum-free interval[3], n (months)	n = 141	n = 84	n = 225
Mean ± SD	3.2 ± 1.87	3.3 ± 1.86	3.3 ± 1.86
Median (range)	3.7 (0-7)	3.7 (0-6)	3.7 (0-7)
Platinum-free interval[3], n (months)	n = 141	n = 84	n = 225
Time since initial cancer diagnosis (months)			
Mean ±SD	20.7 ± 12.09	26.2 ± 27.69	22.8 ± 19.64
Median (range)	15.9 (8;73)	16.0 (8;207)	16.0 (8;207)
Size of residual disease at the end of the primary debulking surgery or attempted debulking surgery, cm (%)			
≤2.0	95 (66.4)	69 (79.3)	164 (71.3)
>2.0	21 (14.7)	3 (3.4)	24 (10.4)
Not Applicable	2 (1.4)	0 (0.0)	2 (0.9)
Unknown	25 (17.5)	15 (17.2)	40 (17.4)
Number of target lesions at study entry, n			
Mean (mean ± SD)	2.3 ± 1.26	2.4 ± 1.28	2.3 ± 1.26
Median (range)	2.0 (1;5)	2.0 (1;5)	2.0 (1;5)
RECIST sum of diameters at study entry, n (mm)			
Mean ± SD	73.6 ± 63.05	68.5 ± 57.28	71.7 ± 60.86
Median (range)	61.0 (10;359)	48.0 (10;339)	59.5 (10;359)
CA-125 Levels at study entry, U/mL			
Mean ± SD	1556.3 ± 5865.51	808.3 ± 1352.35	1273.4 ± 4706.65
Median (range)	248.0 (6;64480)	242.0 (4;8634)	245.0 (4;64480)

[1]Non-unique.

[2]Time from last dose of platinum-based therapy to randomization date.

[3]Time from last platinum-dose to prior progression.

Overview of Efficacy in FR(100%) Patients

Efficacy results demonstrate that the primary endpoint of PFS in the FR(100%) PROC patient population failed to meet the pre-specified PFS futility bound. A total of 110 PFS events had occurred as of the data cut-off on 17 March 2014: 75 patients (52.4%) in the vintafolide + PLD arm and 35 patients (40.2%) in the placebo + PLD arm. A total of 120 patients (52.2%) were censored for the PFS analysis. Censoring occurred at the date of the last radiologic assessment not indicating progression, prior post discontinuation of anticancer therapy, or for more than 2 missed scheduled assessments. The overall median duration of follow-up was 2.8 months (3.0 months on the vintafolide + PLD arm and 1.7 months on the placebo + PLD arm). Median PFS was 5.6 months in patients treated with vintafolide + PLD and 5.9 months in patients treated with placebo + PLD. There was no significant difference between the two treatment arms relative to PFS (HR: 0.950; 95% CI: 0.624, 1.446; 1-sided p-value by stratified log-rank test: 0.4098) as reported in Table 2. The hazard ratio point estimate of 0.950 for PFS failed to meet the pre-specified PFS futility bound (HR=0.80). Consequently, the study was stopped early with enrollment closure on 20 May 2014.

These primary efficacy analysis results were evaluated methodologically and were internally consistent and robust with no signs of systematic bias. The stratified hazard ratios for the 6 sensitivity analyses ranged from 0.917 to 0.992, consistent with the primary PFS analysis hazard ratio of 0.950. The sensitivity analyses indicated that the handling of assessment schedules, initiation of post-study treatment, or inclusion of ineligible patients were unlikely to have influenced the results of primary PFS analysis. Subgroup analyses of PFS using unadjusted hazard ratios showed that stratification by region, ECOG status, platinum failure, treatment-free interval, baseline CA-125, sum of diameters of target lesions, and randomization schedule also had minimal effect on between arm comparisons. Analyses of the frequency of unscheduled CTs and length of time between assessments did not reveal any imbalances in disease assessment between treatment arms.

An interim OS analysis was pre-specified to occur at the same time as the interim PFS analysis. For this secondary analysis of OS, 171 patients (74.3%) were censored. A total of 59 deaths had occurred (vintafolide + PLD arm: 37; placebo +PLD arm: 22). The overall median duration of follow-up was 5.9 months (6.1 months on the vintafolide + PLD arm and 4.3 months on the placebo + PLD arm). Given the relative immaturity of the OS data, firm conclusions cannot be drawn. Median OS for vintafolide + PLD was 17.8 months compared to 14.8 months in the placebo + PLD arm. There was not a statistically significant difference in OS between treatment arms (HR: 0.878, 95% CI: 0.515, 1.497; 1-sided p-value by stratified log-rank test: 0.3166). The observed OS hazard ratio of 0.878 was less than the pre-specified futility bound of 1.51. Cox multivariate subgroup analyses did not demonstrate any significant effects of baseline patient and disease characteristics on OS. The number of lines and types of post-study therapy were balanced between arms.

Table 2: Summary of Primary and Secondary Efficacy Analyses Results: FR(100%) Population

	Vintafolide+ PLD N=143	**Placebo+ PLD N=87**
Progression-free survival, n (%)		
PFS events	75 (52.4)	35 (40.2)
Progressions	65 (45.5)	28 (32.2)
Deaths	10 (7.0)	7 (8.0)
Censored[1]	68 (47.6)	52 (59.8)
Median PFS, [95% CI] (months)	**5.6 [4.2, 7.3]**	**5.9 [2.7, 9.8]**
PFS Rate at 3 months, (%) [95% CI]	69.4 [60.3, 76.9]	62.6 [49.8, 73.0]
PFS Rate at 6 months, (%) [95% CI]	44.3 [34.3, 53.8]	43.1 [27.2, 58.0]
Hazard ratio (stratified Cox proportional hazards model[2]) [95% CI]	0.950 [0.624, 1.446]	
One-sided stratified log-rank test p-value[3]	0.4098	
Hazard ratio (unstratified Cox proportional hazards model) [95% CI]	1.030 [0.688, 1.542]	
One-sided unstratified log-rank test p-value	0.5586	
Overall survival (OS), n (%)		
Number of OS events	37 (25.9)	22 (25.3)
Number censored	106 (74.1)	65 (74.7)
Median OS, [95% CI] months	**17.8 [9.7, --]**	**14.8 [11.3, --]**
OS Rate at 12 months, (%) [95% CI]	60.9 [48.4, 71.2]	58.2 [39.0, 73.2]
OS Rate at 18 months, (%) [95% CI]	49.4 [30.3, 66.0]	33.9 [12.0, 57.7]
Hazard ratio (stratified Cox model[2]) [95% CI]	0.878 [0.515, 1.497]	
One-sided stratified log-rank test p-value[3]	0.3166	
Hazard ratio (unstratified Cox model) [95% CI]	0.901 [0.531, 1.529]	
One-sided unstratified log-rank test p-value	0.3489	

[1]Censoring at the date of the last radiologic assessment, for anticancer therapy and missed scheduled assessments. Percentages are based on N.
[2]Using Cox proportional hazards model including the same stratification parameters.
[3]One-sided log-rank test stratified for Region, Platinum Failure, Baseline CA-125, and Protocol Version.

There were no statistically significant differences between treatment arms for the exploratory objectives of overall response rate, duration of response, disease control rate, duration of disease control, PFS2, CA-125 (confirmed/non-confirmed) response rate, CA-125 PFS, combined RECIST/CA-125 response rate and combined RECIST/CA-125 PFS. Positive trends favorable to the vintafolide + PLD arm included disease control rate, CA-125 response rate, CA-125 PFS and combined RECIST/CA125 PFS.

Overview of Safety:

The primary safety analyses were to be conducted in FR(0-100%) patients who received at least one dose of study drug, analyzed according to actual treatment received.

Vintafolide and PLD Treatment Administration

A total of 896 cycles of vintafolide + PLD were administered to 189 patients, and 491 cycles of placebo + PLD were administered to 120 patients; the mean number of cycles was somewhat higher in the vintafolide + PLD arm (4.7 cycles/patient) than in the placebo + PLD arm (4.1 cycles/patient). The average time between cycles was similar across treatment arms ranging from 11.8 days (placebo + PLD patients) to 13.4 days (vintafolide + PLD patients). Delays in at least one cycle occurred for 47.6% and 45.0% of patients in the vintafolide + PLD and placebo + PLD arms, respectively; the most common reasons for delays (adverse event and scheduling) occurred with comparable frequency in both arms.

In the vintafolide + PLD arm, at least one dose omission of vintafolide occurred in 73.5% of the patients and 7.9% of the patients had a PLD dose omission. In the placebo + PLD arm, at least one dose omission of placebo occurred in 67.5% of the patients and 5.8% of the patients had a PLD dose omission. Dose adjustments were substantially less prevalent; PLD was adjusted more often in both treatment arms. The primary reasons for dose adjustments were similar across treatment arms and included maintaining the prior dose level and non-hematological toxicity.

The mean dose intensity per day was 0.5 mg/day of vintafolide and 1.6 mg/m2/day of PLD for the vintafolide + PLD Arm. The mean dose intensity per day was 0.5 mg/day of placebo and 1.7 mg/m^2/day of PLD in the placebo + PLD arm. Relative dose intensities were similar between arms and were high, suggesting that a high proportion of the patients were able to tolerate treatment. The mean relative dose intensities of vintafolide (84.2%) and placebo (87.2%) were similar. Likewise, the mean relative dose intensity of PLD was comparable in both treatment arms (vintafolide + PLD arm 91.1% and placebo + PLD 94.5%). The similarity of PLD dose intensity between arms suggests that the difference in the median cumulative PLD dose was due to longer treatment time in the vintafolide + PLD arm.

Table 3. Vintafolide and PLD Administration

	Vintafolide + PLD N=189		**Placebo + PLD** N=120	
	Vintafolide	**PLD**	**Placebo**	**PLD**
Total No .of treatment cycles[1], n	896	840	491	458
Mean (SD)	4.7 (3.42)		4.1 (3.58)	
Median (range)	4.0 (1;19)		2.5 (1;20)	
No. of patients with at least:				
One dose not administered, n (%)	139 (73.5)	15 (7.9)	81 (67.5)	7 (5.8)
One dose adjustment[2], n (%)	32 (16.9)	56 (29.6)	10 (8.3)	26 (21.7)
Cumulative dose[3]	187	187	120	118
Mean (SD)	57.7 (45.54)	208.7 (129.32)	50.8 (49.37)	181.7 (130.11)
Median (range)	47.3 (3;268)	199.5 (49;602)	30.0 (3;273)	136.6 (49;650)
Dose intensity[3]	187	187	120	118
Mean (SD)	0.5 (0.10)	1.6 (0.25)	0.5 (0.10)	1.7 (0.28)
Median (range)	0.5 (0;1)	1.7 (0;2)	0.5 (0;1)	1.8 (1;4)
Relative dose intensity, n	187	187	120	118
Mean (SD), %	84.2 (13.63)	91.1 (14.22)	87.2 (14.30)	94.5 (15.44)
Median (range), %	87.5 (33;108)	97.3 (21;125)	89.2 (33;112)	99.3 (55;217)

[1]At least 1 dose of vintafolide/placebo/PLD received.

[2]Number of patients with at least 1 adjusted dose of vintafolide/placebo/PLD. SD=standard deviation.

[3]Cumlative Dose and Dose intensity for vintafolide/placebo unit of measure is mg; for PLD units is mg/m^2.

Vintafolide+PLD and Placebo+PLD Safety

The majority of patients in both arms experienced at least 1 TEAE regardless of causality as summarized in Table 4. Overall, most of the drug-related TEAEs were Grade 1 or 2 in severity in both treatment arms. Drug-related TEAEs and ≥Grade 3 TEAE's, occurred more often in the vintafolide + PLD patients than in the placebo + PLD patients. Fewer than 10% of patients discontinued study therapy due to an adverse event, with comparable frequencies between arms. Regardless of causality, SAE's and fatal AE's occurred with similar frequencies in both arms. The only drug-related fatal adverse event (eosinophilic pneumonia) in the study was considered to be related to study therapy but unexpected for both vintafolide and PLD. There were no substantive qualitative or quantitative differences in the toxicity or safety profiles of either vintafolide +PLD or placebo +PLD based upon FR status (i.e., FR(0-100%) versus FR(100%)).

Table 4. Overview of Treatment-emergent Adverse Events

	Vintafolide + PLD N=189	Placebo + PLD N=120	All N=309
Number of patients who experienced at least 1, n (%) Treatment-emergent adverse event (TEAE)	186 (98.4)	116 (96.7)	302 (97.7)
TEAE related[1] to study treatment	178 (94.2)	101 (84.2)	279 (90.3)
TEAE leading to vintafolide/placebo withdrawal	14 (7.4)	7 (5.8)	21 (6.8)
TEAE leading to PLD withdrawal	12 (6.3%)	7 (5.8%)	19 (6.1%)
TEAE Grade ≥3	137 (72.5)	70 (58.3)	207 (67.0)
Serious TEAE	79 (41.8)	41 (34.2)	120 (38.8)
Fatal TEAE	5 (2.6)	3 (2.5)	8 (2.6)
Number of patients who experienced at least 1 Treatment-emergent cardiac disorder, n (%)[2]	23 (12.2)	8 (6.7)	31 (10.0)
p-value	0.1253		
Difference in proportion, % [95%CI][3]	5.5 [-1.5, 12.0]		
Treatment-emergent visual disorder resulting in loss of visual acuity, n (%)[4]	6 (3.2)	3 (2.5)	9 (2.9)
p-value	1.0000		
Difference in proportion [95%CI][3]	0.7 [-4.2, 4.7]		
TEAEs belonging to the class of PLD and vinca-alkaloids, n (%)	175 (92.6)	106 (88.3)	281 (90.9)
p-value	0.2258		
Difference in proportion [95%CI][3]	4.3 [-2.3, 11.9]		

TEAE = adverse event with onset/worsening on or after the start date and time of the first dose of study drug (PLD or vintafolide/placebo) through 30 days after the last dose of study drug (PLD or vintafolide/placebo).

[1]Possibly, probably, or definitely related to study treatment or missing.

[2]Captured all Preferred Terms in the Cardiac Disorder system order class.

[3]Miettinen and Nurminen method.

[4]Captured with the following Preferred Terms: "blindness," "vision blurred," visual acuity reduced," "visual impairment," or "visual impairment."

A total of 302 patients experienced at least 1 treatment-emergent adverse event (TEAE) during the study. TEAEs occurring in >25% of patients overall included: neutropenia, anemia, nausea, stomatitis, constipation, abdominal pain, vomiting, diarrhea, fatigue, decreased appetite, peripheral sensory neuropathy, and palmer-plantar erythrodysesthesia syndrome. TEAEs occurring with ≥10% difference in the vintafolide + PLD arm than the placebo + PLD arm included: anemia, constipation, abdominal pain, fatigue, pyrexia, decreased appetite, muscular weakness, peripheral sensory neuropathy, depression, dyspnea, dysphonia, and alopecia.

Drug related TEAEs were observed more commonly in the vintafolide + PLD arm (94.2%) than in the placebo + PLD arm (84.2%) and occurred in most SOCs. Drug related TEAEs occurring in >25% of patients overall included: neutropenia, anemia, nausea, stomatitis, constipation, fatigue, and palmer-plantar erythrodysesthesia syndrome. Drug related TEAEs occurring with ≥10% difference in the vintafolide + PLD arm than the placebo + PLD arm included: neutropenia, anemia, constipation, abdominal pain, fatigue, decreased appetite, muscular weakness, peripheral sensory neuropathy, and alopecia.

Patients who had TEAEs that resulted in withdrawal of vintafolide/placebo were discontinued from the study. Patients who had TEAEs resulting in withdrawal of PLD, were allowed to continue in the study. Adverse events

leading to discontinuation of treatment with vintafolide or placebo occurred with comparable frequencies between treatment arms (vintafolide + PLD: 7.4% of patients; placebo + PLD: 5.8%). TEAEs leading to vintafolide or placebo discontinuation in ≥2 patients included: small bowel obstruction, hypersensitivity, peripheral sensory neuropathy, and generalized pruritus. Adverse events leading to discontinuation of treatment with PLD also occurred with comparable frequencies between treatment arms (vintafolide + PLD: 6.3%; placebo + PLD: 5.8%). Small intestinal obstruction and palmar-plantar erythrodysesthesia syndrome were the only TEAEs leading to withdrawal of PLD that occurred in ≥2 patients (vintafolide + PLD: 1.1%; placebo + PLD: versus 0.8%).

There were a total of 120 patients (38.8%) who had a total 234 serious TEAEs irrespective of causality (41.8% of vintafolide + PLD-treated patients and 34.2% placebo + PLD-treated patients). SAEs occurring with ≥2% frequency in the vintafolide + PLD arm than the placebo + PLD arm included: anemia, vomiting, abdominal pain, large intestinal obstruction, pulmonary embolism, pleural effusion. SAEs occurring with ≥2% frequency in the placebo + PLD arm than the vintafolide + PLD arm included: small bowel obstruction and fatigue.

Treatment-related SAEs were observed more commonly in the vintafolide + PLD arm (20.6%) than in the placebo + PLD arm (7.5%). Treatment-related SAEs occurring with ≥2% greater difference in the vintafolide + PLD arm over the placebo + PLD arm include: neutropenia, anemia, nausea, vomiting, and abdominal pain. Thrombocytopenia and stomatitis were the only drug-related SAEs occurring more commonly in the placebo + PLD arm than in the vintafolide + PLD arm.

A total of 535 TEAEs that were Grade 3 or greater in severity occurred in 207 (67.0%) patients overall, with a higher incidence in the vintafolide + PLD arm (72.5%) than the placebo + PLD arm (58.3%). The most commonly represented TEAEs by SOC were gastrointestinal disorders (30.1%), blood and lymphatic disorders (29.1%), skin and subcutaneous tissue disorders (12.6%), and metabolism and nutrition disorders (10.0%). Grade 3 and greater TEAEs occurring with ≥2% greater difference in the vintafolide + PLD arm over the placebo + PLD arm include neutropenia, anemia, abdominal pain, fatigue, GGT increased, hyponatremia, hypokalemia, muscular weakness, peripheral sensory neuropathy, pulmonary embolism, and pleural effusion. Grade 3 and greater TEAEs occurring more frequently in the placebo + PLD arm than in the vintafolide + PLD arm included thrombocytopenia, PPE syndrome, and maculo-papular rash.

A total of 295 treatment-related adverse events of Grade 3 and greater severity occurred in 157 (50.8%) patients overall, with a higher incidence in the vintafolide + PLD arm (57.1%) than the placebo + PLD arm (40.8%). Treatment-related Grade 3 or greater TEAEs occurring with ≥2% greater difference in the vintafolide + PLD arm over the placebo + PLD arm included: neutropenia, anemia, nausea, abdominal pain, vomiting, fatigue, GGT increase, and peripheral sensory neuropathy. Grade 3 and greater TEAEs occurring more frequently in the placebo + PLD arm than in the vintafolide + PLD arm included thrombocytopenia, PPE syndrome, and maculo-papular rash.

A total of eight (2.6%) patients experienced fatal TEAEs during the study. Fatal TEAEs occurred with low frequency overall and at a comparable rate in both treatment arms (vintafolide + PLD arm 2.6% versus placebo + PLD arm 2.5%). Fatal TEAEs occurring in more than 1 patient by SOC term include: respiratory disorder (n=5) and nervous system disorder (n=2). One treatment-related fatal TEAE occurred in the vintafolide + PLD treatment arm; eosinophilic pneumonia, which was an unexpected TEAE for vintafolide + PLD.

The occurrence of cardiac TEAEs did not differ significantly between treatment arms. Cardiac disorders affected 12.2% and 6.7% of vintafolide + PLD and placebo + PLD-treated patients, respectively (p=0.1253, CI% [-1.5, 12.0]). None of the selected preferred terms for cardiac disorders showed a statistically significant difference

between treatment arms. Visual disorders resulting in loss of visual acuity affected 3.2% of vintafolide + PLD patients (n=6) and 2.5% and placebo + PLD-treated patients (n=3); (p=1.0000 CI% [-4.2, 4.7]). None of the selected preferred terms for visual TEAEs resulting in loss of acuity showed a statistically significant difference between treatment arms. TEAEs related to PLD and vinca-alkaloid treatment affected 92.6% and 88.3% of vintafolide + PLD and placebo + PLD-treated patients, respectively (p=0.2258, CI% [-2.3, 11.9]). The following TEAE's occurred significantly more common in the vintafolide + PLD arm than in the placebo + PLD arm: constipation, abdominal pain, anemia, peripheral sensory neuropathy, alopecia and peripheral motor neuropathy. The nature and frequency of these TEAEs were anticipated with vintafolide therapy given its mechanism of action.

The occurrence of drug-related cardiac TEAEs and drug related TEAEs resulting in loss of visual acuity did not differ significantly across treatment arms. Cardiac disorders affected 4.2% and 0.8% of vintafolide + PLD and placebo + PLD-treated patients, respectively (p=0.1612, CI% [-0.7, 7.4]. Visual disorders resulting in loss of visual acuity affected 2.1% and 0.0% of vintafolide + PLD and placebo + PLD-treated patients, respectively (p=0.1603 CI% [-1.0, 5.3]). However, drug-related TEAEs belonging to the class of PLD and vinca-alkaloids were significantly different occurring in 83.6% and 70.8% of patients in the vintafolide + PLD and placebo + PLD treatment arms, respectively(p=0.0101, CI% [3.3, 22.7]). For drug-related TEAEs belonging to the class of PLD and vinca alkaloids, the following TEAEs occurred more commonly in the vintafolide + PLD arm than in the placebo + PLD arm: constipation; anemia; peripheral sensory neuropathy; abdominal pain; alopecia; and peripheral motor neuropathy.

Although not designated a TEAE of special interest in the protocol, thromboembolic events were raised as a potential concern by the DSMB members during the 05 February 2013 DSMB interim safety meeting. After careful review of the events during each interim safety meeting, DSMB members recommended study continuation as planned. Thromboembolic events occurred in 21 patients (11.1%) in the vintafolide + PLD arm and in 7 patients (5.8%) in the placebo + PLD arm. Drug-related thromboembolic events occurred in 7 patients (3.7%) in the vintafolide + PLD arm, and in no patient in the placebo + PLD arm. The seven patients in the vintafolide + PLD arm experienced a total of 8 treatment related thrombotic TEAEs. Three patients developed Grade 3 pulmonary embolus, and one patient developed grade 2 pulmonary embolus. Three patients experienced deep venous thrombosis (1 event Grade 2, 2 events Grade 3) and 1 patient developed a grade 2 venous thrombosis.

Serum chemistry results of Grades 3 and 4 toxicity were relatively uncommon in both treatment arms; decreased sodium and increased GGT were the most common Grades 3 and 4 toxicities observed overall. Toxicities were generally more common in the vintafolide + PLD treatment arm than in the placebo + PLD treatment arm.

Hematology results of Grades 3 and 4 anemia and neutropenia occurred more frequently in the vintafolide + PLD arm than in the placebo + PLD arm; however, Grade 3-4 thrombocytopenia was equally represented in both treatment arms. In spite of the higher rates of neutropenia in the vintafolide + PLD arm than in the placebo + PLD arm, the rates of febrile neutropenia were low and comparable (2.1% versus 2.5%, respectively).

Overall, patients had a mean baseline LVEF of 64.3% (SD of 6.33) which ranged from 42 to 85%. The overall worst mean change from baseline was -1.7% (SD of 6.20) which ranged from -27 to 15%. There were minimal differences between treatment arms.

Etarfolatide Safety

A total of 364 patients received ^{99m}Tc-etarfolatide (321 were later randomized to study treatment and 43 were never randomized). ^{99m}Tc-etarfolatide-emergent AEs occurring in ≥ 2% of patients in any treatment arm included: nausea, constipation, vomiting and fatigue. ^{99m}Tc-etarfolatide-emergent drug related AEs occurring in ≥ 2% of patients in any treatment arm included: nausea, constipation and fatigue. The only serious TEAE that occurred in more than 1 patient was vomiting; all others occurred in only 1 patient. Drug-related serious TEAEs occurred in 3 (0.8%) patients: two occurrences of vomiting, and one occurrence each of nausea and anemia. Overall, treatment with ^{99m}Tc-etarfolatide was well tolerated and the adverse event profiles were consistent with those previously reported.

Conclusions:

Overall, the interim results of this randomized Phase 3 study failed to meet the pre-specified futility PFS hazard ratio bound of 0.80 for the comparison of vintafolide + PLD treatment arm and the placebo + PLD treatment in FR(100%) PROC patients. Following a year of rapid study enrollment (i.e., 57% of all patients enrolled within a 12 month period), an event-trigged interim analysis for futility was conducted. With median duration of follow-up of 2.8 months, 52.2% of patients were censored for the PFS analysis. Median PFS was 5.6 months in patients treated with vintafolide + PLD and 5.9 months in patients treated with placebo + PLD. The observed PFS HR of 0.950 [(95% CI: 0.624, 1.446); 1-sided stratified log-rank p=0.4098] failed to cross the pre-specified futility bound of HR=0.8. Because of the high censoring rate (74.3%), OS results must be interpreted with caution. Median OS for vintafolide + PLD was 17.8 months compared to 14.8 months in the placebo + PLD arm. The observed OS HR of 0.878 [(95% CI: 0.515, 1.497); 1-sided stratified log-rank p=0.3166) was less than the pre-specified futility bound of HR=1.51. Based upon relatively short duration of follow-up and high censoring rates in both treatment arms, it is unclear if the addition of vintafolide to PLD failed to improve PFS over PLD monotherapy, or if insufficient observation hindered demonstration of the vintafolide + PLD combination efficacy.

Overall, the safety data suggest that, with appropriate monitoring, EC145 + PLD is well tolerated by patients with platinum-resistant ovarian cancer. The adverse event profiles of PLD alone and in combination with vintafolide were consistent with those previously reported in the literature. Other than the drug-related fatal TEAE of eosinophilic pneumonia, there were no unanticipated safety issues with either vintafolide + PLD or placebo + PLD. Taken together, the safety data suggests that the adverse event profile of vintafolide + PLD is predictable, manageable, and well tolerated when administered to patients with advanced platinum resistant ovarian cancer.

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