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

Summary

EudraCT number	2011-000348-11
Trial protocol	CZ ES BE PL HU GB
Global end of trial date	02 February 2016
Results information	
Result version number	v1 (current)
This version publication date	12 September 2018
First version publication date	12 September 2018
Summary attachment (see zip file)	EC-FV-06 CSR Synopsis (FEB-2017) (EC-FV-06 CSR Synopsis (FEB-2017).pdf)

Trial information

Trial identification	
Sponsor protocol code	EC-FV-06
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01170650
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Endocyte, Inc.
Sponsor organisation address	3000 Kent Avenue, Suite A1-100, West Lafayette, United States, 47906
Public contact	Christopher Jordan, Endocyte, Inc., 001 3176080769, cjordan@endocyte.com
Scientific contact	Christopher Jordan, Endocyte, Inc., 001 3176080769, cjordan@endocyte.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Compare progression-free survival (PFS), based upon investigator assessment using RECIST v 1.1 in participants with platinum-resistant ovarian cancer who receive combination therapy with vintafolide and pegylated liposomal doxorubicin (PLD) (i.e., vintafolide + PLD) with that of participants with platinum-resistant ovarian cancer who receive PLD and placebo. The primary analysis will be conducted in FR (100%) participants as determined by 99mTc-etarfolatide scan.

Protection of trial subjects:

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), Health Insurance Portability and Accountability Act (HIPAA) or other local regulatory requirements for protection of personal information, and other applicable regulatory requirements and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The ICF will be approved and reviewed by the sponsor prior to IRB/IEC review.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 124
Country: Number of subjects enrolled	Canada: 77
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Poland: 5
Worldwide total number of subjects	321
EEA total number of subjects	71

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	203
From 65 to 84 years	117
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in April 2011. <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. Once supply had been secured, enrollment increased such that ~57% of patients were enrolled within 12 months of the first planned interim analysis.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	321
Number of subjects completed	230

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/Exclusion: 91

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study EC-FV-06 is double-blinded in order to limit the occurrence of conscious or unconscious bias in the conduct and interpretation of the clinical trial arising from the influence which the knowledge of treatment may have on the execution of the clinical study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vintafolide + PLD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EC145
Investigational medicinal product code	
Other name	Vintafolide
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2.5mg IV on days 1, 3, 5 of weeks 1 and 3 of a 28 day cycle.

Investigational medicinal product name	PLD
Investigational medicinal product code	
Other name	Doxorubicin pegylated liposomal
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

50mg/m2 IBW IV on day 1 of 28 day cycle

Arm title	Placebo + PLD

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	PLD
Investigational medicinal product code	
Other name	Doxorubicin pegylated liposomal
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

50mg/m2 IBW IV on day 1 of 28 day cycle

Number of subjects in period 1[1]	Vintafolide + PLD	Placebo + PLD
Started	143	87
Completed	143	87

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The baseline period data include only those who completed the treatment whereas the worldwide number enrolled includes all patients enrolled.

Period 2

Period 2 title	First Interim Analysis
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Vintafolide + PLD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EC145
Investigational medicinal product code	
Other name	Vintafolide
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2.5mg IV on days 1, 3, 5 of weeks 1 and 3 of a 28 day cycle.

Investigational medicinal product name	PLD
Investigational medicinal product code	
Other name	Doxorubicin pegylated liposomal
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

50mg/m2 IBW IV on day 1 of 28 day cycle

Arm title	Placebo + PLD

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	PLD
Investigational medicinal product code	
Other name	Doxorubicin pegylated liposomal
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravascular use

Dosage and administration details:

50mg/m2 IBW IV on day 1 of 28 day cycle

Number of subjects in period 2	Vintafolide + PLD	Placebo + PLD
Started	143	87
Completed	143	87

Baseline characteristics

Reporting groups	
Reporting group title	Vintafolide + PLD
Reporting group description: -	
Reporting group title	Placebo + PLD
Reporting group description: -	

Reporting group values	Vintafolide + PLD	Placebo + PLD	Total
Number of subjects	143	87	230
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.8	61.0	
standard deviation	± 9.99	± 10.64	-
Gender categorical Units: Subjects			
Female	143	87	230
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	14	10	24
Black/African American	8	0	8
White	121	75	196
Unknown	0	1	1
ECOG Units: Subjects			
00	71	51	122
01	72	36	108
Type of Cancer Units: Subjects			
Ovarian	123	73	196
Primary Peritoneal	13	12	25
Fallopian Tube	7	2	9
Regimen Units: Subjects			
Primary platinum therapy only	64	36	100
Primary and secondary platinum therapy	58	36	94
Additional therapy	21	15	36

End points

End points reporting groups	
Reporting group title	Vintafolide + PLD
Reporting group description: -	
Reporting group title	Placebo + PLD
Reporting group description: -	
Reporting group title	Vintafolide + PLD
Reporting group description: -	
Reporting group title	Placebo + PLD
Reporting group description: -	

Primary: Progression-free survival	
End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
22 April 2011 - 17 March 2014	

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: Subjects				
PFS Events	75	35		
Progressions	65	28		
Deaths	10	7		
Censored	68	52		

Statistical analyses

Statistical analysis title	Efficacy Analysis
Comparison groups	Vintafolide + PLD v Placebo + PLD
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Regression, Cox

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Primary

End point timeframe:

22 April 2011 - 17 March 2014

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
median (confidence interval 95%)				
PFS Rate at 3 months	69.4 (60.3 to 76.9)	62.6 (49.8 to 73.0)		
PFS Rate at 6 months	44.3 (34.3 to 53.8)	43.1 (27.2 to 58.0)		

Statistical analyses

Statistical analysis title	Efficacy Analysis
Comparison groups	Vintafolide + PLD v Placebo + PLD
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Regression, Cox

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

22 April 2011 - 17 March 2014

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: Events				
Number of OS Events	37	22		
Number Censored	106	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

22 April 2011 - 17 March 2014

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
median (confidence interval 95%)				
OS Rate at 12 months	60.9 (48.4 to 71.2)	58.2 (39.0 to 73.2)		
OS Rate at 18 months	49.4 (30.3 to 66.0)	33.9 (12.0 to 57.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of target lesions at study entry

End point title	Number of target lesions at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: lesions				
median (full range (min-max))	2.0 (1 to 5)	2.0 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: RECIST sum of diameters at study entry

End point title	RECIST sum of diameters at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: mm				
arithmetic mean (standard deviation)	73.6 (± 63.05)	68.5 (± 57.28)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: RECIST sum of diameters at study entry

End point title	RECIST sum of diameters at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: mm				
median (full range (min-max))	61.0 (10 to 359)	48.0 (10 to 339)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CA-125 Levels at study entry

End point title	CA-125 Levels at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: U/mL				
arithmetic mean (standard deviation)	1556.3 (± 5865.51)	808.3 (± 1352.35)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CA-125 Levels at study entry

End point title	CA-125 Levels at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: U/mL				
median (full range (min-max))	248.0 (6 to 64480)	242.0 (4 to 8634)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Treatment-free survival

End point title	Treatment-free survival

End point description:

End point type	Other pre-specified

End point timeframe:

Basline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
arithmetic mean (standard deviation)	5.7 (± 4.71)	5.7 (± 3.72)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Treatment-free survival

End point title	Treatment-free survival

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
median (full range (min-max))	5.1 (0 to 38)	5.3 (1 to 24)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Platinum-free interval

End point title	Platinum-free interval

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	84		
Units: months				
arithmetic mean (standard deviation)	3.2 (± 1.87)	3.3 (± 1.86)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Platinum-free interval

End point title	Platinum-free interval

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	84		
Units: months				
median (full range (min-max))	3.7 (0 to 7)	3.7 (0 to 6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time since initial cancer diagnosis

End point title	Time since initial cancer diagnosis

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
arithmetic mean (standard deviation)	20.7 (± 12.09)	26.2 (± 27.69)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time since initial cancer diagnosis

End point title	Time since initial cancer diagnosis

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: months				
median (full range (min-max))	15.9 (8 to 73)	16.0 (8 to 207)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Size of residual disease at the end of the primary debulking surgery or attempted debulking surgery (cm)

End point title	Size of residual disease at the end of the primary debulking surgery or attempted debulking surgery (cm)

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: Subjects				
<2.0	95	69		
>2.0	21	3		
Not Applicable	2	0		
Unknown	25	15		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of target lesions at study entry

End point title	Number of target lesions at study entry

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline

End point values	Vintafolide + PLD	Placebo + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	87		
Units: lesions				
arithmetic mean (standard deviation)	2.3 (± 1.26)	2.4 (± 1.28)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 22 April 2011 - 17 March 2014	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups	
Reporting group title	Vintafolide + PLD
Reporting group description: -	
Reporting group title	Placebo + PLD
Reporting group description: -	

Serious adverse events	Vintafolide + PLD	Placebo + PLD	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 189 (41.80%)	41 / 120 (34.17%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events			
Investigations			
Weight decreased			
subjects affected / exposed	3 / 189 (1.59%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
international normalized ratio increased			
subjects affected / exposed	2 / 189 (1.06%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Nervous system disorders			
Brain edema			

subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Cerebral infarction			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Cerebral thrombosis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 189 (2.12%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	4 / 39	2 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Neutropenia			
subjects affected / exposed	5 / 189 (2.65%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	5 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Anaemia			
subjects affected / exposed	4 / 189 (2.12%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	4 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Thrombocytopenia			
subjects affected / exposed	1 / 189 (0.53%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	1 / 39	2 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 189 (2.12%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	3 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	

Fatigue			
subjects affected / exposed	1 / 189 (0.53%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Sudden death			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	10 / 189 (5.29%)	9 / 120 (7.50%)	
occurrences causally related to treatment / all	3 / 39	1 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Vomiting			
subjects affected / exposed	9 / 189 (4.76%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	7 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Abdominal pain			
subjects affected / exposed	8 / 189 (4.23%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	6 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Constipation			
subjects affected / exposed	6 / 189 (3.17%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	5 / 39	2 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Intestinal obstruction			
subjects affected / exposed	6 / 189 (3.17%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Nausea			
subjects affected / exposed	6 / 189 (3.17%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	6 / 39	1 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Ascites			

subjects affected / exposed	4 / 189 (2.12%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Large intestinal obstruction			
subjects affected / exposed	4 / 189 (2.12%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Stomatitis			
subjects affected / exposed	2 / 189 (1.06%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	2 / 39	2 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Diarrhoea			
subjects affected / exposed	3 / 189 (1.59%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 189 (1.06%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Hiatus hernia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	7 / 189 (3.70%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	3 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Pleural effusion			
subjects affected / exposed	6 / 189 (3.17%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Deep vein thrombosis			

subjects affected / exposed	2 / 189 (1.06%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Acute respiratory failure			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Dyspnoea			
subjects affected / exposed	0 / 189 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	1 / 3	
Eosinophilic pneumonia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Aspiration Pneumonia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	1 / 3	
Respiratory distress			
subjects affected / exposed	1 / 189 (0.53%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	1 / 5	0 / 3	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	3 / 189 (1.59%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 189 (1.06%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Staphylococcal sepsis			

subjects affected / exposed	2 / 189 (1.06%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
Urinary tract infection			
subjects affected / exposed	0 / 189 (0.00%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	0 / 3	
infectious peritonitis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 39	0 / 9	
deaths causally related to treatment / all	0 / 5	1 / 3	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vintafolide + PLD	Placebo + PLD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 189 (98.41%)	116 / 120 (96.67%)	
Investigations			
Weight decreased			
subjects affected / exposed	27 / 189 (14.29%)	9 / 120 (7.50%)	
occurrences (all)	36	36	
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 189 (10.05%)	5 / 120 (4.17%)	
occurrences (all)	24	24	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 189 (7.94%)	2 / 120 (1.67%)	
occurrences (all)	17	17	
Hypotension			
subjects affected / exposed	10 / 189 (5.29%)	2 / 120 (1.67%)	
occurrences (all)	12	12	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	60 / 189 (31.75%)	19 / 120 (15.83%)	
occurrences (all)	79	79	

Headache			
subjects affected / exposed	46 / 189 (24.34%)	23 / 120 (19.17%)	
occurrences (all)	69	69	
Dizziness			
subjects affected / exposed	32 / 189 (16.93%)	18 / 120 (15.00%)	
occurrences (all)	50	50	
Dysgeusia			
subjects affected / exposed	20 / 189 (10.58%)	10 / 120 (8.33%)	
occurrences (all)	30	30	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	79 / 189 (41.80%)	39 / 120 (32.50%)	
occurrences (all)	118	118	
Anaemia			
subjects affected / exposed	71 / 189 (37.57%)	27 / 120 (22.50%)	
occurrences (all)	98	98	
Thrombocytopenia			
subjects affected / exposed	19 / 189 (10.05%)	9 / 120 (7.50%)	
occurrences (all)	28	28	
Leukopenia			
subjects affected / exposed	18 / 189 (9.52%)	6 / 120 (5.00%)	
occurrences (all)	24	24	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	112 / 189 (59.26%)	49 / 120 (40.83%)	
occurrences (all)	161	161	
Asthenia			
subjects affected / exposed	37 / 189 (19.58%)	16 / 120 (13.33%)	
occurrences (all)	53	53	
Pyrexia			
subjects affected / exposed	39 / 189 (20.63%)	10 / 120 (8.33%)	
occurrences (all)	49	49	
Oedema peripheral			
subjects affected / exposed	33 / 189 (17.46%)	12 / 120 (10.00%)	
occurrences (all)	45	45	
Chills			

subjects affected / exposed	12 / 189 (6.35%)	6 / 120 (5.00%)	
occurrences (all)	18	18	
Influenza like illness			
subjects affected / exposed	8 / 189 (4.23%)	7 / 120 (5.83%)	
occurrences (all)	15	15	
Pain			
subjects affected / exposed	14 / 189 (7.41%)	1 / 120 (0.83%)	
occurrences (all)	15	15	
Malaise			
subjects affected / exposed	10 / 189 (5.29%)	4 / 120 (3.33%)	
occurrences (all)	14	14	
Chest pain			
subjects affected / exposed	11 / 189 (5.82%)	2 / 120 (1.67%)	
occurrences (all)	13	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	115 / 189 (60.85%)	67 / 120 (55.83%)	
occurrences (all)	182	182	
Stomatitis			
subjects affected / exposed	99 / 189 (52.38%)	54 / 120 (45.00%)	
occurrences (all)	153	153	
Constipation			
subjects affected / exposed	101 / 189 (53.44%)	39 / 120 (32.50%)	
occurrences (all)	140	140	
Abdominal pain			
subjects affected / exposed	87 / 189 (46.03%)	26 / 120 (21.67%)	
occurrences (all)	113	113	
Vomiting			
subjects affected / exposed	68 / 189 (35.98%)	44 / 120 (36.67%)	
occurrences (all)	112	112	
Diarrhoea			
subjects affected / exposed	57 / 189 (30.16%)	29 / 120 (24.17%)	
occurrences (all)	86	86	
Dyspepsia			
subjects affected / exposed	37 / 189 (19.58%)	20 / 120 (16.67%)	
occurrences (all)	57	57	

Abdominal distension			
subjects affected / exposed	37 / 189 (19.58%)	17 / 120 (14.17%)	
occurrences (all)	54	54	
Abdominal pain upper			
subjects affected / exposed	22 / 189 (11.64%)	10 / 120 (8.33%)	
occurrences (all)	32	32	
Small intestinal obstruction			
subjects affected / exposed	13 / 189 (6.88%)	10 / 120 (8.33%)	
occurrences (all)	23	23	
Ascites			
subjects affected / exposed	15 / 189 (7.94%)	6 / 120 (5.00%)	
occurrences (all)	21	21	
Abdominal pain lower			
subjects affected / exposed	13 / 189 (6.88%)	6 / 120 (5.00%)	
occurrences (all)	19	19	
Dysphagia			
subjects affected / exposed	15 / 189 (7.94%)	3 / 120 (2.50%)	
occurrences (all)	18	18	
Dry mouth			
subjects affected / exposed	11 / 189 (5.82%)	6 / 120 (5.00%)	
occurrences (all)	17	17	
Oral pain			
subjects affected / exposed	11 / 189 (5.82%)	5 / 120 (4.17%)	
occurrences (all)	16	16	
Flatulence			
subjects affected / exposed	8 / 189 (4.23%)	6 / 120 (5.00%)	
occurrences (all)	14	14	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	46 / 189 (24.34%)	9 / 120 (7.50%)	
occurrences (all)	55	55	
Cough			
subjects affected / exposed	30 / 189 (15.87%)	20 / 120 (16.67%)	
occurrences (all)	50	50	
Dysphonia			

subjects affected / exposed	24 / 189 (12.70%)	1 / 120 (0.83%)	
occurrences (all)	25	25	
Oropharyngeal pain			
subjects affected / exposed	17 / 189 (8.99%)	4 / 120 (3.33%)	
occurrences (all)	21	21	
Pleural effusion			
subjects affected / exposed	14 / 189 (7.41%)	4 / 120 (3.33%)	
occurrences (all)	18	18	
Pulmonary embolism			
subjects affected / exposed	10 / 189 (5.29%)	3 / 120 (2.50%)	
occurrences (all)	13	13	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	72 / 189 (38.10%)	45 / 120 (37.50%)	
occurrences (all)	117	117	
Rash			
subjects affected / exposed	31 / 189 (16.40%)	19 / 120 (15.83%)	
occurrences (all)	50	50	
Alopecia			
subjects affected / exposed	34 / 189 (17.99%)	8 / 120 (6.67%)	
occurrences (all)	42	34	
Skin hyperpigmentation			
subjects affected / exposed	24 / 189 (12.70%)	15 / 120 (12.50%)	
occurrences (all)	39	39	
Rash maculo-papular			
subjects affected / exposed	19 / 189 (10.05%)	14 / 120 (11.67%)	
occurrences (all)	33	33	
Pruritus			
subjects affected / exposed	20 / 189 (10.58%)	12 / 120 (10.00%)	
occurrences (all)	32	32	
Dry skin			
subjects affected / exposed	19 / 189 (10.05%)	9 / 120 (7.50%)	
occurrences (all)	28	28	
Erythema			

subjects affected / exposed	13 / 189 (6.88%)	7 / 120 (5.83%)	
occurrences (all)	20	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	36 / 189 (19.05%)	16 / 120 (13.33%)	
occurrences (all)	52	52	
Anxiety			
subjects affected / exposed	29 / 189 (15.34%)	8 / 120 (6.67%)	
occurrences (all)	37	37	
Depression			
subjects affected / exposed	24 / 189 (12.70%)	3 / 120 (2.50%)	
occurrences (all)	27	27	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	36 / 189 (19.05%)	17 / 120 (14.17%)	
occurrences (all)	53	53	
Myalgia			
subjects affected / exposed	28 / 189 (14.81%)	11 / 120 (9.17%)	
occurrences (all)	39	39	
Muscular weakness			
subjects affected / exposed	31 / 189 (16.40%)	0 / 120 (0.00%)	
occurrences (all)	31	31	
Arthralgia			
subjects affected / exposed	20 / 189 (10.58%)	7 / 120 (5.83%)	
occurrences (all)	27	27	
Pain in extremity			
subjects affected / exposed	14 / 189 (7.41%)	7 / 120 (5.83%)	
occurrences (all)	21	21	
Muscle spasms			
subjects affected / exposed	14 / 189 (7.41%)	3 / 120 (2.50%)	
occurrences (all)	17	17	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	23 / 189 (12.17%)	16 / 120 (13.33%)	
occurrences (all)	39	39	
Upper respiratory tract infection			

subjects affected / exposed	6 / 189 (3.17%)	6 / 120 (5.00%)	
occurrences (all)	12	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	84 / 189 (44.44%)	38 / 120 (31.67%)	
occurrences (all)	122	122	
Hypomagnesaemia			
subjects affected / exposed	21 / 189 (11.11%)	10 / 120 (8.33%)	
occurrences (all)	31	31	
Hypokalaemia			
subjects affected / exposed	20 / 189 (10.58%)	8 / 120 (6.67%)	
occurrences (all)	28	28	
Dehydration			
subjects affected / exposed	20 / 189 (10.58%)	6 / 120 (5.00%)	
occurrences (all)	26	26	
Hypoalbuminaemia			
subjects affected / exposed	10 / 189 (5.29%)	3 / 120 (2.50%)	
occurrences (all)	13	13	
Hyponatraemia			
subjects affected / exposed	10 / 189 (5.29%)	0 / 120 (0.00%)	
occurrences (all)	10	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2011	Change of protocol from v1 to v3. Inclusion of section "Rationale and Justification for Quality of Life Assessments", modification of study objectives, RECIST v1.1 language added into separate appendix, addition of stratification variable based upon EC20 scan status, and modification of existing language, addition of language to section or clarification of existing language for general study design, primary and secondary endpoint definitions, analysis endpoints and populations, sample size determination, interim and final analyses and efficacy analyses.
05 February 2013	Change of protocol from v3 to v5. Change randomization from 2:1 to 1:1, folate receptor expression status nomenclatures modified, addition of use of EuroQoL EQ-5D-3L questionnaire, modification of study objectives, addition of a 4+/- day allowance for radiographic CT assessments and clarified post-baseline assessments are determined from first dose of vintafolide/placebo and/or PLD, modified inclusion and exclusion criteria, changed stratification variable based upon baseline etarfolatide scan status, updated emergency unblinding procedure, simplified QoL data collection, and modified statistical methods (changed primary objective to PFS, added hierarchical step-down testing for PFS and OS, changed sample size in FR(100%) from 256 to 350, revised interim analysis plan).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 August 2011	Enrollment was suspended August 2011 through April 2012 due to an interruption in the study's PLD supply.	30 April 2012

Notes:

Limitations and caveats

None reported