Clinical trial results:
A phase II Controlled Study of PM01183 in Platinum-Resistant / Refractory Advanced Ovarian Cancer Patients.

Summary

EudraCT number	2011-002172-16
Trial protocol	ES
Global end of trial date	25 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	PM1183-B-002-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Av de los Reyes 1, Poligono Industrial La Mina , Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical DevelopmentDepartment of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., 34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical DevelopmentDepartment of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., 34 91846 60 00, clinicaltrials@pharmamar.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	Final
Date of interim/final analysis	29 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2014
Global end of trial reached?	Yes
Global end of trial date	25 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of PM01183 in patients with platinum-resistant / refractory advanced ovarian cancer.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as approved by the 59th World Medical Association General Assembly, held at Seoul in 2008) and was consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. Study personnel involved in conducting this trial was qualified by education, training, and experience to perform their respective task(s).
The Sponsor provided insurance or indemnity in accordance with the applicable regulatory requirements.

Background therapy:

Patients were to receive standard antiemetic prophylaxis according to American Society of Clinical Oncology (ASCO) guidelines before each treatment administration:
• Corticosteroids (dexamethasone i.v. or equivalent, at institutional standard antiemetic doses).
• Serotonin (5-HT3) antagonists (ondansetron 8 mg i.v. or equivalent).
If necessary, in addition to the above, 10 mg of metoclopramide every eight hours could be administered orally or the duration of treatment with 5-HT3 antagonists and/or dexamethasone could be extended (according to Investigator criteria). Additional antiemetics could be used after Cycle 1 upon agreement with the Sponsor.

Evidence for comparator: -

Actual start date of recruitment	19 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Spain: 36
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	55
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eighty-one patients were enrolled between 19 December 2011 and 22 March 2013 at nine study centers (France and Spain). There were 52 patients treated with PM01183 in the Experimental Arm: 22 in an unrandomized first stage; 30 in the randomized second stage. Twenty-nine patients were randomized to topotecan in the second stage Control Arm

Pre-assignment

Screening details:

Sign IC;Age≥18 year;Histologically/cytologically confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer;Platinum-resistant/refractory disease;FIGO stages IIC through IV and measurable disease as per RECIST v.1.1 or by GCIG criteria;Adequate hematological/renal/metabolic/hepatic function;At least 3 weeks since last prior therapy

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

-First stage: 18 evaluable patients were to be given PM01183 to explore the activity of PM01183. If the minimum threshold of antitumor activity was met (at least two of the 18 patients with confirmed tumor responses)
- Second stage: 60 evaluable patients were to be randomized (stratified according to platinum-resistance or refractoriness), 30 per arm, to an PM01183 Arm or to a Control Arm (Topotecan). Patients discontinuing topotecan could be considered for crossover to PM01183 treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	PM01183

Arm description:

There were 52 patients treated with PM01183 in the Experimental Arm: 22 in an unrandomized first stage; 30 in the randomized second stage.
All patients in this arm received PM01183 7.0 mg FD on Day 1 i.v. as a 1-h infusion q3wk (three weeks = one treatment cycle).

Arm type	Experimental
Investigational medicinal product name	PM01183
Investigational medicinal product code	PM01183
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PM01183 was supplied as a lyophilized powder for concentrate for solution for infusion with two strengths: 1 mg/vial and 4 mg/vial. Before use, the 1-mg vial and 4-mg vial was reconstituted with 2 mL and 8 mL of water for injection respectively to give a solution containing 0.5 mg/mL of PM01183. For administration to patients as i.v. infusion, reconstituted vials were further diluted with glucose 50 mg/mL (5%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion.
All patients in this arm received PM01183: 7.0 mg FD on Day 1 i.v. as a 1-h infusion q3wk (three weeks = one treatment cycle).

Arm title	Topotecan

Arm description:

During the second stage, patients were randomized the Control Arm: Topotecan.
Topotecan was administered either as a standard (daily) or weekly regimen. The daily dose/regimen was based on approved topotecan dosing for relapsed ovarian cancer. The weekly regimen and dose/regimen was based on clinical practice reported in the literature.

Arm type	Active comparator

Investigational medicinal product name	Topotecan
Investigational medicinal product code	Topotecan
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard Daily Regimen: Topotecan: i.v. as a 30-min infusion daily on Days 1–5 q3wk (3 weeks = 1 treatment cycle).
The starting topotecan dose depended on the patient's ECOG PS, CrCL, and on the number of line of prior chemotherapy lines:
-1.50 mg/m2/daily for patients with ECOG PS=0, CrCL≥60 mL/min and not more than one line.
-1.25 mg/m2/daily for patients with ECOG PS=1 or 2, or CrCL 41–59 mL/min, or more than one line.
-0.75 mg/m2/daily for patients with CrCL 30–40 mL/min.
Weekly Regimen:- Topotecan: i.v. as a 30-min infusion weekly on Days 1, 8 and 15 q4wk (4 weeks = 1 treatment cycle).
The starting topotecan dose depended on the patient's ECOG PS and CrCL:
-4.0 mg/m2 for patients with ECOG PS=0 or 1 and CrCL≥60 mL/min.
-3.0 mg/m2 for patients with ECOG PS=2 or CrCL 41–59 ml/min.
-2.4 mg/m2 for patients with calculated CrCL 30–40 mL/min.
Regardless of the starting dose, patients received topotecan at the same schedule

Number of subjects in period 1	PM01183	Topotecan
Started	52	29
Completed	0	0
Not completed	52	29
Adverse event, serious fatal	-	1
Physician decision	5	3
Consent withdrawn by subject	4	2
Adverse event, non-fatal	5	-
Progressive disease	38	23

Baseline characteristics

Reporting groups	
Reporting group title	PM01183
Reporting group description:	
There were 52 patients treated with PM01183 in the Experimental Arm: 22 in an unrandomized first stage; 30 in the randomized second stage. All patients in this arm received PM01183 7.0 mg FD on Day 1 i.v. as a 1-h infusion q3wk (three weeks = one treatment cycle).	
Reporting group title	Topotecan
Reporting group description:	
During the second stage, patients were randomized the Control Arm: Topotecan. Topotecan was administered either as a standard (daily) or weekly regimen. The daily dose/regimen was based on approved topotecan dosing for relapsed ovarian cancer. The weekly regimen and dose/regimen was based on clinical practice reported in the literature.	

Reporting group values	PM01183	Topotecan	Total
Number of subjects	52	29	81
Age categorical Units: Subjects			
18–49 years	7	6	13
50–69 years	37	12	49
≥ 70 years	8	11	19
Age continuous Units: years			
median	59	61	
full range (min-max)	35 to 81	35 to 80	-
Gender categorical Units: Subjects			
Female	52	29	81
Male	0	0	0
ECOG PS			
ECOG PS=Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	26	11	37
PS 1	24	14	38
PS 2	2	4	6
Race Units: Subjects			
Caucasian	44	22	66
Unk	8	7	15
Primary tumor site Units: Subjects			
Ovarian	44	23	67
Peritoneal	7	4	11
Fallopian tube	1	2	3
Histology type Units: Subjects			
Papillary serous	38	19	57
Endometrioid	4	2	6

Undifferentiated carcinoma	4	2	6
Mixed epithelial ovarian	2	0	2
Mucinous	2	1	3
Clear cell	1	3	4
Unspecified/unknown	1	2	3
Histology grade Units: Subjects			
Well differentiated	8	0	8
Moderately differentiated	9	8	17
Poorly differentiated	24	9	33
Unknown	11	12	23
Disease stage at inclusion Units: Subjects			
Locally advanced	20	16	36
Metastatic	32	13	45
Visceral metastasis Units: Subjects			
Yes	20	8	28
No	32	21	53
Ascites Units: Subjects			
Yes	11	10	21
No	41	19	60
Platinum status			
Platinum-resistant disease was defined as disease relapse or progression less than six months after last platinum-containing chemotherapy; platinum-refractory disease was defined as disease that did not respond during last platinum-containing chemotherapy			
Units: Subjects			
Refractory	19	13	32
Resistant	33	16	49
Platinum resistance Units: Subjects			
Primary resistance	30	18	48
Secondary resistance	22	11	33
Patients with PFI			
PFI, platinum-free interval;			
Units: Subjects			
< 3 months	20	15	35
3–6 months	32	14	46
Disease evaluation			
GCIG, Gynecological Cancer Intergroup criteria;RECIST, Response Evaluation Criteria in Solid Tumors v.1.1			
Units: Subjects			
RECIST (measurable disease)	43	22	65
GCIG (non-measurable disease)	9	7	16
Patients with CA-125 Units: Subjects			
≥2× ULN	38	20	58
<2× ULN	14	9	23
Radiotherapy Units: Subjects			
Yes	2	0	2

No	50	29	79
Surgery (cytoreduction) Units: Subjects			
Yes	38	24	62
No	14	5	19
Chemotherapy lines Units: Subjects			
1 line	18	13	31
2 lines	26	12	38
3 lines	8	4	12
Best response to last prior therapy Units: Subjects			
Complete Response	7	1	8
Partial Response	11	11	22
Stable Disease	16	5	21
Progressive Disease	14	7	21
Unk	4	5	9
Weight Units: Kg			
median	64.5	62	
full range (min-max)	45 to 110	50 to 96	-
BSA			
BSA=body surface area			
Units: m2			
median	1.7	1.68	
full range (min-max)	1.44 to 2.27	1.47 to 2.05	-
Signs and symptoms per patient Units: number			
median	1	1	
full range (min-max)	0 to 4	0 to 6	-
Albumin Units: g/dL			
median	4	3.7	
full range (min-max)	2.8 to 4.8	3.1 to 4.4	-
Alpha-1-acid glycoprotein			
n=45 for the Experimental Arm; n=23 for the Control Arm			
Units: mg/dL			
median	114	135	
full range (min-max)	44 to 454	13.2 to 374	-
Time from first diagnosis to first infusion Units: months			
median	18.8	14	
full range (min-max)	2.6 to 109.4	3.8 to 81.2	-
Number of sites involved Units: number			
median	2	2	
full range (min-max)	1 to 6	1 to 5	-
Platinum-free interval Units: months			
median	3.6	2.3	
full range (min-max)	0.1 to 6	0 to 5.9	-

Time from last platinum to PM01183 treatment start			
Units: months			
median	6.9	5.8	
full range (min-max)	0.8 to 36.9	0.7 to 20.3	-
CA-125			
Units: IU/mL			
median	218.3	165	
full range (min-max)	10.3 to 4013	9.3 to 14408	-
TTP last regimen			
Units: months			
median	5.5	5.5	
full range (min-max)	0.2 to 24.8	1.1 to 11.1	-

End points

End points reporting groups

Reporting group title	PM01183

Reporting group description:

There were 52 patients treated with PM01183 in the Experimental Arm: 22 in an unrandomized first stage; 30 in the randomized second stage.
All patients in this arm received PM01183 7.0 mg FD on Day 1 i.v. as a 1-h infusion q3wk (three weeks = one treatment cycle).

Reporting group title	Topotecan

Reporting group description:

During the second stage, patients were randomized the Control Arm: Topotecan.
Topotecan was administered either as a standard (daily) or weekly regimen. The daily dose/regimen was based on approved topotecan dosing for relapsed ovarian cancer. The weekly regimen and dose/regimen was based on clinical practice reported in the literature.

Subject analysis set title	First stage - PM01183
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the first stage, patients were to be given PM01183 as a 1-hour infusion q3wk to explore the activity of PM01183 in this setting. If the minimum threshold of antitumor activity was met (at least two patients of the first 18 evaluable patients with confirmed tumor responses by any of the standard response assessment criteria)

Subject analysis set title	Second stage - PM01183
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the second stage, patients were to be randomized (stratified according to platinum-resistance or refractoriness), to an Experimental Arm PM01183 at the same dose and schedule as in the first stage.

Primary: Confirmed responses

End point title	Confirmed responses

End point description:

The overall response rate (ORR) was defined as the percentage of patients with a complete or partial response according to RECIST v.1.1 (or GCIG criteria in patients with disease not measurable per RECIST).
CR=Complete response
PR=Partial response
SD=Stable disease
PD=Progressive disease

End point type	Primary

End point timeframe:

Overall period

End point values	PM01183	Topotecan	First stage - PM01183	Second stage - PM01183
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	52	29	22	30
Units: number of subjects				
Complete response	1	0	0	1
Partial response	11	0	7	4
Stable disease	26	15	11	15
Progressive disease	13	14	4	9
Not evaluable	1	0	0	1

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	PM01183 v Topotecan
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	Fisher exact

Secondary: Response by RECIST

End point title	Response by RECIST

End point description:

The overall response rate (ORR) was defined as the percentage of patients with a complete or partial response according to RECIST v.1.1

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183	Topotecan	First stage - PM01183	Second stage - PM01183
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	43[1]	22[2]	17[3]	26[4]
Units: number of subjects				
CR+PR	10	0	5	5

Notes:

[1] - % patients (95%CI): 23.3% (11.8–38.6%)

[2] - % patients (95%CI): 0.0% (0.0-15.4%)

[3] - % patients (95%CI): 29.4% (10.3-56%)

[4] - % patients (95%CI): 19.2% (6.6-39.4%)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit

End point title	Clinical benefit

End point description:

Clinical benefit was defined as CR+PR+SD≥ 4 months.

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183	Topotecan	First stage - PM01183	Second stage - PM01183
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	52[5]	29[6]	22[7]	30[8]
Units: number of subjects				
CR+PR+SD≥ 4 months	22	4	10	12

Notes:

[5] - % patients (95%CI): 42.3% (28.7–56.8%)

[6] - % patients (95%CI): 13.8% (3.9–31.7%)

[7] - % patients (95%CI): 45.5% (24.4–67.8%)

[8] - % patients (95%CI): 40.0% (22.7–59.4%)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DR), defined as the time from the date when the response criteria (PR or CR, whichever was reached first) were fulfilled, to the first date when PD, recurrence or death was documented.

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183	Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[9]	0[10]		
Units: months				
median (confidence interval 95%)	4.6 (2.5 to 6.9)	(to)		

Notes:

[9] - PM01183 responders
Events: 9 (75.0%)

[10] - Topotecan responders

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS), defined as the time from the date of first infusion to the date of PD, death (of any cause), or last tumor evaluation.

Progression-free survival rate at six months (PFS6), defined as the Kaplan-Meier estimate of the percentage of patients who were alive and progression-free at six months after the first infusion.

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183	Topotecan	First stage - PM01183	Second stage - PM01183
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	52[11]	29[12]	22[13]	30[14]
Units: months				
median (confidence interval 95%)	4 (2.7 to 5.6)	2 (1.4 to 2.8)	4.5 (2.5 to 6.7)	3.9 (2.5 to 5.7)

Notes:

[11] - Events: 41 (78.8%)
PFS6 (95%CI): 32.4% (18.7–46.2%)
[12] - Events: 26 (89.7%)
PFS6 (95%CI): 7.4% (0–17.1%)
[13] - Events: 18 (81.8%)
PFS6 (95%CI): 34.5% (12.8–56.1%)
[14] - Events: 23 (76.7%)
PFS6 (95%CI): 31.0% (13.4–48.5%)

Attachments (see zip file)	PFS/Progression-free survival.bmp

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Topotecan v Second stage - PM01183
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067 [15]
Method	Logrank

Notes:

[15] - PM01183 second stage vs topotecan

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS), defined as the time from the date of first infusion to the date of death (of any cause) or last patient contact.
Overall survival rate at six months (OS6), defined as the Kaplan-Meier estimate of the percentage of patients who were alive at six months after the first infusion.
Overall survival rate at 12 months (OS12), defined as the Kaplan-Meier estimate of the percentage of patients who were alive at 12 months after the first infusion.

Fifteen patients in Control Arm subsequently crossed over and received PM01183

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183	Topotecan	First stage - PM01183	Second stage - PM01183
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	52[16]	29[17]	22[18]	30[19]
Units: months				
median (confidence interval 95%)	10.6 (9.5 to 18.1)	8.5 (3.3 to 15.6)	12.6 (9.2 to 22)	9.7 (7.7 to 19.3)

Notes:

[16] - Events: 43 (82.7%)
OS6 (95%CI): 84.5% (74.7–94.4%)
OS12 (95%CI): 47.2% (33.5–60.9%)
[17] - Events: 23 (79.3%)
OS6 (95%CI): 55.2% (37.1–73.3%)
OS12 (95%CI): 36.9% (19.1–54.8%)
[18] - Events: 20 (90.9%)
OS6 (95%CI): 86.4% (72.0–100%)
OS12 (95%CI): 50.0% (29.1–70.9%)
[19] - Events: 23 (76.7%)
OS6 (95%CI): 83.1% (69.5–96.6%)
OS12 (95%CI): 45.0% (26.9–63.1%)

Attachments (see zip file)	OS/Overall survival.bmp

Statistical analyses

Statistical analysis title	Differences between treatments
Comparison groups	Topotecan v Second stage - PM01183
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2871 [20]
Method	Logrank

Notes:

[20] - PM01183 second stage vs topotecan

Secondary: PM01183 Pharmacokinetic parameters

End point title	PM01183 Pharmacokinetic parameters

End point description:

The complete plasma concentration-time profiles of PM01183 were analyzed by standard non-compartmental methods (NCA).
AUC, area under the concentration-time curve from time zero to infinity

End point type	Secondary

End point timeframe:

Blood samples (4 mL) for the analysis of PM01183 were collected prior to, during, and after Day 1 of the first and second cycles in all available patients

End point values	First stage - PM01183			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: units				
median (full range (min-max))				
Cycle 1 at 7.0 mg dose: Cmax (µg/L)	145 (57.7 to 468)			
Cycle 1 at 7.0 mg dose: AUC (h*µg/L)	697.9 (346.5 to 2648)			
Cycle 2 at 7.0 mg dose: Cmax (µg/L)	131 (91.6 to 587)			
Cycle 2 at 7.0 mg dose: AUC (h*µg/L)	716 (387.1 to 2936)			
Cycle 2 at 5.5 mg dose: Cmax (µg/L)	181 (143 to 266)			
Cycle 2 at 5.5 mg dose: AUC (h*µg/L)	746.6 (733.7 to 1703)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Topotecan
Reporting group description:	
In the second-stage Control Arm, topotecan was administered as a 30-min i.v. infusion either in a dose range of 0.75–1.50 mg/m2 on Days 1 to 5 q3wk (standard regimen, referred to as 'daily') or 2.4–4.0 mg/m2 on Days 1, 8 and 15 every four weeks (q4wk) (weekly regimen) according to the Investigator's preference.	
Reporting group title	PM01183
Reporting group description:	
PM01183 was administered as a 7.0 mg flat dose (FD) 1-h intravenous (i.v.) infusion every three weeks (q3wk) in both stages.	

Serious adverse events	Topotecan	PM01183	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 29 (41.38%)	18 / 52 (34.62%)	
number of deaths (all causes)	23	43	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wound evisceration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 29 (10.34%)	8 / 52 (15.38%)	
occurrences causally related to treatment / all	3 / 3	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 29 (13.79%)	6 / 52 (11.54%)	
occurrences causally related to treatment / all	7 / 7	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 29 (3.45%)	5 / 52 (9.62%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 29 (6.90%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Proctalgia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 29 (6.90%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillosis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopnemonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Topotecan	PM01183	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)	51 / 52 (98.08%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 52 (0.00%)	
occurrences (all)	9	0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 29 (62.07%)	48 / 52 (92.31%)	
occurrences (all)	53	255	
Mucosal inflammation			

subjects affected / exposed	1 / 29 (3.45%)	4 / 52 (7.69%)	
occurrences (all)	2	5	
Oedema peripheral			
subjects affected / exposed	4 / 29 (13.79%)	4 / 52 (7.69%)	
occurrences (all)	13	19	
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	10 / 52 (19.23%)	
occurrences (all)	3	12	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 29 (13.79%)	9 / 52 (17.31%)	
occurrences (all)	8	22	
Cough			
subjects affected / exposed	0 / 29 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	9	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 29 (10.34%)	4 / 52 (7.69%)	
occurrences (all)	4	12	
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 52 (5.77%)	
occurrences (all)	1	4	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 29 (3.45%)	5 / 52 (9.62%)	
occurrences (all)	2	16	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 52 (1.92%)	
occurrences (all)	6	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 29 (3.45%)	4 / 52 (7.69%)	
occurrences (all)	3	9	
Headache			

subjects affected / exposed	2 / 29 (6.90%)	7 / 52 (13.46%)	
occurrences (all)	3	12	
Neurotoxicity			
subjects affected / exposed	2 / 29 (6.90%)	1 / 52 (1.92%)	
occurrences (all)	2	10	
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 29 (17.24%)	4 / 52 (7.69%)	
occurrences (all)	16	21	
Neuropathy peripheral			
subjects affected / exposed	0 / 29 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 29 (37.93%)	24 / 52 (46.15%)	
occurrences (all)	35	64	
Neutropenia			
subjects affected / exposed	9 / 29 (31.03%)	11 / 52 (21.15%)	
occurrences (all)	11	14	
Thrombocytopenia			
subjects affected / exposed	4 / 29 (13.79%)	7 / 52 (13.46%)	
occurrences (all)	9	9	
Febrile neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 29 (62.07%)	23 / 52 (44.23%)	
occurrences (all)	46	53	
Ascites			
subjects affected / exposed	5 / 29 (17.24%)	7 / 52 (13.46%)	
occurrences (all)	11	30	
Constipation			
subjects affected / exposed	14 / 29 (48.28%)	30 / 52 (57.69%)	
occurrences (all)	30	89	
Diarrhoea			

subjects affected / exposed	7 / 29 (24.14%)	7 / 52 (13.46%)	
occurrences (all)	12	9	
Dyspepsia			
subjects affected / exposed	2 / 29 (6.90%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Intestinal obstruction			
subjects affected / exposed	1 / 29 (3.45%)	3 / 52 (5.77%)	
occurrences (all)	1	5	
Nausea			
subjects affected / exposed	13 / 29 (44.83%)	36 / 52 (69.23%)	
occurrences (all)	22	127	
Vomiting			
subjects affected / exposed	12 / 29 (41.38%)	33 / 52 (63.46%)	
occurrences (all)	17	78	
Abdominal pain upper			
subjects affected / exposed	0 / 29 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 29 (17.24%)	7 / 52 (13.46%)	
occurrences (all)	20	18	
Dry skin			
subjects affected / exposed	3 / 29 (10.34%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	2 / 52 (3.85%)	
occurrences (all)	5	8	
Musculoskeletal pain			
subjects affected / exposed	2 / 29 (6.90%)	3 / 52 (5.77%)	
occurrences (all)	4	4	
Myalgia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 52 (5.77%)	
occurrences (all)	1	11	
Arthralgia			

subjects affected / exposed	0 / 29 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)	2 / 52 (3.85%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 29 (17.24%)	13 / 52 (25.00%)	
occurrences (all)	7	31	
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	3 / 52 (5.77%)	
occurrences (all)	2	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2012	The protocol amendment included the following changes: 1) Due to the global shortage of pegylated liposomal doxorubicin (PLD) which resulted in a lack of PLD supplies for clinical use worldwide, topotecan substituted PLD in the planned Control Arm. 2) Some data suggested that the weekly topotecan schedule was better tolerated and less myelotoxic than the standard schedule. Investigators were able to choose which topotecan schedule to administer to patients allocated to the Control Arm during the second stage of the study. 3) In order to improve patient safety in the Control Arm, the criteria for defining the starting dose of the daily topotecan regimen was slightly modified, the ECOG PS requirement was made stricter, and the extent of prior chemotherapy was taken into account to allocate the daily topotecan starting dose. 4) The exclusion criterion #1b was modified to clarify that patients with grade ≥ 3 ascites were not eligible. 5) Albumin level requirements at inclusion were changed to a minimum of 3.0 g/dL (inclusion criteria #8e).
04 December 2013	The protocol amendment included the following changes: • Planned end-of-study date was extended to 18 months after accrual of the last evaluable patient. • The follow-up assessments of patients showing documented disease progression or starting a new antitumor therapy were updated: every three months until the clinical cut-off, with the purpose of collecting information on survival. • A new secondary endpoint (overall survival rate at 12 months [OS12]) was included. • Exploratory analysis of Homologous Recombination Deficiency (HRD Assay) could be performed on patients responding to treatment, if considered relevant. • Polymorphisms and somatic mutations of genes involved in DNA repair mechanisms, or related to the mechanism of action of PM01183 or to the disease, could also be analyzed in tumor tissue, if relevant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported