



Clinical trial results:

A Randomized-Controlled Three-arm Phase II Study of Lurbinectedin (PM01183) Alone or In Combination with Gemcitabine and a control arm with Docetaxel as Second-Line Treatment in Unresectable Non-Small Cell Lung Cancer (NSCLC) Patients.

Summary

EudraCT number	2013-000548-25
Trial protocol	ES IT BE FR
Global end of trial date	24 November 2016

Results information

Result version number	v1 (current)
This version publication date	24 October 2018
First version publication date	24 October 2018

Trial information

Trial identification

Sponsor protocol code	PM1183-B-004-13
-----------------------	-----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Avenida de los Reyes, 1 Polígono Industrial "La Mina", Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharmamar, S.A, 34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharmamar, 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	13 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2016
Global end of trial reached?	Yes
Global end of trial date	24 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity as progression-free survival at four months (PFS4) of PM01183 alone or in combination with gemcitabine as second-line treatment in unresectable NSCLC patients, using single agent docetaxel as a reference in the control arm as current standard of care.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

All patients treated in PM01183-containing arms (Arms B or C) will receive standard antiemetic prophylaxis, according to American Society of Clinical Oncology (ASCO) guidelines before each treatment administration, as follows:

- Corticosteroids (i.v. dexamethasone or equivalent, at institutional standard antiemetic doses).
- Serotonin (5-HT₃) antagonists (8 mg i.v. ondansetron or equivalent).

If necessary, in addition to the above, 10 mg metoclopramide every eight hours could be administered orally, or the duration of treatment with 5-HT₃ antagonists and/or dexamethasone could be extended (depending on the Investigator's own criteria).

Prophylactic antiemetic medication for the docetaxel arm (Arm A) will follow institutional guidelines. In addition, these patients have to receive 8 mg oral dexamethasone every 12-hours starting the night before docetaxel administration, for a total of six consecutive doses.

Evidence for comparator: -

Actual start date of recruitment	11 September 2013
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	Spain: 32
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	69
EEA total number of subjects	67

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)	38
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

69 patients were enrolled between 11/09/2013 and 2/10/2015 at 13 centers. 68 patients were treated: 22 in Arm A, 21 in Arm B, and 25 in Arm C. The first dose of the first cycle was administered on 17/09/2013 and the last dose of the last cycle was administered on 3/11/2016. The last patient, last follow-up was on 26/11/2016

Pre-assignment

Screening details:

Voluntary written IC; Histologically/cytologically confirmed unresectable NSCLC; failed one prior line of CT-based therapy for unresectable disease; Age 18-75 years; ECOG PS ≤ 1; Adequate hematological, renal, metabolic and hepatic function; three weeks since the last prior therapy; Washout period for radiotherapy; Pregnancy/contraception.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Docetaxel 75 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk

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

Dosage and administration details:

Docetaxel 75 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk

Arm title	Arm B
------------------	-------

Arm description:

In the first protocol version, PM01183 7 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

After protocol amendment 3, PM01183 3.2 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

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

Dosage and administration details:

In the first protocol version, PM01183 7 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

After protocol amendment 3, PM01183 3.2 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

Arm title	Arm C
------------------	-------

Arm description:

Gemcitabine 800 mg/m², 30-min i.v. infusion, immediately followed by PM01183 3.0 mg Flat dose, 1-h

i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (in the first protocol version) or PM01183 1.6 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (after protocol amendment 3)

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

Dosage and administration details:

In the first protocol version, PM01183 3.0 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

After protocol amendment 3, PM01183 1.6 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

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

Dosage and administration details:

Gemcitabine 800 mg/m², 30-min i.v. infusion

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	22	22	25
Completed	0	0	0
Not completed	22	22	25
Treatment-unrelated AE	1	-	3
Physician decision	5	3	2
Consent withdrawn by subject	-	1	3
Treatment-related AE	2	-	4
No treated	-	1	-
Study termination	-	-	1
Treatment-related death	-	2	-
Non-treatmentrelated death	2	2	2
Progressive disease	12	13	10

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description: Docetaxel 75 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk	
Reporting group title	Arm B
Reporting group description: In the first protocol version, PM01183 7 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles After protocol amendment 3, PM01183 3.2 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles	
Reporting group title	Arm C
Reporting group description: Gemcitabine 800 mg/m ² , 30-min i.v. infusion, immediately followed by PM01183 3.0 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (in the first protocol version) or PM01183 1.6 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (after protocol amendment 3)	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	22	22	25
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	10	13
From 65-84 years	7	12	12
Age continuous			
Units: years			
median	61.5	65.0	64.0
full range (min-max)	49 to 72	46 to 74	41 to 75
Gender categorical			
Units: Subjects			
Female	5	5	9
Male	17	17	16
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	6	11	10
PS 1	16	11	15
Race			
Units: Subjects			
Caucasian	21	22	25
Unknown	1	0	0
Histology type			
Units: Subjects			
Non-squamous-cell	17	18	19
Squamous-cell	4	4	6
Not specified	1	0	0
Histology grade			
Units: Subjects			
Well differentiated	0	1	0
Moderately differentiated	2	5	1

Poorly differentiated	7	3	9
Unknown	13	13	15
Stage at diagnosis			
Units: Subjects			
Early	1	1	2
Locally advanced	4	7	4
Metastatic	15	14	18
Unknown	2	0	1
Stage at study entry			
Units: Subjects			
Locally advanced	1	0	2
Metastatic	21	22	23
Surgery			
Units: Subjects			
Yes	3	5	3
No	19	17	22
Radiotherapy			
Units: Subjects			
Yes	9	10	10
No	13	12	15
Prior chemotherapy			
Number of prior lines			
Units: Subjects			
1 line	19	21	23
2 lines	3	1	2
Best response to last prior platinum based chemotherapy			
NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; UK, unknown			
Units: Subjects			
PR	11	11	9
SD	5	8	10
PD	5	3	5
NA	1	0	0
UK	0	0	1
Weight			
Units: Kg			
median	70.5	74.0	77.0
full range (min-max)	45.0 to 90.8	39.0 to 124.0	40.0 to 136.0
BSA			
BSA, body surface area			
Units: m2			
median	1.8	1.9	1.9
full range (min-max)	1.4 to 2.1	1.4 to 2.3	1.3 to 2.5
Signs and symptoms per patient			
Units: Signs and symptoms			
median	1	1	1
full range (min-max)	0 to 4	0 to 4	0 to 5
Albumin			
Units: g/dL			
median	4.3	3.9	4.0
full range (min-max)	3.1 to 4.7	3.2 to 5.0	3.3 to 4.8
Alpha-1-acid glycoprotein			

Units: mg/dL median full range (min-max)	172 144 to 251	141 65 to 243	159 57 to 247
Time from first diagnosis to first infusion Units: months median full range (min-max)	8.0 2.4 to 48.0	11.4 3.3 to 42.7	9.2 1.9 to 109.3
Number of sites involved at baseline Units: sites median full range (min-max)	3 1 to 6	3 1 to 6	3 1 to 6
Platinum-free interval Units: months median full range (min-max)	3.5 1.0 to 16.3	5.6 0.7 to 36.8	3.9 1.0 to 20.8
PFS to last prior line			
PFS, progression-free survival			
Units: months median full range (min-max)	5.7 0.1 to 18.2	6.7 1.1 to 36.9	5.4 1.1 to 17.4

Reporting group values	Total		
Number of subjects	69		
Age categorical Units: Subjects			
Adults (18-64 years)	38		
From 65-84 years	31		
Age continuous Units: years median full range (min-max)	-		
Gender categorical Units: Subjects			
Female	19		
Male	50		
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	27		
PS 1	42		
Race Units: Subjects			
Caucasian	68		
Unknown	1		
Histology type Units: Subjects			
Non-squamous-cell	54		
Squamous-cell	14		
Not specified	1		
Histology grade Units: Subjects			

Well differentiated	1		
Moderately differentiated	8		
Poorly differentiated	19		
Unknown	41		
Stage at diagnosis			
Units: Subjects			
Early	4		
Locally advanced	15		
Metastatic	47		
Unknown	3		
Stage at study entry			
Units: Subjects			
Locally advanced	3		
Metastatic	66		
Surgery			
Units: Subjects			
Yes	11		
No	58		
Radiotherapy			
Units: Subjects			
Yes	29		
No	40		
Prior chemotherapy			
Number of prior lines			
Units: Subjects			
1 line	63		
2 lines	6		
Best response to last prior platinum based chemotherapy			
NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; UK, unknown			
Units: Subjects			
PR	31		
SD	23		
PD	13		
NA	1		
UK	1		
Weight			
Units: Kg			
median			
full range (min-max)	-		
BSA			
BSA, body surface area			
Units: m2			
median			
full range (min-max)	-		
Signs and symptoms per patient			
Units: Signs and symptoms			
median			
full range (min-max)	-		
Albumin			
Units: g/dL			
median			

full range (min-max)	-		
Alpha-1-acid glycoprotein			
Units: mg/dL			
median			
full range (min-max)	-		
Time from first diagnosis to first infusion			
Units: months			
median			
full range (min-max)	-		
Number of sites involved at baseline			
Units: sites			
median			
full range (min-max)	-		
Platinum-free interval			
Units: months			
median			
full range (min-max)	-		
PFS to last prior line			
PFS, progression-free survival			
Units: months			
median			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Docetaxel 75 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk	
Reporting group title	Arm B
Reporting group description: In the first protocol version, PM01183 7 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles After protocol amendment 3, PM01183 3.2 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles	
Reporting group title	Arm C
Reporting group description: Gemcitabine 800 mg/m ² , 30-min i.v. infusion, immediately followed by PM01183 3.0 mg Flat dose, 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (in the first protocol version) or PM01183 1.6 mg/m ² , 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles (after protocol amendment 3)	

Primary: Progression-free survival at four months

End point title	Progression-free survival at four months ^[1]
End point description: The primary analysis of efficacy was based on the percentage of patients who were alive and progression-free at 16 weeks (~4 months) after randomization.	
End point type	Primary
End point timeframe: 16 weeks (~4 months) after randomization	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The exact binomial estimator and its 95%CI was used.

A pre-planned Bayesian supportive analysis test comparing PFS4 was performed. The Bayes quadratic loss estimator following a noninformative prior distribution and their 95% credible region were:

-A: 29.2% 95%CI(13.2, 48.4)

-B: 19.0% 95%CI(5.7, 37.9)

-C: 28.0% 95%CI(12.6, 46.7)

The three 95% confidence intervals overlap when comparing the PFS4 Bayesian estimator, then statistically significant differences were not found in PFS4

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	19 ^[2]	23 ^[3]	
Units: percent				
number (confidence interval 95%)	27.3 (10.7 to 50.2)	15.8 (3.4 to 39.6)	26.1 (10.2 to 48.4)	

Notes:

[2] - 1 no treated, 1 no tumour assesment, 1 major protocol desviation

[3] - 2 no tumour assesment

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
End point description: Objective response per RECIST v.1.1 PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TF, treatment failure (defined as symptomatic deterioration or death due to progression or treatment discontinuation due to any treatment-related toxicity occurred before any appropriate tumor assessments had been performed).	
End point type	Secondary
End point timeframe: Overall period	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	19 ^[4]	23 ^[5]	
Units: subjects				
PR	2	0	4	
SD	10	7	11	
PD	8	8	6	
TF	2	4	2	

Notes:

[4] - 1 no treated, 1 no tumour assesment, 1 major protocol desviation

[5] - 2 no tumour assesment

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate

End point title	Response rate
End point description:	
End point type	Secondary
End point timeframe: Overall period	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	19 ^[6]	23 ^[7]	
Units: percent				
number (confidence interval 95%)	9.1 (1.1 to 29.2)	0 (0 to 17.6)	17.4 (5.0 to 38.8)	

Notes:

[6] - 1 no treated, 1 no tumour assesment, 1 major protocol desviation

[7] - 2 no tumour assesment

Statistical analyses

Secondary: Duration of Response

End point title	Duration of Response ^[8]
End point description:	
Duration of response (DR) was 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.	
999, Not applicable	
No patients with CR or PR to treatment as per the RECIST v.1.1 criteria were found in Arm B.	
End point type	Secondary
End point timeframe:	
Overall period	

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No patients with CR or PR to treatment as per the RECIST v.1.1 criteria were found in Arm B.

End point values	Arm A	Arm C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23 ^[9]		
Units: months				
median (confidence interval 95%)	1.2 (0.8 to 1.6)	6.1 (2.0 to 999)		

Notes:

[9] - 2 no tumour assesment

Statistical analyses

Statistical analysis title	Kaplan meier analysis and log rank test
Statistical analysis description:	
A statistically significant longer median DR was observed for Arm C compared to Arm A (6.1 months vs. 1.2 months; p=0.0177)	
Comparison groups	Arm C v Arm A
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0177
Method	Logrank

Secondary: Progression-free survival

End point title	Progression-free survival
End point description:	
PFS rate at six months (PFS6) was 18.2% (95% CI, 2.1–34.3%) in Arm A, 16.7% (95% CI, 0–33.9%) in Arm B, and 17.5% (95% CI, 0–35.2%) in Arm C.	
PFS, progression-free survival; PFS6, progression-free survival rate at six months.	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	19 ^[10]	23 ^[11]	
Units: months				
median (confidence interval 95%)	3.1 (1.8 to 4.0)	1.9 (1.5 to 3.0)	3.3 (1.9 to 5.7)	

Notes:

[10] - 1 no treated, 1 no tumour assesment, 1 major protocol desviation

[11] - 2 no tumour assesment

Statistical analyses

Statistical analysis title	Progression-free survival
Statistical analysis description:	
No statistically significant difference was detected among the three study arms in terms of median PFS	
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3873
Method	Logrank

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival at 1 year (OS12) was 38.4% (95% CI, 17.6–59.2%) in Arm A; 27.9% (95% CI, 7.1–48.6%) in Arm B; and 17.4% (95% CI, 1.9–32.9%) in Arm C 999, Not applicable	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	19 ^[12]	23 ^[13]	
Units: months				
median (confidence interval 95%)	9.4 (3.1 to 999)	5.5 (3.0 to 8.0)	7.2 (4.5 to 10.6)	

Notes:

[12] - 1 no treated, 1 no tumour assesment, 1 major protocol desviation

[13] - 2 no tumour assesment

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description:	
No statistically significant difference was detected among the three study arms in terms of median OS	
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3526
Method	Logrank

Secondary: Quality of Life

End point title	Quality of Life
End point description:	
The mean QoL scores self-reported by patients using the Lung Cancer Symptom Scale (LCSS) at baseline and after the start of the therapy in visits 3 or 6 (+/- 1 visit) and visit 9 for those patients in maintenance therapy. Higher LCSS scores indicate more severe problems. Total score was calculated as the mean of the total scores of all nine patient items 000 or 999, Not applicable	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	20	25	
Units: points				
arithmetic mean (confidence interval 95%)				
Baseline	27.2 (18.4 to 36.1)	36.4 (25.0 to 47.7)	38.1 (27.7 to 48.5)	
Cycle 3	29.5 (14.5 to 44.5)	32.2 (19.5 to 44.9)	36.4 (25.4 to 47.5)	
Cycle 6	24.3 (17.4 to 31.1)	55.4 (000 to 999)	35.4 (-11.7 to 82.5)	
Cycle 9	999 (999 to 999)	38.1 (-74.8 to 151.1)	999 (999 to 999)	

Statistical analyses

Statistical analysis title	Wilcoxon signed ranktest repeat analysis
Statistical analysis description:	
Changes in QoL scores over time were calculated and tested for statistical significance by means of Wilcoxon signed ranks test repeat-measure analyses of variance.	
Comparison groups	Arm A v Arm B v Arm C

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9026 ^[14]
Method	Wilcoxon signed ranks test repeat analys

Notes:

[14] - Arm A p-value=0.9026; Arm B p-value=0.9862; Arm C p-value=0.8057

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.0
--------------------	------

Reporting groups

Reporting group title	Arm A
-----------------------	-------

Reporting group description:

Docetaxel 75 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk

Reporting group title	Arm B
-----------------------	-------

Reporting group description:

PM01183 3.2 mg/m², 1-h i.v. infusion (at a fixed rate), on D1, q3wk, up to 6 cycles

Reporting group title	Arm C
-----------------------	-------

Reporting group description:

Gemcitabine 800 mg/m², 30-min i.v. infusion, immediately followed by PM01183 1.6 mg/m², 1-h i.v. infusion, both on D1 and D8, q3wk, up to 6 cycles

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)	9 / 21 (42.86%)	18 / 25 (72.00%)
number of deaths (all causes)	14	17	21
number of deaths resulting from adverse events	2	4	2
Vascular disorders			
Shock			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Death			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Asthenia/Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Oesophagobronchial fistula			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pulmonary oedema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	8 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 21 (14.29%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	3 / 25 (12.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	3 / 25 (12.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Necrotising fasciitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 21 (0.00%)	4 / 25 (16.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Staphylococcal sepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	20 / 21 (95.24%)	25 / 25 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	2 / 25 (8.00%)
occurrences (all)	0	6	3

Hypertension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	3 / 25 (12.00%) 3
Hypotension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 3
General disorders and administration site conditions			
Asthenia/Fatigue subjects affected / exposed occurrences (all)	16 / 22 (72.73%) 30	16 / 21 (76.19%) 32	17 / 25 (68.00%) 35
Influenza like illness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 21 (4.76%) 1	1 / 25 (4.00%) 1
Mucosal inflammation subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 5	2 / 21 (9.52%) 3	5 / 25 (20.00%) 7
Pyrexia subjects affected / exposed occurrences (all)	7 / 22 (31.82%) 10	5 / 21 (23.81%) 8	7 / 25 (28.00%) 14
Chest pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2	3 / 25 (12.00%) 3
General physical health deterioration subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Injection site reaction subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 21 (4.76%) 1	1 / 25 (4.00%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	8 / 22 (36.36%) 13	5 / 21 (23.81%) 7	4 / 25 (16.00%) 4
Dyspnoea			

subjects affected / exposed occurrences (all)	8 / 22 (36.36%) 11	5 / 21 (23.81%) 7	7 / 25 (28.00%) 9
Haemoptysis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 21 (0.00%) 0	1 / 25 (4.00%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	3 / 25 (12.00%) 4
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 21 (4.76%) 1	0 / 25 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2	2 / 25 (8.00%) 2
Investigations Platelet count decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 21 (9.52%) 4	3 / 25 (12.00%) 6
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	4 / 25 (16.00%) 5
Weight decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 21 (0.00%) 0	3 / 25 (12.00%) 3
Headache subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Neuropathy peripheral subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4	1 / 21 (4.76%) 1	2 / 25 (8.00%) 5
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 22 (13.64%)	7 / 21 (33.33%)	15 / 25 (60.00%)
occurrences (all)	4	11	29
Neutropenia			
subjects affected / exposed	4 / 22 (18.18%)	3 / 21 (14.29%)	13 / 25 (52.00%)
occurrences (all)	4	8	21
Thrombocytopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	4 / 25 (16.00%)
occurrences (all)	1	0	5
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 22 (13.64%)	5 / 21 (23.81%)	6 / 25 (24.00%)
occurrences (all)	3	6	7
Diarrhoea			
subjects affected / exposed	3 / 22 (13.64%)	3 / 21 (14.29%)	4 / 25 (16.00%)
occurrences (all)	5	4	10
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	6 / 21 (28.57%)	13 / 25 (52.00%)
occurrences (all)	2	7	23
Stomatitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	3 / 25 (12.00%)
occurrences (all)	1	0	4
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)	8 / 21 (38.10%)	6 / 25 (24.00%)
occurrences (all)	4	10	13
Abdominal distension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 21 (28.57%) 7	3 / 25 (12.00%) 4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
Rash			
subjects affected / exposed	3 / 22 (13.64%)	1 / 21 (4.76%)	1 / 25 (4.00%)
occurrences (all)	3	5	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	3 / 25 (12.00%)
occurrences (all)	2	0	3
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	3 / 21 (14.29%)	0 / 25 (0.00%)
occurrences (all)	2	4	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	2 / 25 (8.00%)
occurrences (all)	6	0	2
Pain in extremity			
subjects affected / exposed	1 / 22 (4.55%)	3 / 21 (14.29%)	3 / 25 (12.00%)
occurrences (all)	1	3	3
Muscle spasms			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	1 / 25 (4.00%)
occurrences (all)	1	1	1

Lung infection subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 21 (0.00%) 0	0 / 25 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	0 / 21 (0.00%) 0	1 / 25 (4.00%) 1
Folliculitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 21 (4.76%) 1	1 / 25 (4.00%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	10 / 21 (47.62%) 13	8 / 25 (32.00%) 10
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	3 / 21 (14.29%) 3	1 / 25 (4.00%) 1
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2	1 / 21 (4.76%) 1	1 / 25 (4.00%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2	0 / 25 (0.00%) 0
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 21 (4.76%) 1	1 / 25 (4.00%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2013	<p>The protocol amendment included the following main changes:</p> <ol style="list-style-type: none"> 1) Gene-expression profiling (GEP) was done in circulating tumor and invasive cell (CTIC)-enriched fractions purified from an additional blood sample collected from patients who consented to the PGx sub-study and used to determine a PGx model of PM01183 in NSCLC. 2) The restriction to include only patients with measurable disease was removed (inclusion criterion #5) and patients with non-measurable disease as defined by RECIST v 1.1 were allowed in the trial. 3) The exclusion criterion #7 was modified to clarify that patients who have previously received gemcitabine treatment were eligible.
02 October 2013	<p>The protocol amendment included the following main changes:</p> <ol style="list-style-type: none"> 1) The duration of the docetaxel infusion was changed from 30 minutes to one hour, in accordance with the drug's Summary of Product Characteristics. 2) The exclusion criterion #8 was modified to clarify that both women and men must agree to use a medically acceptable method of contraception (i.e., intrauterine device [IUD], oral contraceptive, subdermal implant, double barrier and/or complete abstinence [non-periodic]) throughout the treatment period and for 6 months after treatment discontinuation.
09 April 2015	<ol style="list-style-type: none"> 1) Due to data from a pooled analysis of phase II single-agent trials suggesting that grade 3/4 neutropenia and thrombocytopenia could be more frequent in patients with lower BSA values, the dose of PM01183 was adjusted according to BSA. In consequence, the PM01183 starting dose for the combination arm (Arm C) was changed to 1.6 mg/m². In addition, in order to improve tolerability, the singleagent PM01183 starting dose was reduced by 20% from the original PM01183 RD of 4.0 mg/m² (or 7 mg FD) found in the FiH trial (PM1183-A-001-08) (23). Therefore, the starting PM01183 dose in Arm B of this trial was changed to 3.2 mg/m². In addition, a clarification as to the capping of BSA-adjusted PM01183 dose at a BSA of 2.0 m² and the rounding of the dose to the first decimal point was included. Furthermore, the maintenance dose in arms B and C was changed from 5.0 mg FD to 2.6 mg/m² 2) EC #6.b #6.c were modified to clarify that all patients at study entry were required to have ALT and AST ≤ 3.0 x ULN and total bilirubin had to be within the normal range 3) IC #7 was modified to clarify the time lapse between completion of any prior radiotherapy and study entry. Therefore, patients who received a total dose of radiation ≥ 30Gy needed to complete a 4-week period between the end of radiotherapy and study entry, whereas those who received a total dose of radiation < 30Gy only needed to complete a 2-week period before entering the study 4) EC #1d was modified to clarify the diagnostic tests accepted for the diagnosis of chronic active hepatitis B and C 5) The secondary prophylactic treatment with G-CSF has been clarified for the different study arms 6) The restriction in the use of aprepitant was expanded to any directly-related compound 7) Planned end-of-study date was extended to 18 months after accrual of the last evaluable patient 8) The Appendix 5 of the protocol was updated with the most recent version of the Declaration of Helsinki

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported