Clinical trial results:
A Phase 2, Randomized Study of MLN0128 (a Dual TORC1/2 Inhibitor), MLN0128+MLN1117 (a PI3K Inhibitor), Weekly Paclitaxel, or the Combination of Weekly Paclitaxel and MLN0128 in Women With Advanced, Recurrent, or Persistent Endometrial Cancer

Summary

EudraCT number	2014-005394-37
Trial protocol	BE ES DE NL IT
Global end of trial date	23 October 2020

Results information

Result version number	v1
This version publication date	13 November 2021
First version publication date	13 November 2021

Trial information

Trial identification

Sponsor protocol code	C31004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02725268
WHO universal trial number (UTN)	U1111-1168-1824

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	Millennium Pharmaceuticals, Inc., 40 Lansdowne Street, Cambridge, United States, 02139
Public contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.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	23 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to determine if sapanisertib in combination with weekly paclitaxel improves progression-free survival (PFS) compared to weekly paclitaxel alone.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	United States: 59
Worldwide total number of subjects	241
EEA total number of subjects	118

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)	123
From 65 to 84 years	118
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 60 investigative sites in Australia, Belgium, Germany, Italy, Netherlands, Norway, Spain, United Kingdom, Canada and the United States from 01 April 2016 to 30 October 2020.

Pre-assignment

Screening details:

The female participants with a diagnosis of endometrial carcinoma were enrolled and randomized into 1:1:1:1 ratio to receive single agent paclitaxel, paclitaxel in combination with sapanisertib, single agent sapanisertib or sapanisertib in combination with MLN1117.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel 80 mg/m^2

Arm description:

Paclitaxel 80 milligrams per square meter (mg/m^2), IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 13.00 weeks).

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m^2 intravenous solution for injection.

Arm title	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg

Arm description:

Paclitaxel 80 mg/m^2, IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle along with sapanisertib 4 milligrams (mg), capsule, orally on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 20.14 and 18.50 weeks).

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel intravenous solution for injection.

Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Sapanisertib Capsules

Arm title	Sapanisertib 30 mg
Arm description:	
Sapanisertib 30 mg, capsule, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 6.14 weeks).	
Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Sapanisertib capsules	

Arm title	Sapanisertib 4 mg + MLN1117 200 mg
Arm description:	
Sapanisertib 4 mg, capsule, orally and MLN1117 200 mg, capsule, orally on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 7.43 weeks).	
Arm type	Experimental
Investigational medicinal product name	MLN1117
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
MLN1117 Capsules	
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Sapanisertib Capsules	

Number of subjects in period 1	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg
Started	90	90	41
Completed	18	20	3
Not completed	72	70	38
Adverse event, serious fatal	58	59	30
Consent Withdrawal by Subject	8	6	8
Other Reason: Site Terminated by Sponsor	-	1	-

Lost to follow-up	4	3	-
Other Reason: Reason not Specified	2	1	-

Number of subjects in period 1	Sapanisertib 4 mg + MLN1117 200 mg
Started	20
Completed	2
Not completed	18
Adverse event, serious fatal	16
Consent Withdrawal by Subject	1
Other Reason: Site Terminated by Sponsor	-
Lost to follow-up	1
Other Reason: Reason not Specified	-

Baseline characteristics

Reporting groups	
Reporting group title	Paclitaxel 80 mg/m^2
Reporting group description:	
Paclitaxel 80 milligrams per square meter (mg/m^2), IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 13.00 weeks).	
Reporting group title	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Reporting group description:	
Paclitaxel 80 mg/m^2, IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle along with sapanisertib 4 milligrams (mg), capsule, orally on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 20.14 and 18.50 weeks).	
Reporting group title	Sapanisertib 30 mg
Reporting group description:	
Sapanisertib 30 mg, capsule, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 6.14 weeks).	
Reporting group title	Sapanisertib 4 mg + MLN1117 200 mg
Reporting group description:	
Sapanisertib 4 mg, capsule, orally and MLN1117 200 mg, capsule, orally on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 7.43 weeks).	

Reporting group values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg
Number of subjects	90	90	41
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
Adolescents (12 - 17 years)	0	0	0
Adults (18 - 64 years)	44	45	21
From 65 - 84 years	46	45	20
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.7	64.4	64.0
standard deviation	± 7.14	± 7.63	± 6.99
Gender categorical Units: Subjects			
Male	0	0	0
Female	90	90	41
Race/ Ethnicity, Customized Units: Subjects			
White	77	78	37
Black or African American	3	4	0

Native Hawaiian or Other Pacific Islander	1	0	1
Asian	6	3	1
Other	0	2	2
Not Reported	3	3	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	5	3
Non-Hispanic and Latino	84	80	37
Not Reported	3	5	1
Region of Enrollment Units: Subjects			
Australia	5	6	3
Belgium	5	10	2
Germany	6	4	1
Italy	14	22	9
Netherlands	2	3	0
Norway	3	1	1
Spain	10	7	5
United Kingdom	9	4	6
Canada	15	10	2
United States	21	23	12
Height			
Number analyzed is the number of participants with data available for height at Baseline.			
Units: cm			
arithmetic mean	160.60	160.23	159.01
standard deviation	± 6.335	± 5.798	± 6.471
Weight			
Number analyzed is the number of participants with data available for weight at Baseline.			
Units: kg			
arithmetic mean	73.29	72.13	75.35
standard deviation	± 18.783	± 18.433	± 17.969

Reporting group values	Sapanisertib 4 mg + MLN1117 200 mg	Total	
Number of subjects	20	241	
Age categorical Units: Subjects			
In Utero	0	0	
Preterm newborn infants (gestional age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days - 23 months)	0	0	
Children (2 - 11 years)	0	0	
Adolescents (12 - 17 years)	0	0	
Adults (18 - 64 years)	13	123	
From 65 - 84 years	7	118	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.0		
standard deviation	± 10.20	-	

Gender categorical Units: Subjects			
Male	0	0	
Female	20	241	
Race/ Ethnicity, Customized Units: Subjects			
White	18	210	
Black or African American	1	8	
Native Hawaiian or Other Pacific Islander	0	2	
Asian	1	11	
Other	0	4	
Not Reported	0	6	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	15	
Non-Hispanic and Latino	15	216	
Not Reported	1	10	
Region of Enrollment Units: Subjects			
Australia	2	16	
Belgium	3	20	
Germany	0	11	
Italy	4	49	
Netherlands	0	5	
Norway	0	5	
Spain	6	28	
United Kingdom	2	21	
Canada	0	27	
United States	3	59	
Height			
Number analyzed is the number of participants with data available for height at Baseline.			
Units: cm			
arithmetic mean	162.67		
standard deviation	± 5.854	-	
Weight			
Number analyzed is the number of participants with data available for weight at Baseline.			
Units: kg			
arithmetic mean	71.81		
standard deviation	± 18.613	-	

End points

End points reporting groups

Reporting group title	Paclitaxel 80 mg/m^2
Reporting group description:	
Paclitaxel 80 milligrams per square meter (mg/m^2), IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 13.00 weeks).	
Reporting group title	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Reporting group description:	
Paclitaxel 80 mg/m^2, IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle along with sapanisertib 4 milligrams (mg), capsule, orally on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 20.14 and 18.50 weeks).	
Reporting group title	Sapanisertib 30 mg
Reporting group description:	
Sapanisertib 30 mg, capsule, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 6.14 weeks).	
Reporting group title	Sapanisertib 4 mg + MLN1117 200 mg
Reporting group description:	
Sapanisertib 4 mg, capsule, orally and MLN1117 200 mg, capsule, orally on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 7.43 weeks).	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS is defined as the time in months from the date of randomization to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST v1.1, PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. ITT population included all randomized participants. For a participants who had not progressed and was last known to be alive, PFS was censored at the last response assessment that is stable disease (SD) or better.	
End point type	Primary
End point timeframe:	
Up to approximately 30 months	

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	90	41	20
Units: months				
median (confidence interval 95%)	3.7 (2.3 to 4.5)	5.6 (3.8 to 6.2)	2.1 (1.9 to 3.5)	2.0 (1.5 to 3.3)

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for PFS

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.178 [2]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.12

Notes:

[1] - null

[2] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 2 for PFS

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.092 [4]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	2.86

Notes:

[3] - null

[4] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 3 for PFS

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.147 [6]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	4.49

Notes:

[5] - null

[6] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Secondary: Number of Participants who Experienced at Least One Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants who Experienced at Least One Treatment-emergent Adverse Event (TEAE)

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Safety population included all participant who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From the first dose of study drug through 30 days after the last dose of study drug (Up to approximately 54 months)

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	86	41	20
Units: participants	87	86	41	20

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time in months from the date of randomization to the date of death. ITT population included all randomized participants. Participants without documentation of death at the time of analysis were censored at the date last known to be alive.

End point type	Secondary

End point timeframe:
Up to approximately 54 months

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	90	41	20
Units: months				
median (confidence interval 95%)	12.7 (9.8 to 19.6)	13.8 (9.9 to 19.1)	12.5 (9.0 to 15.7)	11.1 (2.7 to 17.5)

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for OS
Statistical analysis description:	
The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.	
Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.968 [8]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.5

Notes:

[7] - null

[8] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 2 for OS
Statistical analysis description:	
The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.	
Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.145 [10]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.37

Notes:

[9] - null

[10] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 3 for OS

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.243 [12]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.73

Notes:

[11] - null

[12] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Secondary: Time to Tumor Progression (TTP)

End point title	Time to Tumor Progression (TTP)

End point description:

TTP is defined as the time in months from the date of randomization to the date of first documentation of progression. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. ITT population included all randomized participants . For a participants who had not progressed, TTP was censored at the last response assessment that is SD or better.

End point type	Secondary

End point timeframe:

Up to 30 months

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	90	41	20
Units: months				
median (confidence interval 95%)	3.7 (2.5 to 5.4)	5.7 (3.8 to 7.2)	2.3 (1.9 to 4.2)	2.2 (1.8 to 3.7)

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for TTP

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.17 [14]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.11

Notes:

[13] - null

[14] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 2 for TTP

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.224 [16]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.68

Notes:

[15] - null

[16] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Statistical analysis title	Statistical Analysis 3 for TTP

Statistical analysis description:

The hazard ratio was obtained using a stratified Cox proportional hazard model adjusted for histological subtype, lines of prior chemotherapy and prior taxane therapy. A hazard ratio of <1 was considered statistically significant.

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.244 [18]
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	3.96

Notes:

[17] - null

[18] - The p-value was obtained using stratified log-rank test with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants who achieved a best response of a complete response (CR) or partial response (PR). Per RECIST v1.1, CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. Safety population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 30 months

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	86	41	20
Units: percentage of participants				

number (not applicable)	18.4	24.4	4.9	0

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for ORR
Statistical analysis description:	
The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).	
Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	2.9

Notes:

[19] - null

Statistical analysis title	Statistical Analysis 2 for ORR
Statistical analysis description:	
The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).	
Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Odds ratio (OR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	1.14

Notes:

[20] - null

Statistical analysis title	Statistical Analysis 3 for ORR
Statistical analysis description:	
The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).	
Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[21]
Parameter estimate	Odds ratio (OR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[21] - null

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as the percentage of participants with CR or PR or SD (SD of any duration). Per RECIST v1.1, CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Safety population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 30 months

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	86	41	20
Units: percentage of participants				
number (not applicable)	57.5	80.2	34.1	35.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for CBR

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[22]
Parameter estimate	Odds ratio (OR)
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	5.96

Notes:

[22] - null

Statistical analysis title	Statistical Analysis 2 for CBR

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[23]
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.86

Notes:

[23] - null

Statistical analysis title	Statistical Analysis 3 for CBR

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[24]
Parameter estimate	Odds ratio (OR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.21

Notes:

[24] - null

Secondary: Clinical Benefit Rate (CBR) at Week 16 (CBR-16)

End point title	Clinical Benefit Rate (CBR) at Week 16 (CBR-16)

End point description:

CBR-16 is defined as the percentage of participants who achieved CR or PR of any duration or have SD with a duration of at least 16 weeks. Per RECIST v1.1, CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Safety population included participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 16

End point values	Paclitaxel 80 mg/m^2	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg	Sapanisertib 30 mg	Sapanisertib 4 mg + MLN1117 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	86	41	20
Units: percentage of participants				
number (not applicable)	36.8	51.2	17.1	5.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for CBR-16

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[25]
Parameter estimate	Odds ratio (OR)
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	7.67

Notes:

[25] - null

Statistical analysis title	Statistical Analysis 2 for CBR-16

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 30 mg

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[26]
Parameter estimate	Odds ratio (OR)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.51

Notes:

[26] - null

Statistical analysis title	Statistical Analysis 3 for CBR-16

Statistical analysis description:

The odds ratio and 95% confidence intervals were obtained using a stratified CMH model with histological subtype, lines of prior chemotherapy and prior taxane therapy (original stratification values).

Comparison groups	Paclitaxel 80 mg/m^2 v Sapanisertib 4 mg + MLN1117 200 mg
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[27]
Parameter estimate	Odds ratio (OR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.67

Notes:

[27] - null

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to the end of study (approximately up to 54 months)

Adverse event reporting additional description:

At each visit investigator had to document any occurrence of AEs and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of relation to study treatment. All-cause mortality:ITT population(n= 90,90,41,20). Serious and other(non-serious) AEs:Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Paclitaxel 80 mg/m^2

Reporting group description:

Paclitaxel 80 milligrams per square meter (mg/m^2), IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 13.00 weeks).

Reporting group title	Sapanisertib 4 mg + MLN1117 200 mg

Reporting group description:

Sapanisertib 4 mg, capsule, orally and MLN1117 200 mg, capsule, orally on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 7.43 weeks).

Reporting group title	Sapanisertib 30 mg

Reporting group description:

Sapanisertib 30 mg, capsule, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 6.14 weeks).

Reporting group title	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg

Reporting group description:

Paclitaxel 80 mg/m^2, IV, injection, weekly on Days 1, 8, and 15 of a 28-day cycle along with sapanisertib 4 milligrams (mg), capsule, orally on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle until disease progression, unacceptable toxicity, or withdraw consent (the median exposure was 20.14 and 18.50 weeks).

Serious adverse events	Paclitaxel 80 mg/m^2	Sapanisertib 4 mg + MLN1117 200 mg	Sapanisertib 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 87 (26.44%)	7 / 20 (35.00%)	14 / 41 (34.15%)
number of deaths (all causes)	58	16	30
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Malignant ascites	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Lymphoedema	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue	Additional description: null		

subjects affected / exposed	0 / 87 (0.00%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Pyrexia	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea exertional	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Hypoxia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	1 / 20 (5.00%)	0 / 41 (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

Electrocardiogram QT prolonged	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	1 / 20 (5.00%)	0 / 41 (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
Waist circumference increased	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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

Cardiac disorders			
Acute myocardial infarction	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Atrial tachycardia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anaemia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discoloured vomit	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Ileus	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction	Additional description: null		

subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	2 / 20 (10.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	2 / 20 (10.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	4 / 4	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Rash	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Urinary tract obstruction	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Hydronephrosis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
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	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Abdominal abscess	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Bacteraemia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	1 / 20 (5.00%)	0 / 41 (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
Kidney infection	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Pneumonia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis	Additional description: null		

subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Staphylococcal infection	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (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
Urosepsis	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal infection	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucose tolerance impaired	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	1 / 20 (5.00%)	0 / 41 (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
Hyperglycaemia	Additional description: null		

subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 86 (54.65%)		
number of deaths (all causes)	59		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant ascites	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension	Additional description: null		

subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoedema	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Malaise	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pain	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia	Additional description: null		

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Pulmonary embolism	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory failure	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood glucose increased	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Waist circumference increased	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Foot fracture	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract stoma complication	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial tachycardia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident	Additional description: null		

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia	Additional description: null		

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Discoloured vomit	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faecaloma	Additional description: null		

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus	Additional description: null		

subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Rash	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract obstruction	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cystitis	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney infection	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis	Additional description: null		

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal infection	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Glucose tolerance impaired	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Paclitaxel 80 mg/m^2	Sapanisertib 4 mg + MLN1117 200 mg	Sapanisertib 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 87 (97.70%)	20 / 20 (100.00%)	41 / 41 (100.00%)
Vascular disorders			
Deep vein thrombosis	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	3	1	0
Hypertension	Additional description: null		
subjects affected / exposed	9 / 87 (10.34%)	1 / 20 (5.00%)	2 / 41 (4.88%)
occurrences (all)	18	1	2
Hypotension	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia	Additional description: null		
subjects affected / exposed	7 / 87 (8.05%)	10 / 20 (50.00%)	9 / 41 (21.95%)
occurrences (all)	7	14	10
Chills	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Fatigue	Additional description: null		
subjects affected / exposed	39 / 87 (44.83%)	7 / 20 (35.00%)	18 / 41 (43.90%)
occurrences (all)	54	7	24
Oedema peripheral	Additional description: null		
subjects affected / exposed	18 / 87 (20.69%)	1 / 20 (5.00%)	2 / 41 (4.88%)
occurrences (all)	23	1	2
Peripheral swelling	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	2 / 20 (10.00%)	0 / 41 (0.00%)
occurrences (all)	6	2	0
Pyrexia	Additional description: null		
subjects affected / exposed	12 / 87 (13.79%)	4 / 20 (20.00%)	5 / 41 (12.20%)
occurrences (all)	18	6	7
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	7	0	0

Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: null		
subjects affected / exposed	21 / 87 (24.14%)	1 / 20 (5.00%)	8 / 41 (19.51%)
occurrences (all)	30	1	9
Dyspnoea	Additional description: null		
subjects affected / exposed	18 / 87 (20.69%)	3 / 20 (15.00%)	6 / 41 (14.63%)
occurrences (all)	20	3	7
Epistaxis	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	8	0	1
Oropharyngeal pain	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	0 / 20 (0.00%)	3 / 41 (7.32%)
occurrences (all)	3	0	3
Pulmonary embolism	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	0 / 20 (0.00%)	3 / 41 (7.32%)
occurrences (all)	3	0	3
Psychiatric disorders			
Anxiety	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	1 / 20 (5.00%)	3 / 41 (7.32%)
occurrences (all)	3	1	3
Depression	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	0 / 20 (0.00%)	5 / 41 (12.20%)
occurrences (all)	3	0	5
Insomnia	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences (all)	6	1	1
Investigations			
Alanine aminotransferase increased	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	6 / 20 (30.00%)	1 / 41 (2.44%)
occurrences (all)	5	9	2
Aspartate aminotransferase increased	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	6 / 20 (30.00%)	2 / 41 (4.88%)
occurrences (all)	3	8	3
Blood alkaline phosphatase increased	Additional description: null		
subjects affected / exposed	4 / 87 (4.60%)	0 / 20 (0.00%)	4 / 41 (9.76%)
occurrences (all)	4	0	5

Blood creatinine increased	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	4 / 20 (20.00%)	3 / 41 (7.32%)
occurrences (all)	5	4	6
Blood glucose increased	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	2 / 20 (10.00%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Gamma-glutamyltransferase increased	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	0 / 20 (0.00%)	5 / 41 (12.20%)
occurrences (all)	8	0	7
Neutrophil count decreased	Additional description: null		
subjects affected / exposed	8 / 87 (9.20%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	10	0	0
Platelet count decreased	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	2 / 20 (10.00%)	1 / 41 (2.44%)
occurrences (all)	2	2	1
Protein total decreased	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	1 / 20 (5.00%)	3 / 41 (7.32%)
occurrences (all)	1	1	3
Weight decreased	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	3 / 20 (15.00%)	7 / 41 (17.07%)
occurrences (all)	2	3	7
White blood cell count decreased	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	13	0	1
Cardiac disorders			
Tachycardia	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	3
Nervous system disorders			
Dizziness	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	2 / 20 (10.00%)	3 / 41 (7.32%)
occurrences (all)	3	2	4
Dysgeusia	Additional description: null		
subjects affected / exposed	10 / 87 (11.49%)	2 / 20 (10.00%)	6 / 41 (14.63%)
occurrences (all)	10	2	6
Headache	Additional description: null		

subjects affected / exposed	4 / 87 (4.60%)	1 / 20 (5.00%)	6 / 41 (14.63%)
occurrences (all)	6	1	6
Neuropathy peripheral	Additional description: null		
subjects affected / exposed	12 / 87 (13.79%)	0 / 20 (0.00%)	3 / 41 (7.32%)
occurrences (all)	23	0	3
Paraesthesia	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences (all)	7	1	1
Peripheral sensory neuropathy	Additional description: null		
subjects affected / exposed	7 / 87 (8.05%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	11	0	0
Taste disorder	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	2
Tremor	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	1 / 20 (5.00%)	3 / 41 (7.32%)
occurrences (all)	2	1	3
Blood and lymphatic system disorders			
Anaemia	Additional description: null		
subjects affected / exposed	32 / 87 (36.78%)	6 / 20 (30.00%)	5 / 41 (12.20%)
occurrences (all)	57	10	6
Leukopenia	Additional description: null		
subjects affected / exposed	8 / 87 (9.20%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	15	3	0
Neutropenia	Additional description: null		
subjects affected / exposed	10 / 87 (11.49%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences (all)	13	4	3
Ear and labyrinth disorders			
Vertigo	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	2 / 20 (10.00%)	0 / 41 (0.00%)
occurrences (all)	2	4	0
Gastrointestinal disorders			
Abdominal distension	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	5	0	2
Abdominal pain	Additional description: null		

subjects affected / exposed	13 / 87 (14.94%)	4 / 20 (20.00%)	6 / 41 (14.63%)
occurrences (all)	16	6	10
Abdominal pain lower	Additional description: null		
subjects affected / exposed	4 / 87 (4.60%)	3 / 20 (15.00%)	0 / 41 (0.00%)
occurrences (all)	5	3	0
Abdominal pain upper	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	4 / 20 (20.00%)	4 / 41 (9.76%)
occurrences (all)	7	5	5
Constipation	Additional description: null		
subjects affected / exposed	25 / 87 (28.74%)	5 / 20 (25.00%)	14 / 41 (34.15%)
occurrences (all)	33	5	15
Diarrhoea	Additional description: null		
subjects affected / exposed	31 / 87 (35.63%)	13 / 20 (65.00%)	15 / 41 (36.59%)
occurrences (all)	49	16	24
Dry mouth	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	2 / 20 (10.00%)	2 / 41 (4.88%)
occurrences (all)	2	2	2
Dyspepsia	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	1 / 20 (5.00%)	3 / 41 (7.32%)
occurrences (all)	5	1	3
Gastrooesophageal reflux disease	Additional description: null		
subjects affected / exposed	4 / 87 (4.60%)	3 / 20 (15.00%)	3 / 41 (7.32%)
occurrences (all)	5	3	3
Haemorrhoids	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	5	0	1
Nausea	Additional description: null		
subjects affected / exposed	29 / 87 (33.33%)	16 / 20 (80.00%)	30 / 41 (73.17%)
occurrences (all)	44	23	64
Stomatitis	Additional description: null		
subjects affected / exposed	4 / 87 (4.60%)	2 / 20 (10.00%)	10 / 41 (24.39%)
occurrences (all)	5	2	11
Vomiting	Additional description: null		
subjects affected / exposed	20 / 87 (22.99%)	15 / 20 (75.00%)	31 / 41 (75.61%)
occurrences (all)	38	30	62
Skin and subcutaneous tissue disorders			

Alopecia	Additional description: null		
subjects affected / exposed	31 / 87 (35.63%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	37	0	1
Dry skin	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	6	1	0
Pruritus	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	1 / 20 (5.00%)	6 / 41 (14.63%)
occurrences (all)	3	1	7
Rash	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	4 / 41 (9.76%)
occurrences (all)	7	0	5
Rash maculo-papular	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	6	0	2
Renal and urinary disorders			
Dysuria	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	5	1	0
Haematuria	Additional description: null		
subjects affected / exposed	7 / 87 (8.05%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	9	0	0
Proteinuria	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: null		
subjects affected / exposed	11 / 87 (12.64%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	14	0	0
Back pain	Additional description: null		
subjects affected / exposed	14 / 87 (16.09%)	3 / 20 (15.00%)	3 / 41 (7.32%)
occurrences (all)	16	3	3
Groin pain	Additional description: null		
subjects affected / exposed	0 / 87 (0.00%)	2 / 20 (10.00%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Muscular weakness	Additional description: null		

subjects affected / exposed	4 / 87 (4.60%)	1 / 20 (5.00%)	0 / 41 (0.00%)
occurrences (all)	5	1	0
Myalgia	Additional description: null		
subjects affected / exposed	12 / 87 (13.79%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences (all)	18	1	1
Pain in extremity	Additional description: null		
subjects affected / exposed	7 / 87 (8.05%)	1 / 20 (5.00%)	1 / 41 (2.44%)
occurrences (all)	7	1	1
Infections and infestations			
Nasopharyngitis	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	0 / 20 (0.00%)	2 / 41 (4.88%)
occurrences (all)	3	0	2
Sinusitis	Additional description: null		
subjects affected / exposed	5 / 87 (5.75%)	0 / 20 (0.00%)	0 / 41 (0.00%)
occurrences (all)	7	0	0
Upper respiratory tract infection	Additional description: null		
subjects affected / exposed	7 / 87 (8.05%)	0 / 20 (0.00%)	1 / 41 (2.44%)
occurrences (all)	7	0	1
Urinary tract infection	Additional description: null		
subjects affected / exposed	9 / 87 (10.34%)	3 / 20 (15.00%)	6 / 41 (14.63%)
occurrences (all)	13	3	6
Metabolism and nutrition disorders			
Decreased appetite	Additional description: null		
subjects affected / exposed	16 / 87 (18.39%)	8 / 20 (40.00%)	20 / 41 (48.78%)
occurrences (all)	25	11	27
Dehydration	Additional description: null		
subjects affected / exposed	1 / 87 (1.15%)	2 / 20 (10.00%)	6 / 41 (14.63%)
occurrences (all)	1	7	7
Hyperglycaemia	Additional description: null		
subjects affected / exposed	8 / 87 (9.20%)	5 / 20 (25.00%)	15 / 41 (36.59%)
occurrences (all)	12	7	34
Hypoalbuminaemia	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	1 / 20 (5.00%)	4 / 41 (9.76%)
occurrences (all)	6	2	5
Hypocalcaemia	Additional description: null		

subjects affected / exposed	2 / 87 (2.30%)	2 / 20 (10.00%)	1 / 41 (2.44%)
occurrences (all)	6	4	2
Hypokalaemia	Additional description: null		
subjects affected / exposed	6 / 87 (6.90%)	0 / 20 (0.00%)	3 / 41 (7.32%)
occurrences (all)	11	0	4
Hypomagnesaemia	Additional description: null		
subjects affected / exposed	11 / 87 (12.64%)	1 / 20 (5.00%)	7 / 41 (17.07%)
occurrences (all)	29	1	10
Hyponatraemia	Additional description: null		
subjects affected / exposed	3 / 87 (3.45%)	2 / 20 (10.00%)	4 / 41 (9.76%)
occurrences (all)	6	2	6
Hypophosphataemia	Additional description: null		
subjects affected / exposed	2 / 87 (2.30%)	1 / 20 (5.00%)	2 / 41 (4.88%)
occurrences (all)	4	2	2

Non-serious adverse events	Paclitaxel 80 mg/m^2 + Sapanisertib 4 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 86 (100.00%)		
Vascular disorders			
Deep vein thrombosis	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	5		
Hypertension	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	5		
Hypotension	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia	Additional description: null		
subjects affected / exposed	26 / 86 (30.23%)		
occurrences (all)	39		
Chills	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	7		
Fatigue	Additional description: null		

subjects affected / exposed	40 / 86 (46.51%)		
occurrences (all)	65		
Oedema peripheral	Additional description: null		
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	13		
Peripheral swelling	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	5		
Pyrexia	Additional description: null		
subjects affected / exposed	13 / 86 (15.12%)		
occurrences (all)	20		
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: null		
subjects affected / exposed	4 / 86 (4.65%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: null		
subjects affected / exposed	19 / 86 (22.09%)		
occurrences (all)	29		
Dyspnoea	Additional description: null		
subjects affected / exposed	25 / 86 (29.07%)		
occurrences (all)	35		
Epistaxis	Additional description: null		
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	13		
Oropharyngeal pain	Additional description: null		
subjects affected / exposed	4 / 86 (4.65%)		
occurrences (all)	5		
Pulmonary embolism	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	9		
Psychiatric disorders			
Anxiety	Additional description: null		
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	7		
Depression	Additional description: null		

subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Insomnia	Additional description: null		
subjects affected / exposed	17 / 86 (19.77%)		
occurrences (all)	17		
Investigations			
Alanine aminotransferase increased	Additional description: null		
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	7		
Aspartate aminotransferase increased	Additional description: null		
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	8		
Blood alkaline phosphatase increased	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	8		
Blood creatinine increased	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Blood glucose increased	Additional description: null		
subjects affected / exposed	0 / 86 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	15		
Neutrophil count decreased	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	22		
Platelet count decreased	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Protein total decreased	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Weight decreased	Additional description: null		

subjects affected / exposed	17 / 86 (19.77%)		
occurrences (all)	20		
White blood cell count decreased	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	20		
Cardiac disorders			
Tachycardia	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Nervous system disorders			
Dizziness	Additional description: null		
subjects affected / exposed	14 / 86 (16.28%)		
occurrences (all)	17		
Dysgeusia	Additional description: null		
subjects affected / exposed	15 / 86 (17.44%)		
occurrences (all)	16		
Headache	Additional description: null		
subjects affected / exposed	13 / 86 (15.12%)		
occurrences (all)	15		
Neuropathy peripheral	Additional description: null		
subjects affected / exposed	22 / 86 (25.58%)		
occurrences (all)	32		
Paraesthesia	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	12		
Peripheral sensory neuropathy	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	15		
Taste disorder	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Tremor	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	6		
Blood and lymphatic system disorders			

Anaemia	Additional description: null		
subjects affected / exposed	48 / 86 (55.81%)		
occurrences (all)	93		
Leukopenia	Additional description: null		
subjects affected / exposed	12 / 86 (13.95%)		
occurrences (all)	19		
Neutropenia	Additional description: null		
subjects affected / exposed	19 / 86 (22.09%)		
occurrences (all)	42		
Ear and labyrinth disorders			
Vertigo	Additional description: null		
subjects affected / exposed	4 / 86 (4.65%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal distension	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	11		
Abdominal pain	Additional description: null		
subjects affected / exposed	22 / 86 (25.58%)		
occurrences (all)	25		
Abdominal pain lower	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	5		
Abdominal pain upper	Additional description: null		
subjects affected / exposed	13 / 86 (15.12%)		
occurrences (all)	16		
Constipation	Additional description: null		
subjects affected / exposed	20 / 86 (23.26%)		
occurrences (all)	33		
Diarrhoea	Additional description: null		
subjects affected / exposed	48 / 86 (55.81%)		
occurrences (all)	122		
Dry mouth	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	10		
Dyspepsia	Additional description: null		

subjects affected / exposed	13 / 86 (15.12%)		
occurrences (all)	14		
Gastrooesophageal reflux disease	Additional description: null		
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	11		
Haemorrhoids	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Nausea	Additional description: null		
subjects affected / exposed	53 / 86 (61.63%)		
occurrences (all)	83		
Stomatitis	Additional description: null		
subjects affected / exposed	22 / 86 (25.58%)		
occurrences (all)	34		
Vomiting	Additional description: null		
subjects affected / exposed	24 / 86 (27.91%)		
occurrences (all)	43		
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: null		
subjects affected / exposed	27 / 86 (31.40%)		
occurrences (all)	30		
Dry skin	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	8		
Pruritus	Additional description: null		
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	16		
Rash	Additional description: null		
subjects affected / exposed	17 / 86 (19.77%)		
occurrences (all)	27		
Rash maculo-papular	Additional description: null		
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Renal and urinary disorders			
Dysuria	Additional description: null		

subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	6		
Haematuria	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	10		
Proteinuria	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: null		
subjects affected / exposed	22 / 86 (25.58%)		
occurrences (all)	29		
Back pain	Additional description: null		
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	18		
Groin pain	Additional description: null		
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Muscular weakness	Additional description: null		
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	9		
Myalgia	Additional description: null		
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	14		
Pain in extremity	Additional description: null		
subjects affected / exposed	16 / 86 (18.60%)		
occurrences (all)	21		
Infections and infestations			
Nasopharyngitis	Additional description: null		
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	7		
Sinusitis	Additional description: null		
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	4		
Upper respiratory tract infection	Additional description: null		

subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Urinary tract infection	Additional description: null		
subjects affected / exposed	19 / 86 (22.09%)		
occurrences (all)	24		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: null		
subjects affected / exposed	33 / 86 (38.37%)		
occurrences (all)	45		
Dehydration	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	13		
Hyperglycaemia	Additional description: null		
subjects affected / exposed	17 / 86 (19.77%)		
occurrences (all)	30		
Hypoalbuminaemia	Additional description: null		
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	13		
Hypocalcaemia	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Hypokalaemia	Additional description: null		
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	18		
Hypomagnesaemia	Additional description: null		
subjects affected / exposed	19 / 86 (22.09%)		
occurrences (all)	25		
Hyponatraemia	Additional description: null		
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	8		
Hypophosphataemia	Additional description: null		
subjects affected / exposed	12 / 86 (13.95%)		
occurrences (all)	28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2016	The primary purpose of this amendment was to revise dosing regimens for sapanisertib, Added EudraCT number and Millennium corporate identification to Title page. Updated study overview diagram, schedule of events section. Added alternative names for sapanisertib and MLN1117. Decreased the dose of sapanisertib in Arms B and D from 8 mg to 4 mg. Added the combination of sapanisertib + MLN1117 for the investigator to consider when assessing whether AE is possibly related to study drug. Revised maximum dose reduction from 2 to 3 for sapanisertib. Revised paclitaxel, sapanisertib dose reduction guidelines. Added magnetic resonance imaging (MRI) as an optional method of disease assessment Clarified that PK samples was to be collected from participants in Arm B, C, and D only. Added description suspected expected SAEs reporting. Updated Product Complaint contact information.
19 May 2016	The primary purpose of this amendment was to revise the study population to exclude participants with a known severe hypersensitivity reaction to prior paclitaxel exposure, active hepatitis B and hepatitis C in D infections and were lactating and breastfeeding to have a positive serum pregnancy test. Added an exclusion criterion regarding history of severe hypersensitivity reaction to paclitaxel.
17 April 2017	The primary purpose of this amendment was to update the dosing conditions for the subjects receiving weekly sapanisertib in Arm C, to update the pharmacokinetic (PK) sampling schedule to reflect the dosing change in Arm C, to clarify the procedure and/or timing for collection and clinical laboratory evaluations, to clarify the sapanisertib and paclitaxel dosing instructions, to update the window for obtaining informed consent and to update the procedure for reporting drug exposure during pregnancy with birth events. Added a PK sample collection at 3 to 6 hours postdose on Cycle 1 Day 1 for participants receiving weekly sapanisertib in Arm C. Replaced references relating to QD or QD5D dosing with appropriate dosing instructions. Clarified that informed consent may be signed more than 28 days before Cycle 1 Day 1.
25 September 2017	The primary purpose of this amendment was to update those sections affected by nonclinical data for sapanisertib metabolism by specific cytochrome P (CYP) isoforms. Removed the exclusion criterion relating to treatment with strong CYP inhibitors or inducers. Updated the list of concomitant medications prohibited during the study. Updated the description of potential drug-drug interactions in Arm D. Updated the list of CYP inhibitors or inducers. Removed dietary restrictions related to CYP inhibitors and inducers.
22 January 2018	The primary purpose of this amendment was to update the sample size of the study to reflect changes in study design and the closure of enrollment into Arms C and D. Update the Global Clinical Lead of the study. Added the sensitivity analysis of efficacy endpoints may be performed.
01 March 2020	The primary purpose of this amendment was to remove in-home glucose monitoring., long-term follow up (PFS follow up and/or OS follow up) for participants after end of treatment. Update the Global Clinical Lead of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported