



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/m²), 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/m² intravenous solution for injection.

| | |
|------------------|---|
| Arm title | Paclitaxel 80 mg/m ² + Sapanisertib 4 mg |
|------------------|---|

Arm description:

Paclitaxel 80 mg/m², 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 (gestational 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/m²), 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/m², 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 | | | | |
| | 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 |
| 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 | | | | |
| | 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 |
| 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 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 1 / 87 (1.15%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 1 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations Blood glucose increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 87 (0.00%) | 1 / 20 (5.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 1 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------------------|----------------|----------------|
| Electrocardiogram QT prolonged subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 1 / 20 (5.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 1 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Waist circumference increased subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications Foot fracture | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose subjects affected / exposed | Additional description: null | | |
| | 0 / 87 (0.00%) | 0 / 20 (0.00%) | 1 / 41 (2.44%) |
| | 0 / 0 | 0 / 0 | 0 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract stoma complication subjects affected / exposed | Additional description: null | | |
| | 1 / 87 (1.15%) | 0 / 20 (0.00%) | 0 / 41 (0.00%) |
| | 0 / 1 | 0 / 0 | 0 / 0 |
| | 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 | Additional description: null | | |
| 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 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 3 / 86 (3.49%) | | |
| | 0 / 3 | | |
| | 0 / 0 | | |
| Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 2 / 86 (2.33%) | | |
| | 0 / 2 | | |
| | 0 / 0 | | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 1 / 86 (1.16%) | | |
| | 0 / 1 | | |
| | 0 / 0 | | |
| Investigations Blood glucose increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 86 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 1 / 86 (1.16%) | | |
| | 0 / 1 | | |
| | 0 / 0 | | |
| Platelet count decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 1 / 86 (1.16%) | | |
| | 0 / 1 | | |
| | 0 / 0 | | |
| Transaminases increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 0 / 86 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Waist circumference increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: null | | |
| | 1 / 86 (1.16%) | | |
| | 0 / 3 | | |
| | 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 | |
| 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 | |
| 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 subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 3 / 87 (3.45%) 5 | 4 / 20 (20.00%) 4 | 3 / 41 (7.32%) 6 |
| Blood glucose increased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 0 / 87 (0.00%) 0 | 2 / 20 (10.00%) 3 | 0 / 41 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 6 / 87 (6.90%) 8 | 0 / 20 (0.00%) 0 | 5 / 41 (12.20%) 7 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 8 / 87 (9.20%) 10 | 0 / 20 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Platelet count decreased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 2 / 87 (2.30%) 2 | 2 / 20 (10.00%) 2 | 1 / 41 (2.44%) 1 |
| Protein total decreased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 1 / 87 (1.15%) 1 | 1 / 20 (5.00%) 1 | 3 / 41 (7.32%) 3 |
| Weight decreased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 2 / 87 (2.30%) 2 | 3 / 20 (15.00%) 3 | 7 / 41 (17.07%) 7 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 5 / 87 (5.75%) 13 | 0 / 20 (0.00%) 0 | 1 / 41 (2.44%) 1 |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 1 / 87 (1.15%) 1 | 0 / 20 (0.00%) 0 | 3 / 41 (7.32%) 3 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache | Additional description: null | | |
| | 3 / 87 (3.45%) 3 | 2 / 20 (10.00%) 2 | 3 / 41 (7.32%) 4 |
| | Additional description: null | | |
| | 10 / 87 (11.49%) 10 | 2 / 20 (10.00%) 2 | 6 / 41 (14.63%) 6 |
| | 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 subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 31 / 87 (35.63%) 37 | 0 / 20 (0.00%) 0 | 1 / 41 (2.44%) 1 |
| Dry skin subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 6 / 87 (6.90%) 6 | 1 / 20 (5.00%) 1 | 0 / 41 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 3 / 87 (3.45%) 3 | 1 / 20 (5.00%) 1 | 6 / 41 (14.63%) 7 |
| Rash subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 5 / 87 (5.75%) 7 | 0 / 20 (0.00%) 0 | 4 / 41 (9.76%) 5 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 5 / 87 (5.75%) 6 | 0 / 20 (0.00%) 0 | 1 / 41 (2.44%) 2 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) | | | |
| | Additional description: null | | |
| | 5 / 87 (5.75%) 5 | 1 / 20 (5.00%) 1 | 0 / 41 (0.00%) 0 |
| | Additional description: null | | |
| | 7 / 87 (8.05%) 9 | 0 / 20 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| | Additional description: null | | |
| | 1 / 87 (1.15%) 4 | 0 / 20 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Groin pain subjects affected / exposed occurrences (all) Muscular weakness | | | |
| | Additional description: null | | |
| | 11 / 87 (12.64%) 14 | 0 / 20 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| | Additional description: null | | |
| | 14 / 87 (16.09%) 16 | 3 / 20 (15.00%) 3 | 3 / 41 (7.32%) 3 |
| | Additional description: null | | |
| | 0 / 87 (0.00%) 0 | 2 / 20 (10.00%) 2 | 0 / 41 (0.00%) 0 |
| | 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 subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 48 / 86 (55.81%) | | |
| | 93 | | |
| Leukopenia subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 12 / 86 (13.95%) | | |
| | 19 | | |
| Neutropenia subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 19 / 86 (22.09%) | | |
| | 42 | | |
| | | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | Additional description: null | | |
| | 4 / 86 (4.65%) | | |
| | 7 | | |
| | | | |
| Gastrointestinal disorders | Additional description: null | | |
| | 6 / 86 (6.98%) | | |
| | 11 | | |
| | Additional description: null | | |
| | 22 / 86 (25.58%) | | |
| | 25 | | |
| | Additional description: null | | |
| | 3 / 86 (3.49%) | | |
| | 5 | | |
| | Additional description: null | | |
| | 13 / 86 (15.12%) | | |
| | 16 | | |
| | Additional description: null | | |
| | 20 / 86 (23.26%) | | |
| | 33 | | |
| | Additional description: null | | |
| | 48 / 86 (55.81%) | | |
| | 122 | | |
| | Additional description: null | | |
| | 8 / 86 (9.30%) | | |
| | 10 | | |
| | 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 | Additional description: null | | |
| 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 | Additional description: null | | |
| 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