# Clinical trial results:
# A Phase 2 Trial of MLN0264 in Previously Treated Patients With Metastatic or Recurrent Adenocarcinoma of the Stomach or Gastroesophageal Junction Expressing Guanylyl Cyclase C (GCC)

## Summary

| | |
|---|---|
| EudraCT number | 2014-000804-88 |
| Trial protocol | IT GB ES BE |
| Global end of trial date | 15 January 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 31 January 2017 |
| First version publication date | 31 January 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | C26002 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02202759 |
| WHO universal trial number (UTN) | U1111-1155-9023 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Millennium Pharmaceuticals, Inc. |
| Sponsor organisation address | 40 Landsdowne Street, Cambridge, MA, United States, 02139 |
| Public contact | Medical Director, Takeda, +1 877-825-3327, |
| Scientific contact | Medical 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 | 15 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 January 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy, safety and tolerability of MLN0264 in patients with recurrent or metastatic guanylyl cyclase C (GCC)-positive adenocarcinoma of the stomach or gastroesophageal junction.

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 | 04 August 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | United States: 22 |
| Worldwide total number of subjects | 38 |
| EEA total number of subjects | 16 |

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) | 15 |
| From 65 to 84 years | 23 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 24 investigative sites in Belgium, Spain, United Kingdom and the United States from 04 August 2014 to 15 January 2016.

### Pre-assignment

Screening details:

Participants with a diagnosis of metastatic or recurrent adenocarcinoma of the stomach or gastroesophageal junction expressing Guanylyl Cyclase C (GCC) were enrolled in 1 treatment group, MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MLN0264 1.8 mg/kg (GCC Low) |

Arm description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Low (combined H-score 10-59). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MLN0264 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle

| | |
|---|---|
| **Arm title** | MLN0264 1.8 mg/kg (GCC Intermediate) |

Arm description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 9 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score 60-119). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MLN0264 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle

| **Arm title** | MLN0264 1.8 mg/kg (GCC High) |
|---|---|

Arm description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 8 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score >120). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | MLN0264 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection/infusion |
| Routes of administration | Intramuscular and intravenous use |

Dosage and administration details:

1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle

| **Number of subjects in period 1** | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) |
|---|---|---|---|
| Started | 9 | 15 | 14 |
| Completed | 0 | 0 | 0 |
| Not completed | 9 | 15 | 14 |
| Consent withdrawn by subject | 2 | 1 | 1 |
| Study Terminated by Sponsor | 3 | 3 | 3 |
| Reason not Specified | 4 | 11 | 10 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | MLN0264 1.8 mg/kg (GCC Low) |

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Low (combined H-score 10-59). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Reporting group title | MLN0264 1.8 mg/kg (GCC Intermediate) |
|---|---|

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 9 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score 60-119). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Reporting group title | MLN0264 1.8 mg/kg (GCC High) |
|---|---|

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 8 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score >120). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Reporting group values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) |
|---|---|---|---|
| Number of subjects | 9 | 15 | 14 |
| Age categorical<br>Units: Subjects | | | |
| 31 to 81 years | 9 | 15 | 14 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 60.1 | 62.9 | 62.9 |
| standard deviation | ± 7.7 | ± 12.78 | ± 7.86 |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 1 | 5 | 1 |
| Male | 8 | 10 | 13 |
| Height<br>Units: cm | | | |
| arithmetic mean | 169.7 | 167.8 | 171.1 |
| standard deviation | ± 7.49 | ± 9.85 | ± 9.38 |
| Weight<br>Units: kg | | | |
| arithmetic mean | 71.51 | 71.67 | 72.75 |
| standard deviation | ± 11.25 | ± 17.06 | ± 12.59 |
| Body Surface Area | | | |

| | | | |
|---|---|---|---|
| Units: m^2 | | | |
| arithmetic mean | 1.83 | 1.81 | 1.85 |
| standard deviation | ± 0.168 | ± 0.252 | ± 0.201 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 38 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| 31 to 81 years | 38 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Female | 7 | | |
| Male | 31 | | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Body Surface Area | | | |
| Units: m^2 | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | MLN0264 1.8 mg/kg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264.

| **Reporting group values** | MLN0264 1.8 mg/kg | | |
|---|---|---|---|
| Number of subjects | 38 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| 31 to 81 years | 38 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |

| | | | |
|---|---|---|---|
| Gender, Male/Female<br>Units: participants | | | |
| Female | 7 | | |
| Male | 31 | | |
| Height<br>Units: cm<br>arithmetic mean<br>standard deviation | <br><br><br>± | | |
| Weight<br>Units: kg<br>arithmetic mean<br>standard deviation | <br><br><br>± | | |
| Body Surface Area<br>Units: m^2<br>arithmetic mean<br>standard deviation | <br><br><br>± | | |

## End points

### End points reporting groups

| Reporting group title | MLN0264 1.8 mg/kg (GCC Low) |
|---|---|

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Low (combined H-score 10-59). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Reporting group title | MLN0264 1.8 mg/kg (GCC Intermediate) |
|---|---|

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 9 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score 60-119). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Reporting group title | MLN0264 1.8 mg/kg (GCC High) |
|---|---|

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 8 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264. Participants with guanylyl cyclase C (GCC) protein expression=Intermediate (combined H-score >120). Total H-score 0-600 is the combined score of cytoplasmic staining 0-300 and apical staining 0-300 and is based on the percentage of tumor cells with staining intensity 1+, 2+ and 3+.

| Subject analysis set title | MLN0264 1.8 mg/kg |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264.

### Primary: Overall Response Rate (ORR) Based on Response Evaluation Criteria in Solid Tumors (RECIST)

| End point title | Overall Response Rate (ORR) Based on Response Evaluation Criteria in Solid Tumors (RECIST)[1] |
|---|---|

End point description:

ORR is defined as the percentage of participants with complete response (CR) or partial response (PR) as assessed by the investigator using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. CR: Disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR: At least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions.

| End point type | Primary |
|---|---|

End point timeframe:

Day 21, every other cycle, starting with Cycle 2 until disease progression, death or study closure (up to 17 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned for this endpoint.

| End point values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 14 | 13 | |
| Units: percentage of participants | 0 | 14 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

| End point title | Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug will be determined by the Investigator.

| End point type | Secondary |
|---|---|

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 10.7 months)

| End point values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 15 | 14 | |
| Units: participants | | | | |
| AEs | 8 | 15 | 14 | |
| SAEs | 2 | 5 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Potentially Clinically Significant Laboratory Evaluation Findings

| End point title | Number of Participants With Potentially Clinically Significant Laboratory Evaluation Findings |
|---|---|

End point description:

Participants with at least one post-baseline potentially clinically significant serum chemistry, hematology, coagulation or urinalysis result. Clinically significant results are those that were assessed by the investigator to be Grade 3 or higher using the National Cancer Institute Common Terminology

Criteria for Adverse Events (NCI CTCAE). Grade 3=severe, Grade 4=life threatening or disabling and Grade 5=Death.

| End point type | Secondary |
|---|---|

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 10.7 months)

| **End point values** | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: participants | | | | |
| Chemistry | 8 | | | |
| Hematology | 13 | | | |
| Coagulation | 24 | | | |
| Urinalysis | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Potentially Clinically Significant Vital Signs Findings

| End point title | Number of Participants With Potentially Clinically Significant Vital Signs Findings |
|---|---|

End point description:

Participants with at least one potentially clinically significant post-baseline vital sign finding including measurements of diastolic and systolic blood pressure, heart rate, and oral temperature.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 of each 21 day cycle and 30 days after the last dose of study medication (Up to 10.7 months)

| **End point values** | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: participants | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

| End point title | Progression Free Survival (PFS) |
|---|---|

End point description:

PFS is defined as the time in days from the date of first study drug administration to the date of first documentation of disease progression or death.

| End point type | Secondary |
|---|---|

End point timeframe:

Time Frame: Day 21 of every other 21-day cycle starting with Cycle 2, 30 days after the last dose of study medication, and then every 12 weeks for up to an additional 6 months (Up to 16.7 months)

| **End point values** | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 14 | 13 | |
| Units: days | | | | |
| median (full range (min-max)) | 40 (38 to 311) | 49 (38 to 316) | 87 (39 to 427) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response

| End point title | Duration of Response |
|---|---|

End point description:

Duration of response is defined as the time in days from the date of first documentation of a confirmed response to the date of first documentation of disease progression.

| End point type | Secondary |
|---|---|

End point timeframe:

From first documented response until disease progression (Up to 16.7 months)

| **End point values** | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2[2] | | | |
| Units: days | | | | |
| median (full range (min-max)) | 45.5 (1 to 90) | | | |

Notes:

[2] - Only two subjects had data collected due to early termination.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate

| End point title | Disease Control Rate |
|---|---|

End point description:

Disease control rate is defined as the percentage of participants with complete response (CR) or partial response (PR) or stable disease (SD) with a minimum of 12 weeks' duration. CR: Disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR: At least a 30% decrease in the sum of the Longest Diameter (LD) of target lesions, taking as reference the baseline sum LD and no new lesions. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD) of target lesions, taking as reference the smallest sum LD since the treatment started and no new lesions. Investigator response is based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 21 of every other 21-day cycle starting with Cycle 2, 30 days after the last dose of study medication, and then every 12 weeks for up to an additional 6 months (Up to 16.7 months)

| **End point values** | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 14 | 13 | |
| Units: percentage of participants | 11 | 36 | 54 | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Overall Survival (OS)**

| End point title | Overall Survival (OS) |
|---|---|

End point description:

Overall survival is defined as the time in days from the date of first study drug administration to the date of death.

| End point type | Secondary |
|---|---|

End point timeframe:

Until death or 6 months after the last patient completes treatment—whichever occurs first (Up to 17 months)

| **End point values** | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 14 | 13 | |
| Units: days | | | | |
| median (full range (min-max)) | 230 (79 to 394) | 156 (49 to 505) | 206 (24 to 427) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Cmax: Maximum Observed Serum Concentration for MLN0264

| End point title | Cmax: Maximum Observed Serum Concentration for MLN0264 |
|---|---|

End point description:

Maximum observed serum concentration (Cmax) is the peak serum concentration of a drug after administration, obtained directly from the serum concentration-time curve.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycles 1-3 predose and 10 minutes, 4 hours, and 3, 4, 8 and 15 days postdose. Cycles 4+ predose, 10 minutes, 4 hours, and 4 and 8 days postdose.

| End point values | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 0[3] | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |

Notes:

[3] - No data was collected for this analysis due to early termination.

### Statistical analyses

No statistical analyses for this end point

## Secondary: MLN0264 Serum Concentrations

| End point title | MLN0264 Serum Concentrations |
|---|---|

End point description:

Blood samples were collected and sent to a laboratory to be tested for serum concentrations of MLN0264.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycles 1-3 pre-dose and 10 minutes, 4 hours, and 3, 4, 8 and 15 days post-dose; Cycles 4-9 and 11-14 pre-dose and 10 minutes post-dose; End of Treatment.

| End point values | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1, Pre-Dose (n=37) | 0 (± 0) | | | |
| Cycle 1 Day 1, 10 Minutes Post-Dose (n=37) | 37.0434 (± 9.93577) | | | |
| Cycle 1 Day 1, 4 Hours Post-Dose (n=38) | 26.047 (± 6.27538) | | | |
| Cycle 1 Day 3, 48 Hours Post-Dose (n=35) | 7.0839 (± 1.64899) | | | |

| | | | | |
|---|---|---|---|---|
| Cycle 1 Day 4, 72 Hours Post-Dose (n=35) | 4.4939 (± 1.25657) | | | |
| Cycle 1 Day 8, 168 Hours Post-Dose (n=38) | 1.6795 (± 0.71586) | | | |
| Cycle 1 Day 15, 336 Hours Post-Dose (n=36) | 0.5778 (± 0.22063) | | | |
| Cycle 2 Day 1, Pre-Dose (n=36) | 0.7466 (± 2.68737) | | | |
| Cycle 2 Day 1, 10 Minutes Post-Dose (n=36) | 32.1622 (± 9.61463) | | | |
| Cycle 2 Day 1, 4 Hours Post-Dose (n=36) | 26.0278 (± 9.43156) | | | |
| Cycle 2 Day 3, 48 Hours Post-Dose (n=36) | 7.7186 (± 2.04169) | | | |
| Cycle 2 Day 4, 72 Hours Post-Dose (n=33) | 4.914 (± 1.05592) | | | |
| Cycle 2 Day 8, 168 Hours Post-Dose (n=35) | 1.7813 (± 0.49456) | | | |
| Cycle 2 Day 15, 336 Hours Post-Dose (n=36) | 0.6959 (± 0.27579) | | | |
| Cycle 3 Day 1, Pre-Dose (n=19) | 0.4905 (± 0.77805) | | | |
| Cycle 3 Day 1, 10 Minutes Post-Dose (n=19) | 31.1505 (± 8.74114) | | | |
| Cycle 3 Day 1, 4 Hours Post-Dose (n=19) | 25.1787 (± 5.49543) | | | |
| Cycle 3 Day 3, 48 Hours Post-Dose (n=14) | 6.736 (± 1.5694) | | | |
| Cycle 3 Day 4, 72 Hours Post-Dose (n=15) | 5.887 (± 3.05461) | | | |
| Cycle 3 Day 8, 168 Hours Post-Dose (n=18) | 1.5078 (± 0.48401) | | | |
| Cycle 3 Day 15, 336 Hours Post-Dose (n=18) | 0.6807 (± 0.25869) | | | |
| Cycle 4 Day 1, Pre-Dose (n=16) | 0.3916 (± 0.16462) | | | |
| Cycle 4 Day 1, 10 Minutes Post-Dose (n=15) | 32.3427 (± 8.33045) | | | |
| Cycle 5 Day 1, Pre-Dose (n=7) | 0.4757 (± 0.18995) | | | |
| Cycle 5 Day 1, 10 Minutes Post-Dose (n=7) | 33.9286 (± 7.14793) | | | |
| Cycle 6 Day 1, Pre-Dose (n=8) | 0.4915 (± 0.34173) | | | |
| Cycle 6 Day 1, 10 Minutes Post-Dose (n=8) | 30.385 (± 7.79913) | | | |
| Cycle 6 Day 4, 72 Hours Post-Dose (n=7) | 5.0676 (± 1.54862) | | | |
| Cycle 6 Day 8, 168 Hours Post-Dose (n=6) | 1.691 (± 0.40781) | | | |
| Cycle 7 Day 1, Pre-Dose (n=3) | 0.5097 (± 0.20409) | | | |
| Cycle 7 Day 1, 10 Minutes Post-Dose (n=3) | 31.0133 (± 8.2343) | | | |
| Cycle 8 Day 1, Pre-Dose (n=3) | 0.5677 (± 0.2418) | | | |
| Cycle 8 Day 1, 10 Minute Post-Dose (n=3) | 31.6467 (± 8.93229) | | | |
| Cycle 9 Day 1, Pre-Dose (n=2) | 0.929 (± 0.49639) | | | |
| Cycle 9 Day 1, 10 Minutes Post-Dose (n=2) | 32.35 (± 6.77408) | | | |

| | | | | |
|---|---|---|---|---|
| Cycle 11 Day 1, Pre-Dose (n=1) | 0.776 (± 0) | | | |
| Cycle 11 Day 1, 10 Minutes Post-Dose (n=1) | 56.84 (± 0) | | | |
| Cycle 12 Day 1, Pre-Dose (n=1) | 0.735 (± 0) | | | |
| Cycle 12 Day 1, 10 Minutes Post-Dose (n=1) | 49.88 (± 0) | | | |
| Cycle 13 Day 1, Pre-Dose (n=1) | 0.887 (± 0) | | | |
| Cycle 13 Day 1, 10 Minutes Post-Dose (n=1) | 41.64 (± 0) | | | |
| Cycle 14 Day 1, Pre-Dose (n=1) | 1.026 (± 0) | | | |
| Cycle 14 Day 1, 10 Minutes Post-Dose (n=1) | 41.92 (± 0) | | | |
| End of Treatment (n=26) | 0.3323 (± 0.21216) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Total Antibodies (Conjugated and Unconjugated)

| | |
|---|---|
| End point title | Serum Concentration of Total Antibodies (Conjugated and Unconjugated) |

End point description:

Blood samples were collected and sent to a laboratory to be tested for conjugated and unconjugated antibodies.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Cycles 1-3 pre-dose and 10 minutes, 4 hours, and 3, 4, 8 and 15 days post-dose; Cycles 4-9 and 11-14 pre-dose and 10 minutes post-dose; End of Treatment.

| **End point values** | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1, Pre-Dose (n=37) | 0 (± 0) | | | |
| Cycle 1 Day 1, 10 Minutes Post-Dose (n=37) | 41.8154 (± 10.05341) | | | |
| Cycle 1 Day 1, 4 Hours Post-Dose (n=38) | 35.7626 (± 8.46954) | | | |
| Cycle 1 Day 3, 48 Hours Post-Dose (n=35) | 16.0664 (± 3.26969) | | | |
| Cycle 1 Day 4, 72 Hours Post-Dose (n=35) | 11.7461 (± 2.60098) | | | |
| Cycle 1 Day 8, 168 Hours Post-Dose (n=38) | 6.1851 (± 1.73972) | | | |
| Cycle 1 Day 15, 336 Hours Post-Dose (n=36) | 3.3926 (± 1.00149) | | | |
| Cycle 2 Day 1, Pre-Dose (n=36) | 2.5995 (± 3.79916) | | | |

| | | | | |
|---|---|---|---|---|
| Cycle 2 Day 1, 10 Minutes Post-Dose (n=35) | 43.4749 (± 9.71796) | | | |
| Cycle 2 Day 1, 4 Hours Post-Dose (n=36) | 35.6691 (± 10.26134) | | | |
| Cycle 2 Day 3, 48 Hours Post-Dose (n=36) | 18.4167 (± 4.07769) | | | |
| Cycle 2 Day 4, 72 Hours Post-Dose (n=33) | 13.3398 (± 3.23987) | | | |
| Cycle 2 Day 8, 168 Hours Post-Dose (n=35) | 7.3613 (± 1.87974) | | | |
| Cycle 2 Day 15, 336 Hours Post-Dose (n=36) | 4.3511 (± 1.47322) | | | |
| Cycle 3 Day 1, Pre-Dose (n=19) | 2.5274 (± 1.54088) | | | |
| Cycle 3 Day 1, 10 Minutes Post-Dose (n=19) | 41.3674 (± 11.88629) | | | |
| Cycle 3 Day 1, 4 Hours Post-Dose (n=19) | 33.2692 (± 9.4253) | | | |
| Cycle 3 Day 3, 48 Hours Post-Dose (n=14) | 15.95 (± 5.08026) | | | |
| Cycle 3 Day 4, 72 Hours Post-Dose (n=15) | 12.8393 (± 4.56059) | | | |
| Cycle 3 Day 8, 168 Hours Post-Dose (n=18) | 7.5035 (± 2.01984) | | | |
| Cycle 3 Day 15, 336 Hours Post-Dose (n=18) | 4.2384 (± 1.66059) | | | |
| Cycle 4 Day 1, Pre-Dose (n=16) | 2.9082 (± 1.03729) | | | |
| Cycle 4 Day 1, 10 Minutes Post-Dose (n=15) | 45.4333 (± 13.8498) | | | |
| Cycle 5 Day 1, Pre-Dose (n=7) | 3.2396 (± 0.88493) | | | |
| Cycle 5 Day 1, 10 Minutes Post-Dose (n=7) | 43.0629 (± 7.30566) | | | |
| Cycle 6 Day 1, Pre-Dose (n=8) | 3.081 (± 1.29133) | | | |
| Cycle 6 Day 1, 10 Minutes Post-Dose (n=8) | 39.93 (± 10.13066) | | | |
| Cycle 6 Day 4, 72 Hours Post-Dose (n=7) | 14.7957 (± 4.09897) | | | |
| Cycle 6 Day 8, 168 Hours Post-Dose (n=6) | 9.6217 (± 1.53148) | | | |
| Cycle 7 Day 1, Pre-Dose (n=3) | 3.3417 (± 1.64015) | | | |
| Cycle 7 Day 1, 10 Minutes Post-Dose (n=3) | 42.1667 (± 8.725528) | | | |
| Cycle 8 Day 1, Pre-Dose (n=3) | 3.0573 (± 1.21148) | | | |
| Cycle 8 Day 1, 10 Minute Post-Dose (n=3) | 32.6333 (± 5.9498) | | | |
| Cycle 9 Day 1, Pre-Dose (n=2) | 3.044 (± 0.98429) | | | |
| Cycle 9 Day 1, 10 Minutes Post-Dose (n=2) | 45.8 (± 7.04278) | | | |
| Cycle 11 Day 1, Pre-Dose (n=1) | 4.242 (± 0) | | | |
| Cycle 11 Day 1, 10 Minutes Post-Dose (n=1) | 44.3 (± 0) | | | |
| Cycle 12 Day 1, Pre-Dose (n=1) | 4.102 (± 0) | | | |
| Cycle 12 Day 1, 10 Minutes Post-Dose (n=1) | 47.38 (± 0) | | | |
| Cycle 13 Day 1, Pre-Dose (n=1) | 4.99 (± 0) | | | |

| | | | | |
|---|---|---|---|---|
| Cycle 13 Day 1, 10 Minutes Post-Dose (n=1) | 55.26 (± 0) | | | |
| Cycle 14 Day 1, Pre-Dose (n=1) | 5.675 (± 0) | | | |
| Cycle 14 Day 1, 10 Minutes Post-Dose (n=1) | 61.5 (± 0) | | | |
| End of Treatment (n=26) | 2.5393 (± 1.32302) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Monomethyl Auristatin E (MMAE)

| End point title | Serum Concentration of Monomethyl Auristatin E (MMAE) |
|---|---|

End point description:

Blood samples were collected and sent to a laboratory to be tested for MMAE.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycles 1-3 pre-dose and 10 minutes, 4 hours, and 3, 4, 8 and 15 days post-dose; Cycles 4-9 and 11-14 pre-dose and 10 minutes post-dose; End of Treatment.

| End point values | MLN0264 1.8 mg/kg | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 38 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1, Pre-Dose (n=37) | 0 (± 0) | | | |
| Cycle 1 Day 1, 10 Minutes Post-Dose (n=37) | 0.473 (± 0.6503) | | | |
| Cycle 1 Day 1, 4 Hours Post-Dose (n=38) | 2.659 (± 1.5489) | | | |
| Cycle 1 Day 3, 48 Hours Post-Dose (n=35) | 6.153 (± 3.2773) | | | |
| Cycle 1 Day 4, 72 Hours Post-Dose (n=35) | 5.856 (± 3.4519) | | | |
| Cycle 1 Day 8, 168 Hours Post-Dose (n=38) | 2.945 (± 1.8899) | | | |
| Cycle 1 Day 15, 336 Hours Post-Dose (n=36) | 0.532 (± 0.6693) | | | |
| Cycle 2 Day 1, Pre-Dose (n=36) | 0.116 (± 0.1118) | | | |
| Cycle 2 Day 1, 10 Minutes Post-Dose (n=35) | 0.425 (± 0.2697) | | | |
| Cycle 2 Day 1, 4 Hours Post-Dose (n=36) | 2.665 (± 1.7137) | | | |
| Cycle 2 Day 3, 48 Hours Post-Dose (n=36) | 6.746 (± 4.2361) | | | |
| Cycle 2 Day 4, 72 Hours Post-Dose (n=33) | 6.111 (± 3.6283) | | | |
| Cycle 2 Day 8, 168 Hours Post-Dose (n=35) | 2.898 (± 2.2974) | | | |

| | | | | |
|---|---|---|---|---|
| Cycle 2 Day 15, 336 Hours Post-Dose (n=36) | 0.579 (± 0.6221) | | | |
| Cycle 3 Day 1, Pre-Dose (n=19) | 0.094 (± 0.124) | | | |
| Cycle 3 Day 1, 10 Minutes Post-Dose (n=18) | 0.428 (± 0.4487) | | | |
| Cycle 3 Day 1, 4 Hours Post-Dose (n=19) | 2.302 (± 1.8893) | | | |
| Cycle 3 Day 3, 48 Hours Post-Dose (n=14) | 4.493 (± 2.6877) | | | |
| Cycle 3 Day 4, 72 Hours Post-Dose (n=15) | 3.638 (± 1.857) | | | |
| Cycle 3 Day 8, 168 Hours Post-Dose (n=18) | 2.135 (± 1.703) | | | |
| Cycle 3 Day 15, 336 Hours Post-Dose (n=17) | 0.342 (± 0.3637) | | | |
| Cycle 4 Day 1, Pre-Dose (n=16) | 0.081 (± 0.0865) | | | |
| Cycle 4 Day 1, 10 Minutes Post-Dose (n=15) | 0.304 (± 0.1781) | | | |
| Cycle 5 Day 1, Pre-Dose (n=7) | 0.084 (± 0.0331) | | | |
| Cycle 5 Day 1, 10 Minutes Post-Dose (n=7) | 0.278 (± 0.1325) | | | |
| Cycle 6 Day 1, Pre-Dose (n=8) | 0.093 (± 0.0654) | | | |
| Cycle 6 Day 1, 10 Minutes Post-Dose (n=7) | 0.322 (± 0.2232) | | | |
| Cycle 6 Day 4, 72 Hours Post-Dose (n=7) | 6.183 (± 3.3587) | | | |
| Cycle 6 Day 8, 168 Hours Post-Dose (n=6) | 2.417 (± 1.6379) | | | |
| Cycle 7 Day 1, Pre-Dose (n=3) | 0.044 (± 0.0083) | | | |
| Cycle 7 Day 1, 10 Minutes Post-Dose (n=3) | 0.115 (± 0.0439) | | | |
| Cycle 8 Day 1, Pre-Dose (n=3) | 0.058 (± 0.0103) | | | |
| Cycle 8 Day 1, 10 Minute Post-Dose (n=3) | 0.132 (± 0.0425) | | | |
| Cycle 9 Day 1, Pre-Dose (n=2) | 0.021 (± 0.0291) | | | |
| Cycle 9 Day 1, 10 Minutes Post-Dose (n=2) | 0.158 (± 0.0721) | | | |
| Cycle 11 Day 1, Pre-Dose (n=1) | 0.093 (± 0) | | | |
| Cycle 11 Day 1, 10 Minutes Post-Dose (n=1) | 0.186 (± 0) | | | |
| Cycle 12 Day 1, Pre-Dose (n=1) | 0.087 (± 0) | | | |
| Cycle 12 Day 1, 10 Minutes Post-Dose (n=1) | 0.167 (± 0) | | | |
| Cycle 13 Day 1, Pre-Dose (n=1) | 0.074 (± 0) | | | |
| Cycle 13 Day 1, 10 Minutes Post-Dose (n=1) | 0.132 (± 0) | | | |
| Cycle 14 Day 1, Pre-Dose (n=1) | 0.081 (± 0) | | | |
| Cycle 14 Day 1, 10 Minutes Post-Dose (n=1) | 0.165 (± 0) | | | |
| End of Treatment (n=25) | 0.173 (± 0.3359) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Reduction From Baseline in Tumor Size

| End point title | Percentage of Participants With Reduction From Baseline in Tumor Size |
|---|---|

End point description:

The percentage of participants with the best percentage of tumor reduction from baseline in the sum of the diameter was calculated.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 21 of every other 21-day cycle starting with Cycle 2, 30 days after the last dose of study medication, and then every 12 weeks for up to an additional 6 months (Up to 16.7 months)

| End point values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 14 | 13 | |
| Units: percentage of participants | 3 | 6 | 11 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Guanylyl Cyclase C (GCC) H-score Assessed by Immunohistochemistry (IHC)

| End point title | Guanylyl Cyclase C (GCC) H-score Assessed by Immunohistochemistry (IHC) |
|---|---|

End point description:

Analysis of GCC protein expression levels in tumor tissue (fresh biopsy pretreatment and whenever a biopsy is considered medically safe and technically feasible) was performed using a semiquantitative immunohistochemistry (IHC) assay and the total GCC H-Score was determined. GCC H-score is based on the sum of the 0 to 300 H-score for cytoplasmic staining and the 0 to 300 H-score for apical staining for a total possible H-score 0 to 600. Separate consent was required to obtain archival tumor specimens for GCC expression assessment prior to screening.

| End point type | Secondary |
|---|---|

End point timeframe:

From pre-screening through end of study (approximately 20 months)

| End point values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 15 | 14 | |
| Units: scores on a scale | | | | |
| arithmetic mean (full range (min-max)) | 74.8 (27 to 100) | 154.6 (110 to 230) | 344.3 (260 to 480) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Antitherapeutic Antibodies (ATA)

| End point title | Number of Participants With Antitherapeutic Antibodies (ATA) |
|---|---|

End point description:

Blood samples were collected to assess the immunogenicity of MLN0264 (ATA development) using a laboratory test. Neutralizing ATA assessment was performed for ATA-positive samples only.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose of each 21 day cycle and 30 days after last dose of study medication (Up to 10.7 months)

| End point values | MLN0264 1.8 mg/kg (GCC Low) | MLN0264 1.8 mg/kg (GCC Intermediate) | MLN0264 1.8 mg/kg (GCC High) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 9 | 15 | 14 | |
| Units: participants | 0 | 3 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose through 30 days after the last dose of study drug (up to 10.7 Months)

Adverse event reporting additional description:

At each visit the investigator documented any occurrence of AEs and abnormal laboratory findings. Any event spontaneously reported by participant or observed by investigator was recorded, irrespective of relation to study treatment. Non-serious unsolicited AEs reported below. Non-serious solicited AEs reported in the outcome measure section.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | MLN0264 1.8 mg/kg |

Reporting group description:

MLN0264 1.8 mg/kg, 30-minute intravenous (IV) infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 14 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264.

| **Serious adverse events** | MLN0264 1.8 mg/kg | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | Additional description: One treatment-emergent death occurred during treatment with MLN0264 with and is not related. | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tumour hemorrhage | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | | |
| 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** | MLN0264 1.8 mg/kg | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 38 (97.37%) | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | | |
| occurrences (all) | 16 | | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 38 (31.58%) | | |
| occurrences (all) | 14 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Orthopnoea | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 4 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 4 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 5 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 7 | | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 4 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 6 | | |
| Tremor | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 5 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | | |
| occurrences (all) | 7 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | | |
| occurrences (all) | 11 | | |
| Ascites | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 5 | | |
| Nausea | | | |
| subjects affected / exposed | 20 / 38 (52.63%) | | |
| occurrences (all) | 30 | | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | | |
| occurrences (all) | 13 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | | |
| occurrences (all) | 6 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Proteinuria | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 5 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 3 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 3 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 38 (28.95%) | | |
| occurrences (all) | 13 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | | |
| occurrences (all) | 4 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | | |
| occurrences (all) | 2 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | | |
| occurrences (all) | 4 | | |

| | | | |
|---|---|---|---|
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all) | 4 / 38 (10.53%)<br>5 | | |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 38 (5.26%)<br>2 | | |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 38 (5.26%)<br>3 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 March 2014 | Amendment 1: The purpose of this amendment was to provide clarification and ensure consistency in the Schedule of Events. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported