Clinical trial results:
Phase 2 Trial of MLN0264 in Previously Treated Patients with Advanced or Metastatic Pancreatic Adenocarcinoma Expressing Guanylyl Cyclase C (GCC)

Summary

EudraCT number	2014-000805-11
Trial protocol	IT ES BE GB
Global end of trial date	15 January 2016

Results information

Result version number	v2 (current)
This version publication date	29 June 2017
First version publication date	31 January 2017
Version creation reason	• Correction of full data set Updates due to QA comments from ClinicalTrials.gov.

Trial information

Trial identification

Sponsor protocol code	C26003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02202785
WHO universal trial number (UTN)	U1111-1155-8964

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 advanced or metastatic guanylyl cyclase C (GCC)-positive adenocarcinoma of the pancreas.

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	24 September 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: 5
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	43
EEA total number of subjects	23

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)	21
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 26 investigative sites in Belgium, Spain, United Kingdom and the United States from 24 September 2014 to 15 January 2016.

Pre-assignment

Screening details:

Participants with a diagnosis of Pancreatic adenocarcinoma 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 4 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	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 10 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	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 6 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	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	11	15	17
Completed	0	0	0
Not completed	11	15	17
Consent withdrawn by subject	-	1	-
Study Terminated by Sponsor	1	6	4
Lost to follow-up	-	1	-
Reason not Specified	10	7	13

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 4 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 10 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 6 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	11	15	17
Age categorical Units: Subjects			
44 to 81 years	11	15	17
Age Continuous Units: years			
arithmetic mean	63.1	65.5	62.9
standard deviation	± 11.2	± 7.41	± 10.88
Gender, Male/Female Units: Participants			
Female	8	11	4
Male	3	4	13
Race/Ethnicity, Customized Units: Subjects			
White	9	15	17
Black or African American	1	0	0
Not Reported	1	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	3	1	0
Not Hispanic or Latino	8	14	17

Study Specific Characteristic | Height Units: cm			

Subject analysis sets

Subject analysis set title	MLN0264 1.8 mg/kg
Subject analysis set type	Safety 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 10 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264.

Subject analysis set title	MLN0264 1.8 mg/kg
Subject analysis set type	Sub-group 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 10 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	MLN0264 1.8 mg/kg	
Number of subjects	43	1	
Age categorical Units: Subjects			
44 to 81 years			
Age Continuous Units: years arithmetic mean standard deviation	±	±	
Gender, Male/Female Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White	41	1	
Black or African American	1	0	
Not Reported	1	0	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4	0	
Not Hispanic or Latino	39	1	
Study Specific Characteristic | Height Units: cm arithmetic mean standard deviation	±	±	
Study Specific Characteristic | Weight Units: kg arithmetic mean standard deviation	±	±	
Study Specific Characteristic | Body Surface Area Units: m^2 arithmetic mean standard deviation	±	±	

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 4 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 10 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 6 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	Safety 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 10 cycles). The dose may be decreased, delayed or discontinued in participants who develop treatment-associated nonhematologic and hematologic toxicity to MLN0264.

Subject analysis set title	MLN0264 1.8 mg/kg
Subject analysis set type	Sub-group 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 10 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 16 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 was 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	11	13	15	
Units: percentage of participants	0	8	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:

Day 1 of each 21 day cycle and 30 days after the last dose of study medication (Up to 7.9 months)

End point values	MLN0264 1.8 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Participants				
Chemistry	20			
Hematology	16			
Coagulation	23			
Urinalysis	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. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.	
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 13.9 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	11	13	15	
Units: days				
median (full range (min-max))	39 (9 to 82)	42 (21 to 218)	41 (16 to 137)	

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 7.9 months)	

End point values	MLN0264 1.8 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Participants	0			

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 from the date of first documentation of a Partial Response or better to the date of first documentation of disease progression or relapse based on investigator assessment using RECIST version 1.1 guidelines. Per RECIST version 1.1 for target lesions and assessed by MRI: CR, Disappearance of all target lesions; PR, >=30% decrease in the sum of the longest diameter of target lesions.

End point type	Secondary

End point timeframe:

From first documented response until disease progression (Up to 16 months)

End point values	MLN0264 1.8 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: days				
median (full range (min-max))	103 (103 to 103)			

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. Investigator response is based on the 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. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum longest diameter (LD) since the treatment started.

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 13.9 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	11	13	15	
Units: percentage of participants	0	23	20	

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 16 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	11	15	17	
Units: days				
median (full range (min-max))	162 (36 to 282)	140 (43 to 443)	162 (49 to 435)	

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:

Cmax was not a pre-specified secondary outcome measure. No data was collected.

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[2]			
Units: µg/mL				
arithmetic mean (standard deviation)	()			

Notes:

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

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 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	43			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose	0 (± 0)			
Cycle 1 Day 1, 10 Minutes Post-Dose	0.296 (± 0.1624)			
Cycle 1 Day 1, 4 Hours Post-Dose	2.438 (± 1.3015)			
Cycle 1 Day 3, 48 Hours Post-Dose (n=41)	5.202 (± 2.811)			
Cycle 1 Day 4, 72 Hours Post-Dose (n=39)	4.918 (± 2.3653)			
Cycle 1 Day 8, 168 Hours Post-Dose (n=43)	2.994 (± 2.1173)			
Cycle 1 Day 15, 336 Hours Post-Dose (n=37)	0.58 (± 0.5073)			
Cycle 2 Day 1, Pre-Dose (n=37)	0.128 (± 0.1304)			
Cycle 2 Day 1, 10 Minutes Post-Dose (n=37)	0.405 (± 0.3351)			
Cycle 2 Day 1, 4 Hours Post-Dose (n=37)	2.665 (± 1.6053)			
Cycle 2 Day 3, 48 Hours Post-Dose (n=34)	6.223 (± 3.5926)			
Cycle 2 Day 4, 72 Hours Post-Dose (n=32)	5.808 (± 3.6296)			
Cycle 2 Day 8, 168 Hours Post-Dose (n=34)	2.789 (± 2.0437)			

Cycle 2 Day 15, 336 Hours Post-Dose (n=28)	0.56 (± 0.5332)			
Cycle 3 Day 1, Pre-Dose (n=9)	0.145 (± 0.1318)			
Cycle 3 Day 1, 10 Minutes Post-Dose (n=9)	0.395 (± 0.3514)			
Cycle 3 Day 1, 4 Hours Post-Dose (n=9)	2.237 (± 1.6402)			
Cycle 3 Day 3, 48 Hours Post-Dose (n=8)	6.563 (± 5.2034)			
Cycle 3 Day 4, 72 Hours Post-Dose (n=8)	6.563 (± 6.2902)			
Cycle 3 Day 8, 168 Hours Post-Dose (n=7)	2.826 (± 2.0234)			
Cycle 3 Day 15, 336 Hours Post-Dose (n=7)	1.155 (± 1.2808)			
Cycle 4 Day 1, Pre-Dose (n=7)	0.232 (± 0.2877)			
Cycle 4 Day 1, 10 Minutes Post-Dose (n=7)	0.446 (± 0.4029)			
Cycle 5 Day 1, Pre-Dose (n=5)	0.09 (± 0.0594)			
Cycle 5 Day 1, 10 Minutes Post-Dose (n=5)	0.249 (± 0.1004)			
Cycle 6 Day 1, Pre-Dose (n=5)	0.105 (± 0.0469)			
Cycle 6 Day 1, 10 Minutes Post-Dose (n=5)	0.269 (± 0.1037)			
Cycle 6 Day 4, 72 Hours Post-Dose (n=5)	4.234 (± 1.3134)			
Cycle 6 Day 8, 168 Hours Post-Dose (n=5)	2.002 (± 0.9691)			
Cycle 7 Day 1, Pre-Dose (n=2)	0.125 (± 0.0365)			
Cycle 7 Day 1, 10 Minutes Post-Dose (n=2)	0.277 (± 0.0806)			
Cycle 8 Day 1, Pre-Dose (n=2)	0.108 (± 0.0288)			
Cycle 8 Day 1, 10 Minute Post-Dose (n=2)	0.257 (± 0.0481)			
Cycle 9 Day 1, Pre-Dose (n=2)	0.05 (± 0.019)			
Cycle 9 Day 1, 10 Minutes Post-Dose (n=2)	0.19 (± 0.0361)			
Cycle 10 Day 1, Pre-Dose (n=1)	0.132 (± 0)			
Cycle 10 Day 1, 10 Minutes Post-Dose (n=1)	0.385 (± 0)			
End of Treatment (n=27)	0.137 (± 0.1695)			

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. An 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.

End point type	Secondary

End point timeframe:

From the first dose through 30 days after the last dose of study medication (Up to 7.9 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	11	15	17	
Units: Participants				
AEs	11	15	17	
SAEs	3	7	9	

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:

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 is 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 18 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	11	15	17	
Units: Scores on a scale				
arithmetic mean (full range (min-max))				
Guanylyl Cyclase C (GCC) H-score Assessed by Immun	29.6 (10 to 55)	84 (60 to 110)	204.2 (120 to 355)	

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 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	43			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose	0 (± 0)			
Cycle 1 Day 1, 10 Minutes Post-Dose	36.647 (± 10.0936)			
Cycle 1 Day 1, 4 Hours Post-Dose	27.898 (± 8.4886)			
Cycle 1 Day 3, 48 Hours Post-Dose (n=41)	6.95 (± 1.9173)			
Cycle 1 Day 4, 72 Hours Post-Dose (n=39)	4.758 (± 1.5349)			
Cycle 1 Day 8, 168 Hours Post-Dose (n=43)	1.563 (± 0.5818)			
Cycle 1 Day 15, 336 Hours Post-Dose (n=37)	0.582 (± 0.2331)			
Cycle 2 Day 1, Pre-Dose (n=37)	0.261 (± 0.1643)			
Cycle 2 Day 1, 10 Minutes Post-Dose (n=37)	30.856 (± 9.9483)			
Cycle 2 Day 1, 4 Hours Post-Dose (n=37)	26.691 (± 7.9664)			
Cycle 2 Day 3, 48 Hours Post-Dose (n=35)	7.021 (± 2.4977)			
Cycle 2 Day 4, 72 Hours Post-Dose (n=32)	4.432 (± 1.6115)			
Cycle 2 Day 8, 168 Hours Post-Dose (n=34)	1.681 (± 0.78)			
Cycle 2 Day 15, 336 Hours Post-Dose (n=27)	0.692 (± 0.3038)			

Cycle 3 Day 1, Pre-Dose (n=9)	0.431 (± 0.1481)				
Cycle 3 Day 1, 10 Minutes Post-Dose (n=9)	34.978 (± 5.335)				
Cycle 3 Day 1, 4 Hours Post-Dose (n=9)	26.393 (± 3.3557)				
Cycle 3 Day 3, 48 Hours Post-Dose (n=8)	9.486 (± 2.9593)				
Cycle 3 Day 4, 72 Hours Post-Dose (n=8)	6.579 (± 1.8102)				
Cycle 3 Day 8, 168 Hours Post-Dose (n=7)	1.701 (± 0.4201=				

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 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	43			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, Pre-Dose	0 (± 0)			
Cycle 1 Day 1, 10 Minutes Post-Dose	37.599 (± 9.4299)			
Cycle 1 Day 1, 4 Hours Post-Dose	32.974 (± 8.1824)			
Cycle 1 Day 3, 48 Hours Post-Dose (n=41)	14.051 (± 4.0368)			
Cycle 1 Day 4, 72 Hours Post-Dose (n=39)	10.546 (± 3.6488)			
Cycle 1 Day 8, 168 Hours Post-Dose (n=43)	5.252 (± 1.7703)			
Cycle 1 Day 15, 336 Hours Post-Dose (n=37)	2.958 (± 1.1577)			
Cycle 2 Day 1, Pre-Dose (n=37)	1.668 (± 0.7608)			
Cycle 2 Day 1, 10 Minutes Post-Dose (n=37)	35.963 (± 10.9226)			
Cycle 2 Day 1, 4 Hours Post-Dose (n=37)	32.134 (± 9.7822)			
Cycle 2 Day 3, 48 Hours Post-Dose (n=35)	14.194 (± 4.8398)			
Cycle 2 Day 4, 72 Hours Post-Dose (n=32)	10.948 (± 4.2741)			
Cycle 2 Day 8, 168 Hours Post-Dose (n=34)	6.312 (± 2.7008)			
Cycle 2 Day 15, 336 Hours Post-Dose (n=27)	3.923 (± 1.7465)			
Cycle 3 Day 1, Pre-Dose (n=9)	2.654 (± 1.0757)			
Cycle 3 Day 1, 10 Minutes Post-Dose (n=9)	39.5 (± 6.058)			
Cycle 3 Day 1, 4 Hours Post-Dose (n=9)	37.549 (± 8.2628)			
Cycle 3 Day 3, 48 Hours Post-Dose (n=8)	19.181 (± 3.726)			
Cycle 3 Day 4, 72 Hours Post-Dose (n=8)	15.808 (± 2.0101)			
Cycle 3 Day 8, 168 Hours Post-Dose (n=7)	6.631 (± 3.8091)			
Cycle 3 Day 15, 336 Hours Post-Dose (n=7)	5.279 (± 1.9171)			
Cycle 4 Day 1, Pre-Dose (n=7)	3.252 (± 1.3859)			

Cycle 4 Day 1, 10 Minutes Post-Dose (n=7)	42.194 (± 8.8085)			
Cycle 5 Day 1, Pre-Dose (n=5)	2.734 (± 1.2045)			
Cycle 5 Day 1, 10 Minutes Post-Dose (n=5)	44.244 (± 27.1286)			
Cycle 6 Day 1, Pre-Dose (n=5)	2.854 (± 1.7255)			
Cycle 6 Day 1, 10 Minutes Post-Dose (n=5)	36.304 (± 12.1646)			
Cycle 6 Day 4, 72 Hours Post-Dose (n=5)	12.667 (± 3.4384)			
Cycle 6 Day 8, 168 Hours Post-Dose (n=5)	8.04 (± 3.1264)			
Cycle 7 Day 1, Pre-Dose (n=2)	1.997 (± 0.7877)			
Cycle 7 Day 1, 10 Minutes Post-Dose (n=2)	37.13 (± 4.9922)			
Cycle 8 Day 1, Pre-Dose (n=2)	1.901 (± 0.5834)			
Cycle 8 Day 1, 10 Minute Post-Dose (n=2)	66.24 (± 43.7558)			
Cycle 9 Day 1, Pre-Dose (n=2)	1.462 (± 0.4547)			
Cycle 9 Day 1, 10 Minutes Post-Dose (n=2)	34.79 (± 2.0789)			
Cycle 10 Day 1, Pre-Dose (n=1)	1.282 (± 0)			
Cycle 10 Day 1, 10 Minutes Post-Dose (n=1)	26.32 (± 0)			
End of Treatment (n=27)	2 (± 1.248)			

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 each 21-day cycle, 30 days after the last dose of study medication, and then every 12 weeks for up to an additional 6 months (Approximately 13.9 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	10	15	15	
Units: percentage of participants	50	64	73	

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 7.9 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	11	15	17	
Units: Participants	0	0	0	

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 7.9 Months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

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 IV infusion, Day 1 of each 21-day cycle, for up to 1 year or until disease progression or unacceptable toxicity occurs (Up to 10 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	19 / 43 (44.19%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration	Additional description: One treatment-emergent death occurred during treatment and is not related.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Device failure			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis	Additional description: One treatment-emergent death occurred during treatment and is not related.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bile duct obstruction			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure	Additional description: One treatment-emergent death occurred during treatment and is not related.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure	Additional description: One treatment-emergent death occurred during treatment and is not related.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Candida sepsis			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 43 (2.33%)		
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	42 / 43 (97.67%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	11		
Fatigue			

subjects affected / exposed	16 / 43 (37.21%)		
occurrences (all)	22		
Oedema peripheral			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Anxiety			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	8		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	7		
Thrombocytopenia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	10 / 43 (23.26%)		
occurrences (all)	14		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	19 / 43 (44.19%)		
occurrences (all)	23		
Dry mouth			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	14 / 43 (32.56%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	15		
Nausea			

subjects affected / exposed	17 / 43 (39.53%)		
occurrences (all)	19		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	6		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	9		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 43 (30.23%)		
occurrences (all)	15		
Dehydration			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	16		
Hypokalaemia			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	7		
Hyponatraemia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 4		

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