Clinical trial results:
A Phase 1 Dose Escalation Study of MLN8237, an Aurora A Kinase Inhibitor, in Adult Patients With Nonhematological Malignancies, Followed by a Phase 2 of MLN8237 in Lung, Breast, Head and Neck, or Gastroesophageal Malignancies.

Summary

EudraCT number	2008-006981-27
Trial protocol	CZ
Global end of trial date	25 April 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	C14007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01045421
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc
Sponsor organisation address	40 Landsdowne Street, Cambridge, United States, 02139
Public contact	Drug Information Call Center, Millennium Pharmaceuticals, Inc, 001 5107402412, medical@mlnm.com
Scientific contact	Drug Information Call Center, Millennium Pharmaceuticals, Inc, 001 5107402412, medical@mlnm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1: The primary objective of the phase 1 portion of this study is to assess the safety and tolerability of MLN8237, formulated as an enteric-coated tablet (ECT), on a 7-day dosing schedule for determining the recommended dose and schedule of MLN8237 to be used in phase 2.

Phase 2: The primary objective of the phase 2 portion of this study is to estimate the antitumor activity of MLN8237 as measured by overall response rate (ORR) in patients with advanced, unresectable nonhematological malignancies (NSCLC, SCLC, adenocarcinoma of the breast, HNSCC, or adenocarcinoma of the esophagus/gastroesophageal junction or stomach).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 155
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Czech Republic: 69
Country: Number of subjects enrolled	France: 40
Worldwide total number of subjects	273
EEA total number of subjects	118

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	180
From 65 to 84 years	92
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 42 investigative sites in France, Poland, the Czech Republic, and the United States from 16 February 2010 to 25 April 2014.

Pre-assignment

Screening details:

Subjects with a historical diagnosis of relapsed or refractory advanced nonhematological malignancies were enrolled in 1 of the 2 stages, Phase 1 (lead-in alisertib dose escalation stage) and Phase 2 (efficacy and safety assessment stage for alisertib dose determined in Phase 1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: MLN8237 10 mg

Arm description:

MLN8237 (alisertib) 10 milligram (mg), enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 10 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 1: MLN8237 20 mg

Arm description:

MLN8237 (alisertib) 20 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 20 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 1: MLN8237 40 mg

Arm description:

MLN8237 (alisertib) 40 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 40 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 1: MLN8237 50 mg

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 1: MLN8237 60 mg

Arm description:

MLN8237 (alisertib) 60 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 60 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 1: MLN8237 50 mg- Pancreatic Cancer

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with pancreatic cancer during Phase 1 portion of the study.

Arm type	Experimental

Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 2: MLN8237 50 mg- Breast Cancer

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with breast cancer during Phase 2 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 2: MLN8237 50 mg- Gastric Cancer

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with gastric cancer during Phase 2 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 2: MLN8237 50 mg- HNSCC

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with head and neck squamous cell carcinoma (HNSCC) during Phase 2 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of

rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 2: MLN8237 50 mg- NSCLC

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with non-small cell lung cancer (NSCLC) during Phase 2 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Arm title	Phase 2: MLN8237 50 mg- SCLC

Arm description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with small cell lung cancer (SCLC) during Phase 2 portion of the study.

Arm type	Experimental
Investigational medicinal product name	MLN8237 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy.

Number of subjects in period 1	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg
Started	1	3	4
Completed	1	3	4
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Death	-	-	-
Other	-	-	-
Progressive Disease	-	-	-

Number of subjects in period 1	Phase 1: MLN8237 50 mg	Phase 1: MLN8237 60 mg	Phase 1: MLN8237 50 mg- Pancreatic

			Cancer
Started	12	3	1
Completed	11	2	1
Not completed	1	1	0
Consent withdrawn by subject	1	-	-
Death	-	-	-
Other	-	-	-
Progressive Disease	-	1	-

Number of subjects in period 1	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC
Started	53	55	55
Completed	53	50	53
Not completed	0	5	2
Consent withdrawn by subject	-	-	-
Death	-	1	1
Other	-	3	-
Progressive Disease	-	1	1

Number of subjects in period 1	Phase 2: MLN8237 50 mg- NSCLC	Phase 2: MLN8237 50 mg- SCLC
Started	26	60
Completed	23	58
Not completed	3	2
Consent withdrawn by subject	-	-
Death	2	-
Other	-	1
Progressive Disease	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Included all subjects enrolled in this study.	

Reporting group values	Overall Trial	Total	
Number of subjects	273	273	
Age categorical Units: Subjects			
18-64 years	180	180	
65-84 years	92	92	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	117	117	
Male	156	156	
Race/Ethnicity Units: Subjects			
Hispanic or Latino	12	12	
Not Hispanic or Latino	248	248	
Not reported	13	13	
Race/Ethnicity Units: Subjects			
White	249	249	
Black or African American	15	15	
Asian	4	4	
Chinese	1	1	
Other	1	1	
Not reported	3	3	
Region of Enrollment Units: Subjects			
Czech Republic	69	69	
France	40	40	
Poland	9	9	
United States	155	155	
Disease stage at study entry Units: Subjects			
IA	1	1	
II	1	1	
III	4	4	
IIIA	3	3	
IIIB	10	10	
IIIC	1	1	
IV	201	201	
IVA	24	24	
IVB	3	3	
IVC	25	25	

Eastern Cooperative Oncology Group (ECOG) performance status			
ECOG performance status assesses a subject's physical ability on a 6-point scale: 0=fully active, able to carry on all predisease activities without restriction; 1=restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2=ambulatory (>50% of waking hours), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead.			
Units: Subjects			
0= Fully Active	85	85	
1= Restricted Activity	188	188	

Subject analysis sets

Subject analysis set title	Phase 1: MLN8237- All Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 10, 20, 30, 40, 50, or 60 mg enteric-coated tablets, orally, twice daily, for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects enrolled in dose-escalation or pancreatic cancer cohort during Phase 1 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- Breast Cancer
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with breast cancer during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- Gastric Cancer
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with gastric cancer during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- HNSCC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with HNSCC during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- NSCLC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with NSCLC during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- SCLC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with SCLC during Phase 2 portion of the study.

Subject analysis set title	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study. Included subjects from dose-escalation cohort or pancreatic cancer cohort who received alisertib 50 mg twice daily.

Subject analysis set title	Phase 1: MLN8237 60 mg
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 60 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Reporting group values	Phase 1: MLN8237- All Subjects	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer
Number of subjects	24	53	55
Age categorical Units: Subjects			
18-64 years	17	37	33
65-84 years	7	16	21
85 years and over	0	0	1
Gender categorical Units: Subjects			
Female	9	53	12
Male	15	0	43
Race/Ethnicity Units: Subjects			
Hispanic or Latino	3	4	2
Not Hispanic or Latino	19	48	49
Not reported	2	1	4
Race/Ethnicity Units: Subjects			
White	18	49	51
Black or African American	3	1	3
Asian	2	1	0
Chinese	0	0	0
Other	0	1	0
Not reported	1	1	1
Region of Enrollment Units: Subjects			
Czech Republic	0	19	20
France	0	10	8
Poland	0	1	0
United States	24	23	27
Disease stage at study entry Units: Subjects			
IA	1	0	0
II	0	0	0
III	1	0	1
IIIA	1	1	0
IIIB	0	3	0
IIIC	0	1	0

IV	19	48	54
IVA	1	0	0
IVB	1	0	0
IVC	0	0	0
Eastern Cooperative Oncology Group (ECOG) performance status			
ECOG performance status assesses a subject's physical ability on a 6-point scale: 0=fully active, able to carry on all predisease activities without restriction; 1=restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2=ambulatory (>50% of waking hours), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead.			
Units: Subjects			
0= Fully Active	4	23	21
1= Restricted Activity	20	30	34

Reporting group values	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC	Phase 2: MLN8237 50 mg- SCLC
Number of subjects	55	26	60
Age categorical Units: Subjects			
18-64 years	38	17	38
65-84 years	17	9	22
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	12	28
Male	52	14	32
Race/Ethnicity Units: Subjects			
Hispanic or Latino	1	1	1
Not Hispanic or Latino	50	25	57
Not reported	4	0	2
Race/Ethnicity Units: Subjects			
White	53	22	56
Black or African American	2	2	4
Asian	0	1	0
Chinese	0	1	0
Other	0	0	0
Not reported	0	0	0
Region of Enrollment Units: Subjects			
Czech Republic	8	7	15
France	11	3	8
Poland	1	0	7
United States	35	16	30
Disease stage at study entry Units: Subjects			
IA	0	0	0
II	1	0	0
III	2	0	0
IIIA	0	0	1
IIIB	0	5	2

IIIC	0	0	0
IV	2	21	57
IVA	23	0	0
IVB	2	0	0
IVC	25	0	0
Eastern Cooperative Oncology Group (ECOG) performance status			
ECOG performance status assesses a subject's physical ability on a 6-point scale: 0=fully active, able to carry on all predisease activities without restriction; 1=restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2=ambulatory (>50% of waking hours), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead.			
Units: Subjects			
0= Fully Active	17	7	13
1= Restricted Activity	38	19	47

Reporting group values	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)	Phase 1: MLN8237 60 mg	
Number of subjects	13	3	
Age categorical Units: Subjects			
18-64 years 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female Male			
Race/Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not reported			
Race/Ethnicity Units: Subjects			
White Black or African American Asian Chinese Other Not reported			
Region of Enrollment Units: Subjects			
Czech Republic France Poland United States			
Disease stage at study entry Units: Subjects			
IA II III			

IIIA IIIB IIIC IV IVA IVB IVC			
Eastern Cooperative Oncology Group (ECOG) performance status			
ECOG performance status assesses a subject's physical ability on a 6-point scale: 0=fully active, able to carry on all predisease activities without restriction; 1=restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2=ambulatory (>50% of waking hours), capable of all self care, unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4=completely disabled, cannot carry on any self care, totally confined to bed/chair; 5=dead.			
Units: Subjects			
0= Fully Active 1= Restricted Activity			

End points

End points reporting groups

Reporting group title	Phase 1: MLN8237 10 mg
Reporting group description:	
MLN8237 (alisertib) 10 milligram (mg), enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.	
Reporting group title	Phase 1: MLN8237 20 mg
Reporting group description:	
MLN8237 (alisertib) 20 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.	
Reporting group title	Phase 1: MLN8237 40 mg
Reporting group description:	
MLN8237 (alisertib) 40 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.	
Reporting group title	Phase 1: MLN8237 50 mg
Reporting group description:	
MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.	
Reporting group title	Phase 1: MLN8237 60 mg
Reporting group description:	
MLN8237 (alisertib) 60 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.	
Reporting group title	Phase 1: MLN8237 50 mg- Pancreatic Cancer
Reporting group description:	
MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with pancreatic cancer during Phase 1 portion of the study.	
Reporting group title	Phase 2: MLN8237 50 mg- Breast Cancer
Reporting group description:	
MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with breast cancer during Phase 2 portion of the study.	
Reporting group title	Phase 2: MLN8237 50 mg- Gastric Cancer
Reporting group description:	
MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with gastric cancer during Phase 2 portion of the study.	
Reporting group title	Phase 2: MLN8237 50 mg- HNSCC
Reporting group description:	
MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with head and neck squamous cell carcinoma (HNSCC) during Phase 2 portion of the study.	
Reporting group title	Phase 2: MLN8237 50 mg- NSCLC

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with non-small cell lung cancer (NSCLC) during Phase 2 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- SCLC

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with small cell lung cancer (SCLC) during Phase 2 portion of the study.

Subject analysis set title	Phase 1: MLN8237- All Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 10, 20, 30, 40, 50, or 60 mg enteric-coated tablets, orally, twice daily, for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects enrolled in dose-escalation or pancreatic cancer cohort during Phase 1 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- Breast Cancer
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with breast cancer during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- Gastric Cancer
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with gastric cancer during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- HNSCC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with HNSCC during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- NSCLC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with NSCLC during Phase 2 portion of the study.

Subject analysis set title	Phase 2: MLN8237 50 mg- SCLC
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with SCLC during Phase 2 portion of the study.

Subject analysis set title	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease,

unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study. Included subjects from dose-escalation cohort or pancreatic cancer cohort who received alisertib 50 mg twice daily.

Subject analysis set title	Phase 1: MLN8237 60 mg
Subject analysis set type	Full analysis

Subject analysis set description:

MLN8237 (alisertib) 60 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy during Phase 1 portion of the study.

Primary: Phase 1: Number of Subjects With Dose-Limiting Toxicities (DLTs)

End point title	Phase 1: Number of Subjects With Dose-Limiting Toxicities (DLTs)[1][2]

End point description:

Toxicity as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)v4.0.DLT=any of the following considered drug-related by investigator:Grade 4 (G4) neutropenia (absolute neutrophil count <500 cells/cubic meter [cells/mm^3]) for >7 days;G4 neutropenia with coincident fever;G4 thrombocytopenia for >7 days;Platelet count <10,000 cells/mm3;G3 thrombocytopenia, clinically significant bleeding;Delay in initiation of next cycle by >7 days due to treatment-related toxicity;>=G3 nonhematological toxicity except >=G3 nausea/emesis occurred in the absence of optimal antiemetic therapy;>=G3 diarrhea occurred in the absence of optimal supportive therapy with loperamide/comparable antidiarrheal;G3 fatigue for <1 week;Other G3 nonhematological toxicity that were safely,reliably controlled to <=G2 with treatment.DLT-Evaluable population:Phase 1 subjects who experienced DLT in Cycle 1/completed >=85% of planned alisertib doses,had sufficient follow-up data for DLT.

End point type	Primary

End point timeframe:

Cycle 1 of Phase 1

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: Statistical comparison was not planned to be reported for this outcome.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: DLTs were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	4	12
Units: subjects	0	0	0	2

End point values	Phase 1: MLN8237 60 mg	Phase 1: MLN8237 50 mg- Pancreatic Cancer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	1		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Subjects With Objective Response

End point title	Phase 2: Percentage of Subjects With Objective Response[3][4]

End point description:

Percentage of subjects with objective response based assessment of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis less than [<] 10 millimeter [mm]). No new lesions. PR was defined as greater than or equal to (>=) 30 percent (%) decrease under baseline of the sum of diameters of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. No unequivocal progression of non-target disease. No new lesions. Response-Evaluable population included all subjects with measurable disease who received at least 1 dose of alisertib and had at least 1 post-baseline response assessment.

End point type	Primary

End point timeframe:

Baseline until complete response or partial response, assessed every 2 cycles up to end of study (up to 50 cycles)

Notes:

[3] - 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: Statistical comparison was not planned to be reported for this outcome.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tumor assessment was planned to be performed for only the Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	47	45	23
Units: percentage of subjects				
number (confidence interval 95%)	18 (9 to 32)	9 (2 to 20)	9 (2 to 21)	4 (0 to 22)

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: percentage of subjects				
number (confidence interval 95%)	21 (10 to 35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS)[5]

End point description:

PFS was defined as the time from randomization (or the first dose of study treatment for non-randomized studies) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. Tumor progression as per RECIST 1.1 was defined as at least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1or more new lesions is also considered progression. Safety population included all subjects who received any amount of alisertib.

End point type	Secondary

End point timeframe:

Baseline until progressive disease, assessed every 2 cycles up to end of study (up to 50 cycles)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tumor assessment was planned to be performed for only the Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	55	55	26
Units: days				
median (confidence interval 95%)	164 (78 to 239)	49 (41 to 78)	72 (43 to 96)	92 (72 to 120)

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: days				
median (confidence interval 95%)	49 (42 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Disease Progression (TTP)

End point title	Phase 2: Time to Disease Progression (TTP)[6]

End point description:

Time in days from start of study treatment to first documentation of objective tumor progression. Tumor progression as per RECIST 1.1 was defined as at least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1or more new lesions is also considered progression. Safety population included all subjects who received any amount of alisertib.

End point type	Secondary

End point timeframe:

Baseline until disease progression, assessed every 2 cycles up to end of study (up to 50 cycles)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tumor assessment was planned to be performed for only the Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	55	55	26
Units: days				
median (confidence interval 95%)	164 (78 to 239)	46 (40 to 86)	72 (43 to 96)	92 (74 to 144)

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: days				
median (confidence interval 95%)	78 (42 to 114)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR)[7]

End point description:

Time in days from first documentation of objective tumor response to objective tumor progression/death due to any cancer. Duration of tumor response=(date of first documentation of objective tumor progression or death due to cancer minus date of first CR/PR that was subsequently confirmed plus 1).CR: complete disappearance of all target lesions, non-target disease, except nodal disease;all nodes decreased to normal; no new lesions.PR:>=30% decrease under baseline of sum of diameters of all target lesions; no unequivocal progression of non-target disease; no new lesions. Tumor progression: >=20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study; absolute increase of >=5 mm; appearance of >=1 new lesions is also considered progression. A subset of response-evaluable population who had objective tumor response. '+/-99999' in median and 95% CI=not estimable as the 1 participant in the group was censored.

End point type	Secondary

End point timeframe:

Baseline up to Week 50

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tumor assessment was planned to be performed for only the Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	4	4	1
Units: days				
median (confidence interval 95%)	169 (85 to 313)	198 (146 to 501)	79 (46 to 95)	99999 (-99999 to 99999)

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: days				
median (confidence interval 95%)	125 (93 to 365)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects Reporting One or More Treatment-emergent Adverse Events and Serious Adverse Events

End point title	Phase 2: Number of Subjects Reporting One or More Treatment-emergent Adverse Events and Serious Adverse Events[8]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; or congenital anomaly; or a medically important event. Safety population included all subjects who received any amount of alisertib.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after the last dose of study drug

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary outcome was planned to be summarized only for Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	55	55	26
Units: subjects				
Adverse Events	52	52	54	26
Serious Adverse Events	23	30	19	8

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: subjects				
Adverse Events	57			
Serious Adverse Events	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Cmax- Maximum Observed Plasma Concentration for Alisertib

End point title	Phase 1: Cmax- Maximum Observed Plasma Concentration for Alisertib[9]

End point description:

Maximum observed plasma concentration (Cmax) is the peak plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve. Pharmacokinetic (PK)-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Days 1 and 7 assessment were available. '99999' in geometric coefficient of variation (CV) signifies not available. For Phase 1, MLN8237 10 mg group, geometric CV was not estimable as only 1 subject was evaluable for this group. In addition, geometric CV was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Days 1 and 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours post-dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	4	13
Units: nanomole (nM)				
geometric mean (geometric coefficient				

of variation)				
Day 1 (n = 1, 3, 4, 13, 3)	297 (± 99999)	602 (± 15)	949 (± 49)	1619 (± 39)
Day 7 (n = 1, 3, 3, 12, 2)	981 (± 99999)	1279 (± 35)	1830 (± 39)	2907 (± 49)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: nanomole (nM)				
geometric mean (geometric coefficient of variation)				
Day 1 (n = 1, 3, 4, 13, 3)	1696 (± 37)			
Day 7 (n = 1, 3, 3, 12, 2)	3027 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Tmax- Time to Reach the Maximum Plasma Concentration (Cmax) for Alisertib

End point title	Phase 1: Tmax- Time to Reach the Maximum Plasma Concentration (Cmax) for Alisertib[10]

End point description:

Tmax: Time to reach the maximum plasma concentration (Cmax), equal to time (hours) to Cmax. PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Day 1 and Day 7 assessment were available. '99999' in full range signifies not available. Full range was not summarized if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Days 1 and 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	4	13
Units: hours				
median (full range (min-max))				
Day 1 (n = 1, 3, 4, 13, 3)	2.9 (2.9 to 2.9)	2 (2 to 2.9)	3.2 (2.8 to 6)	2.2 (1.7 to 11)
Day 7 (n = 1, 3, 3, 12, 2)	3.1 (3.1 to 3.1)	3 (1 to 6)	3 (2 to 6)	2.4 (0 to 8)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: hours				
median (full range (min-max))				
Day 1 (n = 1, 3, 4, 13, 3)	6 (3 to 7.9)			
Day 7 (n = 1, 3, 3, 12, 2)	2.8 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: AUC(0-tau): Area Under the Plasma Concentration-time Curve From Time 0 to Time Tau Over the Dosing Interval for Alisertib

End point title	Phase 1: AUC(0-tau): Area Under the Plasma Concentration-time Curve From Time 0 to Time Tau Over the Dosing Interval for Alisertib[11]

End point description:

Area under the plasma concentration-time curve during a dosing interval, where tau is the length of the dosing interval. PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Days 1 and 7 assessment were available. '99999' in geometric CV signifies not available. For Phase 1, MLN8237 10 mg group, geometric CV was not estimable as only 1 subject was evaluable for this group. In addition, geometric CV was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Days 1 and 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	4	13
Units: nanomole*hour (nM*hr)				
geometric mean (geometric coefficient of variation)				
Day 1 (n = 1, 3, 4, 13, 3)	2640 (± 99999)	3495 (± 19)	5015 (± 57)	10736 (± 48)
Day 7 (n = 1, 3, 3, 11, 2)	8660 (± 99999)	10184 (± 24)	13694 (± 59)	20867 (± 49)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: nanomole*hour (nM*hr)				
geometric mean (geometric coefficient of variation)				
Day 1 (n = 1, 3, 4, 13, 3) Day 7 (n = 1, 3, 3, 11, 2)	13932 (± 42) 28709 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Terminal Phase Elimination Half-life (T1/2) for Alisertib

End point title	Phase 1: Terminal Phase Elimination Half-life (T1/2) for Alisertib[12]

End point description:

Terminal phase elimination half-life (T1/2) is the time required for half of the drug to be eliminated from the plasma. PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Day 7 assessment was available. '99999' in standard deviation signifies not available. For Phase 1, MLN8237 10 mg group, standard deviation was not estimable as only 1 subject was evaluable for this group. In addition, standard deviation was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Day 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	2	9
Units: hours				
arithmetic mean (standard deviation)	20.6 (± 99999)	16 (± 1.2)	19 (± 99999)	20.8 (± 10.3)

End point values	Phase 1: MLN8237 60			

	mg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: hours				
arithmetic mean (standard deviation)	27.8 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Rac- Accumulation Ratio for Alisertib

End point title	Phase 1: Rac- Accumulation Ratio for Alisertib[13]

End point description:

Rac was estimated as a ratio of AUC (0-tau) at Day 7 and AUC (0-tau) at Day 1. Area under the plasma concentration-time curve during a dosing interval, where tau is the length of the dosing interval.PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Days 1 and 7 assessment were available. '99999' in standard deviation signifies not available. For Phase 1, MLN8237 10 mg group, standard deviation was not estimable as only 1 subject was evaluable for this group. In addition, standard deviation was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Days 1 and 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	3	11
Units: ratio				
arithmetic mean (standard deviation)	3.3 (± 99999)	3 (± 1)	2.3 (± 0.4)	2.2 (± 0.9)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: ratio				
arithmetic mean (standard deviation)	2.4 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Peak to Trough Ratio for Alisertib

End point title	Phase 1: Peak to Trough Ratio for Alisertib[14]

End point description:

Peak to trough ratio was estimated as a ratio of Cmax at Day 7 and the minimum observed plasma concentration (Ctrough) of alisertib at Day 7. Cmax is the peak plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve. Ctrough is the minimum plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve. PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Days 1 and 7 assessment were available. '99999' in standard deviation signifies not available. For Phase 1, MLN8237 10 mg group, standard deviation was not estimable as only 1 subject was evaluable for this group. In addition, standard deviation was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Day 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	3	11
Units: ratio				
arithmetic mean (standard deviation)	1.7 (± 99999)	2.1 (± 0.7)	2.3 (± 1.4)	2.3 (± 0.8)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: ratio				
arithmetic mean (standard deviation)	1.8 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Steady State Oral Clearance (CLss/F) for Alisertib

End point title	Phase 1: Steady State Oral Clearance (CLss/F) for Alisertib[15]

End point description:

CL/F is apparent clearance of the drug from the plasma, calculated as the drug dose divided AUC(0-tau), expressed in liter per hour (L/hr). PK-Evaluable population included all subjects who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters in Phase 1 where Day 7 assessment was available. '99999' in geometric CV signifies not available. For Phase 1, MLN8237 10 mg group, geometric CV was not estimable as only 1 subject was evaluable for this group. In addition, geometric CV was not estimated if evaluable participants were less than 3, as per investigator's discretion.

End point type	Secondary

End point timeframe:

Day 7: predose, 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours postdose

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were planned to be analyzed for only the Phase 1 portion of the study.

End point values	Phase 1: MLN8237 10 mg	Phase 1: MLN8237 20 mg	Phase 1: MLN8237 40 mg	Phase 1: MLN8237 50 mg (Including Pancreatic Cancer)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	1	3	3	11
Units: L/hr				
geometric mean (geometric coefficient of variation)	2.2 (± 99999)	3.8 (± 22)	5.6 (± 72)	4.6 (± 39)

End point values	Phase 1: MLN8237 60 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: L/hr				
geometric mean (geometric coefficient of variation)	4 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Relationship Between Clinical Response and Molecular Markers of Response

End point title	Phase 2: Relationship Between Clinical Response and Molecular Markers of Response[16]

End point description:

End point type	Secondary

End point timeframe:

12 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This outcome was planned to be performed for only the Phase 2 portion of the study.

End point values	Phase 2: MLN8237 50 mg- Breast Cancer	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	0[18]	0[19]	0[20]
Units: subjects				

Notes:

[17] - This endpoint was not analyzed.

[18] - This endpoint was not analyzed.

[19] - This endpoint was not analyzed.

[20] - This endpoint was not analyzed.

End point values	Phase 2: MLN8237 50 mg- SCLC			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: subjects				

Notes:

[21] - This endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of study drug and no more than 30 days after the last dose of study drug

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 subject or observed by the investigator was recorded, irrespective of the relation to study treatment. Dictionary version was not captured, hence 0.0 is mentioned here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0.0

Reporting groups

Reporting group title	Phase 1: MLN8237- Dose Escalation

Reporting group description:

MLN8237 (alisertib) 10, 20, 30, 40, 50, or 60 mg enteric-coated tablets, orally, twice daily, for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects enrolled in dose escalation cohort during Phase 1 portion of the study.

Reporting group title	Phase 1: MLN8237 50 mg- Pancreatic Cancer

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with pancreatic cancer during Phase 1 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- Breast Cancer

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with breast cancer during Phase 2 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- Gastric Cancer

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with gastric cancer during Phase 2 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- HNSCC

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with HNSCC during Phase 2 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- NSCLC

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with NSCLC during Phase 2 portion of the study.

Reporting group title	Phase 2: MLN8237 50 mg- SCLC

Reporting group description:

MLN8237 (alisertib) 50 mg, enteric-coated tablets, orally, twice daily for 7 days followed by 14 days of rest period in 21-day treatment cycles for a maximum of 24 months, or until progressive disease, unacceptable treatment-related toxicity, or initiation of a different anticancer therapy in subjects with

Serious adverse events	Phase 1: MLN8237-Dose Escalation	Phase 1: MLN8237 50 mg- Pancreatic Cancer	Phase 2: MLN8237 50 mg- Breast Cancer
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 23 (56.52%)	1 / 1 (100.00%)	23 / 53 (43.40%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal cancer			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 1 (100.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer stage unspecified			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour ulceration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oesophageal ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrin D dimer increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femoral neck fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sedation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 1 (100.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 1 (100.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	2 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphthous stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal incontinence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 1 (100.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 1 (100.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute generalised exanthematous pustulosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			

subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal disorder			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Decreased appetite			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 1 (100.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: MLN8237	Phase 2: MLN8237	Phase 2: MLN8237

	50 mg- Gastric Cancer	50 mg- HNSCC	50 mg- NSCLC
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 55 (54.55%)	19 / 55 (34.55%)	8 / 26 (30.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal cancer			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant pleural effusion			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic pain			

subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal cancer metastatic			
subjects affected / exposed	2 / 55 (3.64%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer stage unspecified			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour ulceration			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			

subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oesophageal ulcer			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	3 / 55 (5.45%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 55 (1.82%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hypothermia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oropharyngeal pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibrin D dimer increased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal compression fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sedation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 55 (0.00%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 55 (7.27%)	1 / 55 (1.82%)	3 / 26 (11.54%)
occurrences causally related to treatment / all	2 / 5	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 55 (3.64%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphthous stomatitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 55 (3.64%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 55 (5.45%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal incontinence			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 55 (3.64%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	2 / 55 (3.64%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute generalised exanthematous pustulosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal disorder			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	2 / 55 (3.64%)	0 / 55 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 55 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: MLN8237 50 mg- SCLC		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 60 (46.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal cancer			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant pleural effusion			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pancreatic carcinoma				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion malignant				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small cell lung cancer stage unspecified				
subjects affected / exposed	4 / 60 (6.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 4			
Tumour ulceration				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Bronchial obstruction				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Oesophageal ulcer				

subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	3 / 60 (5.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Fatigue				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				

subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Contrast media allergy				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchospasm				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Haemoptysis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal pain				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibrin D dimer increased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Haemoglobin decreased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arterial injury				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sedation			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Somnolence			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 60 (1.67%)		
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	5 / 60 (8.33%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Keratitis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aphthous stomatitis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colonic obstruction				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecal incontinence				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic ascites				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				

subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Acute generalised exanthematous pustulosis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary incontinence				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal disorder			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			

subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 60 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				

subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Deep vein thrombosis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1: MLN8237-Dose Escalation	Phase 1: MLN8237 50 mg- Pancreatic Cancer	Phase 2: MLN8237 50 mg- Breast Cancer
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	1 / 1 (100.00%)	52 / 53 (98.11%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	9

Weight decreased			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	5 / 53 (9.43%)
occurrences (all)	3	0	6
White blood cell count decreased			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	5 / 53 (9.43%)
occurrences (all)	8	0	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences (all)	2	0	7
Headache			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	11 / 53 (20.75%)
occurrences (all)	2	0	16
Somnolence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	15 / 53 (28.30%)
occurrences (all)	0	0	30
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 23 (17.39%)	1 / 1 (100.00%)	20 / 53 (37.74%)
occurrences (all)	6	2	35
Leukopenia			
subjects affected / exposed	8 / 23 (34.78%)	0 / 1 (0.00%)	18 / 53 (33.96%)
occurrences (all)	13	0	76
Neutropenia			
subjects affected / exposed	10 / 23 (43.48%)	0 / 1 (0.00%)	31 / 53 (58.49%)
occurrences (all)	17	0	159
Thrombocytopenia			
subjects affected / exposed	4 / 23 (17.39%)	1 / 1 (100.00%)	11 / 53 (20.75%)
occurrences (all)	6	1	19
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Fatigue			
subjects affected / exposed	13 / 23 (56.52%)	1 / 1 (100.00%)	29 / 53 (54.72%)
occurrences (all)	20	1	56

Oedema peripheral			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	9 / 53 (16.98%)
occurrences (all)	3	0	12
Pyrexia			
subjects affected / exposed	3 / 23 (13.04%)	0 / 1 (0.00%)	5 / 53 (9.43%)
occurrences (all)	4	0	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 23 (17.39%)	0 / 1 (0.00%)	9 / 53 (16.98%)
occurrences (all)	4	0	14
Abdominal pain upper			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	2 / 53 (3.77%)
occurrences (all)	2	0	3
Aphthous stomatitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	4 / 53 (7.55%)
occurrences (all)	1	0	5
Constipation			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	9 / 53 (16.98%)
occurrences (all)	2	0	12
Diarrhoea			
subjects affected / exposed	10 / 23 (43.48%)	0 / 1 (0.00%)	27 / 53 (50.94%)
occurrences (all)	19	0	58
Nausea			
subjects affected / exposed	11 / 23 (47.83%)	0 / 1 (0.00%)	15 / 53 (28.30%)
occurrences (all)	16	0	34
Stomatitis			
subjects affected / exposed	9 / 23 (39.13%)	0 / 1 (0.00%)	24 / 53 (45.28%)
occurrences (all)	16	0	43
Vomiting			
subjects affected / exposed	8 / 23 (34.78%)	1 / 1 (100.00%)	11 / 53 (20.75%)
occurrences (all)	9	1	20
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 23 (17.39%)	0 / 1 (0.00%)	9 / 53 (16.98%)
occurrences (all)	4	0	11
Dyspnoea			

subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	11 / 53 (20.75%)
occurrences (all)	2	0	15
Oropharyngeal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 23 (43.48%)	0 / 1 (0.00%)	26 / 53 (49.06%)
occurrences (all)	10	0	37
Dry skin			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	5 / 53 (9.43%)
occurrences (all)	0	0	7
Pruritus			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	6 / 53 (11.32%)
occurrences (all)	0	0	6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	3
Confusional state			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	3 / 53 (5.66%)
occurrences (all)	4	0	5
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 1 (0.00%)	6 / 53 (11.32%)
occurrences (all)	1	0	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 1 (0.00%)	6 / 53 (11.32%)
occurrences (all)	0	0	9
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	7 / 53 (13.21%)
occurrences (all)	2	0	10
Musculoskeletal pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 1 (0.00%)	4 / 53 (7.55%)
occurrences (all)	2	0	4
Infections and infestations			

Oral candidiasis			
subjects affected / exposed	5 / 23 (21.74%)	0 / 1 (0.00%)	5 / 53 (9.43%)
occurrences (all)	5	0	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 23 (56.52%)	0 / 1 (0.00%)	13 / 53 (24.53%)
occurrences (all)	16	0	17
Dehydration			
subjects affected / exposed	6 / 23 (26.09%)	0 / 1 (0.00%)	7 / 53 (13.21%)
occurrences (all)	6	0	7
Hypokalaemia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 1 (100.00%)	5 / 53 (9.43%)
occurrences (all)	2	2	6

Non-serious adverse events	Phase 2: MLN8237 50 mg- Gastric Cancer	Phase 2: MLN8237 50 mg- HNSCC	Phase 2: MLN8237 50 mg- NSCLC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 55 (94.55%)	54 / 55 (98.18%)	26 / 26 (100.00%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 55 (1.82%)	1 / 55 (1.82%)	2 / 26 (7.69%)
occurrences (all)	3	1	3
Weight decreased			
subjects affected / exposed	2 / 55 (3.64%)	6 / 55 (10.91%)	2 / 26 (7.69%)
occurrences (all)	2	7	4
White blood cell count decreased			
subjects affected / exposed	4 / 55 (7.27%)	4 / 55 (7.27%)	1 / 26 (3.85%)
occurrences (all)	8	6	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 55 (3.64%)	6 / 55 (10.91%)	5 / 26 (19.23%)
occurrences (all)	2	7	5
Headache			
subjects affected / exposed	1 / 55 (1.82%)	6 / 55 (10.91%)	4 / 26 (15.38%)
occurrences (all)	1	8	5
Somnolence			

subjects affected / exposed	8 / 55 (14.55%)	11 / 55 (20.00%)	3 / 26 (11.54%)
occurrences (all)	10	16	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	37 / 55 (67.27%)	24 / 55 (43.64%)	13 / 26 (50.00%)
occurrences (all)	25	28	22
Leukopenia			
subjects affected / exposed	8 / 55 (14.55%)	14 / 55 (25.45%)	7 / 26 (26.92%)
occurrences (all)	19	30	14
Neutropenia			
subjects affected / exposed	23 / 55 (41.82%)	25 / 55 (45.45%)	15 / 26 (57.69%)
occurrences (all)	64	55	32
Thrombocytopenia			
subjects affected / exposed	14 / 55 (25.45%)	7 / 55 (12.73%)	6 / 26 (23.08%)
occurrences (all)	27	14	9
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 55 (7.27%)	5 / 55 (9.09%)	3 / 26 (11.54%)
occurrences (all)	4	6	3
Fatigue			
subjects affected / exposed	24 / 55 (43.64%)	26 / 55 (47.27%)	15 / 26 (57.69%)
occurrences (all)	33	37	15
Oedema peripheral			
subjects affected / exposed	11 / 55 (20.00%)	2 / 55 (3.64%)	3 / 26 (11.54%)
occurrences (all)	13	2	3
Pyrexia			
subjects affected / exposed	13 / 55 (23.64%)	11 / 55 (20.00%)	3 / 26 (11.54%)
occurrences (all)	14	14	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 55 (5.45%)	1 / 26 (3.85%)
occurrences (all)	6	3	1
Abdominal pain upper			
subjects affected / exposed	6 / 55 (10.91%)	1 / 55 (1.82%)	1 / 26 (3.85%)
occurrences (all)	9	1	2
Aphthous stomatitis			

subjects affected / exposed	6 / 55 (10.91%)	3 / 55 (5.45%)	0 / 26 (0.00%)
occurrences (all)	7	3	0
Constipation			
subjects affected / exposed	11 / 55 (20.00%)	9 / 55 (16.36%)	5 / 26 (19.23%)
occurrences (all)	14	10	6
Diarrhoea			
subjects affected / exposed	21 / 55 (38.18%)	15 / 55 (27.27%)	9 / 26 (34.62%)
occurrences (all)	30	25	13
Nausea			
subjects affected / exposed	18 / 55 (32.73%)	14 / 55 (25.45%)	12 / 26 (46.15%)
occurrences (all)	26	18	17
Stomatitis			
subjects affected / exposed	11 / 55 (20.00%)	14 / 55 (25.45%)	4 / 26 (15.38%)
occurrences (all)	14	18	7
Vomiting			
subjects affected / exposed	16 / 55 (29.09%)	13 / 55 (23.64%)	6 / 26 (23.08%)
occurrences (all)	27	24	18
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 55 (1.82%)	10 / 55 (18.18%)	3 / 26 (11.54%)
occurrences (all)	1	10	3
Dyspnoea			
subjects affected / exposed	9 / 55 (16.36%)	9 / 55 (16.36%)	3 / 26 (11.54%)
occurrences (all)	11	13	4
Oropharyngeal pain			
subjects affected / exposed	2 / 55 (3.64%)	2 / 55 (3.64%)	1 / 26 (3.85%)
occurrences (all)	2	3	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 55 (38.18%)	24 / 55 (43.64%)	11 / 26 (42.31%)
occurrences (all)	26	29	12
Dry skin			
subjects affected / exposed	2 / 55 (3.64%)	4 / 55 (7.27%)	2 / 26 (7.69%)
occurrences (all)	2	5	2
Pruritus			

subjects affected / exposed	6 / 55 (10.91%)	2 / 55 (3.64%)	1 / 26 (3.85%)
occurrences (all)	6	3	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 55 (9.09%)	2 / 55 (3.64%)	0 / 26 (0.00%)
occurrences (all)	5	2	0
Confusional state			
subjects affected / exposed	1 / 55 (1.82%)	2 / 55 (3.64%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Insomnia			
subjects affected / exposed	7 / 55 (12.73%)	6 / 55 (10.91%)	3 / 26 (11.54%)
occurrences (all)	7	6	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 55 (7.27%)	4 / 55 (7.27%)	4 / 26 (15.38%)
occurrences (all)	4	4	4
Back pain			
subjects affected / exposed	6 / 55 (10.91%)	4 / 55 (7.27%)	3 / 26 (11.54%)
occurrences (all)	6	4	3
Musculoskeletal pain			
subjects affected / exposed	0 / 55 (0.00%)	5 / 55 (9.09%)	3 / 26 (11.54%)
occurrences (all)	0	5	3
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	2 / 55 (3.64%)	3 / 55 (5.45%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 55 (27.27%)	12 / 55 (21.82%)	5 / 26 (19.23%)
occurrences (all)	19	15	10
Dehydration			
subjects affected / exposed	3 / 55 (5.45%)	2 / 55 (3.64%)	3 / 26 (11.54%)
occurrences (all)	3	2	5
Hypokalaemia			
subjects affected / exposed	4 / 55 (7.27%)	2 / 55 (3.64%)	2 / 26 (7.69%)
occurrences (all)	6	2	2

Non-serious adverse events	Phase 2: MLN8237 50 mg- SCLC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 60 (91.67%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	18		
Weight decreased			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	8		
White blood cell count decreased			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	32		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	11		
Somnolence			
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 60 (26.67%)		
occurrences (all)	22		
Leukopenia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	21 / 60 (35.00%)		
occurrences (all)	50		
Thrombocytopenia			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	17		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	27 / 60 (45.00%)		
occurrences (all)	28		
Oedema peripheral			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Aphthous stomatitis			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	17 / 60 (28.33%)		
occurrences (all)	31		
Nausea			
subjects affected / exposed	18 / 60 (30.00%)		
occurrences (all)	20		
Stomatitis			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	12		
Vomiting			

subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	9		
Oropharyngeal pain			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	16 / 60 (26.67%)		
occurrences (all)	18		
Dry skin			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		

Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5 3 / 60 (5.00%) 3		
Infections and infestations Oral candidiasis subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	18 / 60 (30.00%) 22 4 / 60 (6.67%) 4 4 / 60 (6.67%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2010	1. Clarified that if treatment was delayed for more than 2 weeks (that is, a rest period of more than 28 days) because of incomplete recovery from treatment-related toxicity, the patient was to be removed from the study. 2. Changed the reporting period for nonserious AEs from "through 30 days after the last dose of study drug" to "through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurred first."
07 July 2010	1. Remove the originally planned 14-day (28-day cycle) dosing schedule in phase 1, and to revise the Schedule of Events for phases 1 and 2 to reflect a 7-day dosing schedule in a 21-day cycle. 2. Enrollment in the phase 1 pancreatic cancer cohort was discontinued approximately 8 months after enrollment was opened because of slow subject accrual.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported