Clinical trial results:
An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS Mutations

Summary

EudraCT number	2015-004535-12
Trial protocol	ES BE NL GB
Global end of trial date	14 December 2020

Results information

Result version number	v1 (current)
This version publication date	07 April 2022
First version publication date	07 April 2022

Trial information

Trial identification

Sponsor protocol code	KO-TIP-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02383927
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kura Oncology, Inc
Sponsor organisation address	12730 High Bluff Drive, San Diego, United States, CA 92130
Public contact	Information desk, Kura Oncology, Inc., 1 8585008800, info@kuraoncology.com
Scientific contact	Information desk, Kura Oncology, Inc., 1 8585008800, info@kuraoncology.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	14 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2020
Global end of trial reached?	Yes
Global end of trial date	14 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the antitumour activity in terms of objective response rate (ORR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, HRAS mutant non-haematological malignancies.

Subjects with HRAS mutations and the following cancers were enrolled in 4 cohorts: thyroid cancer, any solid tumour, head and neck squamous cell cancer (HNSCC), or squamous cell carcinoma (SCC) excluding HNSCC.

Protection of trial subjects:

The protocol, informed consent form (ICF), and other relevant study documentation were approved by the independent ethics committee (IEC)/institutional review boards (IRBs) before initiation of the study. Protocol amendments were approved before initiation, as required.

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Subjects (or their legally acceptable representatives if applicable) provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. No study procedures were performed unless the subject had consented to taking part in the study.

Background therapy:

Supportive care medications considered necessary for the subject’s safety and well-being could be given at the discretion of the Investigator. Additional concomitant therapy that became necessary during the trial and any change to concomitant drugs were recorded.

The following treatments were allowed during the trial:
- Correction of electrolyte deficiency
- Radiotherapy for pain control against non-target lesions if it did not influence bone marrow function
- Total tumour resection in responding subjects who had become candidates for curative resection
- Haematopoietic growth factors and transfusions of blood or blood products in subjects who were experiencing haematological toxicity in accordance with standard institutional practice (not prior to haematological findings unless absolutely clinically necessary and after discussion with the Sponsor’s medical monitor).
- Antiemetic therapy in a subject experiencing gastrointestinal symptoms in accordance with standard clinical practice. If a subject experienced vomiting or nausea, prophylactic antiemetic medications could be administered with subsequent treatment in accordance with standard clinical practice.
- Concurrent use of bisphosphonates as well as thyroid-stimulating hormone (TSH) suppressive therapy

Evidence for comparator:

Not applicable in this non-comparator study.

Actual start date of recruitment	13 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Korea, Republic of: 2
Worldwide total number of subjects	63
EEA total number of subjects	17

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)	38
From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects with thyroid cancer with HRAS mutations were enrolled in Cohort 1;
Subjects with any solid tumour with HRAS mutation were enrolled in Stage 1 of Cohort 2;
Subjects with HNSCC with HRAS mutations were enrolled in Stage 2 of Cohort 2;
Subjects with any SCC (excluding HNSCC) with HRAS mutation were enrolled in Cohort 3.

Pre-assignment

Screening details:

Only consented subjects who met all the eligibility criteria were enrolled in the study. All screening evaluations were to be completed within 4 weeks (28 days) of Cycle 1 Day 1. Screen failure information was not included in the database, therefore screen failures are not reported.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding was used; this was an open-label study with no placebo or comparators.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects with thyroid cancer with HRAS mutations.

Arm type	Experimental
Investigational medicinal product name	Tipifarnib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tipifarnib as monotherapy at a starting dose of 900 mg or 600 mg orally twice daily (BID) on Days 1-7 and 15-21 of each 28-day treatment cycle. The tipifarnib starting dose was updated throughout the study based on emerging data.

On Cycle 1 Day 1, subjects were provided with tipifarnib plus diaries with instructions to record the date and time of each dose.

In the absence of unacceptable tipifarnib-related emergent toxicity or disease progression, subjects could receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may have continued upon agreement of the Investigator and the Sponsor.

Arm title	Cohort 2/Stage 1

Arm description:

Subjects with any solid tumour with HRAS mutation.

Arm type	Experimental
Investigational medicinal product name	Tipifarnib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tipifarnib as monotherapy at a starting dose of 900 mg or 600 mg orally twice daily (BID) on Days 1-7 and 15-21 of each 28-day treatment cycle. The tipifarnib starting dose was updated throughout the study based on emerging data.

On Cycle 1 Day 1, subjects were provided with tipifarnib plus diaries with instructions to record the date and time of each dose.

In the absence of unacceptable tipifarnib-related emergent toxicity or disease progression, subjects could receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may have continued upon agreement of the Investigator and the Sponsor.

Arm title	Cohort 2/Stage 2

Arm description:

Subjects with HNSCC with HRAS mutations.

Arm type	Experimental
Investigational medicinal product name	Tipifarnib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tipifarnib as monotherapy at a starting dose of 900 mg or 600 mg orally twice daily (BID) on Days 1-7 and 15-21 of each 28-day treatment cycle. The tipifarnib starting dose was updated throughout the study based on emerging data.

On Cycle 1 Day 1, subjects were provided with tipifarnib plus diaries with instructions to record the date and time of each dose.

In the absence of unacceptable tipifarnib-related emergent toxicity or disease progression, subjects could receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may have continued upon agreement of the Investigator and the Sponsor.

Arm title	Cohort 3

Arm description:

Subjects with any SCC (excluding HNSCC) with HRAS mutation.

Arm type	Experimental
Investigational medicinal product name	Tipifarnib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tipifarnib as monotherapy at a starting dose of 900 mg or 600 mg orally twice daily (BID) on Days 1-7 and 15-21 of each 28-day treatment cycle. The tipifarnib starting dose was updated throughout the study based on emerging data.

On Cycle 1 Day 1, subjects were provided with tipifarnib plus diaries with instructions to record the date and time of each dose.

In the absence of unacceptable tipifarnib-related emergent toxicity or disease progression, subjects could receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may have continued upon agreement of the Investigator and the Sponsor.

Number of subjects in period 1	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2
Started	13	10	30
Completed	0	0	0
Not completed	13	10	30
Physician decision	-	-	2
Adverse event, non-fatal	4	1	3
Termination by symptomatic deterioration	-	-	6
Other reasons	1	-	-
Study Terminated by Sponsor	-	-	-
Subject request to withdraw from treatment	-	1	4
Disease Progression	8	8	15

Number of subjects in period 1	Cohort 3
Started	10
Completed	0
Not completed	10
Physician decision	-
Adverse event, non-fatal	5
Termination by symptomatic deterioration	-
Other reasons	-
Study Terminated by Sponsor	1
Subject request to withdraw from treatment	-
Disease Progression	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Subjects with thyroid cancer with HRAS mutations.	
Reporting group title	Cohort 2/Stage 1
Reporting group description:	
Subjects with any solid tumour with HRAS mutation.	
Reporting group title	Cohort 2/Stage 2
Reporting group description:	
Subjects with HNSCC with HRAS mutations.	
Reporting group title	Cohort 3
Reporting group description:	
Subjects with any SCC (excluding HNSCC) with HRAS mutation.	

Reporting group values	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2
Number of subjects	13	10	30
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.7	59.1	61.0
standard deviation	± 7.4	± 16.9	± 14.4
Gender categorical Units: Subjects			
Female	4	2	8
Male	9	8	22
ECOG performance score Units: Subjects			
Performance score 0	7	3	3
Performance score 1	6	7	27
Type of tumour			
Type of solid tumour at enrolment in the trial.			
Units: Subjects			
Thyroid	13	0	0
Head and neck	0	0	30
Salivary	0	7	0
Skin	0	0	0
Other	0	3	0
Stage of cancer			
Stage of cancer at enrolment			
Units: Subjects			
Stage I	0	0	0
Stage II	0	0	2
Stage III	1	1	2
Stage IV	12	9	26

Reporting group values	Cohort 3	Total	
Number of subjects	10	63	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	67.0		
standard deviation	± 11.7	-	
Gender categorical Units: Subjects			
Female	5	19	
Male	5	44	
ECOG performance score Units: Subjects			
Performance score 0	1	14	
Performance score 1	9	49	
Type of tumour			
Type of solid tumour at enrolment in the trial.			
Units: Subjects			
Thyroid	0	13	
Head and neck	0	30	
Salivary	0	7	
Skin	4	4	
Other	6	9	
Stage of cancer			
Stage of cancer at enrolment			
Units: Subjects			
Stage I	1	1	
Stage II	0	2	
Stage III	0	4	
Stage IV	9	56	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects with thyroid cancer with HRAS mutations.	
Reporting group title	Cohort 2/Stage 1
Reporting group description: Subjects with any solid tumour with HRAS mutation.	
Reporting group title	Cohort 2/Stage 2
Reporting group description: Subjects with HNSCC with HRAS mutations.	
Reporting group title	Cohort 3
Reporting group description: Subjects with any SCC (excluding HNSCC) with HRAS mutation.	

Primary: Antitumor activity by overall objective response rate

End point title	Antitumor activity by overall objective response rate[1]

End point description:

The ORR of tipifarnib was response assessments according to RECIST 1.1.
The estimate of the ORR was calculated based on the maximum likelihood estimator (i.e., crude proportion of subjects whose best overall response was complete response [CR] or partial response [PR]). The estimate of the ORR was accompanied by 2-sided 95% confidence interval (CI) .The 95% CI was estimated using the Wilson score test-based method.

End point type	Primary

End point timeframe:

From baseline to end of follow-up.

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: No hypothesis testing was planned for efficacy data in this open-label, multicentre, Phase 2 study investigating antitumour activity of tipifarnib in different cohorts of patients with locally advanced unresectable or metastatic, relapsed, and/or refractory tumours that carried HRAS mutations and for whom there was no standard curative therapy available.

End point values	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	23	7
Units: percent				
number (confidence interval 95%)	0.0 (0.0 to 25.9)	0.0 (0.0 to 32.4)	43.5 (25.6 to 63.2)	28.6 (8.2 to 64.1)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) was defined as the time (in months) from first dose (Cycle 1 Day 1) to either first observation of PD or occurrence of death due to any cause within 126 days (approximately 2 time-intervals for tumour assessments) of either first administration of tipifarnib or the last tumour assessment. Observation of PD could have been by either documented radiographic progression (i.e., scan results) or documentation of symptomatic or clinical progression agreed upon and documented by investigators. In subjects without a progression date or with a death date more than 126 days after the first administration of study drugs or the last tumour assessment, the PFS time should have been censored on the date of last tumour assessment or date of first administration of study tipifarnib.

End point type	Other pre-specified

End point timeframe:

From baseline to end of follow-up.

End point values	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	23	7
Units: months				
median (confidence interval 95%)	4.6 (3.1 to 8.4)	6.4 (1.8 to 10.3)	5.5 (3.6 to 9.2)	8.0 (3.7 to 9.3)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of response (DOR)

End point title	Duration of response (DOR)[2]

End point description:

DOR was the number of days from start date of PR or CR (whichever response was achieved first) to the first date that PD was documented (in subjects with an objective response). Disease progression was determined by the Investigator using RECIST 1.1.
The DOR was right-censored at the date for subjects who achieved CR or PR and met one of the following conditions: 1) when non-protocol anticancer treatment started before documentation of disease progression, 2) when death prior to documented disease progression or documented disease progression after more than 1 missed disease assessment visit, or 3) when alive and did not have documentation of disease progression before a data analysis cut-off date (therefore, analysis cut-off date was used as the censoring date).
Data are presented for cohorts for which median and 95% CI were calculable (Kaplan-Meier analysis) (only Cohort 2/Stage 2).

End point type	Other pre-specified

End point timeframe:

From baseline to end of follow-up.

Notes:

[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: The 95% CI for median DOR was not calculable for Cohorts 1, 2/1, and 3, therefore data for these cohorts were not presented for this endpoint.

End point values	Cohort 2/Stage 2			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: months				
median (confidence interval 95%)	6.2 (3.8 to 14.7)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival

End point title	Overall survival[3]

End point description:

An analysis of overall survival (OS) was conducted to estimate median OS time and corresponding 95% CI and provide a by-subject summary. OS was defined as the time (in months) from first dose (Cycle 1 Day 1) to the occurrence of death due to any cause. In subjects without a death date, the OS was censored on 1) the last date of survival status if alive, 2) a data analysis cut-off date for subjects with no survival status documentation, or 3) the date a subject withdrew consent or was lost to follow-up if there was no additional information.
Data are presented for cohorts for which median and 95% CI were calculable (Kaplan-Meier analysis) (i.e., for all cohorts except Cohort 1). For Cohort 1, the median OS was 36.7 months (95% CI: 8.7; not available).

End point type	Other pre-specified

End point timeframe:

From baseline to end of follow-up.

Notes:

[3] - 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: The 95% CI for median survival was not calculable for Cohort 1, therefore data for this cohort were not presented for this endpoint.

End point values	Cohort 2/Stage 1	Cohort 2/Stage 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	23	7	
Units: months				
median (confidence interval 95%)	13.8 (5.3 to 29.9)	10.8 (7.0 to 14.0)	10.4 (6.2 to 16.1)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Antitumor activity - best overall response

End point title	Antitumor activity - best overall response

End point description:

Best overall response according to RECIST version 1.1 was summarised using descriptive statistics.

End point type	Other pre-specified

End point timeframe:

From baseline to end of follow-up.

End point values	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2	Cohort 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	23	7
Units: Subjects				
Complete response	0	0	0	0
Partial response	0	0	10	2
Stable disease	9	6	11	4
Progressive disease	2	2	2	1
Not evaluable	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first signature of informed consent through the post-treatment follow-up period, defined as 30 days from final administration of study drug or immediately before initiation of any other anticancer therapy, whichever came first.

Adverse event reporting additional description:

The 5% cut-off for reporting of non-SAEs here was based on the percentages within individual cohorts.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Subjects with thyroid cancer with HRAS mutations.
Note, deaths due to the underlying condition were not reported as AEs.

Reporting group title	Cohort 2/Stage 1

Reporting group description:

Subjects with any solid tumour with HRAS mutation.
Note, deaths due to the underlying condition were not reported as AEs.

Reporting group title	Cohort 2/Stage 2

Reporting group description:

Subjects with HNSCC with HRAS mutations.
Note, deaths due to the underlying condition were not reported as AEs.

Reporting group title	Cohort 3

Reporting group description:

Subjects with any SCC (excluding HNSCC) with HRAS mutation.
Note, deaths due to the underlying condition were not reported as AEs.

Serious adverse events	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	5 / 10 (50.00%)	20 / 30 (66.67%)
number of deaths (all causes)	6	9	24
number of deaths resulting from adverse events	0	1	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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 pain			

subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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
Discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
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 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Laryngeal obstruction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Atelectasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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
Fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
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 compression fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Atrial fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hemiplegia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	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	0 / 13 (0.00%)	0 / 10 (0.00%)	3 / 30 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (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
Pancytopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (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
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (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
Enterocolitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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
Soft tissue haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
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 column stenosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	3 / 30 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (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

Herpes zoster			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
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	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	2 / 10 (20.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Discomfort				
subjects affected / exposed	0 / 10 (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 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Hypoxia				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal obstruction				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal oedema				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngeal haemorrhage				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphocyte count decreased				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sinus node dysfunction				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Encephalopathy				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Febrile neutropenia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue haemorrhage				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Pain in extremity				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 10 (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 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 10 (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	Cohort 1	Cohort 2/Stage 1	Cohort 2/Stage 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	10 / 10 (100.00%)	29 / 30 (96.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2

Tumour haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 13 (15.38%)	2 / 10 (20.00%)	1 / 30 (3.33%)
occurrences (all)	9	2	1
Blood pressure fluctuation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 13 (76.92%)	4 / 10 (40.00%)	15 / 30 (50.00%)
occurrences (all)	14	4	20
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	6 / 30 (20.00%)
occurrences (all)	1	2	6
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 10 (30.00%)	4 / 30 (13.33%)
occurrences (all)	1	4	6
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	2 / 10 (20.00%)	4 / 30 (13.33%)
occurrences (all)	1	2	4
Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	5 / 30 (16.67%)
occurrences (all)	0	1	6
Chills			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Face oedema			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	4
Malaise			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	0	2	2
Mucosal inflammation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Feeling hot			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Temperature intolerance			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hernia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	4 / 30 (13.33%)
occurrences (all)	2	1	5
Cough			
subjects affected / exposed	1 / 13 (7.69%)	2 / 10 (20.00%)	4 / 30 (13.33%)
occurrences (all)	1	3	4
Dyspnoea exertional			
subjects affected / exposed	0 / 13 (0.00%)	2 / 10 (20.00%)	1 / 30 (3.33%)
occurrences (all)	0	3	1
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Dysphonia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lung consolidation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 13 (15.38%)	2 / 10 (20.00%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Insomnia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	1 / 30 (3.33%)
occurrences (all)	3	2	1
Confusional state			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Mental status changes			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Claustrophobia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Nervousness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Delirium			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 13 (23.08%)	4 / 10 (40.00%)	7 / 30 (23.33%)
occurrences (all)	5	6	8
Weight decreased			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	7 / 30 (23.33%)
occurrences (all)	3	2	8
Blood bilirubin increased			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	2	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Bilirubin conjugated increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Blood urea increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Blood glucose increased			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Protein urine present			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Prothrombin time prolonged			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood calcitonin increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count decreased			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	3 / 30 (10.00%)
occurrences (all)	6	3	4
Platelet count decreased			

subjects affected / exposed	4 / 13 (30.77%)	5 / 10 (50.00%)	4 / 30 (13.33%)
occurrences (all)	6	8	5
White blood cell count decreased			
subjects affected / exposed	3 / 13 (23.08%)	3 / 10 (30.00%)	5 / 30 (16.67%)
occurrences (all)	10	5	9
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)	3 / 10 (30.00%)	5 / 30 (16.67%)
occurrences (all)	0	8	6
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Wound complication			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 10 (20.00%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Left ventricular dysfunction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	6 / 30 (20.00%)
occurrences (all)	5	2	6
Headache			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	2	1	3
Paraesthesia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	3	0	2
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	2 / 10 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Tremor			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Cognitive disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Ataxia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

Post herpetic neuralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dizziness postural			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 13 (69.23%)	5 / 10 (50.00%)	19 / 30 (63.33%)
occurrences (all)	11	12	32
Neutropenia			
subjects affected / exposed	6 / 13 (46.15%)	2 / 10 (20.00%)	4 / 30 (13.33%)
occurrences (all)	10	3	15
Leukopenia			
subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Thrombocytopenia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Lymphopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Leukocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Lymphocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Cerumen impaction			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Asthenopia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Eye swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Glaucoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Ocular hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 13 (69.23%)	5 / 10 (50.00%)	16 / 30 (53.33%)
occurrences (all)	13	8	24
Vomiting			
subjects affected / exposed	4 / 13 (30.77%)	2 / 10 (20.00%)	14 / 30 (46.67%)
occurrences (all)	4	9	18
Diarrhoea			
subjects affected / exposed	6 / 13 (46.15%)	2 / 10 (20.00%)	10 / 30 (33.33%)
occurrences (all)	10	2	14
Constipation			
subjects affected / exposed	5 / 13 (38.46%)	5 / 10 (50.00%)	8 / 30 (26.67%)
occurrences (all)	6	5	8
Abdominal pain			
subjects affected / exposed	2 / 13 (15.38%)	2 / 10 (20.00%)	3 / 30 (10.00%)
occurrences (all)	3	2	3
Dysphagia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	5 / 30 (16.67%)
occurrences (all)	0	1	5
Dry mouth			
subjects affected / exposed	4 / 13 (30.77%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	4	0	2
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Abdominal distension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Mouth haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Oral pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	5
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Faeces soft			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastritis			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 13 (15.38%)	3 / 10 (30.00%)	4 / 30 (13.33%)
occurrences (all)	2	3	6
Rash			
subjects affected / exposed	3 / 13 (23.08%)	1 / 10 (10.00%)	4 / 30 (13.33%)
occurrences (all)	5	1	4
Alopecia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Rash maculo-papular			
subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Dry skin			
subjects affected / exposed	1 / 13 (7.69%)	2 / 10 (20.00%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Swelling face			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pain of skin			

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Haematuria			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Pollakiuria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Dysuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Polyuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	3 / 30 (10.00%)
occurrences (all)	2	0	4
Neck pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	3 / 30 (10.00%)
occurrences (all)	2	1	3
Arthralgia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	2
Muscular weakness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Trismus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Groin pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Soft tissue haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Skin infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 10 (20.00%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Wound infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Bacterial infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Epididymitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Erysipelas			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 13 (46.15%)	1 / 10 (10.00%)	6 / 30 (20.00%)
occurrences (all)	10	1	6

Hypomagnesaemia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	6 / 30 (20.00%)
occurrences (all)	4	2	7
Hypokalaemia			
subjects affected / exposed	3 / 13 (23.08%)	1 / 10 (10.00%)	3 / 30 (10.00%)
occurrences (all)	6	1	3
Dehydration			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Hyperglycaemia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 10 (20.00%)	0 / 30 (0.00%)
occurrences (all)	4	2	0
Hypercalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Hypocalcaemia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	2 / 30 (6.67%)
occurrences (all)	0	1	3
Hypoalbuminaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	2
Hypermagnesaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 3		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	9 / 10 (90.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tumour haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood pressure fluctuation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Deep vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pain			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Feeling hot			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Temperature intolerance			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hernia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Lung consolidation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Upper respiratory tract congestion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Mental status changes			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Claustrophobia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervousness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Delirium			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	10		
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bilirubin conjugated increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood urea increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood glucose increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood lactate dehydrogenase increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood phosphorus increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood potassium increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood thyroid stimulating hormone decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Haemoglobin decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Protein total decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Protein urine present				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Prothrombin time prolonged				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood calcitonin increased				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	6		
White blood cell count decreased			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Wound complication			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Left ventricular dysfunction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysarthria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ataxia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Lethargy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Post herpetic neuralgia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Dizziness postural subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 15			
Neutropenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Leukopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2			
Lymphopenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Leukocytosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0			
Lymphocytopenia				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cerumen impaction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Asthenopia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eye swelling			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Glaucoma			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Ocular hypertension			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Constipation			

subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Dysphagia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Dry mouth				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	2			
Stomatitis				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Abdominal distension				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Mouth haemorrhage				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Oral pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Abdominal discomfort				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Faeces discoloured				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Faeces soft			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Swelling face			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eczema			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pain of skin			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nocturia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Renal impairment			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Trismus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Soft tissue haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Arthritis			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Wound infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Bacterial infection			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epididymitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Erysipelas			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Hypermagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2015	• Changed secondary objectives and endpoints of PFS and DOR to exploratory objectives and endpoints due to the logistical limitations in the follow-up of subjects. • Limited the enrolment of subjects with malignant thyroid tumour histologies in Cohort 1 only to facilitate a formal analysis of subjects with these histologies. • Changed the dosing of tipifarnib to 900 mg, po, BID daily on Days 1-7 and 15-21 of 28-day treatment cycles. • Updated the sample size language based on input from the Mayo Clinic Foundation IRB to: Eleven study subjects will be enrolled for the first stage of study for each cohort; the study will be terminated if 1 or less response was observed at end of first stage. • To accommodate the scheduling of subjects, - Day 22 ECOG performance status, physical examination, and vital signs were removed. - The visit at Cycle 2 Day 1 and beyond could occur ±2 days if deemed necessary due to scheduling conflicts. - Changed Cycle 1 Day 1 dosing to begin in the evening. • Clarified inclusion criterion 7 to: At least 2 weeks since last radiotherapy. If radiation was localized to the only site of measurable disease, there must be documentation of disease progression of the irradiated site. Subjects must have recovered from all acute toxicities from radiotherapy. • Updated Dose Management and Management of Toxicity to align with the change in dose and schedule, and to ensure consistency within the protocol. • Added coagulation profile.
20 October 2015	Additional precautions were introduced at the request of the FDA to ensure subject safety as follows: • Added ECG testing at Cycle 1 Day 1 and Day 7 at the projected time of Cmax, 2-4 h postdose. Changed Day 15 procedures to Day 7 procedures to collect ECG and laboratory safety evaluations at steady state. • Clarified that treatment could only continue in the absence of disease progression and unmanageable toxicity. • Modified to indicate that if treatment-related treatment-emerging unacceptable haematological or non-haematological toxicity was observed (not manageable with supportive care), treatment was to be until recovery. • Reduced the period until recovery to 4 weeks. If recovery required more than 4 weeks, treatment was to be discontinued. • Defined non-tolerable Grade 2 toxicities as those with moderate symptoms that the subject could not endure for the conduct of instrumental activities of daily life or that persisted ≥7 days. • Clarified unstable neurological symptoms at enrolment as those emerging or rapidly progressing within 4 weeks of Cycle 1 Day 1. • Provided limitations to dose re-escalation: Subjects with SAEs or a recurrence of ≥ Grade 3 toxicity deemed related to tipifarnib would not have dose re-escalated following dose reduction. In addition, subjects experiencing more than 1 dose delay of ≥14 days would not have their dose re escalated. • Clarified the exclusion of subjects with hypersensitivity to structural compounds like tipifarnib. Subjects with hypersensitivity to imidazoles were excluded from enrolment. • Clarified option for dose escalation to 1200 mg BID. At the investigators discretion, the dose could be increased to 1200 mg BID in the absence of DLT at the 900 mg BID. The dose was not escalated to 1200 mg BID in subjects with SAEs or ≥ Grade 2 TEAEs deemed related to tipifarnib and lasted ≥14 days, or in subjects that required dose reductions or dose delays ≥14 days for TEAEs deemed related to tipifarnib.

28 July 2016	• Limited enrolment of Stage 2 of Cohort 2 to subjects with HNSCC with HRAS mutations based on the observed antitumor activity in Stage 1 of Cohort 2. • Allowed for, in exceptional circumstances, dosing delays or skipping of dosing for reasons other than the management of toxicity. This was allowed at the judgement of the investigator if 50% of the total dose was maintained in each cycle. • Reduced the frequency of coagulation and urinalysis testing. • Added HPV status as part of subject medical history. • Added to obtain consent for T81C genetic polymorphism testing as part of the HRAS mutational analysis. • Provided further clarification on which antiepileptic medications could be concomitantly administered with tipifarnib without drug-drug interaction potential.
18 September 2017	•Added a third cohort to explore antitumor activity in SCC subjects regardless of tumour site. •Additional enrolment of up to 30 of subjects in Cohort 3 with HRAS mutant HNSCC allowed after 4 responses in 6 HNSCC subjects in Stages 1 and 2 of Cohort 2. •Updated the statistical rationale for sample size changes of Cohort 2 and 3, and the planned number of subjects for enrolment. •Updated contraception inclusion requirements, provided information on potential effects on reproduction and fertility, and guidance on sperm cryopreservation. •Limited text in Exclusion Criterion 4 to requirements necessary for enrolment. •Aligned timing of pregnancy testing throughout the protocol. •Updated information on IP characteristics and the 300 mg tablet, and revised guidance on crushing or chewing tablets. •Made text on dose reduction and management of toxicity consistent and removed limit on dose reductions prior to subject removal. •Removed intra-subject dose escalation to 1200 mg BID. •Additional clarification on definition of cycle and day when tipifarnib was restarted following a treatment interruption. •Clarification that imaging (MRI or CT) should include all regions necessary to assess tumour response for a subject’s malignancy. •Emphasised that tumour assessment should maintain actual schedule, regardless of treatment delay/discontinuation: tumour assessments approximately every 8 weeks over the first 6 months of study, and thereafter, approximately every 12 weeks. •Updated definition of End of Study. •Streamlined the introduction of the protocol and referred investigators to the most current version of the investigator brochure for further details. •Updated the rationale for study with preliminary data from this ongoing study. •Clarified that substantial amendments needed approval by the Competent Regulatory Authority prior to implementation. •Clarified Sponsor reporting requirements for SUSARs. •Removed further collection of blood biomarkers.

26 September 2017	•Revised the reference list. •Modified Inclusion Criterion 12 to include male contraception guidance to 90 days post end of treatment. •Modified Inclusion Criterion 10 to also include the CKD-EPI formula as an option for the estimation of renal function. •Incorporated France country-specific requirements within the global study protocol including: -Modified Inclusion Criterion 2 to clarify that subjects enrolled in France would have a malignancy that had relapsed or was considered treatment failure to standard of care therapy in a multidisciplinary clinical staff meeting. -Modified the definition of End of Study to clarify that for subjects with evidence of clinical benefit who were enrolled in France, continuation of treatment with tipifarnib may have occurred in a new study protocol. -For subjects enrolled in France, symptom based physical examinations on Cycle 1 Day 1 of Cycle 2 and beyond would include questioning about potential visual changes. If clinically indicated, a visual acuity test would be performed. If abnormal results were observed, subjects would be referred to an ophthalmological consultation. Additional physical examinations would be conducted as clinically indicated. •Incorporated Belgium specific requirements within the global study protocol including: -Included language regarding photosensitivity precaution
01 November 2018	• Reduced starting dose from 900 mg to 600 mg. Updated recommended dose reductions to manage related toxicity to reflect starting dose change. • Modified Inclusion criteria 3: the missense HRAS mutation should be with a VAF >20% per Next Generation Sequencing or other approved methodology approved. • Modified Inclusion criteria 9 to lower allowable elevation in AST and ALT to ≤1.5 x ULN. • Added Inclusion criterion 12: subjects had to have albumin ≥3.5 g/dL except when tumour HRAS mutant VAF was ≥35%, suggesting high sensitivity to tipifarnib. • Added exclusion criterion 8: treatment for noncancer related liver disease (excluding cholestasis) within the prior year. • Expanded Cohort 3 to enrol 20 subjects and extended study to 5 years to account for additional subjects. • Provided additional guidance on management of Grade 2 and 3 renal toxicity. • Added Exclusion Criterion 10: Included strong inhibitors or inducers of CYP3A4 or UGT to prohibited concomitant medication list and excluded subjects taking such drugs. • Added buccal swabs for testing CXCL12 UTR3 status. • Adjusted blood chemistry panel to include evaluation of total CO2. • Added details on when concomitant high dose corticosteroid use was allowed. • Added guidance on expected radiographic imaging methods and scan coverage. • Removed collection of tumour markers at the discretion of the Investigator. • Removed photosensitivity precaution and sun protection guidance as the toxicology program concluded that tipifarnib was not phototoxic. • Removed ECG collection post dosing on Cycle 1 Day 1, Cycle 1 Day 7 and EOT. • Specified that pregnancy testing be done within 72 h of Cycle 1 Day 1 as part of screening. • Removed urinalysis and coagulation assessments at EOT visit. • Clarified language specific to subjects in Germany confirming continued treatment of subjects after the end of study would comply with German Drug Law. • Added guidance on potential effects on reproduction and development.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported