

**Clinical trial results:****INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted combination therapy In patients with BRAFV600 mutant stage 3 unresectable or metastatic Melanoma****Summary**

EudraCT number	2016-005228-27
Trial protocol	GB
Global end of trial date	27 November 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information**Trial identification**

Sponsor protocol code	INTERIM
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03352947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Mrs Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, Cambridge Clinical Trials Unit, 44 01223 348158, cctu@addenbrookes.nhs.uk
Scientific contact	Dr Pippa Corrie, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, 44 01223 216083, pippa.corrie@addenbrookes.nhs.uk

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	25 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2020
Global end of trial reached?	Yes
Global end of trial date	27 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary:

- Assess recruitment rate and treatment compliance of the intermittent dosing schedule as a measure of acceptance of intermittent dosing to patients and physicians
- Evaluate the impact on overall quality of life with intermittent dosing using European Organisation for Research and Treatment of Cancer QLQ-C30
- Estimate the size of clinical efficacy of intermittent dosing compared to continuous dosing, measured by progression-free survival

Secondary:

- Evaluate safety, objective response rate, time to treatment failure and overall survival
- Evaluate skin toxicity as assessed by clinicians and patients using patient reported outcome measures
- Assess factors which influence patients' decision to enter/decline entering the trial
- Evaluate patient experience of participation in this trial (using mixed methods)
- Determine the QoL and cost-effectiveness of intermittent dosing compared with standard continuous dosing in a subset of patients, explore pharmacokinetics of dosing

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicine and Healthcare Product Regulatory Authority. Patients received verbal and written information prior to consenting to the trial, and had time to consider their participation and had an opportunity to ask questions. Consenting patients had a series of screening tests to ensure they were suitable for the study and it was safe to proceed. On registration to the trial the participants were allocated a unique trial identification number which was used on all data forms and samples sent to the Sponsor. This allowed their personal data to remain anonymous. Only the participant's direct care team had access to their recruited participants personal/identifiable information during the trial. All participant related information shared was anonymised, with only reference to the participant's trial identification number being included.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	03 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 79
Worldwide total number of subjects	79
EEA total number of subjects	0

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)	35
From 65 to 84 years	43
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The INTERIM trial planned to recruit approximately 100 patients (50 patients in each arm) with a minimum of 9 months follow up per patient. Recruitment commenced on the 03 November 2017 and closed on the 30 March 2020. 79 patients were randomised into the trial across 19 sites in the UK.

Pre-assignment

Screening details:

A total of 86 patients were assessed for eligibility, 7 patients did not give informed consent. The remaining 79 patients were successfully screened for eligibility and randomised (39 experimental and 40 standard arms) from 20/12/2017 to 28/02/2020 from 19 sites. The cut-off date for the last patient last visit was the 27th of November 2020.

Pre-assignment period milestones

Number of subjects started	79
Number of subjects completed	79

Period 1

Period 1 title	On Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard arm (continuous schedule)

Arm description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 28 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 28 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Arm type	Active comparator
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	L01XE23
Other name	Tafinlar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150mg twice daily, 12 hours apart, on days 1 – 28 of a 28 day cycle.

Investigational medicinal product name	Trametinib
Investigational medicinal product code	L01XE25
Other name	Mekinist
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2mg once daily, on days 1 – 28 of a 28 day cycle

Arm title	Experimental arm (intermittent schedule)
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Arm description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 21 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 14 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	L01XE23
Other name	Tafinlar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150mg twice daily, 12 hours apart, on days 1 – 21 of a 28 day cycle.

Investigational medicinal product name	Trametinib
Investigational medicinal product code	L01XE25
Other name	Mekinist
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2mg once daily, on days 1 – 14 of a 28 day cycle

Number of subjects in period 1	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)
Started	40	39
Completed	40	39

Baseline characteristics

Reporting groups

Reporting group title	Standard arm (continuous schedule)
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Reporting group description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 28 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 28 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Reporting group title	Experimental arm (intermittent schedule)
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Reporting group description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 21 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 14 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Reporting group values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)	Total
Number of subjects	40	39	79
Age categorical			
The median patient age was 67 (ranging from 34 to 85) years old with 54.4% (43 out of 79) female.			
Units: Subjects			
Adults (18-64 years)	23	12	35
From 65-84 years	17	26	43
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	61.3	66.2	
full range (min-max)	38.0 to 78.0	34.0 to 85.0	-
Gender categorical			
Units: Subjects			
Female	21	22	43
Male	19	17	36
ECOG performance status			
Units: Subjects			
Grade 0	19	19	38
Grade 1	17	15	32
Grade 2	4	5	9
AJCC stage at baseline			
Units: Subjects			
IIIc	1	2	3
IVM1a	6	5	11
IVM1b	8	6	14
IVM1c	25	26	51

Presence of brain metastases Units: Subjects			
No	40	39	79
LDH relative to ULN Units: Subjects			
≤ ULN	22	21	43
> ULN and ≤ 2 x ULN	14	13	27
> 2 x ULN	4	5	9

Subject analysis sets

Subject analysis set title	Full analysis population
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis population includes all randomised subjects who gave informed consent, met all eligibility criteria and received treatment on the trial.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all patients randomised and received at least one dose of trial treatment.

Reporting group values	Full analysis population	Safety population	
Number of subjects	78	78	
Age categorical			
The median patient age was 67 (ranging from 34 to 85) years old with 54.4% (43 out of 79) female.			
Units: Subjects			
Adults (18-64 years)	35	35	
From 65-84 years	43	42	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	63.7		
full range (min-max)	34.0 to 85.0		
Gender categorical			
Units: Subjects			
Female	43	43	
Male	36	36	
ECOG performance status			
Units: Subjects			
Grade 0	38	38	
Grade 1	32	31	
Grade 2	9	9	
AJCC stage at baseline			
Units: Subjects			
IIIc	3	3	
IVM1a	11	11	
IVM1b	14	14	
IVM1c	51	50	
Presence of brain metastases			
Units: Subjects			
No	56	56	

LDH relative to ULN			
Units: Subjects			
≤ ULN	43	42	
> ULN and ≤ 2 x ULN	27	27	
> 2 x ULN	9	9	

End points

End points reporting groups

Reporting group title	Standard arm (continuous schedule)
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Reporting group description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 28 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 28 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Reporting group title	Experimental arm (intermittent schedule)
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Reporting group description:

Patients with BRAFV600 mutant stage 3 unresectable or metastatic melanoma who met the trial eligibility criteria were randomised to one trial arm.

Participants self-administered both dabrafenib and trametinib. Dabrafenib was taken orally 150mg twice daily 12 hours apart, on days 1 – 21 of a 28 day cycle. Trametinib was taken orally 2mg once daily, on days 1 – 14 of a 28 day cycle.

Treatment was continued until disease progression or beyond, at the investigator's discretion.

Subject analysis set title	Full analysis population
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Subject analysis set type	Full analysis
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Subject analysis set description:

The full analysis population includes all randomised subjects who gave informed consent, met all eligibility criteria and received treatment on the trial.

Subject analysis set title	Safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety population includes all patients randomised and received at least one dose of trial treatment.

Primary: Recruitment rate

End point title	Recruitment rate ^[1]
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End point description:

End point type	Primary
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End point timeframe:

On Study

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: There are no statistical analyses for these endpoints.

End point values	Full analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: per site per 2 months				
number (not applicable)	0.31			

Statistical analyses

No statistical analyses for this end point

Primary: Overall QoL

End point title	Overall QoL
End point description:	This is defined as the global health status score derived from the standard EORTC QLQ-C30 questionnaire at 6 months from date of randomisation
End point type	Primary
End point timeframe:	On Study

End point values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	21	51	
Units: mean				
least squares mean (confidence interval 95%)	11.43 (3.91 to 18.96)	-1.16 (-10.32 to 7.99)	-13.25 (-26.13 to -0.36)	

Statistical analyses

Statistical analysis title	Overall QoL change from baseline
Statistical analysis description:	The analysis of changes from baseline of the mean score over time and difference between groups will be carried out with repeated measures ANCOVA, adjusting for baseline level, treatment arm, timepoint, interaction between treatment group and time. Time treated as repeated variable within subjects, and the analysis was performed with unstructured or AR(1) covariance matrix mixed model with PROC MIXED. Restricted maximum likelihood will be used in estimation of parameters.
Comparison groups	Experimental arm (intermittent schedule) v Standard arm (continuous schedule) v Safety population
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Primary: Progression-free survival

End point title	Progression-free survival
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End point description:

This is calculated as the duration from date of randomisation to the date of first progression or death from any cause, whichever occurs first.

End point type Primary

End point timeframe:

On Study

End point values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	38	78	
Units: number				
Disease progressed	23	25	48	

Attachments (see zip file) Progression free survival (PFS) over time/pfs_km_plot.png

Statistical analyses

Statistical analysis title	K-M plot
Comparison groups	Standard arm (continuous schedule) v Experimental arm (intermittent schedule)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.45

Secondary: Objective Response Rate

End point title Objective Response Rate

End point description:

Objective response is based on overall best objective response.

End point type Secondary

End point timeframe:

On Study, until a disease progression.

End point values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35 ^[2]	37 ^[3]		
Units: percent				
number (confidence interval 95%)				
Yes	77.14 (59.86 to 89.58)	56.76 (39.49 to 72.9)		

Notes:

[2] - 5 patients missing, 27 patients has an objective response out of 35.

[3] - 1 patients missing, 21 patients has an objective response out of 37.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure
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End point description:

End point type	Secondary
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End point timeframe:

On Study

End point values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: percent				
number (not applicable)				
Yes	26	28		

Attachments (see zip file)	KM-plot of Time to treatment failure/ttf_km_plot.png
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type Secondary

End point timeframe:

On Study

End point values	Standard arm (continuous schedule)	Experimental arm (intermittent schedule)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: percent				
number (not applicable)				
Death	15	21		

Attachments (see zip file) KM-plot of of overall survival/os_km_plot.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE collected during the treatment period and at disease progression.

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Experimental intermittent
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Reporting group description: -

Reporting group title	Standard continuous
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Reporting group description: -

Serious adverse events	Experimental intermittent	Standard continuous	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 38 (52.63%)	18 / 39 (46.15%)	
number of deaths (all causes)	21	15	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Hypotension	Additional description: Hypotension		
subjects affected / exposed	3 / 38 (7.89%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event	Additional description: Thromboembolic event		
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: Fatigue		

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever	Additional description: Fever		
subjects affected / exposed	9 / 38 (23.68%)	7 / 39 (17.95%)	
occurrences causally related to treatment / all	9 / 9	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms	Additional description: Flu like symptoms		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: Dyspnea		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders - Other, Asthma	Additional description: Other, Asthma		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough	Additional description: Productive cough		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion	Additional description: Confusion		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysphasia	Additional description: Dysphasia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema cerebral	Additional description: Edema cerebral		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head pain	Additional description: Other, Head pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression	Additional description: Other, Spinal cord compression		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: Seizure		
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders	Additional description: Other, Chorioretinitis		
Chorioretinitis	Additional description: Other, Chorioretinitis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders	Additional description: Abdominal pain		
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea	Additional description: Diarrhea		
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal hemorrhage	Additional description: Esophageal hemorrhage		

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal varices hemorrhage	Additional description: Esophageal varices hemorrhage		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders	Additional description: Acute kidney injury		
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders	Additional description: Muscle weakness lower limb		
Muscle weakness lower limb	Additional description: Muscle weakness lower limb		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Lung infection	Additional description: Lung infection		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, Infection	Additional description: Other, Infection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypophosphatemia	Additional description: Hypophosphatemia	
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Experimental intermittent	Standard continuous	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 38 (78.95%)	36 / 39 (92.31%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Seborrhoea		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Seborrhoea			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Cysts	Additional description: Other, Cysts		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Cysts			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Papilloma	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Papilloma		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Papilloma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Seborrhoeic keratosis	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Seborrhoeic keratosis		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, Seborrhoeic keratosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vascular disorders	Additional description: Flushing		
Flushing			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Hot flashes	Additional description: Hot flashes		
Hot flashes			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Hypertension	Additional description: Hypertension		

subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	1 / 39 (2.56%) 1	
Hypotension	Additional description: Hypotension		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	4 / 39 (10.26%) 4	
Lymphedema	Additional description: Lymphedema		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 39 (5.13%) 2	
Thromboembolic event	Additional description: Thromboembolic event		
subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	0 / 39 (0.00%) 0	
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed occurrences (all)	13 / 38 (34.21%) 13	12 / 39 (30.77%) 12	
Edema face	Additional description: Edema face		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Edema limbs	Additional description: Edema limbs		
subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	5 / 39 (12.82%) 5	
Facial pain	Additional description: Facial pain		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed occurrences (all)	13 / 38 (34.21%) 13	23 / 39 (58.97%) 25	
Fever	Additional description: Fever		
subjects affected / exposed occurrences (all)	11 / 38 (28.95%) 11	22 / 39 (56.41%) 24	
Flu like symptoms	Additional description: Flu like symptoms		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	4 / 39 (10.26%) 5	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		

subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	

General disorders and administration site conditions - Other, Night sweats	Additional description: Other, Night sweats		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	

Pain	Additional description: Pain		
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)	
occurrences (all)	1	3	

Immune system disorders			
Immune system disorders - Other, Erythema nodosum	Additional description: Other, Erythema nodosum		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	

Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	4 / 38 (10.53%)	5 / 39 (12.82%)	
occurrences (all)	4	5	

Dyspnea	Additional description: Dyspnea		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	

Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	3 / 38 (7.89%)	0 / 39 (0.00%)	
occurrences (all)	4	0	

Hoarseness	Additional description: Hoarseness		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

Nasal congestion	Additional description: Nasal congestion		
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	

Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

Respiratory, thoracic and mediastinal disorders - Other, Asthma	Additional description: Respiratory, thoracic and mediastinal disorders - Other, Asthma		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

Sore throat subjects affected / exposed occurrences (all)	Additional description: Sore throat	
	2 / 38 (5.26%)	1 / 39 (2.56%)
	2	1
Psychiatric disorders Confusion subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Psychiatric disorders - Other, Low mood subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	Additional description: Confusion	
	3 / 38 (7.89%)	2 / 39 (5.13%)
	4	2
	Additional description: Depression	
	0 / 38 (0.00%)	1 / 39 (2.56%)
	0	1
	Additional description: Other, Low mood	
	0 / 38 (0.00%)	1 / 39 (2.56%)
	0	1
	Additional description: Restlessness	
	0 / 38 (0.00%)	1 / 39 (2.56%)
	0	1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Alkaline phosphatase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Creatinine increased subjects affected / exposed occurrences (all) Ejection fraction decreased subjects affected / exposed occurrences (all) GGT increased	Additional description: Alanine aminotransferase increased	
	2 / 38 (5.26%)	1 / 39 (2.56%)
	2	1
	Additional description: Alkaline phosphatase increased	
	0 / 38 (0.00%)	3 / 39 (7.69%)
	0	3
	Additional description: Aspartate aminotransferase increased	
	0 / 38 (0.00%)	2 / 39 (5.13%)
	0	2
	Additional description: Blood bilirubin increased	
1 / 38 (2.63%)	1 / 39 (2.56%)	
1	1	
Additional description: Creatinine increased		
3 / 38 (7.89%)	1 / 39 (2.56%)	
3	1	
Additional description: Ejection fraction decreased		
0 / 38 (0.00%)	4 / 39 (10.26%)	
0	4	
Additional description: GGT increased		

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	4 / 39 (10.26%) 4	
Investigations - Other, Lactate dehydrogenase increased	Additional description: Investigations - Other, Lactate dehydrogenase increased		
subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 2	2 / 39 (5.13%) 1	
Investigations - Other, TSH increased	Additional description: Investigations - Other, TSH increased		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 39 (0.00%) 0	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	7 / 39 (17.95%) 8	
Investigations - Other, Cortisol low	Additional description: Investigations - Other, Cortisol low		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Investigations - Other, Urea increased	Additional description: Other, Urea increased		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 39 (7.69%) 3	
Serum amylase increased	Additional description: Serum amylase increased		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Weight loss	Additional description: Weight loss		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1	
White blood cell decreased	Additional description: White blood cell decreased		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	6 / 39 (15.38%) 6	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	Additional description: Fall		
	2 / 38 (5.26%)	0 / 39 (0.00%)	
	2	0	
Fracture subjects affected / exposed occurrences (all)	Additional description: Fracture		
	0 / 38 (0.00%)	1 / 39 (2.56%)	
	0	1	
Injury, poisoning and procedural complications - Other, Head injury subjects affected / exposed occurrences (all)	Additional description: Other, Head injury		
	0 / 38 (0.00%)	1 / 39 (2.56%)	
	0	1	
Cardiac disorders Acute coronary syndrome subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all)	Additional description: Acute coronary syndrome		
	0 / 38 (0.00%)	1 / 39 (2.56%)	
	0	1	
	Additional description: Palpitations		
	1 / 38 (2.63%)	0 / 39 (0.00%)	
	1	0	
Nervous system disorders Amnesia subjects affected / exposed occurrences (all) Depressed level of consciousness subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Dysarthria subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Dysphasia subjects affected / exposed occurrences (all) Edema cerebral	Additional description: Amnesia		
	1 / 38 (2.63%)	0 / 39 (0.00%)	
	1	0	
	Additional description: Depressed level of consciousness		
	0 / 38 (0.00%)	1 / 39 (2.56%)	
	0	1	
	Additional description: Dizziness		
	3 / 38 (7.89%)	4 / 39 (10.26%)	
	3	4	
	Additional description: Dysarthria		
2 / 38 (5.26%)	0 / 39 (0.00%)		
2	0		
Additional description: Dysgeusia			
2 / 38 (5.26%)	0 / 39 (0.00%)		
2	0		
Additional description: Dysphasia			
1 / 38 (2.63%)	1 / 39 (2.56%)		
1	1		
Additional description: Edema cerebral			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0	
Headache	Additional description: Headache		
subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 7	11 / 39 (28.21%) 12	
Lethargy	Additional description: Lethargy		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	4 / 39 (10.26%) 4	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0	
Nervous system disorders - Other, Peripheral neuropathy	Additional description: Other, Peripheral neuropathy		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Paresthesia	Additional description: Paresthesia		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	4 / 39 (10.26%) 4	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Presyncope	Additional description: Presyncope		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1	
Seizure	Additional description: Seizure		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0	
Spasticity	Additional description: Spasticity		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Stroke	Additional description: Stroke		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	

Blood and lymphatic system disorders			
Anemia	Additional description: Anemia		
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Lymph node pain	Additional description: Lymph node pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, Blocked ear	Additional description: Other, blocked ear		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blurred vision	Additional description: Blurred vision		
subjects affected / exposed	1 / 38 (2.63%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
Cataract	Additional description: Cataract		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Eye pain	Additional description: Eye pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Floater	Additional description: Floaters		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, Red eye	Additional description: Other, Red eye		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, Swollen eyes	Additional description: Swollen eyes		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

Eye disorders - Other, Visual acuity reduced	Additional description: Other, Visual acuity reduced	
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	1	0
Eye Disorders - Other, Worsening eye sight	Additional description: Other, Worsening eye sight	
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)
occurrences (all)	1	0
Uveitis	Additional description: Uveitis	
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
Gastrointestinal disorders		
Abdominal pain	Additional description: Abdominal pain	
subjects affected / exposed	2 / 38 (5.26%)	3 / 39 (7.69%)
occurrences (all)	3	4
Ascites	Additional description: Ascites	
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
Bloating	Additional description: Bloating	
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	3	0
Constipation	Additional description: Constipation	
subjects affected / exposed	4 / 38 (10.53%)	10 / 39 (25.64%)
occurrences (all)	4	11
Dental caries	Additional description: Dental caries	
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	1
Diarrhoea	Additional description: Diarrhea	
subjects affected / exposed	8 / 38 (21.05%)	9 / 39 (23.08%)
occurrences (all)	8	10
Dry mouth	Additional description: Dry mouth	
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)
occurrences (all)	1	3
Dyspepsia	Additional description: Dyspepsia	
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	1	2
Dysphagia	Additional description: Dysphagia	

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Fecal incontinence	Additional description: Fecal incontinence		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Gastroesophageal reflux disease	Additional description: Gastroesophageal reflux disease		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Mucositis oral	Additional description: Mucositis oral		
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Nausea	Additional description: Nausea		
subjects affected / exposed	7 / 38 (18.42%)	13 / 39 (33.33%)	
occurrences (all)	7	16	
Oral pain	Additional description: Oral pain		
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Periodontal disease	Additional description: Periodontal disease		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Rectal pain	Additional description: Rectal pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Toothache	Additional description: Toothache		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	9 / 38 (23.68%)	4 / 39 (10.26%)	
occurrences (all)	9	4	
Hepatobiliary disorders	Additional description: Cholecystitis		
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Bullous dermatitis	Additional description: Bullous dermatitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	4 / 38 (10.53%)	4 / 39 (10.26%)	
occurrences (all)	4	4	
Erythema multiforme	Additional description: Erythema multiforme		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Erythroderma	Additional description: Erythroderma		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders - Other, Skin patches	Additional description: Other, Skin patches		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous disorders - Other, Dermatitis	Additional description: Other, Dermatitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Skin and subcutaneous disorders - Other, Eczema	Additional description: Skin and subcutaneous disorders - Other, Eczema		
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Skin and subcutaneous disorders - Other, Papilloma neck	Additional description: Skin and subcutaneous disorders - Other, Papilloma neck		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous disorders - Other, Rash on left hand	Additional description: Skin and subcutaneous disorders - Other, Rash on left hand		
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, Seborrheic keratosis	Additional description: Other, Seborrheic keratosis		

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, Skin tissue disorder			
Additional description: Other, Skin tissue disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Skin and subcutaneous skin disorders - Other, Transient rash			
Additional description: other, transient rash			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysesthesia syndrome			
Additional description: Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	2	
Pruritus			
Additional description: Pruritus			
subjects affected / exposed	1 / 38 (2.63%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
Purpura			
Additional description: Purpura			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Rash acneiform			
Additional description: Rash acneiform			
subjects affected / exposed	3 / 38 (7.89%)	7 / 39 (17.95%)	
occurrences (all)	3	7	
Rash maculo-papular			
Additional description: Rash maculo-papular			
subjects affected / exposed	1 / 38 (2.63%)	6 / 39 (15.38%)	
occurrences (all)	1	6	
Skin and subcutaneous tissue disorders - Other, Hyperkeratosis			
Additional description: Skin and subcutaneous tissue disorders - Other, Hyperkeratosis			
subjects affected / exposed	0 / 38 (0.00%)	4 / 39 (10.26%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders - Other, Rash			
Additional description: Skin and subcutaneous tissue disorders - Other, Rash			
subjects affected / exposed	8 / 38 (21.05%)	4 / 39 (10.26%)	
occurrences (all)	8	4	
Skin and subcutaneous tissue disorders - Other, Skin lesion			
Additional description: Skin and subcutaneous tissue disorders - Other, Skin lesion			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	2	2	

Skin hyperpigmentation subjects affected / exposed occurrences (all)	Additional description: Skin hyperpigmentation	
	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Skin hypopigmentation subjects affected / exposed occurrences (all)	Additional description: Skin hypopigmentation	
	0 / 38 (0.00%) 0	4 / 39 (10.26%) 4
Skin ulceration subjects affected / exposed occurrences (all)	Additional description: Skin ulceration	
	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2
Urticaria subjects affected / exposed occurrences (all)	Additional description: Urticaria	
	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1
Renal and urinary disorders		
Acute kidney injury subjects affected / exposed occurrences (all)	Additional description: Acute kidney injury	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Chronic kidney disease subjects affected / exposed occurrences (all)	Additional description: Chronic kidney disease	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	Additional description: Urinary incontinence	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Musculoskeletal and connective tissue disorders		
Arthralgia subjects affected / exposed occurrences (all)	Additional description: Arthralgia	
	5 / 38 (13.16%) 6	13 / 39 (33.33%) 15
Back pain subjects affected / exposed occurrences (all)	Additional description: Back pain	
	3 / 38 (7.89%) 3	1 / 39 (2.56%) 1
Muscle weakness lower limb subjects affected / exposed occurrences (all)	Additional description: Muscle weakness lower limb	
	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1
Muscle weakness right-sided subjects affected / exposed occurrences (all)	Additional description: Muscle weakness right-sided	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Myalgia	Additional description: Myalgia	

subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	5 / 39 (12.82%) 7	
Neck pain	Additional description: Neck pain		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 39 (2.56%) 1	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	2 / 39 (5.13%) 2	
Infections and infestations			
Eye infection	Additional description: Eye infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Gum infection	Additional description: Gum infection		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0	
Infections and infestations - Other, Oral thrush	Additional description: Infections and infestations - Other, Oral thrush		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 39 (5.13%) 2	
Infections and infestations - Other, Toe infection	Additional description: Infections and infestations - Other, Toe infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Lung infection	Additional description: Lung infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	4 / 39 (10.26%) 4	
Nail infection	Additional description: Nail infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Infections and infestations - Other, Finger infection	Additional description: Other, Finger infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Infection and infestations - Other, Leg infection	Additional description: Other, Leg infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Infections and infestations - Other, Thrush vaginal	Additional description: Other, Thrush vaginal		

subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Papulopustular rash	Additional description: Papulopustular rash		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Penile infection	Additional description: Penile infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Sepsis	Additional description: Sepsis		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1	
Skin infection	Additional description: Skin infection		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 39 (2.56%) 1	
Soft tissue infection	Additional description: Soft tissue infection		
subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0	
Upper respiratory infection	Additional description: Upper respiratory infection		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	3 / 39 (7.69%) 3	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 39 (5.13%) 2	
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 7	6 / 39 (15.38%) 7	
Dehydration	Additional description: Dehydration		
subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 39 (2.56%) 1	

Hypercalcemia subjects affected / exposed occurrences (all)	Additional description: Hypercalcemia	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Hyperglycemia subjects affected / exposed occurrences (all)	Additional description: Hyperglycemia	
	1 / 38 (2.63%) 1	0 / 39 (0.00%) 0
Hypernatremia subjects affected / exposed occurrences (all)	Additional description: Hypernatremia	
	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Hypoalbuminemia subjects affected / exposed occurrences (all)	Additional description: Hypoalbuminemia	
	0 / 38 (0.00%) 0	4 / 39 (10.26%) 4
Hypoglycemia subjects affected / exposed occurrences (all)	Additional description: Hypoglycemia	
	0 / 38 (0.00%) 0	1 / 39 (2.56%) 1
Hypokalemia subjects affected / exposed occurrences (all)	Additional description: Hypokalemia	
	3 / 38 (7.89%) 3	2 / 39 (5.13%) 2
Hyponatremia subjects affected / exposed occurrences (all)	Additional description: Hyponatremia	
	0 / 38 (0.00%) 0	3 / 39 (7.69%) 4
Hypophosphatemia subjects affected / exposed occurrences (all)	Additional description: Hypophosphatemia	
	1 / 38 (2.63%) 1	2 / 39 (5.13%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2018	To allow patients to be randomised before RECIST measurements are available. To clarify the both MRI and CT scans can be used to measure disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported