Clinical trial results:
Trabectedin for recurrent grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group.

Summary

EudraCT number	2014-002446-47
Trial protocol	BE AT ES NL DE
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	25 March 2020
First version publication date	25 March 2020

Trial information

Trial identification

Sponsor protocol code	1320-BTG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234050
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organization for Research and Treatment of Cancer (EORTC)
Sponsor organisation address	83 Avenue Mounier, Brussels, Belgium, 1200
Public contact	Clinical operations department, European Organization for Research and Treatment of Cancer (EORTC), 0032 27741015/, regulatory@eortc.be
Scientific contact	Clinical operations department, European Organization for Research and Treatment of Cancer (EORTC), 0032 27741015/, regulatory@eortc.be

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	26 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2019
Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this randomized phase II study is to collect data on activity, safety and quality of life of trabectedin therapy in patients with recurrent high-grade meningioma.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).
The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2015
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	Netherlands: 5
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	55
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There was no screening period. Patients were randomized to either treatment arm after verification of their eligibility criteria for inclusion in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard

Arm description:

Treatment in the control arm was left to the discretion of the investigator, according to local standard practice, or as referred to by their national authority. Limited information on the treatment administered was recorded.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Depending on local practice

Arm title	Trabectedin

Arm description:

Trabectedin had to be given as a 24-hour infusion every 3 weeks at a starting dose of 1.5 mg/m2 BSA, until one of the treatment withdrawal criteria had been met. Subjects receiving trabectedin were required to receive dexamethasone pretreatment at 20 mg IV, 30 minutes before starting trabectedin. Trabectedin had to be administered under the supervision of a physician experienced in the use of chemotherapy. Its use had preferably to be confined to personnel specialized in the administration of cytotoxic agents. For this trial, the recommended starting dose was 1.5 mg/m2 BSA, administered as an IV infusion over 24 hours with a 3-week interval between cycles. Administration through a central venous line was strongly recommended.

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin had to be given as a 24-hour infusion every 3 weeks at a starting dose of 1.5 mg/m2 BSA

Number of subjects in period 1	Standard	Trabectedin
Started	29	61
Completed	2	0
Not completed	27	61
Consent withdrawn by subject	2	4
No treatment available in the country	2	-
Adverse event, non-fatal	1	13
due to the IDMC recommendations	-	5
SAE: intratumoral hemorrhage	-	1
Lack of efficacy	22	38

Baseline characteristics

End points

End points reporting groups

Reporting group title	Standard

Reporting group description:

Treatment in the control arm was left to the discretion of the investigator, according to local standard practice, or as referred to by their national authority. Limited information on the treatment administered was recorded.

Reporting group title	Trabectedin

Reporting group description:

Trabectedin had to be given as a 24-hour infusion every 3 weeks at a starting dose of 1.5 mg/m2 BSA, until one of the treatment withdrawal criteria had been met. Subjects receiving trabectedin were required to receive dexamethasone pretreatment at 20 mg IV, 30 minutes before starting trabectedin. Trabectedin had to be administered under the supervision of a physician experienced in the use of chemotherapy. Its use had preferably to be confined to personnel specialized in the administration of cytotoxic agents. For this trial, the recommended starting dose was 1.5 mg/m2 BSA, administered as an IV infusion over 24 hours with a 3-week interval between cycles. Administration through a central venous line was strongly recommended.

Primary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Primary

End point timeframe:

Until progressive disease (PD) every 9 weeks and after PD, every 9 weeks for the first year from randomization and every 12 weeks thereafter.

End point values	Standard	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	57		
Units: months				
median (confidence interval 95%)	4.17 (2.0 to 5.95)	2.43 (2.07 to 3.32)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Standard v Trabectedin

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.997
upper limit	2.028

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 4 weeks of randomization & within 4 weeks of treatment start. On day 1 of each treatment cycle or within 72 hours before. 30 days after last drug administration. Until PD or start of new therapy. Every 9 weeks until resolution or stabilization.

Adverse event reporting additional description:

AEs are evaluated using CTCAE grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Trabectedin

Reporting group description:

Experimental arm

Reporting group title	Standard

Reporting group description:

Standard arm

Serious adverse events	Trabectedin	Standard	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 61 (42.62%)	4 / 27 (14.81%)	
number of deaths (all causes)	40	17	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INTRACRANIAL TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

EMBOLISM			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DEATH			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
FATIGUE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INJECTION SITE THROMBOSIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (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			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

MYOCARDITIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRONTOTEMPORAL DEMENTIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NORMAL PRESSURE HYDROCEPHALUS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMNOLENCE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DIARRHOEA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOCELLULAR INJURY			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL FAILURE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MYALGIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ATYPICAL PNEUMONIA			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN ABSCESS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS EXTERNA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PAROTITIS				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
PERICHONDRITIS				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
PNEUMONIA				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
RESPIRATORY TRACT INFECTION				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
SEPSIS				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	1 / 1	0 / 0		
URINARY TRACT INFECTION				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
UROSEPSIS				
alternative dictionary used: MedDRA 22.1				

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trabectedin	Standard	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 61 (95.08%)	25 / 27 (92.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	2	
Vascular disorders			
BLOOD HYPERTENSION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPERTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 61 (16.39%)	12 / 27 (44.44%)	
occurrences (all)	26	21	
HYPOTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 61 (8.20%)	0 / 27 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
EDEMA LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	1 / 27 (3.70%)	
occurrences (all)	3	2	
FATIGUE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	27 / 61 (44.26%)	11 / 27 (40.74%)	
occurrences (all)	57	19	
FEVER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 61 (9.84%)	2 / 27 (7.41%)	
occurrences (all)	8	2	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	2 / 27 (7.41%)	
occurrences (all)	1	4	
GAIT DISTURBANCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 61 (6.56%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
HYPOTHERMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
MALAISE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
SUDDEN DEATH NOS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
GENITAL EDEMA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
TESTICULAR DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
ALLERGIC RHINITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
ATYPICAL PNEUMONIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
DYSPNEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 61 (9.84%)	0 / 27 (0.00%)	
occurrences (all)	7	0	
EPISTAXIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	2	
HICCUPS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
HYPOXEMIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
PNEUMONITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
SORE THROAT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
CONFUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 61 (6.56%)	2 / 27 (7.41%)	
occurrences (all)	5	2	
DEPRESSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
INSOMNIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
LOW MORALE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
CPK INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
GGT INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
INVESTIGATIONS, OTHER: HYPERPHOSPHATEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
SERUM AMYLASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
WEIGHT GAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 61 (9.84%)	0 / 27 (0.00%)	
occurrences (all)	11	0	
WEIGHT LOSS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	9 / 61 (14.75%)	3 / 27 (11.11%)	
occurrences (all)	13	4	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
FALL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 61 (9.84%)	3 / 27 (11.11%)	
occurrences (all)	9	6	
FRACTURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cardiac disorders			
MYOCARDITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
ATAXIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
CEREBROSPINAL FLUID LEAKAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
COGNITIVE DISTURBANCE			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 61 (4.92%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
CONCENTRATION IMPAIRMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
DIZZINESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
DYSGEUSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	2 / 27 (7.41%)	
occurrences (all)	1	4	
DYSGRAPHIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
DYSPHASIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
EDEMA CEREBRAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
FRONTAL LOBE SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

HEADACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 61 (24.59%)	7 / 27 (25.93%)	
occurrences (all)	21	10	
HYDROCEPHALUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
HYPERSOMNIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
INTRACRANIAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
ISCHEMIA CEREBROVASCULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
IVTH NERVE DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
LETHARGY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
MEMORY IMPAIRMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
MIXED APHASIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
MOTOR SLOWING				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
NEURALGIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)		
occurrences (all)	0	1		
NEUROLOGICAL DECREASE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)		
occurrences (all)	0	1		
PARESTHESIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	3 / 61 (4.92%)	1 / 27 (3.70%)		
occurrences (all)	3	1		
PERIPHERAL MOTOR NEUROPATHY				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)		
occurrences (all)	0	1		
PERIPHERAL SENSORY NEUROPATHY				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)		
occurrences (all)	0	2		
POSITIF BABINSKI (RIGHT SIDE)				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
PYRAMIDAL TRACT SYNDROME				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)		
occurrences (all)	3	0		

SEIZURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 61 (14.75%)	4 / 27 (14.81%)	
occurrences (all)	9	10	
SOMNOLENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
STROKE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
TREMOR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
TRIGEMINAL NERVE DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
NEUTROPENIC SEPSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
PICC DISLOCATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
RENAL FAILURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
EAR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
PERICHONDRITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
VERTIGO			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
VESTIBULAR DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
BLURRED VISION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
EYELID FUNCTION DISORDER			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
WATERING EYES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
CONSTIPATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 61 (24.59%)	3 / 27 (11.11%)	
occurrences (all)	22	3	
DIARRHEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 61 (14.75%)	3 / 27 (11.11%)	
occurrences (all)	11	3	
DYSPHAGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
ESOPHAGEAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
FECAL INCONTINENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	2 / 27 (7.41%)	
occurrences (all)	1	3	
GASTRITIS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
GASTROINTESTINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
NAUSEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	28 / 61 (45.90%)	5 / 27 (18.52%)	
occurrences (all)	55	7	
PAROTITIS (RIGHT SIDE)			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
PERIODONTAL DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
STOMACH PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
TOOTHACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	

VOMITING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	22 / 61 (36.07%)	3 / 27 (11.11%)	
occurrences (all)	35	4	
Hepatobiliary disorders			
DETORIORATION OF LIVER FUNCTIONS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HEPATIC CYTOLYSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
HEPATOTOXICITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
DRY SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
NODULE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
PRURITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
REDNESS DUE TO PORT			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
SKIN ULCERATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
PROTEINURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
URINARY INCONTINENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
Endocrine disorders			
CUSHINGOID			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
BACK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
BONE PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
DISC PROTRUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
MUSCLE WEAKNESS LEFT-SIDED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
MUSCLE WEAKNESS LOWER LIMB			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
MUSCLE WEAKNESS LOWER LIMB			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
MUSCLE WEAKNESS RIGHT-SIDED			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
MUSCLE WEAKNESS UPPER LIMB			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	2	2	
MYALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 61 (11.48%)	3 / 27 (11.11%)	
occurrences (all)	7	3	
MYOSITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
NECK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 61 (6.56%)	2 / 27 (7.41%)	
occurrences (all)	4	3	
Infections and infestations			
BLADDER INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 61 (4.92%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
DEVICE RELATED INFECTION alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
ENTEROCOLITIS INFECTIOUS alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
EYE INFECTION alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
GUM INFECTION alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
LUNG INFECTION alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
MENINGITIS alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
MUCOSAL INFECTION alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
OTITIS EXTERNA alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

PARONYCHIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
SEPSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 61 (6.56%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
SKIN INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
UNKNOWN SUSPECTED INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 61 (4.92%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
WOUND INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 61 (18.03%)	3 / 27 (11.11%)	
occurrences (all)	13	4	
DEHYDRATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPERURICEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPOKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
HYPONATREMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
HYPOPROTEINEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	This amendment includes the addition of additional translational research including next-generation-sequencing and the Illumina 850k methylation assay to analyze potential diagnostic, prognostic and predictive molecular markers within the tumor samples. For this purpose the collected samples will be shipped to the lab in Heidelberg after processing and analysis in the central lab in Magdeburg. Besides this the protocol and the PISIC have been amended to allow the collection of MRI images taken up to 2 years prior to enrollment of the patient with the aim of studying the growth dynamics of grade II and III meningiomas and how these are impacted upon study treatment. In addition, we updated section 7.12 of the protocol which describes the Macdonald criteria that are used to assess tumor response and time to progression. In June 2016 we noticed that the Macdonald criteria were not correctly formulated in this section of the protocol and we decided to communicate the correct criteria to all investigators by means of a 'dear investigator' letter. The changes highlighted in this letter have now been incorporated in this protocol amendment. In addition, the IB v11 of Trabectedin has been released. Upon evaluation of the new IB the following rare risk has been added to the PISIC: "Leakage of fluid from the circulatory system to the surrounding tissues (called Capillary Leak Syndrome) and multi-organ damage has been observed in a few cases. It is not possible to know the frequency at this point." Finally, the following selection criteria has been clarified in the protocol as we received multiple questions from investigators regarding this criteria: "No prior systemic anti-neoplastic therapy for meningioma (patient may have received prior radionuclide therapy)". This amendment has been discussed and agreed by: EORTC HQ and study coordinator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported