



## 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
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##### 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](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:

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**Subjects enrolled per age group**

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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

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## 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
<b>Arm title</b>	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

<b>Arm title</b>	Trabectedin
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Arm description:

Trabectedin had to be given as a 24-hour infusion every 3 weeks at a starting dose of 1.5 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> BSA

<b>Number of subjects in period 1</b>	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/m <sup>2</sup> 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/m <sup>2</sup> 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Trabectedin
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Reporting group description:

Experimental arm

Reporting group title	Standard
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Reporting group description:

Standard arm

<b>Serious adverse events</b>	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	
<b>Investigations</b>			
<b>ALANINE AMINOTRANSFERASE INCREASED</b>			
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	
<b>ASPARTATE AMINOTRANSFERASE INCREASED</b>			
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	
<b>BLOOD CREATINE PHOSPHOKINASE INCREASED</b>			
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	
<b>GAMMA-GLUTAMYLTRANSFERASE INCREASED</b>			
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	
<b>Injury, poisoning and procedural complications</b>			
<b>FALL</b>			
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	
<b>Cardiac disorders</b>			

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

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	
<b>SOMNOLENCE</b>			
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	
<b>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
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	
<b>FEBRILE NEUTROPENIA</b>			
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	
<b>NEUTROPENIA</b>			
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	
<b>Gastrointestinal disorders</b>			
<b>DIARRHOEA</b>			
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	
<b>NAUSEA</b>			
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	
<b>VOMITING</b>			
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	
<b>Hepatobiliary disorders</b>			
<b>HEPATIC FUNCTION ABNORMAL</b>			
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	
<b>HEPATOCELLULAR INJURY</b>			
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	
<b>Renal and urinary disorders</b>			
<b>RENAL FAILURE</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>MYALGIA</b>			
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	
<b>Infections and infestations</b>			
<b>ATYPICAL PNEUMONIA</b>			
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	
<b>BRAIN ABSCESS</b>			
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	
<b>DEVICE RELATED INFECTION</b>			
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	
<b>ESCHERICHIA SEPSIS</b>			
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	
<b>MENINGITIS</b>			
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	
<b>NEUTROPENIC SEPSIS</b>			
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	
<b>OTITIS EXTERNA</b>			
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	

<b>PAROTITIS</b>			
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	
<b>PERICHONDRITIS</b>			
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	
<b>PNEUMONIA</b>			
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	
<b>RESPIRATORY TRACT INFECTION</b>			
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	
<b>SEPSIS</b>			
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	
<b>URINARY TRACT INFECTION</b>			
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	
<b>UROSEPSIS</b>			
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	
<b>Metabolism and nutrition disorders</b>			
<b>DECREASED APPETITE</b>			
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	
<b>DEHYDRATION</b>			
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	
<b>HYPONATRAEMIA</b>			
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 %

<b>Non-serious adverse events</b>	Trabectedin	Standard	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	58 / 61 (95.08%)	25 / 27 (92.59%)	
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
<b>TUMOR PAIN</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	2	
<b>Vascular disorders</b>			
<b>BLOOD HYPERTENSION</b>			
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	
<b>GAIT DISTURBANCE</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 61 (6.56%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
<b>HYPOTHERMIA</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
<b>LOCALIZED EDEMA</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
<b>MALAISE</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
<b>NON-CARDIAC CHEST PAIN</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
<b>PAIN</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 61 (3.28%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
<b>SUDDEN DEATH NOS</b>			
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			
<b>GENITAL EDEMA</b>			
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 occurrences (all)	1 / 61 (1.64%) 1	0 / 27 (0.00%) 0	
<b>PNEUMONITIS</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 27 (3.70%) 1	
<b>SORE THROAT</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 27 (0.00%) 0	
<b>Psychiatric disorders</b>			
<b>ANXIETY</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 27 (0.00%) 0	
<b>CONFUSION</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 5	2 / 27 (7.41%) 2	
<b>DEPRESSION</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	1 / 27 (3.70%) 1	
<b>INSOMNIA</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 27 (0.00%) 0	
<b>LOW MORALE</b>			
alternative dictionary used: CTCAE 4			
subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 27 (3.70%) 1	
<b>Investigations</b>			
<b>ALANINE AMINOTRANSFERASE INCREASED</b>			
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		

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

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

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

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

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

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
<b>GASTROESOPHAGEAL REFLUX DISEASE</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
<b>GASTROINTESTINAL PAIN</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)
occurrences (all)	2	0
<b>MUCOSITIS ORAL</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
<b>NAUSEA</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	28 / 61 (45.90%)	5 / 27 (18.52%)
occurrences (all)	55	7
<b>PAROTITIS (RIGHT SIDE)</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	1 / 61 (1.64%)	0 / 27 (0.00%)
occurrences (all)	1	0
<b>PERIODONTAL DISEASE</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	0 / 61 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
<b>STOMACH PAIN</b>		
alternative dictionary used: CTCAE 4		
subjects affected / exposed	2 / 61 (3.28%)	0 / 27 (0.00%)
occurrences (all)	2	0
<b>TOOTHACHE</b>		
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 occurrences (all)	22 / 61 (36.07%) 35	3 / 27 (11.11%) 4	
Hepatobiliary disorders DETORIORATION OF LIVER FUNCTIONS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  HEPATIC CYTOLYSIS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  HEPATOTOXICITY alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1  3 / 61 (4.92%) 3  1 / 61 (1.64%) 2	0 / 27 (0.00%) 0  0 / 27 (0.00%) 0  0 / 27 (0.00%) 0	
Skin and subcutaneous tissue disorders ALOPECIA alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  DRY SKIN alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  NODULE alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  PRURITUS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)  REDNESS DUE TO PORT	0 / 61 (0.00%) 0  2 / 61 (3.28%) 2  0 / 61 (0.00%) 0  0 / 61 (0.00%) 0	2 / 27 (7.41%) 2  1 / 27 (3.70%) 1  1 / 27 (3.70%) 1  2 / 27 (7.41%) 2	

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

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

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

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

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	<p>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.</p> <p>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.</p> <p>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."</p> <p>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)".</p> <p>This amendment has been discussed and agreed by: EORTC HQ and study coordinator</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported