



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).

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
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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/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

End points

End points reporting groups

Reporting group title	Standard
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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
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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
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End point description:

End point type	Primary
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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

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			

<p>EMBOLISM</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>1 / 1</p> <p>0 / 0</p>	<p>0 / 27 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>HYPOTENSION</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>JUGULAR VEIN THROMBOSIS</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>General disorders and administration site conditions</p> <p>DEATH</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>1 / 1</p> <p>1 / 1</p>	<p>0 / 27 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>FATIGUE</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>2 / 2</p> <p>0 / 0</p>	<p>0 / 27 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>INJECTION SITE THROMBOSIS</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>1 / 1</p> <p>0 / 0</p>	<p>0 / 27 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	
<p>MUCOSAL INFLAMMATION</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	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 occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 61 (1.64%) 0 / 1 0 / 0	0 / 27 (0.00%) 0 / 0 0 / 0	
Nervous system disorders CEREBRAL ISCHAEMIA alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 27 (3.70%) 0 / 1 0 / 0	
DIZZINESS alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 61 (1.64%) 0 / 1 0 / 0	0 / 27 (0.00%) 0 / 0 0 / 0	
FRONTOTEMPORAL DEMENTIA alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 27 (3.70%) 0 / 1 0 / 0	
LETHARGY alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 27 (3.70%) 1 / 1 0 / 0	
NORMAL PRESSURE HYDROCEPHALUS alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 61 (1.64%) 0 / 1 0 / 0	0 / 27 (0.00%) 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			

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

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

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

<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
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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported