Clinical trial results:
Radiation therapy and concurrent plus adjuvant Temsirolimus (CCI-779) versus chemo-irradiation with Temozolomide in newly diagnosed glioblastoma without methylation of the MGMT gene promoter – a randomized multicenter, open-label, Phase II study

Summary

EudraCT number	2008-003003-31
Trial protocol	DE FR NL BE GB AT ES IT
Global end of trial date	16 December 2013

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EORTC 26082 - 22081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01019434
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, 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	16 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2013
Global end of trial reached?	Yes
Global end of trial date	16 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study's primary objective is to document the activity profile of Temsirolimus (CCI-779) by the evaluation of overall survival at 12 months (OS12) in patients with newly diagnosed glioblastoma (GBM) without methylation of the MGMT gene promoter, treated with CCI-779 before and concomitantly to radiotherapy (RT), followed by CCI-779 maintenance therapy.

Protection of trial subjects:

The responsible investigator will ensure that this study is 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 will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ich.org/LOB/media/MEDIA482.pdf).
The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Radiotherapy consisted of a conventionally fractionated regimen, delivering a total dose up to 60 Gy, given in individual doses of 2 Gy, 5 days a week. A single phase treatment volume was strongly recommended. Occasionally, in order to keep the dose to the organs at risk (OAR) within tolerance doses, it was necessary to alter shielding partway through the treatment. Wherever possible the dose to the PTV was at least 54 Gy. The radiotherapy had to start within 8 days of randomization and within 7 weeks after surgery or open biopsy.

Evidence for comparator: -

Actual start date of recruitment	14 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Switzerland: 19

Worldwide total number of subjects	111
EEA total number of subjects	92

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)	97
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Registration period from 14/12/2009 and 20/09/2012.
15 institutions in 9 countries.

Pre-assignment

Screening details:

Newly diagnosed histologically proven supratentorial GBM and after screening:
Demonstration of an unmethylated MGMT-promotor

Pre-assignment period milestones

Number of subjects started	257[1]
Number of subjects completed	111

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 24
Reason: Number of subjects	Methylated MGMT-promotor: 67
Reason: Number of subjects	Other: 55

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 257 patients were registered in the study but 111 only were eligible for randomization. Results are presented for randomized patients only.

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	Temozolomide (TMZ)

Arm description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks. TMZ will be given at 75 mg/m2 daily for the whole period of RT including weekends as registered.
Study period 2 (adjuvant):
TMZ administration pauses for 4 weeks from the end of RT and will continue for 6 4-week cycles (D1-5) at 150/200 mg/m2 as detailed in the registration trial and according to the label in this indication. At the investigators discretion TMZ can be continued up to a maximum of 12 cycles.

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	Temodal
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

Study period 1: TMZ will be given at 75 mg/m2 daily for the whole period of RT including weekends as registered.
Study period 2: TMZ administration pauses for 4 weeks from the end of RT and will continue for 6 4-week cycles (D1-5) at 150/200 mg/m2 as detailed in the registration trial and according to the label in

this indication.

Arm title	Temsirolimus (CCI-779)

Arm description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks.
CCI-779 will be given i.v. once every week at 25 mg. Each treatment should be preceded by supportive medication with a histamine H2-receptor antagonist. A first dose of CCI-779, being 25 mg, will be given on day –7 from RT start.

Study period 2 (maintenance):
CCI-779 administration (given i.v. once every week at 25 mg) is to continue until progression or unacceptable AEs.

Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Will be given i.v. once every week at 25 mg. Each treatment should be preceded by supportive medication with a histamine H2-receptor antagonist. A first dose of CCI-779 will be given on day –7 from RT start, being 25 mg. CCI-779 administration is to continue until progression or unacceptable AEs.

Number of subjects in period 1	Temozolomide (TMZ)	Temsirolimus (CCI-779)
Started	55	56
Completed	12	0
Not completed	43	56
Consent withdrawn by subject	3	1
Physician decision	-	2
Adverse event, non-fatal	7	13
Other	3	4
treatment ongoing	-	1
Lack of efficacy	30	35

Baseline characteristics

Reporting groups	
Reporting group title	Temozolomide (TMZ)

Reporting group description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks. TMZ will be given at 75 mg/m2 daily for the whole period of RT including weekends as registered.
Study period 2 (adjuvant):
TMZ administration pauses for 4 weeks from the end of RT and will continue for 6 4-week cycles (D1-5) at 150/200 mg/m2 as detailed in the registration trial and according to the label in this indication. At the investigators discretion TMZ can be continued up to a maximum of 12 cycles.

Reporting group title	Temsirolimus (CCI-779)

Reporting group description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks.
CCI-779 will be given i.v. once every week at 25 mg. Each treatment should be preceded by supportive medication with a histamine H2-receptor antagonist. A first dose of CCI-779, being 25 mg, will be given on day –7 from RT start.

Study period 2 (maintenance):
CCI-779 administration (given i.v. once every week at 25 mg) is to continue until progression or unacceptable AEs.

Reporting group values	Temozolomide (TMZ)	Temsirolimus (CCI-779)	Total
Number of subjects	55	56	111
Age categorical Units: Subjects			
<50 years	15	14	29
≥50 years	40	42	82
Age continuous Units: years			
median	55.7	54.9	
full range (min-max)	24.4 to 76	28.2 to 74.7	-
Gender categorical Units: Subjects			
Female	19	21	40
Male	36	35	71
Steroids use Units: Subjects			
No	37	40	77
yes, stable/decreasing dose	17	16	33
yes, increasing dose	1	0	1
WHO performance status Units: Subjects			
PS 0	40	32	72
PS 1	14	20	34
PS 2	1	4	5

End points

End points reporting groups

Reporting group title	Temozolomide (TMZ)

Reporting group description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks. TMZ will be given at 75 mg/m2 daily for the whole period of RT including weekends as registered.
Study period 2 (adjuvant):
TMZ administration pauses for 4 weeks from the end of RT and will continue for 6 4-week cycles (D1-5) at 150/200 mg/m2 as detailed in the registration trial and according to the label in this indication. At the investigators discretion TMZ can be continued up to a maximum of 12 cycles.

Reporting group title	Temsirolimus (CCI-779)

Reporting group description:

Study period 1 (concomitant RT-TMZ) and starts within 8 days from randomization:
Focal RT to the tumor area will be administered concomitantly to TMZ at a dose of 60 Gy, given in individual doses of 2 Gy per day for 5 days a week over 6 weeks.
CCI-779 will be given i.v. once every week at 25 mg. Each treatment should be preceded by supportive medication with a histamine H2-receptor antagonist. A first dose of CCI-779, being 25 mg, will be given on day –7 from RT start.

Study period 2 (maintenance):
CCI-779 administration (given i.v. once every week at 25 mg) is to continue until progression or unacceptable AEs.

Primary: Overall survival rate at 12 months (OS12)

End point title	Overall survival rate at 12 months (OS12)[1][2]

End point description:

The primary endpoint (OS12) is evaluated only in the Temsirolimus (CCI-779) arm, in the per protocol population (All patients who are eligible and have started their allocated treatment with at least one dose of the study drug)

The number of patients alive at 1 year will be computed. Patients lost to follow-up or who died before 1 year are considered as failures at the time of analysis.

In case more than 54 eligible patients are recruited in Temsirolimus (CCI-779) arm, the decision rule will be applied as such on the first 54 eligible patients according to their sequential registration numbers.

End point type	Primary

End point timeframe:

All patients will be observed during a minimum follow-up of 1 year.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a non comparative phase II design, no formal statistical test was performed for the primary endpoint.
In the per protocol population, exactly 38 patients treated with CCI-779 (out of 54 eligible) had survived up to 1 year. At least 39 patients were needed to reach the targeted drug activity. The trial was analysed with the conclusion that the therapeutic activity of Temsirolimus (CCI-779) is too low in this disease.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The decision rule defined above was only applied to the treatment arm (CCI-779).

End point values	Temsirolimus (CCI-779)			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: patients				
number (not applicable)				
Failure	16			
Success (alive at 12 months)	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The duration of survival is the time interval between randomization and the date of death due to any cause. Patients not reported dead or lost to follow up will be censored at the date of the last follow up examination. All patients will be followed until death.

Overall survival will be described in the intent-to-treat population (all randomized patients according to the allocated treatment).

End point type	Secondary

End point timeframe:

All patients will have three monthly disease and status assessment after the end of RT until PD or start of
further anti tumoral therapy. After the documentation of first progression, the patient must be followed every 3 months till death.

End point values	Temozolomide (TMZ)	Temsirolimus (CCI-779)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	56		
Units: Months				
median (confidence interval 95%)	16 (13.8 to 18.2)	14.8 (13.3 to 16.4)		

Statistical analyses

Statistical analysis title	Comparison of OS in ITT

Statistical analysis description:

Sensitivity analysis
Comparison of overall survival (CCI-779 versus TMZ) in the intent-to-treat population (all randomized patients according to the allocated treatment).

Comparison groups	Temozolomide (TMZ) v Temsirolimus (CCI-779)

Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.47
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.76

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression free survival (PFS) will be measured from the date of randomization until the date of objective progression or the date of patient's death whichever occurs first. Patients without evidence of progression will be censored at the date of last tumor assessment where non progression was documented. If a patient received a second anti-cancer therapy without prior documentation of disease progression, the patient will be censored at the date of last tumor assessment before starting new anti tumoral therapy.

End point type	Secondary

End point timeframe:

All patients will have three monthly disease and status assessment after the end of radiotherapy until progression or start of further anti-tumoral therapy.

End point values	Temozolomide (TMZ)	Temsirolimus (CCI-779)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	56		
Units: Months				
median (confidence interval 95%)	5.95 (3.25 to 8.02)	5.36 (3.71 to 6.14)		

Statistical analyses

Statistical analysis title	Comparison of PFS in ITT

Statistical analysis description:

Sensitivity analysis
Comparison of progression-free survival (CCI-779 versus TMZ) in the intent-to-treat population (all randomized patients according to the allocated treatment).

Comparison groups	Temozolomide (TMZ) v Temsirolimus (CCI-779)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.86

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Before treatment start, at week 4 and 6 of RT, 4 weeks after the end of RT. Three monthly disease evaluation after the end of RT.
Every 4 weeks for CCI-779/every adjuvant cycle for TMZ.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (xx% AEs are reported as "other" and are not reported as not available from the list of SOC).
AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	TMZ in safety

Reporting group description:

TMZ in safety population

Reporting group title	CCI-779 in safety

Reporting group description:

CCI-779 in safety population

Serious adverse events	TMZ in safety	CCI-779 in safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 53 (28.30%)	26 / 55 (47.27%)	
number of deaths (all causes)	43	46	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Hypertension	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (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			
Chills	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: No information.		
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic injury	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar syndrome	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid retention	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Syncope	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Hepatitis	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin toxicity	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TMZ in safety	CCI-779 in safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 53 (100.00%)	55 / 55 (100.00%)	
Investigations			
HYPER ALKALINE PHOSPHATASE	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 53 (13.21%)	7 / 55 (12.73%)	
occurrences (all)	7	7	
HYPER ALT	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	30 / 53 (56.60%)	40 / 55 (72.73%)	
occurrences (all)	30	40	
HYPER GGT	Additional description: No information.		

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	25 / 53 (47.17%)	33 / 55 (60.00%)	
occurrences (all)	25	33	
HYPER AST	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	19 / 53 (35.85%)	25 / 55 (45.45%)	
occurrences (all)	19	25	
HYPERBILIRUBINEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 53 (11.32%)	2 / 55 (3.64%)	
occurrences (all)	6	2	
HYPERCALCAEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 53 (11.32%)	4 / 55 (7.27%)	
occurrences (all)	6	4	
HYPERCHOLESTEROLEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	23 / 53 (43.40%)	47 / 55 (85.45%)	
occurrences (all)	23	47	
HYPERCREATININEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 53 (24.53%)	6 / 55 (10.91%)	
occurrences (all)	13	6	
HYPERGLYCEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	26 / 53 (49.06%)	36 / 55 (65.45%)	
occurrences (all)	26	36	
HYPERKALEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	14 / 53 (26.42%)	7 / 55 (12.73%)	
occurrences (all)	14	7	
HYPERMAGNESIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	5 / 53 (9.43%)	2 / 55 (3.64%)	
occurrences (all)	5	2	
HYPERPHOSPHATEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 53 (16.98%)	28 / 55 (50.91%)	
occurrences (all)	9	28	
HYPOCALCAEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 53 (15.09%)	14 / 55 (25.45%)	
occurrences (all)	8	14	
HYPERTRIGLYCERIDEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	36 / 53 (67.92%)	51 / 55 (92.73%)	
occurrences (all)	36	51	
HYPOGLYCEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 53 (7.55%)	3 / 55 (5.45%)	
occurrences (all)	4	3	
HYPOKALEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 53 (9.43%)	18 / 55 (32.73%)	
occurrences (all)	5	18	
HYPOMAGNESIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	9 / 55 (16.36%)	
occurrences (all)	1	9	
WEIGHT GAIN	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 53 (16.98%)	6 / 55 (10.91%)	
occurrences (all)	9	6	
WEIGHT LOSS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 53 (11.32%)	13 / 55 (23.64%)	
occurrences (all)	6	13	

Vascular disorders			
FLUSHING	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
HYPERTENSION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 53 (16.98%)	9 / 55 (16.36%)	
occurrences (all)	9	9	
Cardiac disorders			
CONSTIPATION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 53 (15.09%)	6 / 55 (10.91%)	
occurrences (all)	8	6	
DIARRHEA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	13 / 55 (23.64%)	
occurrences (all)	3	13	
DYSPEPSIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	
occurrences (all)	3	4	
MUCOSITIS ORAL	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	25 / 55 (45.45%)	
occurrences (all)	1	25	
NAUSEA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	22 / 53 (41.51%)	12 / 55 (21.82%)	
occurrences (all)	22	12	
VENTRICULAR ARRHYTHMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
VOMITING	Additional description: No information.		

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	10 / 53 (18.87%)	7 / 55 (12.73%)	
occurrences (all)	10	7	
Nervous system disorders			
DIZZINESS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 53 (20.75%)	13 / 55 (23.64%)	
occurrences (all)	11	13	
DYSGEUSIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 53 (7.55%)	13 / 55 (23.64%)	
occurrences (all)	4	13	
EDEMA CEREBRAL	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
HEADACHE	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	20 / 53 (37.74%)	24 / 55 (43.64%)	
occurrences (all)	20	24	
PARESTHESIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
PERIPHERAL MOTOR NEUROPATHY	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 53 (15.09%)	8 / 55 (14.55%)	
occurrences (all)	8	8	
PERIPHERAL SENSORY NEUROPATHY	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			

ANEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 53 (9.43%)	5 / 55 (9.09%)	
occurrences (all)	5	5	
FEBRILE NEUTROPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
LEUKOPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	9 / 53 (16.98%)	4 / 55 (7.27%)	
occurrences (all)	9	4	
LYMPHOCYTOPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	32 / 53 (60.38%)	26 / 55 (47.27%)	
occurrences (all)	32	26	
NEUTROPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 53 (15.09%)	3 / 55 (5.45%)	
occurrences (all)	8	3	
THROMBOCYTOPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 53 (11.32%)	3 / 55 (5.45%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
EDEMA LIMBS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 53 (13.21%)	6 / 55 (10.91%)	
occurrences (all)	7	6	
FATIGUE	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	40 / 53 (75.47%)	43 / 55 (78.18%)	
occurrences (all)	40	43	
FEVER	Additional description: No information.		
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	5 / 53 (9.43%)	16 / 55 (29.09%)	
occurrences (all)	5	16	
LOCALIZED EDEMA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	6 / 55 (10.91%)	
occurrences (all)	2	6	
NON-CARDIAC CHEST PAIN	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
ALLERGIC RHINITIS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
COUGH	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	16 / 55 (29.09%)	
occurrences (all)	2	16	
DYSPNEA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	9 / 55 (16.36%)	
occurrences (all)	3	9	
EPISTAXIS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	5 / 55 (9.09%)	
occurrences (all)	0	5	
PNEUMONITIS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	5 / 55 (9.09%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			

ALOPECIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	33 / 53 (62.26%)	28 / 55 (50.91%)	
occurrences (all)	33	28	
ERYTHEMA MULTIFORME	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	8 / 55 (14.55%)	
occurrences (all)	3	8	
NAIL DISCOLORATION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
NAIL LOSS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
NAIL RIDGING	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
PERIORBITAL EDEMA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	4	
PRURITUS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	10 / 55 (18.18%)	
occurrences (all)	2	10	
RASH ACNEIFORM	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	18 / 55 (32.73%)	
occurrences (all)	0	18	
RASH MACULO-PAPULAR	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	0 / 53 (0.00%)	9 / 55 (16.36%)	
occurrences (all)	0	9	
URTICARIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Psychiatric disorders			
AGITATION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
ANXIETY	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	7 / 55 (12.73%)	
occurrences (all)	0	7	
CONFUSION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	7 / 55 (12.73%)	
occurrences (all)	2	7	
DEPRESSION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 53 (11.32%)	7 / 55 (12.73%)	
occurrences (all)	6	7	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	7 / 55 (12.73%)	
occurrences (all)	2	7	
BACK PAIN	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 53 (5.66%)	8 / 55 (14.55%)	
occurrences (all)	3	8	
Infections and infestations			

CATHETER RELATED INFECTION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 53 (1.89%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
PHARYNGITIS	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
RHINITIS INFECTIVE	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 53 (0.00%)	5 / 55 (9.09%)	
occurrences (all)	0	5	
UPPER RESPIRATORY INFECTION	Additional description: No information.		
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2009	Protocol version 2.0 dated 25 JUN 2009 In this amendment: • An exclusion criterion on hypersensitivity to antihistamines was added on request of the VHP. The rationale for this is the need to take antihistamines before administration of Temsirolimus. Therefore, it should be clarified to protect the patients, that subjects with a hypersensitivity to antihistamines or with medical reasons that don't allow the subjects to take antihistamines can't be included in the study. • The procedure for stopping in case of toxicity was clarified (prolongation of QT interval) • It was clarified that the information on anonymization and sample destruction in the informed consents handles about biological samples as wel (and not only medical data)l. • The details of sample storage and the central laboratory were clarified in the PIS.
06 December 2010	Protocol version 3.0 dated 06 DEC 2010 The reasons for this amendment are: • Need for modification of the protocol and the Patient Information Sheet according to new safety information. • The participating sites had difficulties to be compliant with time of 8 days between randomization and the start of Radiotherapy (RT). This 8-days period has been removed. The RT now has to start within 7 weeks (49 days) of surgery or open biopsy. • The company MDX Health (OMS) in Liège – Belgium is added as testing center for the MGMT test.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27143690