# 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<br>Units: Subjects | | | |
| <50 years | 15 | 14 | 29 |
| ≥50 years | 40 | 42 | 82 |
| Age continuous<br>Units: years | | | |
| median | 55.7 | 54.9 | |
| full range (min-max) | 24.4 to 76 | 28.2 to 74.7 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 19 | 21 | 40 |
| Male | 36 | 35 | 71 |
| Steroids use<br>Units: Subjects | | | |
| No | 37 | 40 | 77 |
| yes, stable/decreasing dose | 17 | 16 | 33 |
| yes, increasing dose | 1 | 0 | 1 |
| WHO performance status<br>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<br><br>In this amendment:<br>• 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.<br>• The procedure for stopping in case of toxicity was clarified (prolongation of QT interval)<br>• 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.<br>• 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<br><br>The reasons for this amendment are:<br>• Need for modification of the protocol and the Patient Information Sheet according to new safety information.<br>• 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.<br>• 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