Clinical trial results:
Cilengitide in subjects with newly diagnosed glioblastoma multiforme and unmethylated MGMT gene promoter - a multicenter, open-label Phase II study, investigating two cilengitide regimens in combination with standard treatment (temozolomide with concomitant radiation therapy, followed by temozolomide maintenance therapy) - CORE.

Summary

EudraCT number	2008-004457-15
Trial protocol	CZ IT FR HU AT ES
Global end of trial date	01 August 2013

Results information

Result version number	v1
This version publication date	23 May 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	EMD121974-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00813943
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Serono
Sponsor organisation address	Frankfurter Str. 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck KGaA , 49 6151725200, service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA Communication Center, 49 6151725200, service@merckgroup.com

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	01 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2013
Global end of trial reached?	Yes
Global end of trial date	01 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of a 5-day administration schedule of 2000 mg cilengitide given in combination with radiation therapy (RTX) and temozolomide (TMZ) standard treatment in the safety run-in part of the trial:

To investigate the overall survival (OS) in subjects receiving 2 different regimens of 2000 mg cilengitide in combination with RTX and TMZ standard treatment in the randomized part of the trial:

Protection of trial subjects:

In this trial highest medical and ethical standards were followed, in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 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	France: 20
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	United States: 65
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 30
Worldwide total number of subjects	265
EEA total number of subjects	127

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)	218
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Mar 2009/Sep 2011. Clinical data cut-off: 07 Feb 2013, Study completion date: Aug 2013.

Pre-assignment

Screening details:

Enrolled: 294 screened for eligibility; 29 excluded (mainly due to non-fulfillment of inclusion or exclusion criteria), 265 subjects randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy

Arm description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

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

Dosage and administration details:

Cilengitide 2000 milligram (mg) will be administered intravenously twice weekly over 1 hour infusion from Weeks -1 to 77 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. If considered beneficial in the opinion of the Investigator, continuation of cilengitide treatment will be optional in subjects without disease progression and after Week 77 since start of treatment.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] will be administered intravenously once daily from Week 1 to 6. From Week 11 onwards, TMZ will be given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 or until disease progression.

Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Route of administration not applicable

Dosage and administration details:

Radiation therapy (RTX) at a dose of 2 gray (Gy) per fraction will be given once daily, 5 days per week from Week 1 to 6, total dose 60 Gy.

Arm title	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy

Arm description:

Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

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

Dosage and administration details:

Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TMZ 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34.

Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Route of administration not applicable

Dosage and administration details:

RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Arm title	Temozolomide + Radiotherapy

Arm description:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

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

Dosage and administration details:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4

weeks until Week 34.

Investigational medicinal product name	Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Intravenous use

Dosage and administration details:

RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Number of subjects in period 1	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy
Started	88	88	89
Completed	83	83	86
Not completed	5	5	3
Ongoing at cut-off date	5	5	3

Baseline characteristics

Reporting groups

Reporting group title	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy

Reporting group description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Reporting group title	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy

Reporting group description:

Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Reporting group title	Temozolomide + Radiotherapy

Reporting group description:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Reporting group values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy
Number of subjects	88	88	89
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.6	55.2	54.5
standard deviation	± 9.63	± 10.44	± 11.64
Gender categorical Units: Subjects			
Female	38	38	34
Male	50	50	55

Reporting group values	Total		
Number of subjects	265		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	110		
Male	155		

End points

End points reporting groups

Reporting group title	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy

Reporting group description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Reporting group title	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy

Reporting group description:

Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Reporting group title	Temozolomide + Radiotherapy

Reporting group description:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all subjects who received any dose of study treatment that is Cilengitide, Temozolomide or Radiotherapy. 1 subject who was randomized to cilengitide 5-times weekly, but who actually received Cilengitide 2-times weekly was allocated to the cilengitide 2-times weekly treatment group for the safety population.

Subject analysis set title	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy-SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Subject analysis set title	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy-SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Subject analysis set title	Temozolomide + Radiotherapy-SAF

Subject analysis set type	Safety analysis

Subject analysis set description:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Safety population included all subjects who received any dose of study treatment that is Cilengitide, Temozolomide or Radiotherapy. 1 subject who was randomized to cilengitide 5-times weekly, but who actually received Cilengitide 2-times weekly was allocated to the cilengitide 2-times weekly treatment group for the safety population.

Primary: Overall survival (OS) time

End point title	Overall survival (OS) time

End point description:

The OS time was defined as the time (in months) from randomization to death or last day known to be alive. Subjects without event were censored at the last date known to be alive or at the clinical cut-off date, whatever was earlier. ITT population included all the participants who were randomized to study treatment.

End point type	Primary

End point timeframe:

Time from randomization to death or last day known to be alive, reported between day of first subject randomized, that was, Jun 2009 until cut-off date, (07 Feb 2013)

End point values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	88	89	
Units: Months				
median (confidence interval 95%)	16.3 (13.2 to 18.1)	14.5 (12.6 to 16.5)	13.4 (12.2 to 14.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Overall Survival Time
Comparison groups	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy v Temozolomide + Radiotherapy
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0328
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.686
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.484
upper limit	0.972

Statistical analysis title	Statistical Analysis 2 for Overall Survival Time
Comparison groups	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy v Temozolomide + Radiotherapy
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3771
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.612
upper limit	1.204

Secondary: Progression free survival (PFS) time - investigator and independent read	
End point title	Progression free survival (PFS) time - investigator and independent read

End point description:

The PFS time was defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Investigator read was the assessment of all imaging by the treating physician at the local trial site. Independent Read was the assessment of all imaging centrally by an Independent Review Committee (IRC). ITT population included all the participants who were randomized to study treatment.

End point type	Secondary

End point timeframe:

Time from randomization to disease progression, death or last tumor assessment, reported between day of first subject randomized, that was, Jun 2009 until cut-off date, (07 Feb 2013).

End point values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	88	89	
Units: Months				
median (confidence interval 95%)				
PFS Time: Independent read	5.6 (3.6 to 5.9)	5.9 (4.2 to 7.6)	4.1 (3.7 to 4.7)	
PFS Time: Investigator read	6.4 (4.2 to 7.9)	7.5 (5.9 to 8.2)	6 (4.1 to 7.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax)

End point title	Maximum observed plasma concentration (Cmax)[1]

End point description:

The Cmax for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[1] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[2]			
Units: nanogram per milliliter				
arithmetic mean (standard deviation)				
Day 1	108527 (± 27197)			
Day 5	150873 (± 97220)			

Notes:

[2] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum plasma concentration (Tmax) and terminal elimination half-life (t1/2)

End point title	Time to maximum plasma concentration (Tmax) and terminal elimination half-life (t1/2)[3]

End point description:

The Tmax and t1/2 for cilengitide were calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[3] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[4]			
Units: hours				
arithmetic mean (standard deviation)				
Tmax: Day 1 (Single dose)	0.97 (± 0.34)			
Tmax: Day 5 (Repeated doses)	1.17 (± 0.34)			
t1/2: Day 1 (Single dose)	2.38 (± 0.8)			
t1/2: Day 5 (Repeated doses)	2.44 (± 0.8)			

Notes:

[4] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to infinity (AUC [0-infinity]) and area under the plasma concentration-time curve from time 0 to 24 hours (AUC [0-24])

End point title	Area under the plasma concentration-time curve from time 0 to infinity (AUC [0-infinity]) and area under the plasma concentration-time curve from time 0 to 24 hours (AUC [0-24])[5]

End point description:

The AUC (0-infinity) and AUC (0-24) for cilengitide were calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[5] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[6]			
Units: hour*ng/mL				
arithmetic mean (standard deviation)				
AUC (0-infinity): Day 1 (Single dose)	280944 (± 75720)			
AUC (0-infinity): Day 5 (Repeated Doses)	335263 (± 105435)			
AUC (0-24): Day 1 (Single dose)	269941 (± 82850)			
AUC (0-24): Day 5 (Repeated doses)	316137 (± 110425)			

Notes:

[6] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration at pre-dose (Cpre) and plasma concentration at end of infusion (CT)

End point title	Plasma concentration at pre-dose (Cpre) and plasma concentration at end of infusion (CT)[7]

End point description:

The Cpre and CT for cilengitide were calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[7] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[8]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cpre: Day 1 (Single dose)	6372.7 (± 21135.95)			
Cpre: Day 5 (Repeated doses)	286 (± 319.05)			
CT: Day 1 (Single dose)	108045.5 (± 27981.04)			
CT: Day 5 (Repeated doses)	157470 (± 99849.26)			

Notes:

[8] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent terminal rate constant

End point title	Apparent terminal rate constant[9]

End point description:

The apparent terminal rate constant for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after

dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[9] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[10]			
Units: Per hour				
arithmetic mean (standard deviation)				
Day 1 (Single dose)	0.32 (± 0.11)			
Day 5 (Repeated doses)	0.32 (± 0.11)			

Notes:

[10] - Number of participants analyzed signifies those who were evaluable for this outcome measures.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean residence time from time 0 to infinity (MRT [0-infinity])

End point title	Mean residence time from time 0 to infinity (MRT [0-

End point description:

The MRT (0-infinity) for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[11] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[12]			
Units: hour				
arithmetic mean (standard deviation)				
Day 1 (Single dose)	2.8 (± 0.71)			
Day 5 (Repeated doses)	2.9 (± 0.97)			

Notes:

[12] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma clearance (CL)

End point title	Plasma clearance (CL)[13]

End point description:

The CL for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[13] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[14]			
Units: milliliter per minute				
arithmetic mean (standard deviation)				
Day 1 (Single dose)	125.7 (± 29.93)			
Day 5 (Repeated doses)	109.3 (± 36.61)			

Notes:

[14] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution during the terminal phase (Vz) and apparent volume of distribution at steady state (Vss)

End point title	Apparent volume of distribution during the terminal phase (Vz) and apparent volume of distribution at steady state (Vss)[15]

End point description:

The Vz (after single dose) and Vss (after repeated doses) for cilengitide were calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2. Cilengitide plasma concentrations were determined after dosing on Day 1 (single dose) and Day 5 (repeated doses) of Week 1.

End point type	Secondary

End point timeframe:

Days 1 and 5 of Week 1

Notes:

[15] - 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: Only "Cilengitide (5-times) + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11[16]			
Units: liter				
arithmetic mean (standard deviation)				
Vz	24.7 (± 6.29)			
Vss	19.2 (± 8.54)			

Notes:

[16] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious AEs, treatment-Related AEs, Treatment-Related Serious AEs, AEs leading to death, treatment-related AEs leading to death, AEs of Grade 3 or 4 and treatment-related AEs of Grade 3 or 4

End point title	Number of subjects with adverse events (AEs), serious AEs, treatment-Related AEs, Treatment-Related Serious AEs, AEs leading to death, treatment-related AEs leading to death, AEs of Grade 3 or 4 and treatment-related AEs of Grade 3 or 4

End point description:

An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. Treatment-emergent AEs are the events between first dose of study drug and up to 28 days after last dose of study treatment. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. Treatment-related AEs were the AEs which were suspected to be reasonably related to the study treatment (cilengitide, or radiotherapy, or temozolomide) as per investigator assessment. The severity of AEs was assessed according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTCAE) (Version 3.0): Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening or disabling. Note: Death (Grade 5) was regarded as an outcome.

End point type	Secondary

End point timeframe:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first participant randomized, that was, Jun 2009 until cut-off date (07 Feb 2013).

End point values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy-SAF	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy-SAF	Temozolomide + Radiotherapy-SAF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	89	81	85	
Units: Participants				
AEs	88	80	82	
Serious AEs	47	36	30	
Treatment-related AEs	70	64	56	
Treatment-related serious AEs	13	4	5	
AEs leading to death	8	8	5	
Treatment-related AEs leading to death	2	2	1	
AEs of Grade 3 or 4	57	47	45	
Treatment-related AEs of Grade 3 or 4	25	19	17	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with AEs belonging to Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) thromboembolic events and haemorrhage With NCI−CTC Toxicity Grade 3 or 4

End point title	Number of subjects with AEs belonging to Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) thromboembolic events and haemorrhage With NCI−CTC Toxicity Grade 3 or 4

End point description:

Thromboembolic events (standardized MedDRA query [SMQ]) Grade 3 or 4 AEs encompassed hemiparesis and cerebrovascular accident, pulmonary embolism, and deep vein thrombosis. Thromboembolic events (SMQ) of any grade and of Grade 3 or 4 were generally more frequent in the Cilengitide + Temozolomide/Radiotherapy group than in the Temozolomide/Radiotherapy group but were still in the expected range of this patient population The severity of AEs was assessed according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTCAE) (version 3.0): Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening or disabling. Note: Death (Grade 5) was regarded as an outcome.

End point type	Secondary

End point timeframe:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first participant randomized, that was, Jun 2009 until cut-off date (07 Feb 2013)

End point values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy-SAF	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy-SAF	Temozolomide + Radiotherapy-SAF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	89	81	85	

Units: Participants				
SMQ: Thromboembolic events	17	10	12	
SMQ:Hemorrhage	3	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormal electrocardiogram (ECG) and lab parameters

End point title	Number of subjects with clinically significant abnormal electrocardiogram (ECG) and lab parameters

End point description:

Any clinically significant abnormal ECG and lab finding was planned to be reported as AE only so they have been captured in the below mentioned adverse event section

End point type	Secondary

End point timeframe:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first subject randomized, that was, Jun 2009 until cut-off date (07 Feb 2013).

End point values	Cilengitide (2-times weekly) + Temozolomide + Radiotherapy-SAF	Cilengitide (5-times weekly) + Temozolomide + Radiotherapy-SAF	Temozolomide + Radiotherapy-SAF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: Participants				
Abnormal ECG				
Abnormal Laboratory values				

Notes:

[17] - As stated in the end point description, this outcome measure was not evaluated.

[18] - As stated in the end point description, this outcome measure was not evaluated.

[19] - As stated in the end point description, this outcome measure was not evaluated.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first participant randomized, that is, Jun 2009 until cut-off date (07 Feb 2013)

Adverse event reporting additional description:

Safety population included all participants who received any dose of study treatment that is Cilengitide, Temozolomide or Radiotherapy. 1 participant who was randomized to cilengitide 5-times weekly, but who actually received Cilengitide 2-times weekly was allocated to the cilengitide 2-times weekly treatment group for the safety population

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Cilengitide twice a week + Temozolomide + Radiotherapy

Reporting group description:

In Group A, 2000 mg cilengitide will be administered twice weekly by i.v. infusion throughout the study. Treatment will start 1 week prior to RTX and TMZ standard treatment (Week -1), i.e. as single agent. During Weeks 1-6, cilengitide will be administered in combination with RTX and TMZ and for a further 6 cycles (Week 7-34) in combination with TMZ maintenance treatment, according to the RTX and TMZ standard treatment. After completion of RTX and TMZ standard treatment, subjects continue receiving 2000 mg cilengitide i.v. 2x/week as maintenance for another 10 months.

Reporting group title	Temozolomide + Radiotherapy

Reporting group description:

Subjects in Group C will not receive cilengitide during the study.

Reporting group title	Cilengitide 5 times a week + Temozolomide + Radiotherapy

Reporting group description:

In Group B, treatment with cilengitide as twice weekly i.v. infusion of 2000 mg per infusion will start 1 week prior to RTX and TMZ standard treatment (Week -1), i.e. as single agent. Thereafter, during combination with RTX and TMZ (Weeks 1-6), subjects will receive 2000 mg cilengitide i.v. 5x/week on days of RTX. After this 6-week intense treatment, subjects will receive 2000 mg cilengitide i.v. 2x/week in combination with TMZ maintenance treatment for a further 6 cycles (Week 7-34). After completion of RTX and TMZ standard treatment, subjects continue receiving 2000 mg cilengitide i.v. 2x/week as maintenance for another 10 months.

Serious adverse events	Cilengitide twice a week + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	Cilengitide 5 times a week + Temozolomide + Radiotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 89 (52.81%)	30 / 85 (35.29%)	36 / 81 (44.44%)
number of deaths (all causes)	65	67	61
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASM RECURRENCE			

subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEOPLASM PROGRESSION			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAVY CHAIN DISEASE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
BRAIN STEM GLIOMA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
BRAIN NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED #(INCL CYSTS AND POLYPS)			
subjects affected / exposed	5 / 89 (5.62%)	0 / 85 (0.00%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Vascular disorders			
THROMBOSIS			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			

subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	4 / 89 (4.49%)	3 / 85 (3.53%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HAEMATOMA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
DEVICE MALFUNCTION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONDITION AGGRAVATED			
subjects affected / exposed	1 / 89 (1.12%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
CHEST DISCOMFORT			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHENIA			

subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	1 / 89 (1.12%)	2 / 85 (2.35%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GAIT DISTURBANCE			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
GENERALISED OEDEMA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 89 (1.12%)	3 / 85 (3.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TERMINAL STATE			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL DISORDERS AND ADMINISTRATION SITE #CONDITIONS			

subjects affected / exposed	9 / 89 (10.11%)	8 / 85 (9.41%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	1 / 9	1 / 8	0 / 3
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 1
Social circumstances			
SOCIAL STAY HOSPITALISATION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	2 / 89 (2.25%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MEDIASTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG DISORDER			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HYPOXIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PULMONARY EMBOLISM			
subjects affected / exposed	9 / 89 (10.11%)	1 / 85 (1.18%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	3 / 9	0 / 1	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	1 / 1
PNEUMONIA ASPIRATION			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 89 (1.12%)	1 / 85 (1.18%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INSOMNIA			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSYCHOTIC DISORDER			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
AMYLASE INCREASED			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIPASE INCREASED			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

HEPATIC ENZYME INCREASED			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBRIN D DIMER INCREASED			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 89 (0.00%)	2 / 85 (2.35%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BUNDLE BRANCH BLOCK RIGHT			

subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PULSELESS ELECTRICAL ACTIVITY			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
COGNITIVE DISORDER			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL VENTRICLE DILATATION			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL CYST			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRAIN OEDEMA			

subjects affected / exposed	1 / 89 (1.12%)	2 / 85 (2.35%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
APHASIA			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONVULSION			
subjects affected / exposed	5 / 89 (5.62%)	3 / 85 (3.53%)	7 / 81 (8.64%)
occurrences causally related to treatment / all	0 / 5	0 / 3	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSARTHRIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSKINESIA			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	4 / 89 (4.49%)	1 / 85 (1.18%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GRAND MAL CONVULSION			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			

subjects affected / exposed	1 / 89 (1.12%)	3 / 85 (3.53%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIANOPIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
subjects affected / exposed	4 / 89 (4.49%)	5 / 85 (5.88%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HYDROCEPHALUS			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MOTOR DYSFUNCTION			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL DECOMPENSATION			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
PARTIAL SEIZURES			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYRAMIDAL TRACT SYNDROME			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UNRESPONSIVE TO STIMULI			

subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADICULAR PAIN			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
NEUTROPENIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

RETINAL ARTERY EMBOLISM			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOOD POISONING			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETROPERITONEAL HAEMORRHAGE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

TOXIC SKIN ERUPTION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
OLIGURIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROTIC SYNDROME			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY INCONTINENCE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			

subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	2 / 89 (2.25%)	2 / 85 (2.35%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECI PNEUMONIA			

subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO THRIVE			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 89 (1.12%)	0 / 85 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 89 (0.00%)	1 / 85 (1.18%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOVOLAEMIA			
subjects affected / exposed	0 / 89 (0.00%)	0 / 85 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cilengitide twice a week + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	Cilengitide 5 times a week + Temozolomide + Radiotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 89 (93.26%)	76 / 85 (89.41%)	79 / 81 (97.53%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	5 / 89 (5.62%)	3 / 85 (3.53%)	6 / 81 (7.41%)
occurrences (all)	5	3	6
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	22 / 89 (24.72%)	11 / 85 (12.94%)	25 / 81 (30.86%)
occurrences (all)	22	11	25
FATIGUE			
subjects affected / exposed	27 / 89 (30.34%)	19 / 85 (22.35%)	21 / 81 (25.93%)
occurrences (all)	27	19	21
OEDEMA PERIPHERAL			
subjects affected / exposed	9 / 89 (10.11%)	8 / 85 (9.41%)	5 / 81 (6.17%)
occurrences (all)	9	8	5
PYREXIA			
subjects affected / exposed	16 / 89 (17.98%)	8 / 85 (9.41%)	14 / 81 (17.28%)
occurrences (all)	16	8	14
GAIT DISTURBANCE			
subjects affected / exposed	3 / 89 (3.37%)	10 / 85 (11.76%)	7 / 81 (8.64%)
occurrences (all)	3	10	7
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	9 / 89 (10.11%)	3 / 85 (3.53%)	7 / 81 (8.64%)
occurrences (all)	9	3	7
DYSPNOEA			
subjects affected / exposed	5 / 89 (5.62%)	3 / 85 (3.53%)	4 / 81 (4.94%)
occurrences (all)	5	3	4
Psychiatric disorders			

INSOMNIA			
subjects affected / exposed	12 / 89 (13.48%)	12 / 85 (14.12%)	15 / 81 (18.52%)
occurrences (all)	12	12	15
DEPRESSION			
subjects affected / exposed	12 / 89 (13.48%)	2 / 85 (2.35%)	9 / 81 (11.11%)
occurrences (all)	12	2	9
ANXIETY			
subjects affected / exposed	6 / 89 (6.74%)	6 / 85 (7.06%)	7 / 81 (8.64%)
occurrences (all)	6	6	7
Investigations			
PLATELET COUNT DECREASED			
subjects affected / exposed	3 / 89 (3.37%)	5 / 85 (5.88%)	0 / 81 (0.00%)
occurrences (all)	3	5	0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 89 (0.00%)	3 / 85 (3.53%)	5 / 81 (6.17%)
occurrences (all)	0	3	5
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	11 / 89 (12.36%)	3 / 85 (3.53%)	3 / 81 (3.70%)
occurrences (all)	11	3	3
FALL			
subjects affected / exposed	2 / 89 (2.25%)	2 / 85 (2.35%)	5 / 81 (6.17%)
occurrences (all)	2	2	5
Nervous system disorders			
APHASIA			
subjects affected / exposed	7 / 89 (7.87%)	6 / 85 (7.06%)	4 / 81 (4.94%)
occurrences (all)	7	6	4
CONVULSION			
subjects affected / exposed	9 / 89 (10.11%)	10 / 85 (11.76%)	10 / 81 (12.35%)
occurrences (all)	9	10	10
MEMORY IMPAIRMENT			
subjects affected / exposed	7 / 89 (7.87%)	7 / 85 (8.24%)	8 / 81 (9.88%)
occurrences (all)	7	7	8
HEMIPARESIS			
subjects affected / exposed	7 / 89 (7.87%)	6 / 85 (7.06%)	5 / 81 (6.17%)
occurrences (all)	7	6	5

HEADACHE			
subjects affected / exposed	38 / 89 (42.70%)	27 / 85 (31.76%)	33 / 81 (40.74%)
occurrences (all)	38	27	33
DYSGEUSIA			
subjects affected / exposed	6 / 89 (6.74%)	2 / 85 (2.35%)	4 / 81 (4.94%)
occurrences (all)	6	2	4
DIZZINESS			
subjects affected / exposed	6 / 89 (6.74%)	5 / 85 (5.88%)	5 / 81 (6.17%)
occurrences (all)	6	5	5
PARAESTHESIA			
subjects affected / exposed	2 / 89 (2.25%)	0 / 85 (0.00%)	6 / 81 (7.41%)
occurrences (all)	2	0	6
TREMOR			
subjects affected / exposed	6 / 89 (6.74%)	3 / 85 (3.53%)	5 / 81 (6.17%)
occurrences (all)	6	3	5
Blood and lymphatic system disorders			
LEUKOPENIA			
subjects affected / exposed	5 / 89 (5.62%)	7 / 85 (8.24%)	6 / 81 (7.41%)
occurrences (all)	5	7	6
LYMPHOPENIA			
subjects affected / exposed	9 / 89 (10.11%)	7 / 85 (8.24%)	7 / 81 (8.64%)
occurrences (all)	9	7	7
ANAEMIA			
subjects affected / exposed	5 / 89 (5.62%)	1 / 85 (1.18%)	9 / 81 (11.11%)
occurrences (all)	5	1	9
THROMBOCYTOPENIA			
subjects affected / exposed	11 / 89 (12.36%)	17 / 85 (20.00%)	15 / 81 (18.52%)
occurrences (all)	11	17	15
NEUTROPENIA			
subjects affected / exposed	12 / 89 (13.48%)	8 / 85 (9.41%)	9 / 81 (11.11%)
occurrences (all)	12	8	9
Eye disorders			
VISION BLURRED			
subjects affected / exposed	6 / 89 (6.74%)	1 / 85 (1.18%)	2 / 81 (2.47%)
occurrences (all)	6	1	2
Gastrointestinal disorders			

CONSTIPATION			
subjects affected / exposed	26 / 89 (29.21%)	27 / 85 (31.76%)	27 / 81 (33.33%)
occurrences (all)	26	27	27
ABDOMINAL PAIN UPPER			
subjects affected / exposed	5 / 89 (5.62%)	1 / 85 (1.18%)	5 / 81 (6.17%)
occurrences (all)	5	1	5
NAUSEA			
subjects affected / exposed	33 / 89 (37.08%)	30 / 85 (35.29%)	30 / 81 (37.04%)
occurrences (all)	33	30	30
DIARRHOEA			
subjects affected / exposed	8 / 89 (8.99%)	2 / 85 (2.35%)	6 / 81 (7.41%)
occurrences (all)	8	2	6
STOMATITIS			
subjects affected / exposed	5 / 89 (5.62%)	2 / 85 (2.35%)	1 / 81 (1.23%)
occurrences (all)	5	2	1
VOMITING			
subjects affected / exposed	18 / 89 (20.22%)	21 / 85 (24.71%)	18 / 81 (22.22%)
occurrences (all)	18	21	18
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	14 / 89 (15.73%)	11 / 85 (12.94%)	18 / 81 (22.22%)
occurrences (all)	14	11	18
RASH			
subjects affected / exposed	11 / 89 (12.36%)	3 / 85 (3.53%)	8 / 81 (9.88%)
occurrences (all)	11	3	8
PRURITUS			
subjects affected / exposed	9 / 89 (10.11%)	5 / 85 (5.88%)	11 / 81 (13.58%)
occurrences (all)	9	5	11
ERYTHEMA			
subjects affected / exposed	4 / 89 (4.49%)	3 / 85 (3.53%)	5 / 81 (6.17%)
occurrences (all)	4	3	5
URTICARIA			
subjects affected / exposed	2 / 89 (2.25%)	2 / 85 (2.35%)	7 / 81 (8.64%)
occurrences (all)	2	2	7
Renal and urinary disorders			

URINARY INCONTINENCE			
subjects affected / exposed	3 / 89 (3.37%)	3 / 85 (3.53%)	5 / 81 (6.17%)
occurrences (all)	3	3	5
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	4 / 89 (4.49%)	2 / 85 (2.35%)	5 / 81 (6.17%)
occurrences (all)	4	2	5
NECK PAIN			
subjects affected / exposed	6 / 89 (6.74%)	1 / 85 (1.18%)	2 / 81 (2.47%)
occurrences (all)	6	1	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	7 / 89 (7.87%)	2 / 85 (2.35%)	3 / 81 (3.70%)
occurrences (all)	7	2	3
MUSCULAR WEAKNESS			
subjects affected / exposed	9 / 89 (10.11%)	4 / 85 (4.71%)	19 / 81 (23.46%)
occurrences (all)	9	4	19
MUSCLE SPASMS			
subjects affected / exposed	2 / 89 (2.25%)	1 / 85 (1.18%)	5 / 81 (6.17%)
occurrences (all)	2	1	5
BACK PAIN			
subjects affected / exposed	7 / 89 (7.87%)	0 / 85 (0.00%)	3 / 81 (3.70%)
occurrences (all)	7	0	3
PAIN IN EXTREMITY			
subjects affected / exposed	9 / 89 (10.11%)	6 / 85 (7.06%)	3 / 81 (3.70%)
occurrences (all)	9	6	3
Infections and infestations			
ORAL CANDIDIASIS			
subjects affected / exposed	6 / 89 (6.74%)	3 / 85 (3.53%)	6 / 81 (7.41%)
occurrences (all)	6	3	6
NASOPHARYNGITIS			
subjects affected / exposed	9 / 89 (10.11%)	1 / 85 (1.18%)	5 / 81 (6.17%)
occurrences (all)	9	1	5
URINARY TRACT INFECTION			
subjects affected / exposed	6 / 89 (6.74%)	6 / 85 (7.06%)	10 / 81 (12.35%)
occurrences (all)	6	6	10
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	6 / 89 (6.74%)	5 / 85 (5.88%)	10 / 81 (12.35%)
occurrences (all)	6	5	10
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	6 / 89 (6.74%)	1 / 85 (1.18%)	5 / 81 (6.17%)
occurrences (all)	6	1	5
DECREASED APPETITE			
subjects affected / exposed	20 / 89 (22.47%)	18 / 85 (21.18%)	18 / 81 (22.22%)
occurrences (all)	20	18	18
HYPONATRAEMIA			
subjects affected / exposed	3 / 89 (3.37%)	5 / 85 (5.88%)	4 / 81 (4.94%)
occurrences (all)	3	5	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2010	This amendment dated 19 Mar 2010 was substantial and applied to all sites. The main purpose of this amendment was to: • Allow inclusion of subjects with transient increase of transaminases due to narcotic use as a result of general anesthesia for surgery if transaminases were within normal limits prior to surgery and considering that this elevation of transaminases did not reflect a chronic underlying liver disease. • Allow inclusion of subjects with prior low dose RTX for tinea capitis of the head because clinical experience over the last 30 years in treatment of patients with GBM who were irradiated because of tinea capitis did not raise any concerns regarding special early or late side effects of low dose RTX, and therefore to give these patients the opportunity to be treated within this study. • Exclude subjects, only if major surgery was planned and to allow planned minor surgical procedures such as implantation of a port-a-cath or dental extraction as the safety profile of cilengitide so far included no concerns regarding bleeding and wound healing complications for these kinds of minor interventions. • Allow cilengitide re-escalation after first occurrence of Grade 4 toxicity on a case-by-case basis as this is most frequently Grade 4 thrombocytopenia when cilengitide is combined with TMZ and from the known safety profile of both drugs, thrombocytopenia is most likely related to TMZ. • Allow the restart of TMZ treatment for the maintenance phase after discontinuation for Grade 4 hematologic or Grade 3/4 non-hematologic toxicity during the continuous concomitant treatment phase, which is in line with the current Summary of Product Characteristics for TMZ and because TMZ can be well tolerated during maintenance treatment when it is only administered over 5 days every 4 weeks .

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported