



## 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          | v2 (current)   |
| This version publication date  | 18 September 2017  |
| First version publication date | 26 July 2015   |
| Version creation reason        | • Correction of full data set<br>Correction of full data set |

### 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:

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**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:

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**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:

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**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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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  |
| <b>Arm title</b>             | 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 [ $\text{mg}/\text{m}^2$ ] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200  $\text{mg}/\text{m}^2$  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 [ $\text{mg}/\text{m}^2$ ] 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  $\text{mg}/\text{m}^2$  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.

|                  |  |
|------------------|--|
| <b>Arm title</b> | 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Temozolomide + Radiotherapy |
|------------------|-----------------------------|

**Arm description:**

TMZ 75 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup>] 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<br>Units: Subjects |  |  |                             |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 54.6<br>± 9.63 | 55.2<br>± 10.44 | 54.5<br>± 11.64 |
| Gender categorical<br>Units: Subjects                                   |                |                 |                 |
| Female  | 38             | 38              | 34              |
| Male  | 50             | 50              | 55              |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 265   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

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



## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Cilengitide (2-times weekly) + Temozolomide + Radiotherapy     |
| Reporting group description:<br>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 <sup>2</sup> ] 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 <sup>2</sup> 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:<br>Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m <sup>2</sup> 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 <sup>2</sup> 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:<br>TMZ 75 mg/m <sup>2</sup> 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 <sup>2</sup> 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:<br>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:<br>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 <sup>2</sup> ] 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 <sup>2</sup> 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:<br>Cilengitide 2000 mg 5-times weekly over 1 hour intravenous infusion from Weeks -1 to 77, TMZ 75 mg/m <sup>2</sup> 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 <sup>2</sup> 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:  |                            |
| <p>TMZ 75 mg/m<sup>2</sup> 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<sup>2</sup> 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.</p> |                            |
| <b>Primary: Overall survival (OS) time</b>   |                            |
| End point title  | Overall survival (OS) time |
| End point description:   |                            |
| <p>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.</p>  |                            |
| End point type   | Primary                    |
| End point timeframe:   |                            |
| <p>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)</p>  |                            |

| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1 for Overall Survival Time   |
| Comparison groups                       | Temozolomide + Radiotherapy v Cilengitide (2-times weekly) + 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  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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).

| <b>End point values</b>          | 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) <sup>[1]</sup> |
|-----------------|---|

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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[2]</sup>  |  |  |  |
| 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) <sup>[3]</sup> |
|-----------------|--|

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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[4]</sup>  |  |  |  |
| 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]) <sup>[5]</sup> |
|-----------------|--|

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

|  |  |  |  |  |
|--|--|--|--|--|
| <b>End point values</b>                  | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                       | Reporting group  |  |  |  |
| Number of subjects analysed              | 11 <sup>[6]</sup>  |  |  |  |
| 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) <sup>[7]</sup> |
|-----------------|---|

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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[8]</sup>  |  |  |  |
| 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 <sup>[9]</sup> |
|-----------------|--|

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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[10]</sup>   |  |  |  |
| 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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[12]</sup>   |  |  |  |
| 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) <sup>[13]</sup> |
|-----------------|---------------------------------------|

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 <sup>[14]</sup>   |  |  |  |
| 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 (V<sub>z</sub>) and apparent volume of distribution at steady state (V<sub>ss</sub>)

|                 |  |
|-----------------|--|
| End point title | Apparent volume of distribution during the terminal phase (V <sub>z</sub> ) and apparent volume of distribution at steady state (V <sub>ss</sub> ) <sup>[15]</sup> |
|-----------------|--|

End point description:

The V<sub>z</sub> (after single dose) and V<sub>ss</sub> (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

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Cilengitide (5-times weekly) + Temozolomide + Radiotherapy |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 11 <sup>[16]</sup>   |  |  |  |
| 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).

|                             |  |  |                                       |  |
|-----------------------------|--|--|---------------------------------------|--|
| <b>End point values</b>     | Cilengitide (2-times weekly)<br>+<br>Temozolomide<br>+<br>Radiotherapy-SAF | Cilengitide (5-times weekly)<br>+<br>Temozolomide<br>+<br>Radiotherapy-SAF | Temozolomide<br>+<br>Radiotherapy-SAF |  |
| Subject group type          | Subject analysis set   | Subject analysis set   | Subject analysis set                  |  |
| Number of subjects analysed | 0 <sup>[17]</sup>  | 0 <sup>[18]</sup>  | 0 <sup>[19]</sup>                     |  |
| 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 | 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.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Temozolomide + Radiotherapy |
|-----------------------|-----------------------------|

Reporting group description:

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

| Serious adverse events  | Cilengitide twice a week + Temozolomide + Radiotherapy | Cilengitide 5 times a week + Temozolomide + Radiotherapy | Temozolomide + Radiotherapy |
|---|--|--|-----------------------------|
| Total subjects affected by serious adverse events                   |  |  |                             |
| subjects affected / exposed   | 47 / 89 (52.81%)                                       | 36 / 81 (44.44%)   | 30 / 85 (35.29%)            |
| number of deaths (all causes)                                       | 65   | 61   | 67                          |
| 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%) | 2 / 81 (2.47%) | 0 / 85 (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          |
| NEOPLASM PROGRESSION   |                |                |                |
| subjects affected / exposed  | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| BRAIN STEM GLIOMA  |                |                |                |
| subjects affected / exposed  | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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          |
| HEAVY CHAIN DISEASE  |                |                |                |
| subjects affected / exposed  | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED #(INCL CYSTS AND POLYPS) |                |                |                |
| subjects affected / exposed  | 5 / 89 (5.62%) | 3 / 81 (3.70%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 5          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all                           | 0 / 2          | 0 / 0          | 0 / 0          |
| Vascular disorders   |                |                |                |
| THROMBOSIS   |                |                |                |
| subjects affected / exposed  | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          | 0 / 0          |
| HYPOTENSION  |                |                |                |
| subjects affected / exposed  | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| HAEMATOMA  |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all      | 1 / 4          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 0          |
| HYPERTENSION   |                |                |                |
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| ASTHENIA   |                |                |                |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| CHEST DISCOMFORT                                     |                |                |                |
| subjects affected / exposed                          | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| CONDITION AGGRAVATED                                 |                |                |                |
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          | 0 / 1          |
| DEVICE MALFUNCTION                                   |                |                |                |
| subjects affected / exposed                          | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| DISEASE PROGRESSION                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                           | 2 / 89 (2.25%) | 2 / 81 (2.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 2          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 1          | 0 / 0          |
| FATIGUE   |                |                |                |
| subjects affected / exposed                           | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all       | 1 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| GENERAL PHYSICAL HEALTH DETERIORATION                 |                |                |                |
| subjects affected / exposed                           | 2 / 89 (2.25%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| TERMINAL STATE  |                |                |                |
| subjects affected / exposed                           | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| PYREXIA   |                |                |                |
| subjects affected / exposed                           | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| NON-CARDIAC CHEST PAIN                                |                |                |                |
| subjects affected / exposed                           | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| GENERALISED OEDEMA                                    |                |                |                |
| subjects affected / exposed                           | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| GAIT DISTURBANCE                                      |                |                |                |
| subjects affected / exposed                           | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1          |
| 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%) | 3 / 81 (3.70%) | 8 / 85 (9.41%) |
| occurrences causally related to treatment / all | 1 / 9           | 0 / 3          | 1 / 8          |
| 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 / 81 (0.00%) | 0 / 85 (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 |                 |                |                |
| DYSпноEA  |                 |                |                |
| subjects affected / exposed                     | 2 / 89 (2.25%)  | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| HAEMOPTYSIS                                     |                 |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%)  | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| PULMONARY EMBOLISM                              |                 |                |                |
| subjects affected / exposed                     | 9 / 89 (10.11%) | 2 / 81 (2.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 3 / 9           | 1 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 1 / 1           | 1 / 1          | 0 / 1          |
| PNEUMONIA ASPIRATION                            |                 |                |                |
| subjects affected / exposed                     | 2 / 89 (2.25%)  | 0 / 81 (0.00%) | 0 / 85 (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          |
| HYPOXIA   |                 |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%)  | 0 / 81 (0.00%) | 0 / 85 (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          |
| MEDIASTINAL HAEMORRHAGE                         |                 |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%)  | 0 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| PLEURAL EFFUSION                                |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| Psychiatric disorders                           |                |                |                |
| MENTAL STATUS CHANGES                           |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 1 / 81 (1.23%) | 1 / 85 (1.18%) |
| 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%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PSYCHOTIC DISORDER                              |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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          |
| WHITE BLOOD CELL COUNT DECREASED                |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| PLATELET COUNT DECREASED                        |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| FIBRIN D DIMER INCREASED                        |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| LIPASE INCREASED                                |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 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%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| Cardiac disorders                               |                |                |                |
| ATRIAL FIBRILLATION                             |                |                |                |
| subjects affected / exposed                     | 2 / 89 (2.25%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| ACUTE MYOCARDIAL INFARCTION                     |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BRADYCARDIA                                     |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| BUNDLE BRANCH BLOCK RIGHT                       |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| PULSELESS ELECTRICAL ACTIVITY                   |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| CARDIAC FAILURE                                 |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| 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                        |                |                |                |
| CONVULSION                                      |                |                |                |
| subjects affected / exposed                     | 5 / 89 (5.62%) | 7 / 81 (8.64%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 5          | 2 / 7          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| COGNITIVE DISORDER                              |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| APHASIA   |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 2 / 81 (2.47%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| CEREBRAL CYST                                   |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 3 / 81 (3.70%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| BRAIN OEDEMA                                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 2 / 85 (2.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| CEREBRAL VENTRICLE DILATATION                   |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| HEADACHE  |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 1 / 81 (1.23%) | 3 / 85 (3.53%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HAEMORRHAGE INTRACRANIAL                        |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| DYSARTHRIA                                      |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| EPILEPSY  |                |                |                |
| subjects affected / exposed                     | 4 / 89 (4.49%) | 2 / 81 (2.47%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DYSKINESIA                                      |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| GRAND MAL CONVULSION                            |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| PARTIAL SEIZURES                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 89 (1.12%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 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%) | 3 / 81 (3.70%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| HEMIANOPIA                                      |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| HYDROCEPHALUS                                   |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HEMIPARESIS                                     |                |                |                |
| subjects affected / exposed                     | 4 / 89 (4.49%) | 3 / 81 (3.70%) | 5 / 85 (5.88%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 3          | 0 / 5          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| MOTOR DYSFUNCTION                               |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 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%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| SOMNOLENCE                                      |                |                |                |
| subjects affected / exposed                     | 2 / 89 (2.25%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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          |
| UNRESPONSIVE TO STIMULI                         |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| Blood and lymphatic system disorders            |                |                |                |
| ANAEMIA   |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |
| PANCYTOPENIA                                    |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 1 / 85 (1.18%) |
| 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%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| FEBRILE NEUTROPENIA                             |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          | 0 / 0          |
| 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 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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%) | 1 / 81 (1.23%) | 0 / 85 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| DYSPHAGIA                                       |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| FOOD POISONING                                  |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 0 / 85 (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          |
| LARGE INTESTINE PERFORATION                     |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| RETROPERITONEAL HAEMORRHAGE                     |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| URINARY INCONTINENCE                            |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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          |
| NEPHROTIC SYNDROME                              |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| OLIGURIA  |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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%) | 0 / 81 (0.00%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| MENINGITIS                                      |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| HERPES ZOSTER                                   |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |



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

|   |                |                |                |
|---|----------------|----------------|----------------|
| HYPONATRAEMIA                                   |                |                |                |
| subjects affected / exposed                     | 0 / 89 (0.00%) | 1 / 81 (1.23%) | 1 / 85 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| HYPERGLYCAEMIA                                  |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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          |
| DECREASED APPETITE                              |                |                |                |
| subjects affected / exposed                     | 1 / 89 (1.12%) | 0 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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 / 81 (0.00%) | 0 / 85 (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          |

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

| Non-serious adverse events                            | Cilengitide twice a week + Temozolomide + Radiotherapy | Cilengitide 5 times a week + Temozolomide + Radiotherapy | Temozolomide + Radiotherapy |
|---|--|--|-----------------------------|
| Total subjects affected by non-serious adverse events |  |  |                             |
| subjects affected / exposed                           | 83 / 89 (93.26%)                                       | 79 / 81 (97.53%)   | 76 / 85 (89.41%)            |
| Vascular disorders                                    |  |  |                             |
| HYPERTENSION  |  |  |                             |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 5 / 89 (5.62%)<br>5 | 6 / 81 (7.41%)<br>6 | 3 / 85 (3.53%)<br>3 |
| General disorders and administration<br>site conditions |                     |                     |                     |
| FATIGUE   |                     |                     |                     |
| subjects affected / exposed                             | 27 / 89 (30.34%)    | 21 / 81 (25.93%)    | 19 / 85 (22.35%)    |
| occurrences (all)                                       | 27                  | 21                  | 19                  |
| OEDEMA PERIPHERAL                                       |                     |                     |                     |
| subjects affected / exposed                             | 9 / 89 (10.11%)     | 5 / 81 (6.17%)      | 8 / 85 (9.41%)      |
| occurrences (all)                                       | 9                   | 5                   | 8                   |
| PYREXIA   |                     |                     |                     |
| subjects affected / exposed                             | 16 / 89 (17.98%)    | 14 / 81 (17.28%)    | 8 / 85 (9.41%)      |
| occurrences (all)                                       | 16                  | 14                  | 8                   |
| ASTHENIA  |                     |                     |                     |
| subjects affected / exposed                             | 22 / 89 (24.72%)    | 25 / 81 (30.86%)    | 11 / 85 (12.94%)    |
| occurrences (all)                                       | 22                  | 25                  | 11                  |
| GAIT DISTURBANCE  |                     |                     |                     |
| subjects affected / exposed                             | 3 / 89 (3.37%)      | 7 / 81 (8.64%)      | 10 / 85 (11.76%)    |
| occurrences (all)                                       | 3                   | 7                   | 10                  |
| Respiratory, thoracic and mediastinal<br>disorders      |                     |                     |                     |
| DYSPNOEA  |                     |                     |                     |
| subjects affected / exposed                             | 5 / 89 (5.62%)      | 4 / 81 (4.94%)      | 3 / 85 (3.53%)      |
| occurrences (all)                                       | 5                   | 4                   | 3                   |
| COUGH   |                     |                     |                     |
| subjects affected / exposed                             | 9 / 89 (10.11%)     | 7 / 81 (8.64%)      | 3 / 85 (3.53%)      |
| occurrences (all)                                       | 9                   | 7                   | 3                   |
| Psychiatric disorders                                   |                     |                     |                     |
| ANXIETY   |                     |                     |                     |
| subjects affected / exposed                             | 6 / 89 (6.74%)      | 7 / 81 (8.64%)      | 6 / 85 (7.06%)      |
| occurrences (all)                                       | 6                   | 7                   | 6                   |
| INSOMNIA  |                     |                     |                     |
| subjects affected / exposed                             | 12 / 89 (13.48%)    | 15 / 81 (18.52%)    | 12 / 85 (14.12%)    |
| occurrences (all)                                       | 12                  | 15                  | 12                  |
| DEPRESSION  |                     |                     |                     |
| subjects affected / exposed                             | 12 / 89 (13.48%)    | 9 / 81 (11.11%)     | 2 / 85 (2.35%)      |
| occurrences (all)                                       | 12                  | 9                   | 2                   |
| Investigations  |                     |                     |                     |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| PLATELET COUNT DECREASED<br>subjects affected / exposed<br>occurrences (all)  | 3 / 89 (3.37%)<br>3    | 0 / 81 (0.00%)<br>0    | 5 / 85 (5.88%)<br>5    |
| NEUTROPHIL COUNT DECREASED<br>subjects affected / exposed<br>occurrences (all)  | 0 / 89 (0.00%)<br>0    | 5 / 81 (6.17%)<br>5    | 3 / 85 (3.53%)<br>3    |
| Injury, poisoning and procedural complications<br>RADIATION SKIN INJURY<br>subjects affected / exposed<br>occurrences (all) | 11 / 89 (12.36%)<br>11 | 3 / 81 (3.70%)<br>3    | 3 / 85 (3.53%)<br>3    |
| FALL<br>subjects affected / exposed<br>occurrences (all)  | 2 / 89 (2.25%)<br>2    | 5 / 81 (6.17%)<br>5    | 2 / 85 (2.35%)<br>2    |
| Nervous system disorders<br>APHASIA<br>subjects affected / exposed<br>occurrences (all)                                     | 7 / 89 (7.87%)<br>7    | 4 / 81 (4.94%)<br>4    | 6 / 85 (7.06%)<br>6    |
| CONVULSION<br>subjects affected / exposed<br>occurrences (all)  | 9 / 89 (10.11%)<br>9   | 10 / 81 (12.35%)<br>10 | 10 / 85 (11.76%)<br>10 |
| DIZZINESS<br>subjects affected / exposed<br>occurrences (all)   | 6 / 89 (6.74%)<br>6    | 5 / 81 (6.17%)<br>5    | 5 / 85 (5.88%)<br>5    |
| DYSGEUSIA<br>subjects affected / exposed<br>occurrences (all)   | 6 / 89 (6.74%)<br>6    | 4 / 81 (4.94%)<br>4    | 2 / 85 (2.35%)<br>2    |
| HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 38 / 89 (42.70%)<br>38 | 33 / 81 (40.74%)<br>33 | 27 / 85 (31.76%)<br>27 |
| HEMIPARESIS<br>subjects affected / exposed<br>occurrences (all)   | 7 / 89 (7.87%)<br>7    | 5 / 81 (6.17%)<br>5    | 6 / 85 (7.06%)<br>6    |
| MEMORY IMPAIRMENT<br>subjects affected / exposed<br>occurrences (all)   | 7 / 89 (7.87%)<br>7    | 8 / 81 (9.88%)<br>8    | 7 / 85 (8.24%)<br>7    |
| PARAESTHESIA  |                        |                        |                        |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 2 / 89 (2.25%)<br>2    | 6 / 81 (7.41%)<br>6    | 0 / 85 (0.00%)<br>0    |
| TREMOR<br>subjects affected / exposed<br>occurrences (all)   | 6 / 89 (6.74%)<br>6    | 5 / 81 (6.17%)<br>5    | 3 / 85 (3.53%)<br>3    |
| Blood and lymphatic system disorders<br>THROMBOCYTOPENIA<br>subjects affected / exposed<br>occurrences (all) | 11 / 89 (12.36%)<br>11 | 15 / 81 (18.52%)<br>15 | 17 / 85 (20.00%)<br>17 |
| ANAEMIA<br>subjects affected / exposed<br>occurrences (all)  | 5 / 89 (5.62%)<br>5    | 9 / 81 (11.11%)<br>9   | 1 / 85 (1.18%)<br>1    |
| NEUTROPENIA<br>subjects affected / exposed<br>occurrences (all)  | 12 / 89 (13.48%)<br>12 | 9 / 81 (11.11%)<br>9   | 8 / 85 (9.41%)<br>8    |
| LYMPHOPENIA<br>subjects affected / exposed<br>occurrences (all)  | 9 / 89 (10.11%)<br>9   | 7 / 81 (8.64%)<br>7    | 7 / 85 (8.24%)<br>7    |
| LEUKOPENIA<br>subjects affected / exposed<br>occurrences (all)   | 5 / 89 (5.62%)<br>5    | 6 / 81 (7.41%)<br>6    | 7 / 85 (8.24%)<br>7    |
| Eye disorders<br>VISION BLURRED<br>subjects affected / exposed<br>occurrences (all)                          | 6 / 89 (6.74%)<br>6    | 2 / 81 (2.47%)<br>2    | 1 / 85 (1.18%)<br>1    |
| Gastrointestinal disorders<br>NAUSEA<br>subjects affected / exposed<br>occurrences (all)                     | 33 / 89 (37.08%)<br>33 | 30 / 81 (37.04%)<br>30 | 30 / 85 (35.29%)<br>30 |
| CONSTIPATION<br>subjects affected / exposed<br>occurrences (all)   | 26 / 89 (29.21%)<br>26 | 27 / 81 (33.33%)<br>27 | 27 / 85 (31.76%)<br>27 |
| DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)  | 8 / 89 (8.99%)<br>8    | 6 / 81 (7.41%)<br>6    | 2 / 85 (2.35%)<br>2    |
| ABDOMINAL PAIN UPPER   |                        |                        |                        |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                         | 5 / 89 (5.62%)<br>5    | 5 / 81 (6.17%)<br>5    | 1 / 85 (1.18%)<br>1    |
| VOMITING<br>subjects affected / exposed<br>occurrences (all)             | 18 / 89 (20.22%)<br>18 | 18 / 81 (22.22%)<br>18 | 21 / 85 (24.71%)<br>21 |
| STOMATITIS<br>subjects affected / exposed<br>occurrences (all)           | 5 / 89 (5.62%)<br>5    | 1 / 81 (1.23%)<br>1    | 2 / 85 (2.35%)<br>2    |
| Skin and subcutaneous tissue disorders                                   |                        |                        |                        |
| URTICARIA<br>subjects affected / exposed<br>occurrences (all)            | 2 / 89 (2.25%)<br>2    | 7 / 81 (8.64%)<br>7    | 2 / 85 (2.35%)<br>2    |
| RASH<br>subjects affected / exposed<br>occurrences (all)                 | 11 / 89 (12.36%)<br>11 | 8 / 81 (9.88%)<br>8    | 3 / 85 (3.53%)<br>3    |
| ERYTHEMA<br>subjects affected / exposed<br>occurrences (all)             | 4 / 89 (4.49%)<br>4    | 5 / 81 (6.17%)<br>5    | 3 / 85 (3.53%)<br>3    |
| ALOPECIA<br>subjects affected / exposed<br>occurrences (all)             | 14 / 89 (15.73%)<br>14 | 18 / 81 (22.22%)<br>18 | 11 / 85 (12.94%)<br>11 |
| PRURITUS<br>subjects affected / exposed<br>occurrences (all)             | 9 / 89 (10.11%)<br>9   | 11 / 81 (13.58%)<br>11 | 5 / 85 (5.88%)<br>5    |
| Renal and urinary disorders  |                        |                        |                        |
| URINARY INCONTINENCE<br>subjects affected / exposed<br>occurrences (all) | 3 / 89 (3.37%)<br>3    | 5 / 81 (6.17%)<br>5    | 3 / 85 (3.53%)<br>3    |
| Musculoskeletal and connective tissue disorders                          |                        |                        |                        |
| ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)           | 4 / 89 (4.49%)<br>4    | 5 / 81 (6.17%)<br>5    | 2 / 85 (2.35%)<br>2    |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)            | 7 / 89 (7.87%)<br>7    | 3 / 81 (3.70%)<br>3    | 0 / 85 (0.00%)<br>0    |
| MUSCLE SPASMS  |                        |                        |                        |

|                                    |                  |                  |                  |
|------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed        | 2 / 89 (2.25%)   | 5 / 81 (6.17%)   | 1 / 85 (1.18%)   |
| occurrences (all)                  | 2                | 5                | 1                |
| MUSCULAR WEAKNESS                  |                  |                  |                  |
| subjects affected / exposed        | 9 / 89 (10.11%)  | 19 / 81 (23.46%) | 4 / 85 (4.71%)   |
| occurrences (all)                  | 9                | 19               | 4                |
| MUSCULOSKELETAL PAIN               |                  |                  |                  |
| subjects affected / exposed        | 7 / 89 (7.87%)   | 3 / 81 (3.70%)   | 2 / 85 (2.35%)   |
| occurrences (all)                  | 7                | 3                | 2                |
| NECK PAIN                          |                  |                  |                  |
| subjects affected / exposed        | 6 / 89 (6.74%)   | 2 / 81 (2.47%)   | 1 / 85 (1.18%)   |
| occurrences (all)                  | 6                | 2                | 1                |
| PAIN IN EXTREMITY                  |                  |                  |                  |
| subjects affected / exposed        | 9 / 89 (10.11%)  | 3 / 81 (3.70%)   | 6 / 85 (7.06%)   |
| occurrences (all)                  | 9                | 3                | 6                |
| Infections and infestations        |                  |                  |                  |
| NASOPHARYNGITIS                    |                  |                  |                  |
| subjects affected / exposed        | 9 / 89 (10.11%)  | 5 / 81 (6.17%)   | 1 / 85 (1.18%)   |
| occurrences (all)                  | 9                | 5                | 1                |
| ORAL CANDIDIASIS                   |                  |                  |                  |
| subjects affected / exposed        | 6 / 89 (6.74%)   | 6 / 81 (7.41%)   | 3 / 85 (3.53%)   |
| occurrences (all)                  | 6                | 6                | 3                |
| UPPER RESPIRATORY TRACT INFECTION  |                  |                  |                  |
| subjects affected / exposed        | 6 / 89 (6.74%)   | 10 / 81 (12.35%) | 5 / 85 (5.88%)   |
| occurrences (all)                  | 6                | 10               | 5                |
| URINARY TRACT INFECTION            |                  |                  |                  |
| subjects affected / exposed        | 6 / 89 (6.74%)   | 10 / 81 (12.35%) | 6 / 85 (7.06%)   |
| occurrences (all)                  | 6                | 10               | 6                |
| Metabolism and nutrition disorders |                  |                  |                  |
| DECREASED APPETITE                 |                  |                  |                  |
| subjects affected / exposed        | 20 / 89 (22.47%) | 18 / 81 (22.22%) | 18 / 85 (21.18%) |
| occurrences (all)                  | 20               | 18               | 18               |
| HYPERGLYCAEMIA                     |                  |                  |                  |
| subjects affected / exposed        | 6 / 89 (6.74%)   | 5 / 81 (6.17%)   | 1 / 85 (1.18%)   |
| occurrences (all)                  | 6                | 5                | 1                |
| HYPONATRAEMIA                      |                  |                  |                  |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 3 / 89 (3.37%) | 4 / 81 (4.94%) | 5 / 85 (5.88%) |
| occurrences (all)           | 3              | 4              | 5              |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 19 March 2010 | <p>This amendment dated 19 Mar 2010 was substantial and applied to all sites. The main purpose of this amendment was to:</p> <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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</li></ul> <p>.</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported