



## Clinical trial results:

### Phase III trial of CCNU/temozolomide (TMZ) combination therapy vs. standard TMZ therapy for newly diagnosed MGMT-methylated glioblastoma patients (CeTeG)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-011252-22 |
| Trial protocol           | DE             |
| Global end of trial date | 06 April 2017  |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)                              |
| This version publication date     | 24 December 2021                          |
| First version publication date    | 24 December 2021                          |
| Summary attachment (see zip file) | journal article (Tzaridis et al 2019.pdf) |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | CeTeG |
|-----------------------|-------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Rheinische Friedrich-Wilhelm-University of Bonn  |
| Sponsor organisation address | Regina-Pacis-Weg 3, Bonn, Germany,   |
| Public contact               | University of Bonn<br>53012 Bonn, Germany<br>General phone number: +49 (0)228 73-0, Rheinische Friedrich-Wilhelm-University of Bonn, +49 228730, |
| Scientific contact           | University of Bonn<br>53012 Bonn, Germany<br>General phone number: +49 (0)228 73-0, Rheinische Friedrich-Wilhelm-University of Bonn, +49 228730, |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 23 January 2019 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 07 March 2017   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 06 April 2017   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

This phase III trial determines whether combined Cecenu and Temozolomide chemotherapy plus standard radiotherapy is superior to TMZ monochemotherapy plus standard radiotherapy alone in patients with newly diagnosed mMGMT GBM patients regarding overall survival.

Protection of trial subjects:

Safety was monitored continuously throughout the trial. The study included the following evaluations of safety and tolerability:

Adverse Events: Adverse events will be reported throughout the study at each visit. Adverse events will be followed by the investigator.

Clinical Laboratory Tests: Laboratory tests at each visit will be performed at the Laboratory of the treating University Medical Center. Between visits, weekly laboratory testings are performed by the general practitioner or oncologist of the patients and results are to be faxed within 24 hours to the local investigator. All laboratory reports will be reviewed by the investigator. This review must be documented, and any clinically relevant changes occurring during the study must be recorded in the adverse event section of the CRF.

Vital Signs

Physical and neurologic examination: Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Karnofsky performance score: Karnofsky performance score is outlined in appendix 1

NOA-07 test battery: the NOA\_07 test battery is outlined in section 9.2.7.

MMST: The MMST is outlined in appendix 2

General safety monitoring: The management of SAE within the study group will be according to ICH GCP, i.e. depending on the criteria expected/unexpected, suspected/ not suspected, dead/alive SAEs have to be announced to the sponsor within the legal time frame. Similarly, the sponsor will announce SAEs to the authorities within the legal time frame. For details see chapter 7 (adverse event reporting). Safety is independently monitored by the Data monitoring and safety board as detailed below.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 06 June 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 129 |
| Worldwide total number of subjects   | 129          |
| EEA total number of subjects         | 129          |

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)                      | 107 |
| From 65 to 84 years                       | 22  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening phase (1-3 weeks after resection): Patients with previously untreated GBM are screened for the trial. After obtaining informed consent for determination of MGMT promoter methylation status and reference neuropathology, a block of paraffinembedded tissue is sent for reference neuropathology review to the Department of Neuropathology, Un

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall trial (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> | Lomustine-Temozolomide |
|------------------|------------------------|

Arm description: -

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Lomustine    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

100 mg/m<sup>2</sup> KOF at day 1 of the course

|  |              |
|--|--------------|
| Investigational medicinal product name | Temozolomide |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

100 mg/m<sup>2</sup> KOF at day 2-6 of the course

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

Arm description: -

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Temozolomide      |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

150-200 mg/m<sup>2</sup> KOF for 5 days of the course

| <b>Number of subjects in period 1</b> | Lomustine-<br>Temozolomide | Temozolomide |
|---------------------------------------|----------------------------|--------------|
| Started                               | 66                         | 63           |
| Completed                             | 53                         | 55           |
| Not completed                         | 13                         | 8            |
| Adverse event, non-fatal              | 6                          | 2            |
| Lost to follow-up                     | 7                          | 6            |

## Baseline characteristics

## End points

### End points reporting groups

|                                |                        |
|--------------------------------|------------------------|
| Reporting group title          | Lomustine-Temozolomide |
| Reporting group description: - |                        |
| Reporting group title          | Temozolomide           |
| Reporting group description: - |                        |

### Primary: overall survival between different treatment groups

|                         |   |
|-------------------------|---|
| End point title         | overall survival between different treatment groups |
| End point description:  |   |
| End point type          | Primary   |
| End point timeframe:    |   |
| 06.06.2011 - 06.04.2017 |   |

| End point values            | Lomustine-Temozolomide | Temozolomide    |  |  |
|-----------------------------|------------------------|-----------------|--|--|
| Subject group type          | Reporting group        | Reporting group |  |  |
| Number of subjects analysed | 66                     | 63              |  |  |
| Units: months               | 38                     | 31              |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | post-hoc sensitivity analyss - overall survival |
| Comparison groups                       | Lomustine-Temozolomide v Temozolomide           |
| Number of subjects included in analysis | 129   |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | other <sup>[1]</sup>                            |
| P-value                                 | = 0.6579  |
| Method                                  | Regression, Cox                                 |
| Parameter estimate                      | Hazard ratio (HR)                               |
| Point estimate                          | 0.9   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.58  |
| upper limit                             | 1.54  |
| Variability estimate                    | Standard deviation                              |

Notes:

[1] - univariate Cox-regression analysis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

06.06.2011 - 06.05.2017

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | CCNU/TMZ |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events                            | CCNU/TMZ       |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 66 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

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

| Non-serious adverse events                            | CCNU/TMZ         |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 40 / 66 (60.61%) |  |  |
| Blood and lymphatic system disorders                  |                  |  |  |
| thrombocytopenia                                      |                  |  |  |
| subjects affected / exposed                           | 40 / 66 (60.61%) |  |  |
| occurrences (all)                                     | 40               |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 March 2012    | <p>Introduction of translational analyses into the trial protocol: collection of serum samples, translational genetic analyses of brain tumor material, experimental MRI sequences. The aim is (1) to obtain data on tumor development, progression, response to therapy and immune reaction and (2) to obtain data that help to differentiate between tumor progression and pseudoprogression.</p> <p>Implementation of new guidelines (CT-3) for the management of SAEs. In-patient treatments for tumor progression are now regarded as an SAE.</p>   |
| 16 November 2012 | <p>5 new study centers entering the trial, expansion of the number of study centers from 12 to 17.</p>   |
| 28 January 2016  | <p>Prolongation of the recruitment time by 10 months (after firstpatient-in). The prolongation of the recruitment time was necessary since the rate of patients with a methylated MGMT promotor was 35.4% and thus lower than in the TMZ registration trial (45%) which was the base of the initial calculation. Due to the reduced rate of MGMT promotormethylated patients, more patients than expected had to be screened for MGMT promotor methylation status than initially calculated thus prolonging recruitment time.</p> <p>Prolongation of the follow-up period: A blinded analysis of the overall survival time 14 months after last-patient-in (36 months after first-patient-in) showed that there is an overall mean risk for the event "death" of 0.1994/patient year which was lower than expected. Due to this unexpected low number of events at this time a lower number of events at the end of the intended follow-up-time could be expected and consequently a lower power. We calculated that with the observed actual event rate and an assumed OR of 2 as planned, the 68 events required for an analysis with a sufficient power of 80% can be reached by a prolongation of the follow-up time to April 2017. The patient information and informed consent form was changed accordingly.</p> <p>Reduction of the observation time for adverse effects to 30 days following the last study-related procedure (excluding follow-up).</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported