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 53012 Bonn, Germany General phone number: +49 (0)228 73-0, Rheinische Friedrich-Wilhelm-University of Bonn, +49 228730,
Scientific contact	University of Bonn 53012 Bonn, Germany 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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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
Arm title	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/m² 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/m² KOF at day 2-6 of the course

Arm title	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/m² KOF for 5 days of the course

Number of subjects in period 1	Lomustine-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[1]
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	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. Implementation of new guidelines (CT-3) for the management of SAEs. In-patient treatments for tumor progression are now regarded as an SAE.
16 November 2012	5 new study centers entering the trial, expansion of the number of study centers from 12 to 17.
28 January 2016	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. 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. Reduction of the observation time for adverse effects to 30 days following the last study-related procedure (excluding follow-up).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported