Clinical trial results:
Clinical Trial Phase IIB randomized, multicenter, of continuation or non-continuation with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment in patients with glioblastoma.

Summary

EudraCT number	2014-000838-39
Trial protocol	ES
Global end of trial date	14 June 2019

Results information

Result version number	v1 (current)
This version publication date	05 November 2020
First version publication date	05 November 2020
Summary attachment (see zip file)	Peer review journal publication (Neurooncology GEINO 1401.pdf)

Trial information

Trial identification

Sponsor protocol code	GEINO14-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Investigación en Neuro-Oncología (GEINO)
Sponsor organisation address	C/ Velázquez no7, 3 planta, Madrid, Spain, 28001
Public contact	Pau Doñate, MFAR Clinical Research, investigacion@mfar.net
Scientific contact	Pau Doñate, MFAR Clinical Research, investigacion@mfar.net

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	30 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2019
Global end of trial reached?	Yes
Global end of trial date	14 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Detect differences in the probability of progression-free survival at 6 months between patients with methylated or unmethylated MGMT and residual disease or not, to receive an additional 6 cycles of temozolomide.

Protection of trial subjects:

The trial was conducted in accordance with applicable regulatory requirements and the principles of the Declaration of Helsinki. The protocol was approved by the ethics committees of all participating centers. All patients provided their signed informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 159
Worldwide total number of subjects	159
EEA total number of subjects	159

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)	159
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From August 22, 2014 to November 27, 2018 166 patients were recruited across 20 centers in Spain.

Pre-assignment

Screening details:

166 patients were screened, seven of whom were deemed to be ineligible. Seventy-nine patients were randomized to stop temozolomide after cycle 6 (control arm) and 80 to continue for up to six additional cycles (cycles 7 to 12) (experimental arm).

Period 1

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

Blinding implementation details:

No blinding was empowered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Patients will recieve no intervention, stop temozolomide after cycle 6

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Experimental arm

Arm description:

Patients will receive 6 additional temozolomide cycles, a total of 12

Arm type	Experimental
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150-200 mg/m2
Administered the first 5 days of a 28 days cycle

Number of subjects in period 1	Control	Experimental arm
Started	79	80
Completed	40	48
Not completed	39	32
Discontinued intervention due to progression	39	31
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Patients will recieve no intervention, stop temozolomide after cycle 6	
Reporting group title	Experimental arm
Reporting group description:	
Patients will receive 6 additional temozolomide cycles, a total of 12	

Reporting group values	Control	Experimental arm	Total
Number of subjects	79	80	159
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	60.4	60.7	
full range (min-max)	31 to 79	29 to 83	-
Gender categorical Units: Subjects			
Female	38	38	76
Male	41	42	83
Residual disease (>10mm) Units: Subjects			
Yes	42	41	83
No	37	39	76
KPS index Units: Subjects			
<70%	2	2	4
>=70%	77	78	155
Residual Neurological symptom Units: Subjects			
Yes	8	19	27
No	71	60	131
NA	0	1	1
DXM dose at inclusion Units: Subjects			
0 mg	70	67	137

0.5-2 mg	6	9	15
>2 mg	3	4	7
Barthel index Units: Subjects			
index 0	9	12	21
index 1	70	68	138
MMSE Units: Subjects			
index <27	10	16	26
index ≥27	60	51	111
NP / ND	9	13	22
Anticonvulsant therapy Units: Subjects			
Yes	38	37	75
No	41	43	84
Initial surgery-Treatment at diagnosis Units: Subjects			
Biopsy	10	7	17
Complete resection by post-op MRI)	35	28	63
Complete resection without post-op MRI	14	20	34
Subtotal resection	20	25	45
MGMT Methylation status Units: Subjects			
Methylated	48	49	97
Unmethylated	31	31	62
IDH1 Mutation status Units: Subjects			
IDH1-R132 mutated by ICH	7	1	8
IDH1-R132 non mutated by ICH	66	71	137
not determined	6	8	14

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Patients will recieve no intervention, stop temozolomide after cycle 6	
Reporting group title	Experimental arm
Reporting group description:	
Patients will receive 6 additional temozolomide cycles, a total of 12	

Primary: Progression free survival at 6 month

End point title	Progression free survival at 6 month
End point description:	
Number of patients (proportion) without progression of disease and time between start of treatment and progression of disease.	
End point type	Primary
End point timeframe:	
6 months after the start of treatment (6 additional cycles of temozolomide for experimental arm or standard of care for control arm)	

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Percentage of subjects free of PD				
median (confidence interval 95%)	55.7 (45.8 to 67.8)	61.3 (51.5 to 72.9)		

Attachments (see zip file)	PFS Kaplan Meier/Captura de pantalla 2020-07-13 a las

Statistical analyses

Statistical analysis title	Log Rank (Mantel-Cox)
Comparison groups	Control v Experimental arm
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.38

Notes:

[1] - p values lower than 0.05 will point to discard the null hypothesis, which assumes no differences between treatment arms.

Secondary: Treatment safety

End point title	Treatment safety

End point description:

Total number of adverse events, type of events and grade. ONLY RELEVANT DIFFERENCES IN TOXICITY BY ARM

End point type	Secondary

End point timeframe:

Through the whole study. 4 years

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Number of patients				
Lymphopenia	33	55		
Thrombocytopenia	17	38		
Nausea and Vomiting	10	30		
Fatigue	21	35		
Leucopenia	20	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Progresion Free survival Median values

End point title	Progresion Free survival Median values

End point description:

Progression free survival assessed by CT scan following the RANO criteria

End point type	Secondary

End point timeframe:

Through the whole study. 4 years. The median follow up for each patient was 33.4 months

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Months				
median (confidence interval 95%)	7.77 (5.70 to 9.83)	9.5 (5.93 to 13.07)		

Attachments (see zip file)	PFS Kaplan Meier/Captura de pantalla 2020-07-13 a las

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time between start of treatment and death

End point type	Secondary

End point timeframe:

Through the whole study. 4 years. The median follow up for each patient was 33.4 months.

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Months				
median (confidence interval 95%)	23.3 (17.9 to 28.7)	18.2 (16.7 to 23.8)		

Attachments (see zip file)	OS Kaplan Meier chart/Captura de pantalla 2020-07-13 a las

Statistical analyses

No statistical analyses for this end point

Secondary: Translational sub-study - Biomarkers MSH6 immunoreactivity.

End point title	Translational sub-study - Biomarkers MSH6 immunoreactivity.

End point description:

MSH6 immunoreactivity.
partial immunoreactivity of MSH6 in patients by treatment arm

End point type	Secondary

End point timeframe:

Baseline determination

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	80		
Units: Patients				
MSH6 partial immunoreactivity	6	5		
no MSH6 partial immunoreactivity	73	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS by arm and MGMT methylation status

End point title	Median PFS by arm and MGMT methylation status

End point description:

Median Progression Free Survival depending on treatment arm in patients with MGMT methylation

End point type	Secondary

End point timeframe:

Through the whole study. 4 years. The median follow up for each patient was 33.4 months

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[2]	49[3]		
Units: Months				
median (confidence interval 95%)	8.5 (6.5 to 10.4)	11.4 (9.2 to 13.6)		

Notes:

[2] - Only patients with MGMT methylated

[3] - Only patients with MGMT methylated

Attachments (see zip file)	PFS Kaplan Meier for patients with MGMT methylatio/Captura

Statistical analyses

No statistical analyses for this end point

Secondary: Median OS by arm and MGMT methylation status

End point title	Median OS by arm and MGMT methylation status

End point description:

Median OS depending on treatment arm in patients with methylated MGMT

End point type	Secondary

End point timeframe:

Through the whole study. 4 years. The median follow up for each patient was 33.4 months

End point values	Control	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[4]	49[5]		
Units: Months				
median (confidence interval 95%)	27.1 (20.3 to 33.9)	20.7 (14.7 to 26.7)		

Notes:

[4] - Only patients with MGMT methylated

[5] - Only patients with MGMT methylated

Attachments (see zip file)	OS Kaplan Meier for patients with MGMT methylation/Captura

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Through the clinical study. About 4 years	
Adverse event reporting additional description:	
In addition, clinically relevant changes on physical examination and abnormal parameters found on complementary examinations (eg radiography, ECG) should also be reported like AE.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Control
Reporting group description:	
Patients will recieve no intervention, stop temozolomide after cycle 6	
Reporting group title	Experimental arm
Reporting group description:	
Patients will receive 6 additional temozolomide cycles, a total of 12	

Serious adverse events	Control	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 79 (6.33%)	9 / 80 (11.25%)	
number of deaths (all causes)	52	63	
number of deaths resulting from adverse events			
Vascular disorders			
Intra-craneal hypertension			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
claudication			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Dysarthria			
subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological impairment			
subjects affected / exposed	0 / 79 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Syncope			
subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General deterioration			
subjects affected / exposed	1 / 79 (1.27%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Femur fracture			

subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Respiratory infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Control	Experimental arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 79 (100.00%)	80 / 80 (100.00%)	
Vascular disorders			
Thromboembolism			
subjects affected / exposed	2 / 79 (2.53%)	0 / 80 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 79 (26.58%)	35 / 80 (43.75%)	
occurrences (all)	21	35	
Anxiety			
subjects affected / exposed	2 / 79 (2.53%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Pain			
subjects affected / exposed	10 / 79 (12.66%)	13 / 80 (16.25%)	
occurrences (all)	10	13	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	2 / 79 (2.53%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Cardiac disorders			
Cardiac events			

subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Neurologic impairment			
subjects affected / exposed	41 / 79 (51.90%)	38 / 80 (47.50%)	
occurrences (all)	41	38	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	20 / 79 (25.32%)	30 / 80 (37.50%)	
occurrences (all)	20	30	
Neutropenia			
subjects affected / exposed	2 / 79 (2.53%)	3 / 80 (3.75%)	
occurrences (all)	2	3	
Anemia			
subjects affected / exposed	8 / 79 (10.13%)	4 / 80 (5.00%)	
occurrences (all)	8	4	
Lymphopenia			
subjects affected / exposed	33 / 79 (41.77%)	55 / 80 (68.75%)	
occurrences (all)	33	55	
Thrombocytopenia			
subjects affected / exposed	17 / 79 (21.52%)	38 / 80 (47.50%)	
occurrences (all)	17	38	
Alkaline phosphatase high			
subjects affected / exposed	4 / 79 (5.06%)	3 / 80 (3.75%)	
occurrences (all)	4	3	
Potassium high			
subjects affected / exposed	6 / 79 (7.59%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Sodium high			
subjects affected / exposed	5 / 79 (6.33%)	7 / 80 (8.75%)	
occurrences (all)	5	7	
GGT high			
subjects affected / exposed	6 / 79 (7.59%)	4 / 80 (5.00%)	
occurrences (all)	6	4	
GOT high			

subjects affected / exposed	3 / 79 (3.80%)	1 / 80 (1.25%)	
occurrences (all)	3	1	
GPT high			
subjects affected / exposed	7 / 79 (8.86%)	5 / 80 (6.25%)	
occurrences (all)	7	5	
Bilirubin high			
subjects affected / exposed	8 / 79 (10.13%)	7 / 80 (8.75%)	
occurrences (all)	8	7	
Ear and labyrinth disorders			
Hearing loss			
subjects affected / exposed	2 / 79 (2.53%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	10 / 79 (12.66%)	30 / 80 (37.50%)	
occurrences (all)	10	30	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	3 / 79 (3.80%)	4 / 80 (5.00%)	
occurrences (all)	3	4	
Renal and urinary disorders			
Creatinine urine			
subjects affected / exposed	6 / 79 (7.59%)	3 / 80 (3.75%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
Bone events			
subjects affected / exposed	4 / 79 (5.06%)	3 / 80 (3.75%)	
occurrences (all)	4	3	
Infections and infestations			
Constipation			
subjects affected / exposed	2 / 79 (2.53%)	6 / 80 (7.50%)	
occurrences (all)	2	6	
Infection			
subjects affected / exposed	5 / 79 (6.33%)	11 / 80 (13.75%)	
occurrences (all)	5	11	
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	19 / 79 (24.05%)	14 / 80 (17.50%)	
occurrences (all)	19	14	
Anorexia			
subjects affected / exposed	1 / 79 (1.27%)	4 / 80 (5.00%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2016	Inclusion of 2 new centers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32328662