Clinical trial results:
PROSPECTIVE, PHASE II CLINICAL TRIAL TO EVALUATE EFFICACY AND SAFETY OF AUTOLOGOUS DENDRITIC CELL VACCINATION IN GLIOBLASTOMA MULTIFORME PATIENTS AFTER COMPLETE SURGICAL RESECTION WITH FLUORESCENCE MICROSCOPE

Summary

EudraCT number	2009-009879-35
Trial protocol	ES
Global end of trial date	01 August 2014

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021
Summary attachment (see zip file)	SPANISH REPORT (DEND_GM_INFORME_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	DEND/GM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01006044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra
Sponsor organisation address	Avda. Pío XII, 36, Pamplona, Spain, 31008
Public contact	UCICEC, Clínica Universidad de Navarra, 34 948 255 400 114, ucicec@unav.es
Scientific contact	UCICEC, Clínica Universidad de Navarra, 34 948 255 400 1148, ucicec@unav.es

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	18 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2014
Global end of trial reached?	Yes
Global end of trial date	01 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessing the impact of treatment on progression-free survival.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	19
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients between 18 and 70 years old, with a histological diagnosis of glioblastoma who have not previously been treated with chemo- or radiotherapy. After obtaining the patient's consent, surgery is performed where the tumour sample is processed.

Pre-assignment

Screening details:

After surgery, early monitoring of the resection will be carried out with DG-MRI in the first 72h. If the residual volume is less than 1 cm3, the screening tests will be completed, and, if applicable, the patient's entry into the clinical trial shall be confirmed. Availability of sufficient tumour tissue processed to produce cell-based vaccines.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Treatment group

Arm description:

26 patients were included in the trial. One patient withdrew consent and another patient died before receiving treatment, resulting in 24 patients receiving treatment. After surgery, standard treatment with concurrent radiotherapy and temozolomide was started, followed by twelve cycles of Temozolamide. In addition, autologous dendritic cells were obtained by leukapheresis and cell culture to prepare individualised cell vaccines. Each patient was given 4 monthly vaccinations, 4 bimonthly vaccinations and then 4 quarterly vaccinations.

Arm type	Experimental
Investigational medicinal product name	autologous dendritic cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Leukapheresis of mononuclear cells is performed after completing a minimum of 7 days without steroid treatment. Immature dendritic cells are generated to prepare vaccines. The cell vaccine will be administered intradermally. The vaccination schedule shall begin as soon as possible after surgery. If possible, the first dose should be administered before starting radiotherapy. Repeat monthly until the first 4 vaccinations are completed. Thereafter, 4 vaccinations will be administered every other month and 4 quarterly. The total dose is 10 millones U unit(s).

Arm title	Historical control group

Arm description:

The overall survival of the treatment group is compared to a historical control group. For historical control, a search was carried out in the CUN medical records system for patients operated on at the centre for glioblastoma since 2007, when fluorescence surgery was first used. 23 patients were selected who met the same inclusion criteria used in the clinical trial, had none of the exclusion criteria, and the clinical information included follow-up until death or up to 24 months.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Treatment group	Historical control group
Started	26	23
Completed	24	23
Not completed	2	0
Consent withdrawn by subject	1	-
death before treatment	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment group

Reporting group description:

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Reporting group values	Treatment group	Historical control group	Total
Number of subjects	26	23	49
Age categorical Units: Subjects			
Age continuous Units: years			
median	59.2	61.1	
inter-quartile range (Q1-Q3)	49.1 to 64.8	53.1 to 70	-
Gender categorical Units: Subjects			
Female	12	9	21
Male	14	14	28

End points

End points reporting groups

Reporting group title	Treatment group

Reporting group description:

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Primary: Survival

End point title	Survival

End point description:

Patient survival is assessed with data of Progresion free survival (PFS) and Overall Survival (OS). Overall survival of the treated group is compared to a historical control group. For historical control group, a search was carried out in the CUN medical records system for patients operated on at the centre for glioblastoma since 2007, when fluorescence surgery was first used.
The addition of tumor lysate-pulsed autologous DCs vaccination to maximal safe resection followed by radiotherapy and concomitant and adjuvant temozolomide is feasible and safe. Its potential benefit in survival in such a selected population still needs to be confirmed in a randomized trial.

End point type	Primary

End point timeframe:

The Survival is assessed during all the trial.

End point values	Treatment group	Historical control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: Hazard Ratio				
number (not applicable)				
HR of mortality	0.56	1		

Statistical analyses

Statistical analysis title	Kaplan-Meier. Cox-regression

Statistical analysis description:

Overall survival of the treated group is compared to a historical control group.

Comparison groups	Treatment group v Historical control group

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Cox

Notes:

[1] - When comparing overall survival between the treatment group and the historical control group using the Wilcoxon test, a p=0.03 was obtained.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All OA occurring during the treatment period or within 30 days after the administration of the last dose of the protocol treatment should be recorded. SAEs must be reported by filling in the SAE form within 24 hours of becoming aware of the SAE.

Adverse event reporting additional description:

No serious adverse events related to the study medication occur. Non-serious adverse events occur in all patients, but most of these are related to concomitant treatment, pharmacological or surgical, as well as to disease progression, not with study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	ND
Dictionary version	ND

Reporting groups

Reporting group title	treatment group

Reporting group description: -

Serious adverse events	treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 24 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
progression - recurrence			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
seizures			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
election crisis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
aphasia			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
dysarthria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
hyporexia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
fever			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
wound infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
deep venous thrombosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
anhedonia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
vomit			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
nausea			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
pneumonia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breathlessness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
desorientation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)		
Gastrointestinal disorders			
dysgeusia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2009	Changes to clarify vaccine administration, correct errors and add partners.
07 October 2009	Include model of oral consent of the patient in the presence of witnesses. Clarify that the administration of GM CSF and interferon alpha will be at the discretion of the investigator. Modify initial application form
28 March 2012	Add intermediate data analysis
13 June 2012	Change of promoter
21 September 2012	Change of principal investigator, due to death.
26 June 2013	Changes on the IMPD

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported