Clinical trial results:
Multicenter, randomized, non-comparative, open-label phase II trial on the efficacy of Ortataxel and Fotemustine in recurrent glioblastoma

Summary

EudraCT number	2012-003618-15
Trial protocol	IT
Global end of trial date	11 November 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020
Summary attachment (see zip file)	study journal article (ortataxelarticle.pdf)

Trial information

Trial identification

Sponsor protocol code	IRFMN-GBM-6272

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01989884
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via Giuseppe La Masa, 19, Milano, Italy, 20156
Public contact	Laboratory of Methodology for Clinical Research, Oncology Department, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, +39 0239014650, elena.biagioli@marionegri.it
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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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2016
Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was primarily aimed at assessing the efficacy of Ortataxel in terms of progression free survival at 6 months (PFS-6) in patients with recurrent glioblastoma.

Protection of trial subjects:

Before any administration of study drug, the following examinations were required: relevant physical examinations (symptom-directed physical examination, neurological examination, weight), a check of patients vital signs, relevant laboratory assessments.
When a patient discontinued the study treatment, regardless of the reason for discontinuation, the patient had to return to the clinic within 30 days (± 7 days) after the last infusion of study for a visit to monitor any possible adverse reactions.

Background therapy:

No background therapy was planned due to the absence of effective therapies for patients with this stage of glioblastoma

Evidence for comparator:

Not comparative trial

Actual start date of recruitment	26 November 2013
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	Italy: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolment started on 26th Nov 2013 and was closed on 23rd Dec 2015. Patients were enrolled from 6 experimental sites. A total of 40 patients were enrolled and assigned to Ortataxel. On October 2014 the calibration was eliminated thanks to an amendment to the protocol. Until October 2014, five patients had been assigned to Fotemustine.

Pre-assignment

Screening details:

Patients with histologically confirmed GBM in recurrence/PD after surgery (or biopsy), standard radiotherapy and chemotherapy with Temozolomide (no more than one prior line of Temozolomide).Patients who had undergone recent surgery for recurrent or PD were eligible provided that 14 days had elapsed and 7 day for core or needle biopsy.

Pre-assignment period milestones

Number of subjects started	38
Number of subjects completed	38

Period 1

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

Arms

Arm title	Ortataxel arm

Arm description:

Ortataxel 75 mg/m² intravenous every 21 days. Study treatment continued until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death.

Arm type	Experimental
Investigational medicinal product name	Ortataxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ortataxel 75 mg/m² administered intravenous every 21 days until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death.

Number of subjects in period 1	Ortataxel arm
Started	38
Completed	38

Baseline characteristics

Reporting groups	
Reporting group title	Ortataxel arm
Reporting group description:	
Ortataxel 75 mg/m² intravenous every 21 days. Study treatment continued until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death.	

Reporting group values	Ortataxel arm	Total	
Number of subjects	38	38	
Age categorical			
age at the enrollment			
Units: Subjects			
Age continuous			
age at the enrollment			
Units: years			
arithmetic mean	57.7		
standard deviation	± 11.4	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	16	16	
Body Mass Index			
Units: Subjects			
Normal weight	21	21	
Overweight	12	12	
Obese	5	5	
Residual disease after initial surgery			
Units: Subjects			
NO	29	29	
yes	9	9	
Further surgery			
Further surgery after the first one			
Units: Subjects			
No	18	18	
yes	20	20	
Time from primary diagnosis to enrollment			
Units: Months			
arithmetic mean	16.8		
standard deviation	± 12.9	-	
Months from last cycle of chemotherapy to enrollment			
Previous treatments - Months from last cycle of chemotherapy to enrollment			
Units: months			
arithmetic mean	6.6		
standard deviation	± 11.9	-	
Months from first progression or recurrence to enrollment			

Previous Treatment - Months from first progression or recurrence to enrollment			
Units: months			
arithmetic mean	2.3		
standard deviation	± 2.6	-	

Subject analysis sets

Subject analysis set title	per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all patients who were registered, with no major violations of the eligibility criteria or during study conduction, who received at least 2 cycles of treatment (unless they interrupted treatment for progressive disease or death) and whose disease is assessed

Subject analysis set title	Intention to treat analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention to treat (ITT) population included all patients who were registered, with no major violations of the eligibility criteria or during study conduction.
2 patients were excluded from the ITT ppopulation due to major violations.

Reporting group values	per protocol analysis set	Intention to treat analysis set	
Number of subjects	35	38	
Age categorical			
age at the enrollment			
Units: Subjects			

Age continuous			
age at the enrollment			
Units: years			
arithmetic mean		57.7	
standard deviation	±	± 11.4	
Gender categorical			
Units: Subjects			
Female		22	
Male		16	
Body Mass Index			
Units: Subjects			
Normal weight		21	
Overweight		12	
Obese		5	
Residual disease after initial surgery			
Units: Subjects			
NO		29	
yes		9	
Further surgery			
Further surgery after the first one			
Units: Subjects			
No		18	
yes		20	
Time from primary diagnosis to enrollment			
Units: Months			

arithmetic mean		16.8	
standard deviation	±	± 12.9	
Months from last cycle of chemotherapy to enrollment			
Previous treatments - Months from last cycle of chemotherapy to enrollment			
Units: months			
arithmetic mean		6.6	
standard deviation	±	± 11.9	
Months from first progression or recurrence to enrollment			
Previous Treatment - Months from first progression or recurrence to enrollment			
Units: months			
arithmetic mean		2.3	
standard deviation	±	± 2.6	

End points

End points reporting groups

Reporting group title	Ortataxel arm

Reporting group description:

Ortataxel 75 mg/m² intravenous every 21 days. Study treatment continued until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death.

Subject analysis set title	per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all patients who were registered, with no major violations of the eligibility criteria or during study conduction, who received at least 2 cycles of treatment (unless they interrupted treatment for progressive disease or death) and whose disease is assessed

Subject analysis set title	Intention to treat analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention to treat (ITT) population included all patients who were registered, with no major violations of the eligibility criteria or during study conduction.
2 patients were excluded from the ITT ppopulation due to major violations.

Primary: progression free survival at 6 months

End point title	progression free survival at 6 months

End point description:

End point type	Primary

End point timeframe:

from patient registration into the trial until progression or death at 6 months, whichever occurs first

End point values	Ortataxel arm	per protocol analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	35		
Units: months	38	35		

Attachments (see zip file)	ortataxelarticle.pdf

Statistical analyses

Statistical analysis title	Primary efficacy endpoint analysis

Statistical analysis description:

The PFS-6 with both 80% and 95% confidence intervals (CI) will be estimated by means of Kaplan-Meier method.
The one-tailed statistical hypotheses are: p0 ≤0.20 (null hypothesis) versus pA 0.35 (alternative hypothesis), where p is the estimated probability of being alive and progression-free at 6 months from registration.
According to the sample size assumptions, the following conclusions based on 58 eligible patients will be possibly drawn:
- if there will be 15 or less patients alive an

Comparison groups	Ortataxel arm v per protocol analysis set
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.02
Method	Logrank

Secondary: Dose-intensity

End point title	Dose-intensity

End point description:

End point type	Secondary

End point timeframe:
during treatment

End point values	Intention to treat analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: mg/m2/week				
arithmetic mean (standard deviation)	23.4 (± 3.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival 9 months

End point title	Overall survival 9 months

End point description:

End point type	Secondary

End point timeframe:
from enrollment untill death or 9 months, whichever occurs first

End point values	per protocol analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: proportion of alive patients at 9 months	35			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from enrollment until 30 days after the end of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4

Reporting groups

Reporting group title	all patients who received the treatment

Reporting group description: -

Serious adverse events	all patients who received the treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 38 (23.68%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Seizure			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock	Additional description: grade 4		
subjects affected / exposed	9 / 38 (23.68%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all patients who received the treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 38 (89.47%)		
Investigations			

Neutropenia subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 7 2 / 38 (5.26%) 2		
Nervous system disorders Asthenia subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 6 / 38 (15.79%) 11 3 / 38 (7.89%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 3 / 38 (7.89%) 13 4 / 38 (10.53%) 8 5 / 38 (13.16%) 15 3 / 38 (7.89%) 8		
Immune system disorders Anaphylactic shock subjects affected / exposed occurrences (all)	 1 / 38 (2.63%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 1 / 38 (2.63%) 3 2 / 38 (5.26%) 2		

Nausea subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2014	the calibration arm with Fotemustine was closed.

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/3072653