Clinical trial results:
A RANDOMIZED PHASE III STUDY OF TEMOZOLOMIDE AND SHORT-COURSE RADIATION VERSUS SHORT-COURSE RADIATION ALONE IN THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME IN ELDERLY PATIENTS

Summary

EudraCT number	2008-001949-26
Trial protocol	NL DE FR IT BE
Global end of trial date	04 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	26062-22061

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00482677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CCTG
Sponsor organisation address	10 Stuart Street, Kingston, Ontario, Canada,
Public contact	James Perry, M.D. Sunnybrook & Women's College Health Sciences Centre, Normand Laperriere, MD Princess Margaret Hospital/University Health Network , 1 416-480-6124, james.perry@swchsc.on.ca
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Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062 , regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062 , regulatory@eortc.be

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	11 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2016
Global end of trial reached?	Yes
Global end of trial date	04 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) rates between short-course radiation therapy alone and shortcourse radiation therapy given together with concurrent and adjuvant temozolomide, in elderly (>65 years of age) patients with newly diagnosed glioblastoma multiforme (GBM, WHO grade IV) , who have had prior surgery/biopsy at diagnosis and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ich.org/LOB/media/MEDIA482.pdf).
The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Radiation Therapy (40 Gy/15 fractions over 3 weeks)

Evidence for comparator:

Phase II studies had demonstrated median survivals of 6 months with temozolomide only in patients older than age 70. Dr. Chinot reported on 32 patients older than age 70 (median age 75) who were treated with temozolomide only in the 5 day per 28 day regimen and median survival was 6.4 months. Dr Glantz reported on 32 patients older than age 70 that were offered temozolomide only or radiotherapy only in a series of 86 patients. The median survival for the temozolomide only group was 6 months as compared to the radiotherapy group median survival of 4.1 months in a non-randomized study.
In addition, a prospective sequential series of patients with GBM and age ≥ 65 treated with radiotherapy (RT) only, RT plus PCV, and RT with temozolomide (adjuvant only) demonstrated increasing median survivals of 11.2, 12.7, and 14.9 months respectively. .
Phase III study of concurrent temodal and radiation therapy followed by 6 months of adjuvant temozolomide have shown a survival advantage over radiotherapy alone in patients age 18-70, with evidence of improved survival in the 60-70 age cohort in the combined modality group. Therefore, in view of the seeming similarity of results of temozolomide alone, RT alone, and the recent phase III study which shows an advantage of combined temozolomide with RT, there is a need to study this populations in a phase III randomized study comparing all three approaches in patients older than age 70.

Actual start date of recruitment	14 November 2007
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	Netherlands: 45
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	France: 70
Country: Number of subjects enrolled	Germany: 50
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Canada: 199
Country: Number of subjects enrolled	Australia: 97
Country: Number of subjects enrolled	Japan: 17
Worldwide total number of subjects	562
EEA total number of subjects	249

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)	0
From 65 to 84 years	562
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients > 65 years of age, with newly diagnosed, histopathologically confirmed, glioblastoma multiforme (GBM, WHO grade IV) who have had prior surgery/biopsy at diagnosis and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.

Pre-assignment

Screening details:

- Patient's age is > 65 years.
- Patient is not deemed suitable by the treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.
-ECOG performance status of 0, 1 or 2.

Pre-assignment period milestones

Number of subjects started	562
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RT alone

Arm description:

Radiation Therapy (40 Gy/15 fractions over 3 weeks)

Arm type	Radiotherapy

No investigational medicinal product assigned in this arm

Arm title	RT + TMZ

Arm description:

Radiation Therapy (40 Gy/15 fractions over 3 weeks) and Concurrent Temozolomide (75 mg/m2, daily, from the first to the last day of radiotherapy to a maximum of 28 days)

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

Dosage and administration details:

Temozolomide (concurrent with radiation) 75 mg/m2. once a day, daily, from the first day to the last day of radiotherapy.
Temozolomide (adjuvant; to start 4 weeks after the end of radiation). 150 mg/m2 in cycle 1; escalate to 200 mg/m2 in cycles 2 onwards in the absence of significant adverse events. in 28-day long cycles (once a day, daily, for the first 5 days within each cycle), until progressive disease (PD) or unacceptable adverse events to a maximum of 12 months.

Number of subjects in period 1	RT alone	RT + TMZ
Started	281	281
Completed	261	25
Not completed	20	256
intercurrent illness (not related to temozolomide)	-	38
Treatment not started	10	10
Consent withdrawn by subject	1	13
Adverse event, non-fatal	2	31
Patient's death	1	15
Treatment ongoing	-	1
Unspecified	-	6
Lack of efficacy	6	142

Baseline characteristics

Reporting groups	
Reporting group title	RT alone
Reporting group description:	
Radiation Therapy (40 Gy/15 fractions over 3 weeks)	
Reporting group title	RT + TMZ
Reporting group description:	
Radiation Therapy (40 Gy/15 fractions over 3 weeks) and Concurrent Temozolomide (75 mg/m2, daily, from the first to the last day of radiotherapy to a maximum of 28 days)	

Reporting group values	RT alone	RT + TMZ	Total
Number of subjects	281	281	562
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
65-70 years	82	83	165
71-75 years	114	117	231
>= 76 years	85	81	166
Gender categorical Units: Subjects			
Female	109	110	219
Male	172	171	343
ECOG performance status Units: Subjects			
PS 0	57	74	131
PS 1	160	141	301
PS 2	64	66	130

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients	

Reporting group values	ITT		
Number of subjects	562		
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		
65-70 years	165		
71-75 years	231		
>= 76 years	166		
Gender categorical Units: Subjects			
Female	219		
Male	343		
ECOG performance status Units: Subjects			
PS 0	131		
PS 1	301		
PS 2	130		

End points

End points reporting groups

Reporting group title	RT alone
Reporting group description:	
Radiation Therapy (40 Gy/15 fractions over 3 weeks)	
Reporting group title	RT + TMZ
Reporting group description:	
Radiation Therapy (40 Gy/15 fractions over 3 weeks) and Concurrent Temozolomide (75 mg/m2, daily, from the first to the last day of radiotherapy to a maximum of 28 days)	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe:	
The duration of survival is the time interval between the date of randomization and the date of death. Patients who were still alive when last traced are censored at the date of last follow up. All	

End point values	RT alone	RT + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	281		
Units: Months				
median (confidence interval 95%)	7.62 (6.97 to 8.38)	9.33 (8.31 to 10.3)		

Statistical analyses

Statistical analysis title	Comparison of OS between arms
Comparison groups	RT alone v RT + TMZ
Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.8

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:

PFS is the time interval between the date of randomization and the date of disease progression or death, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination.

End point values	RT alone	RT + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	281		
Units: Months				
median (confidence interval 95%)	3.94 (3.52 to 4.34)	5.29 (4.6 to 6.21)		

Statistical analyses

Statistical analysis title	Comparison of PFS
Comparison groups	RT alone v RT + TMZ
Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During radiotherapy (± temozolomide)
21-28 days after the end of radiotherapy
In RT only: 4 weeks after RT and every 3 months until death
In RT+TMZ: Every 3 months until death

Adverse event reporting additional description:

AEs are evaluated using CTCAE v3 grading, SAEs using CTCAE v3. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	RT alone

Reporting group description:

Radiotherapy

Reporting group title	RT+TMZ

Reporting group description:

TMZ/RT->adj TMZ

Serious adverse events	RT alone	RT+TMZ	
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 271 (35.06%)	105 / 271 (38.75%)	
number of deaths (all causes)	264	256	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
VASCULAR			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	12 / 271 (4.43%)	28 / 271 (10.33%)	
occurrences causally related to treatment / all	1 / 4	2 / 5	
deaths causally related to treatment / all	0 / 3	0 / 1	
General disorders and administration site conditions			
CONSTITUTIONAL SYMPTOMS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	8 / 271 (2.95%)	9 / 271 (3.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			

alternative dictionary used: CTCAE 3			
subjects affected / exposed	7 / 271 (2.58%)	7 / 271 (2.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY/UPPER RESPIRATORY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	9 / 271 (3.32%)	9 / 271 (3.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 5	
Cardiac disorders			
CARDIAC ARRHYTHMIA			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 271 (0.37%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC GENERAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 271 (0.74%)	8 / 271 (2.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
NEUROLOGY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	43 / 271 (15.87%)	35 / 271 (12.92%)	
occurrences causally related to treatment / all	4 / 5	2 / 5	
deaths causally related to treatment / all	0 / 2	1 / 1	
Blood and lymphatic system disorders			
BLOOD/BONE MARROW			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 271 (0.74%)	4 / 271 (1.48%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHATICS			

alternative dictionary used: CTCAE 3			
subjects affected / exposed	4 / 271 (1.48%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
OCULAR/VISUAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 271 (0.37%)	3 / 271 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	10 / 271 (3.69%)	7 / 271 (2.58%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatobiliary disorders			
HEPATOBILIARY/PANCREAS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 271 (0.00%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATOLOGY/SKIN			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	3 / 271 (1.11%)	4 / 271 (1.48%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL/GENITOURINARY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	4 / 271 (1.48%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Endocrine disorders			
ENDOCRINE			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	2 / 271 (0.74%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL/SOFT TISSUE			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	14 / 271 (5.17%)	17 / 271 (6.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTION			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	17 / 271 (6.27%)	22 / 271 (8.12%)	
occurrences causally related to treatment / all	1 / 5	4 / 5	
deaths causally related to treatment / all	0 / 3	1 / 1	
Metabolism and nutrition disorders			
METABOLIC/LABORATORY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	5 / 271 (1.85%)	3 / 271 (1.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RT alone	RT+TMZ	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 271 (97.05%)	267 / 271 (98.52%)	
Vascular disorders			
VASCULAR			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	26 / 271 (9.59%)	45 / 271 (16.61%)	
occurrences (all)	26	45	

General disorders and administration site conditions			
CONSTITUTIONAL SYMPTOMS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	159 / 271 (58.67%)	172 / 271 (63.47%)	
occurrences (all)	159	172	
PAIN			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	106 / 271 (39.11%)	99 / 271 (36.53%)	
occurrences (all)	106	99	
Immune system disorders			
ALLERGY/IMMUNOLOGY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	4 / 271 (1.48%)	6 / 271 (2.21%)	
occurrences (all)	4	6	
Reproductive system and breast disorders			
SEXUAL/REPRODUCTIVE FUNCTION			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 271 (0.00%)	2 / 271 (0.74%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
PULMONARY/UPPER RESPIRATORY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	46 / 271 (16.97%)	66 / 271 (24.35%)	
occurrences (all)	46	66	
Cardiac disorders			
CARDIAC ARRHYTHMIA			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	4 / 271 (1.48%)	6 / 271 (2.21%)	
occurrences (all)	4	6	
CARDIAC GENERAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	11 / 271 (4.06%)	21 / 271 (7.75%)	
occurrences (all)	11	21	
Nervous system disorders			

NEUROLOGY			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	216 / 271 (79.70%)	237 / 271 (87.45%)	
occurrences (all)	216	237	
Blood and lymphatic system disorders			
BLOOD/BONE MARROW			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	9 / 271 (3.32%)	15 / 271 (5.54%)	
occurrences (all)	9	15	
COAGULATION			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 271 (0.37%)	0 / 271 (0.00%)	
occurrences (all)	1	0	
LYMPHATICS			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	44 / 271 (16.24%)	60 / 271 (22.14%)	
occurrences (all)	44	60	
Ear and labyrinth disorders			
AUDITORY/EAR			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	20 / 271 (7.38%)	22 / 271 (8.12%)	
occurrences (all)	20	22	
Eye disorders			
OCULAR/VISUAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	43 / 271 (15.87%)	35 / 271 (12.92%)	
occurrences (all)	43	35	
Gastrointestinal disorders			
GASTROINTESTINAL			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	113 / 271 (41.70%)	152 / 271 (56.09%)	
occurrences (all)	113	152	
Hepatobiliary disorders			
HEPATOBILIARY/PANCREAS			
alternative dictionary used: CTCAE 3			

subjects affected / exposed occurrences (all)	1 / 271 (0.37%) 1	4 / 271 (1.48%) 4	
Skin and subcutaneous tissue disorders DERMATOLOGY/SKIN alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 107 / 271 (39.48%) 107	 102 / 271 (37.64%) 102	
Renal and urinary disorders RENAL/GENITOURINARY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 40 / 271 (14.76%) 40	 45 / 271 (16.61%) 45	
Endocrine disorders ENDOCRINE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 13 / 271 (4.80%) 13	 16 / 271 (5.90%) 16	
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL/SOFT TISSUE alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 79 / 271 (29.15%) 79	 97 / 271 (35.79%) 97	
Infections and infestations INFECTION alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 54 / 271 (19.93%) 54	 75 / 271 (27.68%) 75	
Metabolism and nutrition disorders METABOLIC/LABORATORY alternative dictionary used: CTCAE 3 subjects affected / exposed occurrences (all)	 13 / 271 (4.80%) 13	 15 / 271 (5.54%) 15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2009	-Deletion in the EudraCT application form of the central facility in the Netherlands (section G4); the samples are sent by the sites directly to the central pathology review facility without any intermediate storage.
30 June 2010	• Change in the drug supply chain of Shering-Plough: The Temodal will continue to be manufactured at Orion, in Finland. The bulk Temodal will the be shipped from Orion to WAG, in Switzerland, for secondary packaging and labeling. The GMP/QA releases for the packaged supplies will be performed by WAG. The drug will be shipped from WAG to Almac UK where the QP release will be performed. Once the QP release completed, the product will be shipped to the country sites directly. • The protocol and Group Specific Appendix have been amended, please note those changes are considered as non-substantial (changes are detailed in the document "GSA-26062-22061-amend 2 annex 1" and "GSA-26062-22061-amend 2"): • The first change is a number of clarifications to the protocol in regards to dose modifications for radiotherapy and the transition from concurrent to adjuvant temozolomide, as well as clarifications for supporting documentation required for radiotherapy. • The second change to the protocol involves a clarification to the eligibility criteria regarding the timing between initial surgery and the start of study therapy. • A third change to the protocol involves follow-up for patients on the temozolomide and radiotherapy arm of the trial (Arm 2 patients).
02 July 2013	1. Changes in the IMP labels: Due to the switch of activities from Schering-Piough to Merck (MSD) and therefore changes in the standard operational procedures for IMP label design, the wording and layout of the IMP labels have changed. 2. Correction on drug supply chain: WAG has been initially declared in our covering letter but does not reflect in the Annex I. Therefore the relevant part of the Annex I has been updated accordingly.
12 August 2013	Merck (MSD) is not able to provide a new stock of TEMOZOLOMIDE within the timelines. The batch being used for the moment on the participating site expires on 30/09/2013 and very soon some sites will be out of stock. As a consequence, we are momentarily obliged to ask participating sites to use commercial drug. The commercial drug will be reimbursed by the EORTC which will then invoice Merck. No patient will be charged for the drug costs.

25 November 2013	Protocol and Group Specific Appendix (GSA) Previous GSA version: 2.0 dated 10AUG2009 New GSA version: 2.1 dated 21MAY2010 Previous Protocol version: 1.0 dated 16APR2007 New Protocol version: 2.0 dated 22FEB2010 Rationale: The first change is a number of clarifications to the protocol in regards to dose modifications for radiotherapy and the transition from concurrent to adjuvant temozolomide, as well as clarifications for supporting documentation required for radiotherapy. The second change to the protocol involves a clarification to the eligibility criteria regarding the timing between initial surgery and the start of study therapy. A third change to the protocol involves follow-up for patients on the temozolomide and radiotherapy arm of the trial (Arm 2 patients). These changes are described on "GSA-26062-22061-amend 2 & GSA-26062-22061-AMEND 2 annex 1" document which will allow you to clearly identify the changes. The following documents have been impacted by this amendment and have been updated: -The Clinical Trial Protocol -The Group Specific Appendix Please note that this amendment doesn't affect the safety, physical or mental integrity of the patients, or on the scientific value of the trial.
17 February 2014	Notification of temozolomide new safety information Merck Sharp & Dohme (MSD), the marketing authorization holder for temozolomide, informed healthcare providers of the following new safety information: • Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide. • Liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. • Liver function tests should be performed: prior to treatment initiation. If abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and risks for the individual patient; after each treatment cycle. • For patients on a 42 day treatment cycle, liver function tests should be repeated midway during this cycle; • For patients with significant liver function abnormalities the benefits and risks of continuing treatment should be carefully considered. Recruitment for this trial has been completed. As a result there are no implications for the management of patients on treatment and thus a protocol amendment is not required. However, patients who are continuing on follow-up will be informed orally of this updated information by their Principal Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported