



Clinical trial results:

Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase III study

Summary

EudraCT number	2004-002714-11
Trial protocol	AT DE GB IT DK BE ES PT HU SE GR
Global end of trial date	14 May 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EORTC 22033-26033
-----------------------	-------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00182819
WHO universal trial number (UTN)	-

Notes:

Sponsors

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	07 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2013
Global end of trial reached?	Yes
Global end of trial date	14 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A randomized study to demonstrate a difference in progression-free survival for primary treatment with temozolomide versus primary irradiation (primary objective).

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki 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 for Good Clinical Practice. The protocol will be approved by the Local, Regional or National Ethics Committees.

Background therapy:

NO background therapy.

Evidence for comparator:

Based on the 3 randomized radiotherapy trials for patients harbouring a low-grade glioma mentioned above there seems to be no survival advantage for immediate radiotherapy or radiation doses above 45 - 50 Gy. Additionally, radiotherapy carries the risk of side effects on cognition. Survival appears to depend mainly on age, grading, histology and neurologic function. Based on the data of the two randomized EORTC trials a group of patients with an inferior prognosis who need immediate therapy can be identified. Therefore a study is proposed for patients carrying prognostic factors for a worse outcome as identified by the previous randomized studies. In this study patients for whom treatment with radiotherapy is commonly prescribed will be randomized between radiotherapy versus chemotherapy with temozolomide.

Temozolomide has been demonstrated to have an activity in low-grade glioma. In particular, several studies have shown a higher chemosensitivity for tumors with loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). The latter is especially true for oligodendrogliomas. For this reason, we propose randomization only after genetic testing and stratification for LOH on 1p. The study will investigate if the use of temozolomide improves the time to progression as compared to radiotherapy. Late toxicity, quality of life and cognitive function are important secondary endpoints.

Actual start date of recruitment	23 September 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Luxembourg: 1
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 29

Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	France: 134
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Australia: 62
Country: Number of subjects enrolled	Canada: 82
Country: Number of subjects enrolled	Egypt: 8
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Switzerland: 39
Country: Number of subjects enrolled	Netherlands: 113
Worldwide total number of subjects	707
EEA total number of subjects	492

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)	686
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Registration period from 23/09/2005 and 26/03/2010.

78 institutions in 19 countries.

Pre-assignment

Screening details:

Histologically proven low grade diffuse glioma and after screening:

Results of genetic testing (1p) available

Patients requiring treatment by at least one of the following:

1. Age ≥ 40 years
2. Radiologically proven progressive lesion
3. Neurological symptoms others than seizures only
4. Intractable seizures

Pre-assignment period milestones

Number of subjects started	707
----------------------------	-----

Number of subjects completed	477
------------------------------	-----

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 50
Reason: Number of subjects	Patient lost to follow-up: 6
Reason: Number of subjects	Patient potentially randomizable: 51
Reason: Number of subjects	Death not due to progression: 1
Reason: Number of subjects	Higher grade transformation: 47
Reason: Number of subjects	Progression or death due to progression: 2
Reason: Number of subjects	Other / missing: 73

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	Radiotherapy (RT)
-----------	-------------------

Arm description:

Treatment should start within 6 weeks of randomization. Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 50.4Gy, once daily 1.8 Gy per fraction, 5 days per week, for a total of 28 fractions.

Arm type	Radiotherapy
----------	--------------

No investigational medicinal product assigned in this arm

Arm title	Temozolomide (TMZ)
-----------	--------------------

Arm description:

Treatment should start within 6 weeks of randomization. Treatment with temozolomide will be continued until disease progression but no longer than 12 treatment cycles (approx. 1 year).

Arm type	Experimental
----------	--------------

Investigational medicinal product name	TEMOZOLOMIDE
Investigational medicinal product code	
Other name	Temodal
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide will be administered continuously at a daily dose of 75 mg/m² daily x 21 days, q 28 days. The drug will be administered orally once a day. The dose administered will be determined using the body surface area (BSA) calculated at the beginning of the treatment. The BSA will be calculated from the height and weight obtained at the pretreatment visit.

Number of subjects in period 1^[1]	Radiotherapy (RT)	Temozolomide (TMZ)
Started	240	237
Completed	199	200
Not completed	41	37
treatment never started, ...	-	4
information not available, treatment never started	18	-
Protocol deviation	23	33

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 707 patients were registered but only 477 patients were eligible for randomization. Results are presented for randomized patients only.

Baseline characteristics

Reporting groups

Reporting group title	Radiotherapy (RT)
-----------------------	-------------------

Reporting group description:

Treatment should start within 6 weeks of randomization. Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 50.4Gy, once daily 1.8 Gy per fraction, 5 days per week, for a total of 28 fractions.

Reporting group title	Temozolomide (TMZ)
-----------------------	--------------------

Reporting group description:

Treatment should start within 6 weeks of randomization. Treatment with temozolomide will be continued until disease progression but no longer than 12 treatment cycles (approx. 1 year).

Reporting group values	Radiotherapy (RT)	Temozolomide (TMZ)	Total
Number of subjects	240	237	477
Age categorical			
Units: Subjects			
<40	92	85	177
>=40	148	152	300
Age continuous			
Units: years			
median	43.5	45	
full range (min-max)	18.4 to 71.8	19.1 to 74.5	-
Gender categorical			
Units: Subjects			
Female	102	100	202
Male	138	137	275
Type of histologically proven low grade			
Units: Subjects			
astrocytoma who grade II	88	79	167
oligoastrocytoma who grade II	58	60	118
oligodendroglioma who grade II	94	98	192
Molecular testing			
Patients having had previous 1p testing in a different laboratory than the one specified for this study had a repeated testing in the central reference laboratory			
Units: Subjects			
1p deleted	98	97	195
1p normal	107	106	213
Undeterminable	35	34	69
MRI contrast enhancement			
Units: Subjects			
No	119	119	238
Yes	121	118	239
WHO performance status			
Units: Subjects			
WHO 0	151	143	294
WHO 1	79	86	165
WHO 2	10	8	18

End points

End points reporting groups

Reporting group title	Radiotherapy (RT)
Reporting group description: Treatment should start within 6 weeks of randomization. Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 50.4Gy, once daily 1.8 Gy per fraction, 5 days per week, for a total of 28 fractions.	
Reporting group title	Temozolomide (TMZ)
Reporting group description: Treatment should start within 6 weeks of randomization. Treatment with temozolomide will be continued until disease progression but no longer than 12 treatment cycles (approx. 1 year).	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description: Defining disease progression as radiological or clinical/neurological progression which ever occurs first, 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. The patient should consistently be followed with the same diagnostic imaging throughout the study.	
End point type	Primary
End point timeframe: The first follow-up (FU) will be performed 3 months after the start of therapy, then at 3-monthly intervals until progression	

End point values	Radiotherapy (RT)	Temozolomide (TMZ)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	237		
Units: Years				
median (confidence interval 95%)	3.82 (3.32 to 4.59)	3.24 (2.81 to 3.62)		

Statistical analyses

Statistical analysis title	PFS: TMZ versus RT in ITT
Statistical analysis description: Comparison of PFS between both arms (Temozolomide versus Radiotherapy) in intent-to-treat population (all randomized patients according to the allocated treatment)	
Comparison groups	Radiotherapy (RT) v Temozolomide (TMZ)

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.48

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
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.	
End point type	Secondary
End point timeframe:	
The first follow-up (FU) will be performed 3 months after the start of therapy, then at 3-monthly intervals until progression. After disease progression Patients are followed every 6 months for survival.	

End point values	Radiotherapy (RT)	Temozolomide (TMZ)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240 ^[1]	237 ^[2]		
Units: Years				
median (confidence interval 95%)	7 (7 to 7)	7 (7 to 7)		

Notes:

[1] - Median was not reached

[2] - Median was not reached

Statistical analyses

Statistical analysis title	OS: TMZ versus RT in ITT
Statistical analysis description:	
Comparison of OS between both arms (Temozolomide versus Radiotherapy) in intent-to-treat population (all randomized patients according to the allocated treatment)	
Comparison groups	Radiotherapy (RT) v Temozolomide (TMZ)

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 6 weeks of randomization, the first follow-up (FU) will be performed 3 months after treatment start, then at 3-monthly intervals until progression.

*Additional evaluations for patients receiving TMZ: Prior to day 1 of each cycle of TMZ

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (xx% AEs are reported as "other" and are not reported as not available from the list of SOC). AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, therefore all AEs (any grade) will be reported in non-SAE section.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.1
--------------------	------

Reporting groups

Reporting group title	Radiotherapy
-----------------------	--------------

Reporting group description:

Only patients randomized in radiotherapy arm and who started radiotherapy are included in the population

Reporting group title	Temozolomide
-----------------------	--------------

Reporting group description:

Only patients randomized in Temozolomide arm and who started Temozolomide are included in the population

Serious adverse events	Radiotherapy	Temozolomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 228 (4.82%)	34 / 235 (14.47%)	
number of deaths (all causes)	57	55	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Colon cancer	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma stage III	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
CD4 lymphocytes decreased	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	2 / 228 (0.88%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	7 / 235 (2.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	

Blood and lymphatic system disorders			
Lymphopenia	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	4 / 235 (1.70%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroesophageal reflux disease	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary incontinence alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	0 / 228 (0.00%)	1 / 235 (0.43%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders Pain in extremity alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	1 / 228 (0.44%)	0 / 235 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Infections and infestations Bronchitis alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	0 / 228 (0.00%)	2 / 235 (0.85%)	
	0 / 0	0 / 2	
	0 / 0	0 / 0	
Oral herpes alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	0 / 228 (0.00%)	1 / 235 (0.43%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Otitis media alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	0 / 228 (0.00%)	1 / 235 (0.43%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: No information.		
	0 / 228 (0.00%)	1 / 235 (0.43%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Pneumonia	Additional description: No information.		

alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 228 (0.44%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Radiotherapy	Temozolomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	200 / 228 (87.72%)	223 / 235 (94.89%)	
Vascular disorders			
VASCULAR	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	4 / 228 (1.75%)	2 / 235 (0.85%)	
occurrences (all)	5	2	
Surgical and medical procedures			
SURGERY/INTRA-OPERATIVE INJURY	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed occurrences (all)	2 / 228 (0.88%) 2	0 / 235 (0.00%) 0	
General disorders and administration site conditions			
CONSTITUTIONAL SYMPTOMS	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	149 / 228 (65.35%) 186	175 / 235 (74.47%) 253	
PAIN	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	113 / 228 (49.56%) 180	128 / 235 (54.47%) 267	
Immune system disorders			
ALLERGY/IMMUNOLOGY	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	3 / 228 (1.32%) 3	12 / 235 (5.11%) 12	
Reproductive system and breast disorders			
SEXUAL/REPRODUCTIVE FUNCTION	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	7 / 228 (3.07%) 9	15 / 235 (6.38%) 17	
Respiratory, thoracic and mediastinal disorders			
PULMONARY/UPPER RESPIRATORY	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	15 / 228 (6.58%) 17	43 / 235 (18.30%) 54	
Cardiac disorders			
CARDIAC(GENERAL)	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed occurrences (all)	10 / 228 (4.39%) 10	14 / 235 (5.96%) 14	
Nervous system disorders			
NEUROLOGY	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			

subjects affected / exposed	162 / 228 (71.05%)	167 / 235 (71.06%)	
occurrences (all)	493	532	
Blood and lymphatic system disorders			
ANEMIA	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	7 / 228 (3.07%)	60 / 235 (25.53%)	
occurrences (all)	7	60	
LEUKOPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	12 / 228 (5.26%)	134 / 235 (57.02%)	
occurrences (all)	12	134	
LYMPHATICS	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	2 / 228 (0.88%)	9 / 235 (3.83%)	
occurrences (all)	2	10	
NEUTROPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	7 / 228 (3.07%)	90 / 235 (38.30%)	
occurrences (all)	7	90	
THROMBOCYTOPENIA	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 228 (0.00%)	19 / 235 (8.09%)	
occurrences (all)	0	19	
Ear and labyrinth disorders			
AUDITORY/EAR	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	41 / 228 (17.98%)	36 / 235 (15.32%)	
occurrences (all)	56	44	
Eye disorders			
OCULAR/VISUAL	Additional description: No information.		
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	36 / 228 (15.79%)	46 / 235 (19.57%)	
occurrences (all)	62	64	
Gastrointestinal disorders			

GASTROINTESTINAL alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	70 / 228 (30.70%)	168 / 235 (71.49%)	
	120	424	
Hepatobiliary disorders HEPATOBIILIAR/PANCREAS alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	2 / 228 (0.88%)	0 / 235 (0.00%)	
	3	0	
Skin and subcutaneous tissue disorders DERMATOLOGY/SKIN alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	112 / 228 (49.12%)	77 / 235 (32.77%)	
	142	118	
Renal and urinary disorders RENAL/GENITOURINARY alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	6 / 228 (2.63%)	16 / 235 (6.81%)	
	6	19	
Endocrine disorders ENDOCRINE alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	9 / 228 (3.95%)	12 / 235 (5.11%)	
	9	15	
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL/SOFT TISSUE alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	22 / 228 (9.65%)	23 / 235 (9.79%)	
	30	28	
Infections and infestations INFECTION alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	24 / 228 (10.53%)	73 / 235 (31.06%)	
	29	111	
Metabolism and nutrition disorders			

METABOLIC/LABORATORY alternative dictionary used: CTCAE 3.0 subjects affected / exposed occurrences (all)	Additional description: No information.		
	4 / 228 (1.75%)	4 / 235 (1.70%)	
	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2006	IB update (Dec 2005) + SUSAR reported since December
22 January 2007	Protocol version 2.0 Substantial changes - the core PIS / informed consent has been amended with toxicity data provided by the company after market exposure with TMZ - Addendum to the patient information sheet / informed consent has been added for the NEW and the ONGOING patients
04 June 2007	protocol version 2.0 updates to the Patient information sheet & informed consent update of the IB
21 May 2010	update in the drug supply chain

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/20378192>

<http://www.ncbi.nlm.nih.gov/pubmed/22560713>