Clinical trial results:
PHASE 2 SINGLE-ARM, OPEN LABEL STUDY OF IRINOTECAN IN COMBINATION WITH TEMOZOLOMIDE IN CHILDREN WITH RECURRENT OR REFRACTORY MEDULLOBLASTOMA AND IN CHILDREN WITH NEWLY DIAGNOSED HIGH-GRADE GLIOMA

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2006-005476-40
Trial protocol	GB FR DK IT PL ES
Global end of trial date	15 December 2011

Results information

Result version number	v2 (current)
This version publication date	26 March 2016
First version publication date	30 July 2015
Version creation reason	• Correction of full data set Correction of identified Timestamp error .

Trial information

Trial identification

Sponsor protocol code	A5961166

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00404495
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the rate of objective confirmed tumor response of irinotecan in combination with temozolomide in children with recurrent or refractory medulloblastoma and in children with newly diagnosed high-grade glioma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2007
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	Poland: 9
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 4
Worldwide total number of subjects	83
EEA total number of subjects	79

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)	61
Adolescents (12-17 years)	22
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

83 subjects were enrolled; 66 subjects were treated with Temozolomide + Irinotecan for medulloblastoma and 17 subjects were treated with Temozolomide + Irinotecan for high-grade glioma.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Temozolomide + Irinotecan for Medulloblastoma

Arm description:

For subjects with medulloblastoma: Irinotecan 10 mg/m^2/Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

Arm type	Experimental
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan 10 milligram per square meter (mg/m^2) per Day on Days 1-5 and Days 8-12 in repeated 3 week cycles.

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

Dosage and administration details:

Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3 week cycles.

Arm title	Temozolomide + Irinotecan for High-Grade Glioma

Arm description:

For subjects with high-grade glioma: Irinotecan 10 mg/m^2/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

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 100-125 mg/m^2 daily on Days 1-5 in repeated 3 week cycles.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan 10 mg/m^2 per Day on Days 1-5 and Days 8-12 in repeated 3 week cycles.

Number of subjects in period 1	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma
Started	66	17
Completed	22	6
Not completed	44	11
Consent withdrawn by subject	1	-
Death	37	11
Not specified	1	-
Lost to follow-up	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Temozolomide + Irinotecan for Medulloblastoma
Reporting group description:	
For subjects with medulloblastoma: Irinotecan 10 mg/m^2/Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.	
Reporting group title	Temozolomide + Irinotecan for High-Grade Glioma
Reporting group description:	
For subjects with high-grade glioma: Irinotecan 10 mg/m^2/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.	

Reporting group values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma	Total
Number of subjects	66	17	83
Age categorical Units: Subjects			
2 years to 12 years	49	12	61
Greater than (>) 12 years to 18 years	17	5	22
Gender categorical Units: Subjects			
Female	21	3	24
Male	45	14	59

End points

End points reporting groups

Reporting group title	Temozolomide + Irinotecan for Medulloblastoma

Reporting group description:

For subjects with medulloblastoma: Irinotecan 10 mg/m^2/Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

Reporting group title	Temozolomide + Irinotecan for High-Grade Glioma

Reporting group description:

For subjects with high-grade glioma: Irinotecan 10 mg/m^2/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

Primary: Percentage of Subjects With Objective Response of Complete Response or Partial Response

End point title	Percentage of Subjects With Objective Response of Complete Response or Partial Response[1]

End point description:

Percentage of subjects with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR). CR persisted on repeat imaging study at least (≥) 4 weeks after initial documentation of response. PR, for bidimensionally measurable disease, was a decrease by ≥50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Best overall response recorded any time while the subject was receiving treatment. External Response Review Committee (ERRC) assessment. Primary Evaluable Population: subset of evaluable population predetermined by 2-stage Optimum Simon design. Medulloblastoma cohort: n=consecutive evaluable subjects up to 46 if 6 responses obtained in first 15 evaluable subjects. Glioma cohort: n=consecutive evaluable subjects up to 29 if 1 response in first 10 evaluable subjects.

End point type	Primary

End point timeframe:

Baseline to 1 Year (medulloblastoma), Baseline to 6 Weeks (high-grade glioma)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification:
Only descriptive data was planned to be collected for this endpoint. No statistical analysis was performe d as per planned analysis.

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	10		
Units: percentage of subjects				
number (confidence interval 95%)	32.6 (19.5 to 48)	0 (0 to 30.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Objective Response of Complete Response or Partial Response, Investigator's Assessment

End point title	Percentage of Subjects With Objective Response of Complete Response or Partial Response, Investigator's Assessment

End point description:

Percentage of subjects with objective response based assessment of confirmed CR or confirmed PR. CR persisted on repeat imaging study ≥4 weeks after initial documentation of response. PR, in case of bidimensionally measurable disease, was a decrease by ≥50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Best overall response could be recorded any time while the subject was receiving treatment. Investigator's assessment. Evaluable local population: Subjects received at least 1 dose of study medication, had measurable disease under study, at least 1 on-study objective tumor assessment, completed at least 2 cycles of study treatment or progressed. Based on investigator's assessment.

End point type	Secondary

End point timeframe:

Baseline to 1 Year (medulloblastoma), Baseline to 6 Weeks (high-grade glioma)

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	17		
Units: percentage of subjects				
number (confidence interval 95%)	34.9 (23.3 to 48)	11.8 (1.5 to 36.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Median duration (50%) of tumor response for subjects with objective disease response: who have not progressed or died due to any cause; with a response and subsequent progression or death due to any cause for duration of response (DR). DR was defined as time from start of first documented objective tumor response (CR or PR) to first documented objective tumor progression or death due to any cause, whichever occurred first. DR (calculated in Weeks) = (the end date for DR minus first subsequent confirmed CR or PR plus 1) divided by 7. Investigator's assessment. Evaluable local population.

End point type	Secondary

End point timeframe:

Baseline to Date of Tumor Response (Up to 1 Year)

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[2]	2[3]		
Units: weeks				
median (full range (min-max))	22.4 (6.9 to 46.6)	36.3 (4 to 68.6)		

Notes:

[2] - Number of subjects analyzed=number of subjects who responded.

[3] - Number of subjects analyzed=number of subjects who responded.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

TTF was defined as the time from the date of first dose of study treatment to the date of the first documentation of progressive disease (PD), the date of treatment discontinuation except completion of treatment, or date of death due to cancer. Investigator's assessment.
Evaluable local population was assessed.

End point type	Secondary

End point timeframe:

Baseline to Date of Treatment Failure (Up to 1 Year)

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	17		
Units: months				
median (confidence interval 95%)	3.8 (2.9 to 5.4)	1.6 (1.3 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Progression (TTP)

End point title	Time to Tumor Progression (TTP)

End point description:

TTP was defined as the time in months from start of study treatment to first documentation of objective tumor progression or death due to cancer, whichever came first. TTP was calculated as (first event date minus the date of first dose of study medication plus 1) divided by 7 multiplied by 4.33. Tumor progression was determined from oncologic assessment data (where data met the criteria for PD). Investigator's assessment. Evaluable local population was analyzed.

End point type	Secondary

End point timeframe:

Baseline to Date of Progression (Up to 1 Year)

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	17		
Units: months				
median (confidence interval 95%)	5.6 (3.8 to 7.4)	1.6 (1.3 to 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Time in months from the start of study treatment to date of death due to any cause. OS was calculated as (the death date minus the date of first dose of study medication plus 1) divided by 7 multiplied by 4.33. Death was determined from adverse event data (where outcome was death) or from follow-up contact data (where the subject current status was death). Investigator's assessment. All subjects were analyzed. One subject in the Temozolomide + Irinotecan for Medulloblastoma cohort did not have recurrent or refractory medulloblastoma and 3 subjects in the Temozolomide + Irinotecan for High-Grade Glioma cohort did not have high-grade glioma, and were not considered evaluable for survival.

End point type	Secondary

End point timeframe:

Baseline to Date of Death (Up to 1 Year After Treatment)

End point values	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	14		
Units: months				
median (confidence interval 95%)	16.7 (13.3 to 19.8)	9.4 (5.8 to 20.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events are reported from time of first dose of study treatment up to 30 days after last dose of study treatment .

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Temozolomide + Irinotecan for Medulloblastoma

Reporting group description:

For subjects with medulloblastoma: Irinotecan 10 mg/m^2/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

Reporting group title	Temozolomide + Irinotecan for High-Grade Glioma

Reporting group description:

For subjects with high-grade glioma: Irinotecan 10 mg/m^2/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m^2 daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

Serious adverse events	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 66 (46.97%)	5 / 17 (29.41%)	
number of deaths (all causes)	7	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood culture positive			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Medulloblastoma			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiopathy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 66 (4.55%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	3 / 66 (4.55%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	4 / 66 (6.06%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 66 (9.09%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Temozolomide + Irinotecan for Medulloblastoma	Temozolomide + Irinotecan for High-Grade Glioma	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 66 (96.97%)	17 / 17 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Melanocytic naevus			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Haematoma			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Hypotension			

subjects affected / exposed	4 / 66 (6.06%)	1 / 17 (5.88%)	
occurrences (all)	7	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	6 / 66 (9.09%)	2 / 17 (11.76%)	
occurrences (all)	6	2	
Catheter site rash			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Catheter site pain			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Catheter site swelling			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Device occlusion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	15 / 66 (22.73%)	4 / 17 (23.53%)	
occurrences (all)	18	4	
Chest pain			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Feeling abnormal			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Feeling hot			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Inflammation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	1 / 66 (1.52%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Peripheral swelling			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	14 / 66 (21.21%)	2 / 17 (11.76%)	
occurrences (all)	15	2	
Xerosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Genital lesion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Penis disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal discomfort			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	13 / 66 (19.70%)	0 / 17 (0.00%)	
occurrences (all)	21	0	
Dyspnoea			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Hiccups			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Pharyngeal erythema			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	6 / 66 (9.09%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Rhinalgia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Respiratory disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	5 / 66 (7.58%)	0 / 17 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Disorientation			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Nightmare			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	5 / 66 (7.58%)	1 / 17 (5.88%)		
occurrences (all)	22	1		
Alanine aminotransferase				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	2	0		
Blood bicarbonate decreased				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	1	0		
Aspartate aminotransferase				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	3	0		
Aspartate aminotransferase increased				
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)		
occurrences (all)	5	0		
Blood bicarbonate increased				
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)		
occurrences (all)	6	0		
Blood creatinine increased				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	1	0		
Blood culture positive				
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)		
occurrences (all)	3	0		
Blood magnesium decreased				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	1	0		
Blood phosphorus decreased				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	1	0		
Blood urea decreased				
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)		
occurrences (all)	4	0		
Blood potassium decreased				
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)		
occurrences (all)	12	0		

C-reactive protein increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Haemoglobin decreased			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Heart rate			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Haemoglobin			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Monocyte count decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Protein total increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Platelet count			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	1 / 66 (1.52%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Weight decreased			
subjects affected / exposed	6 / 66 (9.09%)	0 / 17 (0.00%)	
occurrences (all)	12	0	
Injury, poisoning and procedural complications			

Animal bite			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Fall			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Ligament sprain			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Stoma site pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Post procedural discharge			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Skin abrasion			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Wound			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Aphasia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	5 / 66 (7.58%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Cerebellar syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Cholinergic syndrome			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Cranial nerve disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Convulsion			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Cranial nerve paralysis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	6 / 66 (9.09%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Hydrocephalus			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	4	0	

Hemiparesis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	20 / 66 (30.30%)	5 / 17 (29.41%)	
occurrences (all)	35	7	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyperreflexia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Intracranial pressure increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Meningeal disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Monoparesis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Muscle spasticity			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Neurological symptom			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nystagmus			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Partial seizures			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Pyramidal tract syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Reflexes abnormal			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Slow speech			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Sensory disturbance			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Tardive dyskinesia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	5 / 66 (7.58%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Visual field defect			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tonic convulsion			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Tremor			
subjects affected / exposed	2 / 66 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Eosinopenia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	10 / 66 (15.15%)	1 / 17 (5.88%)	
occurrences (all)	40	1	
Leukopenia			
subjects affected / exposed	6 / 66 (9.09%)	0 / 17 (0.00%)	
occurrences (all)	39	0	
Lymphadenopathy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			

subjects affected / exposed	10 / 66 (15.15%)	0 / 17 (0.00%)	
occurrences (all)	62	0	
Neutropenia			
subjects affected / exposed	15 / 66 (22.73%)	1 / 17 (5.88%)	
occurrences (all)	41	6	
Thrombocytopenia			
subjects affected / exposed	17 / 66 (25.76%)	1 / 17 (5.88%)	
occurrences (all)	54	2	
Ear and labyrinth disorders			
Ear canal erythema			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Deafness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Tinnitus			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Hypoacusis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Conjunctival hyperaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eye pain			

subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Eye movement disorder			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Eyelid ptosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Strabismus			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Keratitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	22 / 66 (33.33%)	4 / 17 (23.53%)	
occurrences (all)	50	4	
Anal erosion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	8 / 66 (12.12%)	1 / 17 (5.88%)	
occurrences (all)	9	1	
Anal haemorrhage			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Anal fissure			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Aphthous stomatitis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Breath odour			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	22 / 66 (33.33%)	4 / 17 (23.53%)	
occurrences (all)	32	5	
Faecal incontinence			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	38 / 66 (57.58%)	10 / 17 (58.82%)	
occurrences (all)	136	12	
Dyspepsia			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal ulcer			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gingival bleeding			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	20 / 66 (30.30%)	7 / 17 (41.18%)	
occurrences (all)	45	12	
Mouth ulceration			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	

Lip oedema			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Oral mucosal eruption			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Odynophagia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Proctalgia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Retching			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	6	0	
Toothache			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	42 / 66 (63.64%)	13 / 17 (76.47%)	
occurrences (all)	106	36	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Alopecia			

subjects affected / exposed	2 / 66 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Dry skin			
subjects affected / exposed	4 / 66 (6.06%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Decubitus ulcer			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Ecchymosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	1 / 66 (1.52%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Petechiae			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pruritus generalised			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Rash macular			

subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	5 / 66 (7.58%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Skin hyperpigmentation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin striae			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin fissures			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Urinary retention			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Urine flow decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Urogenital haemorrhage			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	2 / 66 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	7 / 66 (10.61%)	0 / 17 (0.00%)	
occurrences (all)	9	0	
Bone pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Limb discomfort			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Joint swelling			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	3 / 66 (4.55%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Myalgia			

subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	9 / 66 (13.64%)	1 / 17 (5.88%)	
occurrences (all)	14	1	
Neck pain			
subjects affected / exposed	5 / 66 (7.58%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	5 / 66 (7.58%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Ear infection			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Device related infection			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Herpes zoster			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hordeolum			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	8 / 66 (12.12%)	3 / 17 (17.65%)	
occurrences (all)	14	3	
Oral herpes			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Pharyngitis			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Respiratory tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 66 (3.03%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	7 / 66 (10.61%)	0 / 17 (0.00%)	
occurrences (all)	10	0	
Urinary tract infection			
subjects affected / exposed	5 / 66 (7.58%)	2 / 17 (11.76%)	
occurrences (all)	9	2	

Tonsillitis			
subjects affected / exposed	1 / 66 (1.52%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Viral rhinitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 66 (16.67%)	2 / 17 (11.76%)	
occurrences (all)	17	2	
Hyperalbuminaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Hypochloraemia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Hypermagnesaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			

subjects affected / exposed	4 / 66 (6.06%)	0 / 17 (0.00%)	
occurrences (all)	16	0	
Hypomagnesaemia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Hyponatraemia			
subjects affected / exposed	5 / 66 (7.58%)	0 / 17 (0.00%)	
occurrences (all)	9	0	
Hypophagia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	3 / 66 (4.55%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Malnutrition			
subjects affected / exposed	1 / 66 (1.52%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2007	1) Subjects who had response or achieved SD with temozolomide were eligible to receive irinotecan added to this temozolomide treatment (from first cycle of adjuvant chemotherapy) for maximum period of 1 year until disease progression, unacceptable toxicity, or subject's desire to discontinue therapy, following radiotherapy and/or surgery, or other supportive care. 2) Inclusion criterion modified such that investigators could allow for effect of motor paresis due to disease in assessment in children with relatively stable neurological deficits. 3) Additional exclusion criteria on hypersensitivity/intolerance added. 5) Pathological Assessment section was added: For all high-grade glioma (HGG) subjects, pathological samples used for diagnosis were to be reviewed by a central pathologist. For recurrent medulloblastoma subjects in Cohort 1, pathological samples from initial diagnosis and/or a subsequent biopsy or resection were also reviewed if available. Rebiopsy at relapse not mandated. Central pathologist diagonosis used to determine evaluability. 6) For HGG subjects following 2 cycles of treatment, nonresponders were to discontinue study treatment and be treated with standard therapy. 7) HGG subjects with measurable residual disease were to have this confirmed by a post operative magnetic resonance imaging (MRI) performed within 72 hours of surgery. Subjects were to have a screening scan dated no more than 14 days prior treatment.
25 April 2007	1) Under Exclusion Criteria, chronic inflammatory bowel disease and/or bowel obstruction was added.
24 April 2009	1) This protocol was amended to clarify the maximum time any subject was permitted on treatment and to clarify the duration of post-treatment follow-up. 2) For subjects with recurrent or refractory medulloblastoma, treatment continued (for a maximum of 1 year) until disease progression, unacceptable toxicity, or the subject's desire to discontinue therapy. 3) Subjects were followed up every 3 months for 1 year or until death or lost to follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study had one treatment arm but two distinct cohorts with different diagnostics and treatment durations.

Notes: